COMPOSITIONS AND METHODS FOR THE TREATMENT OF ANORECTAL DISORDERS


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Abstract: Compositions and methods for the treatment of patients with anorectal disorders including colostomy are provided in which certain compounds including, but not limited to, NO donors, calcium channel blockers, cholinergic modulators (including acetylcholine storage blocking agents and acetylcholine vesicle storage blocking agents), Sg(a)1-adrenergic receptor antagonists (including $Sg(a)1$-adrenergic antagonists and $Sg(a)2$-adrenergic antagonists), $Sg(b)$-adrenergic receptor agonists (including $Sg(b)2$-adrenergic antagonists and $Sg(b)3$-adrenergic antagonists), phosphodiesterase inhibitors, cAMP-dependent protein kinase activators (e.g., cAMP mimetics), superoxide scavengers, potassium channel activators (including ATP-sensitive potassium channel activators and activators of the Maxi-K channels), estrogen-like compounds, testosterone-like compounds, benzodiazepines, adrenergic nerve inhibitors, antidiarrheal agents, HMG-CoA reductase inhibitors, smooth muscle relaxants, adenosine receptor modulators, adenylyl cyclase activators, endothelin receptor antagonists, bisphosphonates, cGMP-dependent protein kinase activators (e.g., cGMP mimetics), and combinations thereof are used.
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COMPOSITIONS AND METHODS FOR THE TREATMENT OF
ANORECTAL DISORDERS

CROSS-REFERENCES TO RELATED APPLICATIONS

[01] This application claims priority of U.S. Patent Application Serial No. 60/362,698, filed March 6, 2002, the disclosure of which is incorporated herein by reference in its entirety.

STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[02] This invention was made with government support under Grant Number 1 R43 DK 56563-01 awarded by the National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, The Government has rights in certain aspects of the invention. Additional research funding was from Cellegy Pharmaceuticals, Inc.

REFERENCE TO A "SEQUENCE LISTING," A TABLE, OR A COMPUTER PROGRAM LISTING APPENDIX SUBMITTED ON A COMPACT DISK.

[03] NOT APPLICABLE

BACKGROUND OF THE INVENTION

[04] This invention is directed to compositions and methods for treating anorectal disorders such as anal fissures, anal ulcer, hemorrhoidal diseases, constipation, and
levator spasm by administering to an appropriate anal area (for example, the anal mucosa and the perianal region) of a subject in need of such treatment an agent or combination of agents which relaxes the internal anal sphincter muscle. More specifically, this invention describes compositions and methods for treating anorectal disorders with agents which relax the internal anal sphincter or induce increase in cyclic nucleotides in the anal sphincter muscle or which mimic the actions of cyclic nucleotides or increase mucosal blood flow or reduce intracellular calcium concentrations in the affected anal sphincter muscle tissue, thereby reducing anal sphincter hypertonicity and/or spasm and facilitate healing in patients afflicted with such disorders.

[05] In general, anal fissure (fissure-in-ano), anal ulcer, hemorrhoidal diseases, and levator spasm (proctalgia fugax) are benign conditions of the anorectal area which affect subjects, including humans, of all ages, races, and sexes. While hemorrhoids and anal fissures do not garner the attention given to life threatening diseases, they are responsible for considerable suffering and disability, affecting over 26 million people in the U.S., Europe, and Japan.

[06] Hemorrhoids are specialized vascular areas lying subjacent to the anal mucosa. Symptomatic hemorrhoidal diseases are manifested by bleeding, thrombosis and/or prolapse of the hemorrhoidal tissues. Commonly, internal hemorrhoidal tissue bulges into the anal canal during defecation and results in bleeding and pain. As the tissue enlarges, further bleeding, pain, prolapse and thrombosis can ensue. The thrombosis of hemorrhoids is yet another cause of bleeding and pain.

[07] Levator spasm is a condition affecting women more frequently than men. This syndrome is characterized by spasm of the levator ani muscle, a portion of the anal sphincter complex. The patient suffering from levator spasm may experience severe, episodic rectal pain. A physical exam may reveal spasm of the puborectalis muscle and pain may be reproduced by direct pressure on this muscle. Bleeding is normally not associated with this condition.

[08] Hemorrhoids are the most prevalent anorectal disorder and are the most common cause of hematochezia (i.e., passage of bloody stools). Hemorrhoidal disease is the consequence of distal displacement of the anal cushions, which normally play an important role in continence. The causes of hemorrhoids are not known. The most consistently demonstrated physiological abnormality is increased resting anal pressure (Hancock B.D., Br J Surg 64(2):92-5 (1975); Loder, P.B., Br J Surg 81(7):946-54 (1994)). Patients with non-prolapsing hemorrhoids appear to have higher anal pressures than those
with prolapsing hemorrhoids (Arabi, Y. et al., *Am J Surg* 134(5):608-10 (1977); Sun, W.M. et al., *Br J Surg* 77(4): 458-62, (1990)), although the therapeutic implications of this observation remain unclear. Treatment is dependent on the degree of hemorrhoid prolapse and symptoms. Most cases (first- and second-degree hemorrhoids) generally respond to conservative medical treatment (e.g., dietary changes, sitz baths) or non-surgical procedures (e.g., rubber band ligation). Acutely thrombosed external hemorrhoids are usually characterized by severe anal pain, and internal anal sphincter hypertonia may play a role in the etiology of this pain (Gorfine, S.R., *Dis Colon Rectum* 38(5): 453-7 (1995)). Surgical excision of symptomatic thrombosed external hemorrhoids is indicated within 48 to 72 hours of the onset of pain. Post-hemorrhoidectomy pain is severe, disproportionate to the surgery itself, and requires the use of narcotic analgesics, which unfortunately complicate recovery by causing constipation. Anal dilatation and lateral internal sphincterotomy as treatments to reduce anal sphincter pressure in hemorrhoids have been used successfully, both as stand alone procedures and in conjunction with hemorrhoidectomy (Keighley, M.R. et al., *Br Med J* J2(6196):967-9 (1979); Schouten W.R. et al., *Dis Colon Rectum* 28(12), 869-72 (1986); Galizia et al., *Eur J Surg* 166(3):223-8 (2000)).

Others have reported that the addition of lateral internal sphincterotomy to routine hemorrhoidectomy is unnecessary and carries the added risk of incontinence (Mathai, V. et al., *Br J Surg*. 83(3):380-2 (1996)).

Anal fissure is one of the most common causes of anorectal pain. Anal fissures are tears in the mucosa of the distal anal canal, usually along the posterior midline. An anal fissure or ulcer can be associated with another systemic or local disease, but more frequently presents as an isolated finding. The typical idiopathic fissure or ulcer is confined to the anal mucosa and usually lies in the posterior midline, distal to the dentate line. The exact causes of anal fissures remain unknown. They are often associated with trauma, e.g., passage of a hard stool, but can also occur during bouts of diarrhea, childbirth, or ulceration of a hemorrhoid (Lund, J.N. et al., *Br J Surg*. 83(10): 1335-44 (1996)). An individual with an anal fissure or ulcer frequently experiences anal pain and bleeding, the pain being more pronounced during and after bowel movements, and may last for as long as 3 hours following bowel movements. The most common symptom is pain at defecation, which can be quite severe and last for a variable time afterwards. The pain is chiefly due to an intense spasm of the internal anal sphincter muscle. Most anal fissures are adequately treated with sitz baths, stool softeners, and analgesics. Approximately 60% of acute anal fissures will heal within three weeks using this treatment regimen. Acute anal fissures, which do not heal, become
chronic anal fissures or anal ulcers. Hypertonicity of the internal anal sphincter muscle and mucosal ischemia are thought to play an important role in the pathogenesis of chronic anal fissures (Schouten W.R. et al., *Dis Colon Rectum* 37(7):664-9 (1994); Lund, J.N. et al., *Br J Surg* 83(10): 1335-44 (1996)). Anodermal blood flow at the posterior midline is less than other regions of the anal canal, and perfusion of the posterior mucosa is inversely related to anal pressure. Chronic anal fissures are typically not responsive to conservative medical therapy. Current treatments are therefore directed at relieving sphincter spasm, and include anal dilatation (under anesthesia), or more commonly, lateral sphincterotomy of the internal anal sphincter. Healing occurs following surgical sphincterotomy in 95% of cases.

Successful sphincterotomy (or anal dilatation) is associated with a significant decrease in intra-anal pressure and increase in anodermal blood flow (Lund, J.N. et al., *Br J Surg* 83(10): 1335-44, (1996); Schouten W.R. et al., *Scan J Gastroenterol. Suppl* 218: 78-81 (1996)). However, up to 35% of patients may experience some form of incontinence following the surgical procedure (Sharp, F.R., *Am J Surg* 171(5):512-5 (1996)). Incontinence of stool and flatulence is a humiliating disability with numerous social, medical, and financial implications. There is clearly a large unmet medical need to develop effective, non-surgical treatments for anal fissure and other colorectal conditions, including acute hemorrhoidal disease, hemorrhoidectomy pain, proctalgia fugax, and severe constipation. Considerable recent progress has been made in the understanding of anorectal physiology and pharmacology. These new insights provide important implications and opportunities for the pharmacological management of colorectal disorders.

11 Sphincters are circular groups of smooth muscle that control the orifices of hollow organs. They are present throughout the gastrointestinal tract and control the passage of materials through this system of the body. When constricted, sphincters close orifices leading to or from the hollow organs, such as the stomach, intestine, rectum, etc. In order for the orifice to open, the sphincter must relax. The sphincter that closes the anus (sphincter ani) consists of two sphincter muscle groups. The external anal sphincter is a thin flat plane of striated muscle fibers adherent to the integument surrounding the margin of the anus. It is innervated by motor neurons and is under voluntary control. The internal anal sphincter (IAS) is a ring of smooth muscle that surrounds the anal canal and is formed by a specialized aggregation of involuntary circular smooth muscle fibers of the intestine. The IAS is largely responsible for resting anal sphincter pressure and continence which is maintained by intrinsic myogenic tone and regulated by both intrinsic innervation and extrinsic innervation from the extrinsic autonomic nervous system (Penninckx, F. et al.,


responses to phenylephrine and potassium chloride (a membrane depolarizing agent). However, it remains to be determined whether β-adrenergic agonists offer disease-specific advantages for the treatment of chronic anal fissure.

[14] The IAS relaxes in response to rectal distention (the rectoanal inhibitory reflex). The nerves mediating the rectoanal inhibitory reflex lie entirely within the wall of the gut (enteric inhibitory neurons), and descend from the rectum to the IAS. Electrical field stimulation (EFS) mimics the effects of intrinsic nerve stimulation on isolated smooth muscle strips. IAS strips are relaxed by EFS, an effect that is abolished by the neurotoxin tetrodotoxin, but is unaffected by antagonists of the classical neurotransmitters, acetylcholine or norepinephrine. The inhibitory nerves are thus classified as non-adrenergic, non-cholinergic (NANC) nerves. Adenosine triphosphate (ATP) and vasoactive intestinal peptide (VIP) were first suggested as NANC neurotransmitter candidates since they mimicked the relaxation elicited by electrical stimulation of motor nerve fibers (Burnstock, G. et al., Br J Pharmacol. 46(2):234-42 (1972); Bitar, K.N. et al., Science 216(4545): 531-3 (1982)). However, ATP and VIP, either separately or together, could not account for all inhibitory neurotransmission in gastrointestinal smooth muscle, and their roles have not been established in man (Burleigh, D.E. et al., Gastroenterology 77(3): 484-90 (1979); Burleigh, D.E., J Pharm Pharmacol 35(4):258-60 (1983); Brookes, S.J., J Gastroenterol Hepatol 8(6):590-603 (1993).

[15] Recent studies indicate that NO plays an important role in NANC nerve mediated relaxation of the IAS. In an animal model, Rattan, S. et al., (Rattan, S. et al., Am J Physiol 262 (1 Pt 1):G107-12 (1992) demonstrated that IAS relaxation associated with the rectoanal reflex (induced by rectal balloon distention), or neural stimulation, was blocked by inhibition of NO synthase (NOS) with L-NNA [N⁵-(nitroamidino)-L-2,5-diaminopentanoic acid], but not with D-NNA. Block of the rectoanal reflex by L-NNR was reversed by L-arginine in a stereospecific manner, implicating NO or NO-like substances as mediators of NANC nerve mediated IAS relaxation. NO was shown to directly relax the IAS in a concentration-dependent manner in vitro, mimicking the effect of NANC nerve stimulation by EFS. NANC nerve-mediated relaxation of IAS strips in vitro was blocked by inhibition of NO synthase with L-NNA, and the block was reversed by L-arginine, but not D-arginine (Rattan, S. et al., Am J Physiol 262 (1 Pt 1):G107-12, (1992) and Rattan, S. et al., Gastroenterology 103(1):43-50 (1992)). Similar observations have been made using isolated muscle strips of human IAS (Burleigh Gastroenterology 102(2): 679-83 (1992); O'Kelly, T.J. et al., Br J Surg 80(10): 1337-41, (1993)). The direct release of NO following NANC nerve
stimulation of opossum IAS strips was demonstrated using a specific chemiluminescence detection method (Chakder, S. et al., *Am J Physiol.*, 264 (4Pt 1)G702-7 (1993)). O’Kelly (O’Kelly, T.J. et al., *Dis Colon Rectum* 37(4): 35-7 (1994)) recently demonstrated the presence of NOS in neurons of the myenteric plexus that project throughout the IAS and lay in close proximity to smooth muscle cells. In Hirschsprung’s disease, a condition in which the rectoanal reflex is absent, NOS containing nerves were absent from the non-relaxing segment, but present in the normal segment of the gut (O’Kelly, T.J. et al., *J Pediatric Surgery* 29(2): 294-9 (1994)). These observations fulfill most of the criteria for NO as an inhibitory mediator or neurotransmitter.

[16] A number of potent vasodilators are known to chemically release NO on or within target cells, and thus are known as NO donors. Some NO donors, e.g., nitroglycerin, are widely used therapeutically as coronary vasodilators to treat heart disease. In keeping with the role of NO as an inhibitory neurotransmitter mediating relaxation of the IAS, NO donors are beginning to be explored clinically as drugs to treat anal disorders associated with IAS hypertonicity. Significantly, nitroglycerin (Gorfine, S.R., *Dis Colon Rectum*, 38(5):453-6 (1995); Watson, S.J. et al., *Br J Surgery* 83(6):771-5, 1996; Lund, J.N. et al., *Lancet* 349: 9044 (1997)) and isosorbide dinitrate have been used to effect a reversible chemical sphincterotomy in patients with chronic anal fissure. These drugs reduce maximal resting anal pressure and, improve anodermal blood flow, reduce pain, and heal fissures in a majority of the patients. Nitroglycerin has also been shown to reduce the throbbing pain of acute hemorrhoidal thrombosis and proctalgia fugax (Gorfine, S.R., *Dis Colon Rectum* 38(5):453-6 (1995); Lowenstein, B. et al., *Dis Colon Rectum* 41(5):667-8 (1998)).

[17] U.S. Patents No. 5,504,117 and No. 5,693,676 describe the use of NO donors for the treatment of anorectal conditions. One potential problem associated with topical nitroglycerin therapy is the incidence of headache, particularly at higher doses (Palazzo, F.F. et al., *J R Coll Surg Edinb* 45(3):168-70 (2000)). The headache is presumably due to systemic effects of nitroglycerin and is generally transient, but can affect patient compliance. There is a need for treatment methods strategies which enhance the local effect of nitroglycerin and minimize its systemic side effects. A second potential problem of nitrates is the development of drug tolerance, a problem well documented for nitrate therapy in cardiovascular disease (Fung, H.L. et al., *Cardiovasc Drugs Ther* 8(3):489-99, (1994)). Tolerance, if present, would limit the ability of nitroglycerin to produce a sustained relaxation of the IAS, which may be necessary for healing particularly refractant chronic anal fissures.
However, the recent animal studies show that anorectal smooth muscle does not develop

[18] There is clearly a significant need for other non-surgical treatments of
anorectal disorders, including, for example, anal fissures and other anorectal conditions
associated with anal sphincter spasm and or hypertonicity, including acute hemorrhoidal
diseases and proctalgia fugax.

[19] There is thus a need for alternative methods and compositions for
reducing anal sphincter pressure that complement or supplant nitroglycerin.

[20] The use of a topical or intra-rectal pharmaceutical preparation that
complements or supplants nitroglycerin for the treatment of chronic anal fissures and other
anorectal disorders can provide a more effective alternative to surgery for these painful
disorders.

SUMMARY OF THE INVENTION

[21] The present invention is based on the discovery that compounds such
as NO donors, calcium channel blockers, cholinergic modulators (including acetylcholine
storage blocking agents and acetylcholine vesicle storage blocking agents), α-adrenergic
receptor antagonists (including α1-adrenergic antagonists and α2-adrenergic antagonists), β-
adrenergic receptor agonists (including β2-adrenergic antagonists and β3-adrenergic
agonists), phosphodiesterase inhibitors, cAMP-dependent protein kinase activators (e.g.,
cAMP mimetics), superoxide scavengers, potassium channel activators (including ATP-
sensitive potassium channel activators and activators of the Maxi-K channels), estrogen-like
compounds, testosterone-like compounds, benzodiazepines, adrenergic nerve inhibitors,
antidiarrheal agents, HMG-CoA reductase inhibitors, smooth muscle relaxants, adenosine
receptor modulators, adenylyl cyclase activators, endothelin receptor antagonists,
bisphosphonates, cGMP-dependent protein kinase activators (e.g., cGMP mimetics) are
effective for treating a variety of anorectal disorders including, but not limited to, anal
fissure, hemorrhoids, anorectal ulcers, levator spasm, anorectal itching and burning, non-
specific anorectal pain, itching or burning, chronic idiopathic anal pain, inflammation and
inflammatory lesions in the rectal, anal and perianal region, post-surgical pain in the rectal,
anal and perianal regions, and abnormal elevation of pressure within the lower
gastrointestinal tract, including particularly, abnormally increased resting anal pressures.

[22] In one aspect, the present invention provides a method for treating
anorectal disorders, the method comprising administering to a patient in need thereof a
compound selected from the group consisting of cAMP-dependent protein kinase activators, superoxide scavengers, benzodiazepines, adenosine receptor modulators, antidiarrheal agents, HMG-CoA reductase inhibitors, endothelin receptor antagonists, adenylyl cyclase activators and potassium channel activators (including ATP-sensitive potassium channel activators as well as activators of the Maxi-K channel) in a therapeutically effective amount. In one embodiment, the anorectal disorder is selected from the group consisting of anal fissure, hemorrhoids, levator spasm, anal ulcer, and anorectal pain, burning, or itching, inflammation or inflammatory lesion in the rectal, anal or perianal region, post-surgical rectal, anal or perianal pain, and chronic idiopathic anal pain. In another embodiment, at least two different compounds selected from the group consisting of cAMP-dependent protein kinase activators, superoxide scavengers, benzodiazepines, adenosine receptor modulators, antidiarrheal agents, HMG-CoA reductase inhibitors, endothelin receptor antagonists, adenylyl cyclase activators, testosterone-like compounds and potassium channel activators (including those that are ATP-sensitive and those that activate the Maxi-K channel) are administered to the patient. In another embodiment, a first compound selected from the group consisting of cAMP-dependent protein kinase activators, superoxide scavengers, benzodiazepines, adenosine receptor modulators, antidiarrheal agents, HMG-CoA reductase inhibitors, testosterone-like compounds and potassium channel activators; and a second compound selected from the group consisting of cAMP-dependent protein kinase activators, superoxide scavengers, benzodiazepines, adenosine receptor modulators, antidiarrheal agents, HMG-CoA reductase inhibitors, endothelin receptor antagonists, adenylyl cyclase activators, potassium channel activators, calcium channel blockers, cholinergic modulators (e.g., acetylcholine storage blocking agents), α-adrenergic receptor antagonists, β-adrenergic agonists, adrenergic nerve inhibitors, NO donors, phosphodiesterase inhibitors, estrogen-like compounds, testosterone-like compounds, and smooth muscle relaxants are administered to the patient. The compound may be administered via the oral, parenteral (intravenous, intramuscular or subcutaneous), transdermal, pulmonary or transmucosal (nasal, buccal, cervical, vaginal, anorectal) route for systemic and/or local delivery. For topical administration to the skin and mucous membranes, the compound may be formulated as a gel, ointment, cream, lotion, powder, solution, suspension, spray, paste, oil, or foam. In some embodiments, plastic dilators of the type used to progressively stretch the contracted muscles of the rectum can be impregnated with the compound to deliver the compound topically to the anorectal area while stretching the sphincter muscles. In other embodiments, the compound is delivered continuously.
continuous delivery, a dermal patches containing the compound may be used or an anorectal suppository containing with the compound may be inserted into the anal canal.

[23] In another aspect, the present invention provides a method of treating anorectal disorders, the method comprising administering to a patient in need thereof a compound selected from the group consisting of calcium channel blockers, cholinergic modulators, β-adrenergic agonists, and adrenergic nerve inhibitors. In one embodiment, at least two compounds selected from the group consisting of calcium channel blockers, cholinergic modulators, β-adrenergic agonists, and adrenergic nerve inhibitors are administered to the patient. In another embodiment, a first compound selected from the group consisting of calcium channel blockers, cholinergic modulators, β-adrenergic agonists, and adrenergic nerve inhibitors; and a second compound selected from the group consisting of cAMP-dependent protein kinase activators, superoxide scavengers, benzodiazepines, adenosine receptor modulators, antidiarrheal agents, HMG-CoA reductase inhibitors, endothelin receptor antagonists, adenylyl cyclase activators, potassium channel activators (e.g., ATP-sensitive potassium channel activators), calcium channel blockers, cholinergic modulators (e.g., acetylcholine storage blocking agents), α-adrenergic receptor antagonists, β-adrenergic agonists, adrenergic nerve inhibitors, NO donors, phosphodiesterase inhibitors, estrogen-like compounds, testosterone-like compounds, and smooth muscle relaxants are administered to the patient. The compound may be administered via the oral, parenteral (intravenous, intramuscular or subcutaneous), transdermal, pulmonary or transmucosal (nasal, buccal, cervical, vaginal, anorectal) route for systemic and/or local delivery. For topical administration to the skin and/or mucous membranes, the compounds may be formulated as a gel, ointment, cream, lotion, powder, solution, suspension, spray, paste, oil, or foam. Plastic dilators of the type used to progressively stretch the contracted muscles of the rectum impregnated with the compound can be used to deliver the compound topically to the anorectal region while simultaneously stretching the rectal muscles. The compound may also be delivered continuously via a rectal suppository.

[24] In another aspect, the present invention provides a method of treating an anorectal disorder, the method comprising administering to a patient in need thereof a compound selected from the group consisting of cholinergic modulators and adrenergic nerve inhibitors. In one embodiment, at least two compounds selected from the group consisting of cholinergic modulators and adrenergic nerve inhibitors are administered to the patient. In another embodiment, a first compound selected from the group consisting of cholinergic
modulators and adrenergic nerve inhibitors; and a second compound selected from the group consisting of cAMP-dependent protein kinase activators, superoxide scavengers, benzodiazepines, adenosine receptor modulators, antidiarrheal agents, HMG-CoA reductase inhibitors, endothelin receptor antagonists, adenyl cyclase activators, potassium channel activators, calcium channel blockers, cholinergic modulators, α-adrenergic receptor antagonists, β-adrenergic agonists, adrenergic nerve inhibitors, NO donors, phosphodiesterase inhibitors, estrogen-like compounds, testosterone-like compounds, and smooth muscle relaxants are administered to the patient. Again, the compounds may be administered via the oral, parenteral (intravenous, intramuscular or subcutaneous), transdermal, pulmonary or transmucosal (nasal, buccal, cervical, vaginal, anorectal) route for systemic and/or local delivery. In one embodiment, the compounds are administered topically to the skin and/or mucous membranes and are in a form selected from the group consisting of gel, ointment, cream, lotion, powder, solution, suspension, spray, paste, oil, and foam. In another embodiment, the compound is delivered continuously by inserting a rectal suppository impregnated with the compound.

[25] In yet another aspect, the present invention is directed to a method of treating an anorectal disorder, the method comprising administering to a patient in need thereof a compounds selected from the group consisting of NO donors, β-adrenergic agonists and phosphodiesterase inhibitors. In one embodiment, the method comprises administering to the patient at least two compounds selected from the group consisting of NO donors, β-adrenergic agonists, and phosphodiesterase inhibitors. In another embodiment, a first compound selected from the group consisting of NO donors, β-adrenergic agonists, and phosphodiesterase inhibitors; and a second compound selected from the group consisting of cAMP-dependent protein kinase activators, superoxide scavengers, benzodiazepines, adenosine receptor modulators, antidiarrheal agents, HMG-CoA reductase inhibitors, endothelin receptor antagonists, adenyl cyclase activators, potassium channel activators (e.g., ATP-sensitive potassium channel activators), calcium channel blockers, cholinergic modulators, α-adrenergic receptor antagonists, β-adrenergic agonists, adrenergic nerve inhibitors, NO donors, phosphodiesterase inhibitors, estrogen-like compounds, testosterone-like compounds, and smooth muscle relaxants are administered to the patient. In particular embodiments, the compounds are administered via the oral, parenteral (intravenous, intramuscular or subcutaneous), transdermal, pulmonary or transmucosal (nasal, buccal, cervical, vaginal, anorectal) route for systemic and/or local delivery. For topical
administration to the skin and/or mucous membranes, the compounds are preferably in a form selected from the group consisting of gel, ointment, cream, lotion, powder, solution, suspension, spray, paste, oil, and foam. In other embodiments, the compound is delivered continuously. For continuous delivery, a rectal suppository containing the compositions may be inserted.

[26] In still another aspect, a method of treating an anorectal disorder is provided herein, the method comprising administering to a patient in need thereof a compound selected from the group consisting of NO donors, calcium channel blockers, cholinergic modulators, \( \alpha \)-adrenergic antagonists, \( \beta \)-adrenergic agonists, phosphodiesterase inhibitors, adrenergic nerve inhibitors, and estrogen-like compounds. Again, the compounds may be administered alone or in combination. In one embodiment, at least two compounds selected from the group consisting of NO donors, calcium channel blockers, cholinergic modulators, \( \alpha \)-adrenergic antagonists, \( \beta \)-adrenergic agonists, phosphodiesterase inhibitors, adrenergic nerve inhibitors, and estrogen-like compounds are administered to the patient. In another embodiment, a first compound selected from the group consisting of NO donors, calcium channel blockers, cholinergic modulators, \( \alpha \)-adrenergic antagonists, \( \beta \)-adrenergic agonists, phosphodiesterase inhibitors, adrenergic nerve inhibitors, and estrogen-like compounds; and a second compound selected from the group consisting of cAMP-dependent protein kinase activators, superoxide scavengers, benzodiazepines, adenosine receptor modulators, antidiarrheal agents, HMG-CoA reductase inhibitors, endothelin receptor antagonists, adenylyl cyclase activators, potassium channel activators (e.g., ATP-sensitive potassium channel activators as well as activators of the Maxi-K channel), calcium channel blockers, cholinergic modulators, \( \alpha \)-adrenergic receptor antagonists, \( \beta \)-adrenergic agonists, adrenergic nerve inhibitors, NO donors, phosphodiesterase inhibitors, estrogen-like compounds, testosterone-like compounds, and smooth muscle relaxants are administered to the patient. Administration may be via the oral, parenteral (intravenous, intramuscular or subcutaneous), transdermal, pulmonary or transmucosal (nasal, buccal, cervical, vaginal, anorectal) route for systemic and/or local delivery. For topical administration to the skin and/or mucous membranes, the compounds may be formulated as a gel, ointment, cream, lotion, powder, solution, suspension, spray, paste, oil, or foam. Administration can also be by continuous delivery. For continuous delivery, a rectal suppository containing said compound is inserted.
[27] In still another aspect, a method for treating non-specific pain, itching or burning of the anorectal area, is provided herein, the method comprising administering to a patient in need thereof a compound selected from the group consisting of NO donors, calcium channel blockers, cholinergic modulators (e.g., acetylcholine storage blocking agents and acetylcholine vesicle transport blocking agents), α-adrenergic receptor antagonists (e.g., α₁-adrenergic receptor antagonists and α₂-adrenergic receptor antagonists), β-adrenergic agonists, phosphodiesterase inhibitors, adrenergic nerve inhibitors, estrogen-like compounds, testosterone-like compounds and smooth muscle relaxants. Again, the compounds may be administered alone or in combination. In one embodiment, at least two compounds selected from the group consisting of NO donors, calcium channel blockers, cholinergic modulators, α-adrenergic receptor antagonists (e.g., α₁-adrenergic receptor antagonists and α₂-adrenergic receptor antagonists), β-adrenergic agonists, phosphodiesterase inhibitors, adrenergic nerve inhibitors, estrogen-like compounds, testosterone-like compounds and smooth muscle relaxants are administered to the patient. In another embodiment, a first compound selected from the group consisting of NO donors, calcium channel blockers, cholinergic modulators, α-adrenergic receptor antagonists, β-adrenergic agonists, phosphodiesterase inhibitors, adrenergic nerve inhibitors, estrogen-like compounds, testosterone-like compounds and smooth muscle relaxants; and a second compound selected from the group consisting of cAMP-dependent protein kinase activators, superoxide scavengers, benzodiazepines, adenosine receptor modulators, antidiarrheal agents, HMG-CoA reductase inhibitors, endothelin receptor antagonists, adenylyl cyclase activators, potassium channel activators, calcium channel blockers, cholinergic modulators, α-adrenergic receptor antagonists, β-adrenergic agonists, adrenergic nerve inhibitors, NO donors, phosphodiesterase inhibitors, estrogen-like compounds, testosterone-like compounds, and smooth muscle relaxants are administered to the patient. Administration may be via the oral, parenteral (intravenous, intramuscular or subcutaneous), transdermal, pulmonary or transmucosal (nasal, buccal, cervical, vaginal, anorectal) route for systemic and/or local delivery. For topical administration to the skin and/or mucous membranes, the compounds may be formulated as a gel, ointment, cream, lotion, powder, solution, suspension, spray, paste, oil, or foam. Administration can also be by continuous delivery. For continuous delivery, a rectal suppository providing said compound is inserted.

[28] In still another aspect, a method for treating anorectal disorders is provided, the method comprising administering to a patient in need thereof a compound
selected from the group consisting of cAMP-dependent protein kinase activators, superoxide scavengers, benzodiazepines, adenosine receptor modulators, antidiarrheal agents, HMG-CoA reductase inhibitors, endothelin receptor antagonists, adenylyl cyclase activators, potassium channel activators, calcium channel blockers, cholinergic modulators, β-adrenergic agonists, adrenergic nerve inhibitors, NO donors, phosphodiesterase inhibitors, α-adrenergic receptor antagonists (e.g., α₁-adrenergic receptor antagonists and α₂-adrenergic receptor antagonists) and smooth muscle relaxants. Again, the compounds may be administered alone or in combination. In one embodiment, at least two compounds selected from the group consisting of cAMP-dependent protein kinase activators, superoxide scavengers, benzodiazepines, adenosine receptor modulators, antidiarrheal agents, HMG-CoA reductase inhibitors, endothelin receptor antagonists, adenylyl cyclase activators, potassium channel activators, calcium channel blockers, cholinergic modulators, β-adrenergic agonists, adrenergic nerve inhibitors, NO donors, phosphodiesterase inhibitors, α-adrenergic receptor antagonists and smooth muscle relaxants are administered to the patient. In another embodiment, a first compound selected from the group consisting of cAMP-dependent protein kinase activators, superoxide scavengers, benzodiazepines, adenosine receptor modulators, antidiarrheal agents, HMG-CoA reductase inhibitors, endothelin receptor antagonists, adenylyl cyclase activators, potassium channel activators, calcium channel blockers, cholinergic modulators, β-adrenergic agonists, adrenergic nerve inhibitors, NO donors, phosphodiesterase inhibitors, α₁-adrenergic receptor antagonists, α₂-adrenergic receptor antagonists, acetylcholine storage blocking agents, and smooth muscle relaxants; and a second compound selected from the group consisting of cAMP-dependent protein kinase activators, superoxide scavengers, benzodiazepines, adenosine receptor modulators, antidiarrheal agents, HMG-CoA reductase inhibitors, endothelin receptor antagonists, adenylyl cyclase activators, potassium channel activators, calcium channel blockers, cholinergic modulators, α-adrenergic receptor antagonists, β-adrenergic agonists, adrenergic nerve inhibitors, NO donors, phosphodiesterase inhibitors, estrogen-like compounds, testosterone-like compounds, and smooth muscle relaxants are administered to the patient. Administration may be via the oral, parenteral (intravenous, intramuscular or subcutaneous), transdermal, pulmonary or transmucosal (nasal, buccal, cervical, vaginal, anorectal) route for systemic and/or local delivery. For topical administration to the skin and/or mucous membranes, the compounds may be formulated as a gel, ointment, cream, lotion, powder,
solution, suspension, spray, paste, oil, or foam. Administration can also be by continuous
delivery. For continuous delivery, a rectal suppository with said compound is inserted.

[29] In still another aspect, pharmaceutical kits comprising one or more
containers filled with one or more of the ingredients of the pharmaceutical compounds and/or
compositions of the present invention are provided herein. Such kits can also include, for
example, other compounds and/or compositions (e.g., permeation enhancers, lubricants, etc.),
a device(s) for administering the compound and/or compositions, and written instructions in a
form prescribed by a government agency regulating the manufacture, use or sale of
pharmaceuticals, medical devices or biological products, which instructions can also reflect
approval by the agency of manufacture, use or sale for human administration.

[30] In one of its aspects, the anorectal disorder is a colostomy and the
invention provides a method of treating a colostomy patient, the method comprising
administering to said patient a therapeutically effective amount of a composition comprising
at least one agent selected from the group consisting of NO donors, phosphodiesterase type II
inhibitors, phosphodiesterase type IV inhibitors, phosphodiesterase type V inhibitors,
nonspecific phosphodiesterase inhibitors, superoxide scavengers, β-adrenergic agonists,
calcium channel blockers, L-type Ca^{2+} channel blockers, cAMP-dependent protein kinase
activators, α-adrenergic antagonists (e.g., α_{1}-adrenergic antagonists and α_{2} adrenergic
antagonists), estrogen-like compounds, endothelin receptor antagonists, adenylyl cyclase
activators, potassium channel activators (e.g., ATP-sensitive potassium channel activators),
adenosine receptor modulators, benzodiazepines, and smooth muscle relaxants. The
composition may be administered with a colostomy irrigation fluid to improve (e.g., make
faster or more thorough) the colostomy irrigation.

[31] In one aspect, the present invention provides compositions for the
treatment of anorectal disorders comprising a nitric oxide donor in combination with a second
agent (typically one which modulates levels of cAMP or cGMP). The second agent can be a
phosphodiesterase type V (PDE V) inhibitor, a phosphodiesterase type II (PDE II) inhibitor, a
phosphodiesterase type IV (PDE IV) inhibitor, a nonspecific PDE inhibitor, a β-adrenergic
agonist, a cAMP-dependent protein kinase activator, an estrogen or estrogen-like compound,
or an α_{1}-adrenergic antagonist. The agent can also be a superoxide anion (O_{2}^{-}) scavenger, an
ATP-sensitive K^{+} channel activator, a adrenergic nerve inhibitor, or a smooth muscle
relaxant, although these agents do not directly modulate either cAMP or cGMP levels. The
present invention further provides methods of using these compositions.
[32] In another aspect, the present invention provides compositions for the
treatment of anorectal disorders comprising a phosphodiesterase inhibitor, preferably a PDE
II inhibitor, a PDE IV inhibitor or a PDE V inhibitor, either alone or in combination with
another agent selected from β-adrenergic receptor agonists, α₁-adrenergic antagonists,
estrogens, L-type Ca²⁺ channel blockers, K⁺ channel activators (e.g., ATP-sensitive K⁺
channel activators or activators of the Maxi-K channel) or smooth muscle relaxants, in
combination with a pharmaceutically acceptable carrier. The present invention also provides
methods of using these compositions.

[33] In another aspect, the present invention provides compositions for the
treatment of anorectal disorders comprising a β-adrenergic receptor agonist, preferably a β₂-
or β₃-adrenergic receptor agonist, either alone or in combination with another agent selected
from cAMP-hydrolyzing PDE inhibitors (e.g., a PDE IV inhibitor), nonspecific PDE
inhibitors, α₁-adrenergic antagonists, estrogens or estrogen-like compounds, L-type Ca²⁺
channel blockers, or K⁺ channel activators (e.g., ATP-sensitive K⁺ channel activators or
activators of the Maxi-K channel), and methods of using those compositions.

[34] In yet another aspect, the present invention provides compositions for
the treatment of anorectal disorders comprising an K⁺ channel activator (e.g., ATP-sensitive
K⁺ channel activators or activators of the Maxi-K channel), either alone or in combination
with another agent selected from cAMP-dependent protein kinase activators, α₁-adrenergic
antagonists, estrogens, L-type Ca²⁺ channel blockers, or smooth muscle relaxants, and
methods of using those compositions.

[35] In still another aspect, the present invention provides compositions for
the treatment of anorectal disorders comprising an α₁-adrenergic antagonist, either alone or in
combination with another agent selected from cAMP-hydrolyzing PDE inhibitors (preferably
a PDE IV inhibitor) or smooth muscle relaxants, and methods of using those compositions.

[36] In another aspect, the present invention provides compositions for the
treatment of anorectal disorders comprising β₂-adrenergic agonists, either alone or in
combination with another agent. Methods for the use of these compositions are also
provided. In one group of embodiments, the β₂-adrenergic agonists are used alone. In a
preferred embodiment, the β₂-adrenergic agonists is combined with a phosphodiesterase
inhibitor. In another embodiment, the β₂-adrenergic agonists are combined with one or more
other IAS relaxing agents.

[37] In another aspect, the present invention provides compositions for the
treatment of anorectal disorders comprising adenosine receptor modulators, either alone or in
combination with another agent. Methods for the use of these compositions are also provided. In one group of embodiments, adenosine receptor modulators are used alone. In another group of embodiments, the adenosine receptor modulators are combined with at least one other IAS relaxing agent.

[38] In another aspect, the present invention provides compositions for the treatment of anorectal disorders comprising cyclic nucleotide-dependent protein kinase activators (e.g., cAMP- and cGMP-dependent protein kinase activators), either alone or in combination with another agent. Methods for the use of these compositions are also provided. In one group of embodiments, cGMP-dependent protein kinase activators are used alone. In another group of embodiments, nonspecific cyclic nucleotide-dependent protein kinase activators are used alone. In yet another group of embodiments, nonspecific cyclic nucleotide-dependent protein kinase activators are used in combination with smooth muscle relaxants. In still another group of embodiments, cAMP-dependent protein kinase activators are provided in combination with L-type Ca\(^{2+}\) channel blockers.

[39] In yet another aspect, the present invention provides a composition for the treatment of anorectal disorders comprising a methylxanthine compound. In preferred embodiments, the compound is theophylline or dyphylline. In still another embodiment, the methylxanthine compound is used alone. In still another embodiment, the methylxanthine compound is combined with another IAS relaxing agent.

[40] In yet another aspect, the present invention provides compositions for the treatment of anorectal disorders comprising an estrogen or other estrogenic compound, either alone or in combination with another agent. Methods for the use of these compositions are also provided. In one group of embodiments, estrogenic compounds are used alone. In another group of embodiments, the estrogenic compounds are used in combination with a second agent selected from phosphodiesterase inhibitors, β-adrenergic receptor agonists, α\(_1\)-adrenergic antagonists, L-type Ca\(^{2+}\) channel blockers, K\(^{+}\) channel activators (e.g., ATP-sensitive K\(^{+}\) channel activators or activators of the Maxi-K channel), or smooth muscle relaxants, in combination with a pharmaceutically acceptable carrier. The present invention further provides methods of using these compositions.

[41] In another aspect, the invention provides a promising new approach for treating anal disorders is the topical application of a nitric oxide (NO) donor to an appropriate anal area. Nitric oxide has been shown to bring about a concentration-dependent reduction in the resting tension of internal sphincter smooth muscle strips *in vitro* (Rattan, S. *et al.* *Am J Physiol* **262**:G107-112 (1992)), and NO donors (e.g., nitroglycerin, isosorbide dinitrate,
isosorbide mononitrate, and L-arginine) have been shown to reduce anal pressure in humans. Schouten, W.R. et al., “Pathophysiological aspects and clinical outcome of intra-anal application of isosorbide dinitrate in patients with chronic anal fissure,” *Gut* 39:465-9 (1996); Farid, M., *Br J Surg* 84:1 (1997); and Hechtman, H.B. et al., *Arch. Surg* 131:775-778 (1996). NO has also been shown to mediate adaptive relaxation of other sphincters in the gastrointestinal tract including the lower esophageal sphincter (Conklin et al., *Gastroenterology* 104:1439-1444 (1993); Trottrup et al., *Br J Pharmacol* 104:113-116 (1991)), pyloric sphincter (Bayguinov et al., *Am J Physiol* 264:G975-983 (1993), sphincter of Oddi (Moureille et al., *Gastroenterology* 105:1299-1305 (1993)), and the ileocolic sphincter (Ward et al., *Br J Pharmacol* 105:776-782 (1992)). It is thought that NO or NO-like substances serve as important control mechanisms for the general phenomenon of gastrointestinal adaptive relaxation. Despite the initial promise of NO donors, tachyphylaxis has been observed for members of this class of agents. Surprisingly, the present invention provides compositions that are useful to overcome side effects and problems associated with the current therapies.

[42] Where the compounds discussed above act through mechanisms distinctly different from nitroglycerin, they can be used to complement nitroglycerin therapy, or as stand-alone products.

[43] As noted above, methods of treating anorectal disorders are also provided herein. The methods of the invention comprise administering to a subject a suitable formulation of one or more of the compositions above. In related methods, treatment is carried out by administration of two or more agents in sequence, either by the same route of administration or by different routes of administration.

**BRIEF DESCRIPTION OF THE DRAWINGS**

[44] Figure 1 illustrates a typical waveform pattern for resting IASP in a rat under conditions of a control experiment.

[45] Figure 2 illustrates the waveform pattern for IASP in a rat following administration of 20 µl of a 1% solution of nitroglycerin in propylene glycol.

[46] Figure 3 illustrates the effect of a cGMP mimetic on internal anal sphincter pressure in a rat. The figure shows a waveform pattern for IASP for a rat following administration of 20 µl of a 10% solution of dibutyryl-cGMP in saline.

[47] Figure 4 illustrates the effect of a type V phosphodiesterase inhibitor on internal anal sphincter pressure in a rat. The figure shows a waveform pattern for IASP
for a rat following administration of 20 μl of a 5% solution of zatprinast in 1-methyl-2-pyrrolidinone.

[48] Figure 5 illustrates the effect of a potassium channel opener on internal anal sphincter pressure in a rat. The figure shows a waveform pattern for IASP for a rat following administration of 20 μl of a 4% solution of minoxidil in 62.5% propylene glycol.

[49] Figure 6 illustrates the effect of NTG administered to the IAS as a bolus dose.

[50] Figure 7 illustrates the effect of NTG administered to the IAS by continuous infusion over 4 hours.

[51] Figure 8 illustrates the effect of 8-bromo cAMP infused to the IAS at 20 μg/hour for three hours.

[52] Figure 9 illustrates the effect of dibutyril cAMP infused to the IAS at 20 μg/hour for three hours.

[53] Figure 10 illustrates the effect of a bolus delivery of SOD (200 μg) to the IAS, followed by a bolus dose of NTG (200 μg) in the same vehicle.

[54] Figure 11 illustrates the effect of a bolus delivery of NTG (200 μg) to the IAS, followed by a bolus dose of SOD (200 μg) in the same vehicle.

[55] Figure 12 illustrates the effect on the IAS of a vehicle injection followed after 30 minutes by bolus doses of NTG.

[56] Figure 13 illustrates the effect on the IASP of an i.p. injection of zatprinast followed by bolus doses of NTG applied topically to the IAS.

[57] Figure 14 illustrates the effect on the IASP of a bolus dose of NTG applied topically to the IAS, wherein the first NTG dose is provided at 2.75 hours after a vehicle injection.

[58] Figure 15 illustrates the effect on the IASP of an i.p. injection of zatprinast followed by bolus doses of NTG, wherein the first NTG dose is provided at 2.75 hours after zatprinast injection.

[59] Figure 16 illustrates the effect on the IAS of a vehicle injection followed after 50 minutes by bolus doses of NTG.

[60] Figure 17 illustrates the effect on the IAS of PDE V inhibitor, dipyridamole injected i.p. 50 minutes prior to bolus doses of NTG.

[61] Figure 18 illustrates the effect on the IASP of PDE V inhibitor MBCQ injected i.p. 30 minutes prior to bolus doses of NTG.
[62] Figure 19 illustrates the effect on the IASP of β-agonist isoproterenol delivered to the IAS 30 minutes after saline alone.

[63] Figure 20 illustrates the effect on the IASP of β₂-agonist terbutaline in saline infused continuously at 20 μg/hour.

[64] Figure 21 illustrates the effect on the IASP of β₂-agonist salbutamol in saline infused continuously at 20 μg/hour.

[65] Figure 22 illustrates the effect on the IASP of PDE IV inhibitor rolipram in DMSO/acetone/olive oil infused continuously at 20 μg/hour.

[66] Figure 23 illustrates a bolus dose of salbutamol followed by a single bolus dose of salbutamol and PDE IV inhibitor etazolate.

[67] Figure 24 illustrates a bolus dose of etazolate followed by a single bolus dose of salbutamol and etazolate.

[68] Figure 25 illustrates the effect on the IASP of PDE IV inhibitor Ro 20-1724 in DMSO/acetone/olive oil infused continuously at 20 μg/hour.

[69] Figure 26 illustrates a vehicle control for the treatments provided in Figure 27.

[70] Figure 27 illustrates the effect on the IASP of the specific adenyl cyclase activator forskolin, in DMSO/acetone/olive oil infused continuously at 20 μg/hour.

[71] Figure 28 illustrates the effect on the IASP of the α₁-blocker, prazosin, in DMSO/acetone/olive oil infused continuously at 20 μg/hour.

[72] Figure 29 illustrates the effect on the IASP of the nonspecific PDE inhibitor IBMX, in DMSO/acetone/olive oil infused continuously at 200 μg/hour.

[73] Figure 30 illustrates the effect on the IASP of the nonspecific PDE inhibitor IBMX, in DMSO/acetone/olive oil infused continuously at 20 μg/hour.

[74] Figure 31 illustrates the effect on the IASP of a single bolus dose of the K⁺-ATP channel opener minoxidil in propylene glycol/water.

[75] Figure 32 illustrates the effect on the IASP of the K⁺-ATP channel opener diazoxide, in DMSO/acetone/olive oil infused continuously at 20 μg/hour.

[76] Figure 33 illustrates the effect on the IASP of the Ca²⁺-channel blocker diltiazem in saline infused continuously at 20 μg/hour.

[77] Figure 34 illustrates the effect on the IASP of the Ca²⁺-channel blocker verapamil in saline infused continuously at 20 μg/hour.
[78] Figure 35 illustrates the effect on the IASP of the adrenergic nerve inhibitor 6-hydroxydopamine when administered to the IAS in bolus doses of 200 μg per day for 5 days.

[79] Figure 36 illustrates the effect on the IASP of a control vehicle i.p injection of 1-methyl-2-pyrollidinone followed after 30 minutes by continuous infusion of a sub-threshold dose of isoproterenol in saline (0.2 μg/hour).

[80] Figure 37 illustrates the effect on the IASP of the PDE III/IV inhibitor zardaverine when injected i.p. (10 mg in vehicle) followed after 30 minutes by a continuous infusion of isoproterenol.

[81] Figure 38 illustrates the effect on the IASP of the PDE III/IV inhibitor zardaverine when injected i.p. (7.5 mg in vehicle) followed after 30 minutes by a continuous infusion of 5% dextrose.

[82] Figure 39 illustrates the effect on the IASP of the PDE III/IV inhibitor zardaverine when injected i.p. (7.5 mg in vehicle) followed after 30 minutes by a continuous infusion of a sub-threshold dose of isoproterenol.

[83] Figure 40 illustrates the effect on the IASP of the adenosine antagonist and non-specific PDE inhibitor, theophylline when continuously infused at 200 μg/hour in 5% dextrose.

[84] Figure 41 illustrates the effect on the IASP of theophylline when continuously infused at 20 μg/hour in 5% dextrose.

[85] Figure 42 illustrates the effect on the IASP of theophylline when continuously infused at 2 μg/hour in 5% dextrose.

[86] Figure 43 illustrates the effect on the IASP of dyphylline when continuously infused at 20 μg/hour in 5% dextrose.

[87] Figure 44 illustrates the effect on the IASP of vesamicol when continuously infused at 100 μg/hour as compared to saline.

[88] Figure 45 illustrates the effect on the IASP of yohimbine gel (0.05% and 0.01%) on the IASP when continuously infused at the rate of 100 ul/hr.

[89] Figure 46 illustrates compounds that are useful in the methods and compositions of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

Abbreviations and Definitions
cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; NO, nitric oxide; NTG, nitroglycerin; SOD, superoxide dismutase; PDE, phosphodiesterase; IASP, internal anal sphincter pressure; Rp-cAMPS, Rp-Adenosine-3',5'-cyclic monophosphorothioate; Sp-cAMPS, Sp-Adenosine-3',5'-cyclic monophosphorothioate; 8-CPT cAMP, 8-(4-Chlorophenylthio)-adenosine-3',5'-cyclic monophosphate, sodium salt; Sp-5,6-DCI-cBiMPS, Sp-5,6-dichloro-1-b-D-ribofuranosylbenzimidazole-3',5'-monophosphorothioate; Dibutyryl-cAMP, N6,2'-O-Dibutyryladenosine-3',5'-cyclic monophosphate, sodium salt monohydrate; Sp-8-pCPT-cGMPS, Sp-8-(4-Chlorophenylthio)-quanosine-3',5'-cyclic monophosphate, sodium salt; 8-Bromo-cGMP, 8-Bromoguanosine-3',5'-cyclic monophosphate, sodium salt; Rp-8-Br-cGMPS, Rp-8-Bromoguanosine-3',5'-cyclic monophosphorothioate, sodium salt; Dibutyryl-cGMP, N2,2'-O-Dibutyrylguanosine-3',5'-cyclic monophosphate, sodium salt; EHNA, erythro-9-(2-Hydroxy-3-nonyl)adenine HCl; IBMX, 3-Isobutyl-1-methylxanthine; MY-5445, 1-(3-Chlorophenylamino)-4-phenylphtalazine; Ro 20-1724, 4-(3-Butoxy-4-methoxybenzyl)-2-imidazolidinone; MBCQ, 4-((3,4-(Methyleneoxy) benzyl)amino)-6-chloroquinazoline.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by those of ordinary skill in the art to which this invention belongs. The following references provide one of skill with a general definition of many of the terms used in this invention: Singleton, et al., DICTIONARY OF MICROBIOLOGY AND MOLECULAR BIOLOGY (2d ed. 1994); THE CAMBRIDGE DICTIONARY OF SCIENCE AND TECHNOLOGY (Walker ed., 1988); and Hale & Marham, THE HARPER COLLINS DICTIONARY OF BIOLOGY (1991). As used herein, the following terms have the meanings ascribed to them unless specified otherwise. Although any methods and materials similar or equivalent to those described herein may be used in the practice or testing of the present invention, the preferred methods and materials are described. For purposes of the present invention, the following terms are defined below.

The terms “treatment,” “therapy” and the like include, but are not limited to, changes in the recipient's status. The changes can be either subjective or objective and can relate to features such as symptoms or signs of the disease or condition being treated. For example, if the patient notes decreased itching, reduced bleeding, reduced discomfort or decreased pain, then successful treatment has occurred. Similarly, if the clinician notes objective changes, such as by histological analysis of a biopsy sample, then treatment has also been successful. Alternatively, the clinician may note a decrease in the size of lesions or other abnormalities upon examination of the patient. This would also represent an
improvement or a successful treatment. Preventing the deterioration of a recipient's status is also included by the term. Therapeutic benefit includes any of a number of subjective or objective factors indicating a response of the condition being treated as discussed herein.

[93] “Drug”, “pharmacological agent”, “pharmaceutical agent”, “active agent”, and “agent” are used interchangeably and are intended to have their broadest interpretation as to any therapeutically active substance which is delivered to a living organism to produce a desired, usually beneficial effect.

[94] “Pharmaceutically-acceptable” or “therapeutically-acceptable” refers to a substance which does not interfere with the effectiveness or the biological activity of the active ingredients and which is not toxic to the hosts, which may be either humans or animals, to which it is administered. “Therapeutically-effective amount” refers to the amount of an active agent sufficient to induce a desired biological result. That result may be alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. The term “therapeutically effective amount” is used herein to denote any amount of the formulation that causes a substantial improvement in a disease condition when applied to the affected areas repeatedly over a period of time. The amount will vary with the condition being treated, the stage of advancement of the condition, and the type and concentration of formulation applied. Appropriate amounts in any given instance will be readily apparent to those skilled in the art or capable of determination by routine experimentation.

[95] The term “anorectal area” or “anorectal region” is defined herein to include both the anus and the rectum region of a mammal. More particularly, the term includes the internal anal canal, the external anus and the lower rectum.

[96] The term “perianal area” or “perianal region” is defined herein to include the area around, about or near, but not including, the anorectal area.

[97] “Hypertonicity” refers to being in state of greater than normal muscular tension or incomplete relaxation.

[98] The term “cyclic nucleotide” refers to cyclic adenosine monophosphate and cyclic guanosine monophosphate.

[99] The term “modulation” refers to any systematic variation or graded change in a characteristic (e.g. frequency, concentration, amplitude, effectiveness, etc.) of a sustained oscillation sufficient to affect a biological function. The term “change” includes an increase or decrease in the characteristic.
The term “subject” as used herein includes any animal, such as a mammal, including a human.

The term “anorectal disorder” includes any disorder associated with an anorectal disease, including an acute or chronic anal fissure, an internally or externally thrombosed hemorrhoid, a hemorrhoidal disease, a disorder associated with endoscopic hemorrhoidal ligation or pain caused by such ligation, levator spasm, constipation, and other anorectal disorder associated with hypertonicity or spasm of the anal sphincter muscle. The term also includes inflammation and inflammatory lesions of the rectal, anal and perianal region such as those associated with Inflammatory Bowel Disease, including Crohn’s Disease. The term also refers to post-surgical pain associated with hemorrhoidectomy or other anorectal surgery that is associated with pain and/or intense anal spasms. The term “anal fissure” is also referred to as “anal rhagades” and spasms of the anal sphincter are also referred to as “rectal tenesmus.” Additionally, the term is meant to include pain which can be associated with any of the above disorders or conditions.

The terms “signs, symptoms and causes of anorectal disease” and “signs and symptoms of anorectal disease” include, but are not limited to, anal sphincter hypertonicity; anal and rectal ischemia, itching, inflammation, pain or bleeding; thrombosed or prolapsed hemorrhoidal tissue; spasticity of the levator ani muscle, spasm of the puborectalis muscle or anal sphincter muscles, and linear or ischemic ulcers or crack-like sores in the anal canal or on the margin of the anus.

The term “desirable therapeutic effects” in the treatment of anorectal diseases and conditions includes, but is not limited to, anal sphincter relaxation; reduction of anal sphincter pressure; maintenance of reduced anal sphincter pressure; reduction or elimination of ischemia, itching, inflammation, pain, bleeding, or muscle spasm; restoration or improvement of anoderm blood flow; dilation of blood vessels in the anus and rectum; and partial or complete healing of linear or ischemic ulcers or crack-like sores in the anal canal or on the margin of the anus.

The terms “potassium channel opener” and “potassium channel activator” refer generally to a class of drugs that cause an increased flow of potassium ions from inside an electrically excitable cell to outside the cell via a membrane of the cell which has at least one potassium channel. Potassium channel opener activity may be observed by measuring a hyperpolarization of the cell membrane potential (i.e., a more negative membrane potential) caused by an increase in the flow of potassium ions from inside a cell to outside the cell via a potassium channel in the cell membrane.
[105] The term “pharmaceutical composition” means a composition suitable for pharmaceutical use in a subject, including an animal or human. A pharmaceutical composition generally comprises an effective amount of an active agent and a pharmaceutically acceptable carrier.

[106] The term “pharmaceutically acceptable carrier” encompasses any of the standard pharmaceutical carriers, buffers and excipients, including phosphate-buffered saline solution, water, and emulsions (such as an oil/water or water/oil emulsion), and various types of wetting agents and/or adjuvants. Suitable pharmaceutical carriers and their formulations are described in REMINGTON’S PHARMACEUTICAL SCIENCES (Mack Publishing Co., Easton, 19th ed. 1995). Preferred pharmaceutical carriers depend upon the intended mode of administration of the active agent. Typical modes of administration are described below.

[107] The term “effective amount” means a dosage sufficient to produce a desired result. The desired result may comprise a subjective or objective improvement in the recipient of the dosage.

[108] A “prophylactic treatment” is a treatment administered to a subject who does not exhibit signs of a disease or exhibits only early signs of a disease, wherein treatment is administered for the purpose of decreasing the risk of developing pathology.

[109] A “therapeutic treatment” is a treatment administered to a subject who exhibits signs of pathology, wherein treatment is administered for the purpose of diminishing or eliminating those pathological signs.

[110] The term “appropriate anal area” means any area or tissue of the anus or sphincter that is affected by or subject to anal disorder or disease, including, for example, the external or internal anus, the external or internal anal sphincter, anal sphincter muscle, or external or internal anal canal.

[111] As used herein, the term “NO donor” refers to any organic or inorganic compound that can deliver nitric oxide in a physiologic setting. Also included are those compounds that can be metabolized in vivo into a compound that delivers nitric oxide (e.g., a prodrug form of a NO donor, or a binary NO generating system).

GENERAL
The present invention provides novel, non-invasive methods for treating anorectal disorders using nitric oxide donors and other agents that either interfere with the downstream biochemical events leading to smooth muscle relaxation, or block signals for smooth muscle contraction. Such compounds are effective for treating a variety of anorectal disorders including, but not limited to, an acute or chronic anal fissure, an internally or externally thrombosed hemorrhoid, a hemorrhoidal disease, a disorder associated with endoscopic hemorrhoidal ligation or pain caused by such ligation, levator spasm, constipation, and other anorectal disorder associated with hypertonicity or spasm of the anal sphincter muscle. The term also refers to post-surgical pain associated with hemorrhoidectomy or other anorectal surgery that leads to intense anal spasms. The term "anal fissure" is also referred to as "anal rhabades" and spasms of the anal sphincter are also referred to as "rectal tenesmus." Additionally, the term is meant to include pain which can be associated with any of the above disorders or conditions. The term can include anorectal itching, burning and pain. Suitable compounds for use with the methods of the present invention are described infra and include, in particular, NO donors, calcium channel blockers, cholinergic modulators (including acetylcholine storage blocking agents and acetylcholine vesicle storage blocking agents), α-adrenergic receptor antagonists (e.g., α₁-adrenergic antagonists, α₂-adrenergic antagonists, etc.), β-adrenergic receptor agonists (including β₂-adrenergic antagonists and β₃-adrenergic antagonists), phosphodiesterase inhibitors, cAMP-dependent protein kinase activators (e.g., cAMP mimetics), superoxide scavengers, potassium channel activators (including ATP-sensitive potassium channel activators and activators of the Maxi-K channels), estrogen-like compounds, testosterone-like compounds, benzodiazepines, adrenergic nerve inhibitors, antidiarrheal agents, HMG-CoA reductase inhibitors, smooth muscle relaxants, adenosine receptor modulators, adenylyl cyclase activators, endothelin receptor antagonists, bisphosphonates, cGMP-dependent protein kinase activators (e.g., cGMP mimetics). These compounds may be administered in stand-alone therapy, in combination therapy or as separate dosage forms administered simultaneously or in succession.

The compounds of the present invention may be administered therapeutically to a patient affected with one or more of the above-listed disorders, as well as prior to proctologic examination. Administration can be via the oral, parenteral (intravenous, intramuscular or subcutaneous), transdermal, pulmonary or transmucosal (nasal, buccal, cervical, vaginal, anorectal) route, for systemic and/or local delivery, with local delivery
being preferred. To provide pharmacological therapy in conjunction with traditional muscle stretch therapy used to treat rectal spasms, plastic dilators impregnated with or otherwise providing the compound may be used to deliver the compound topically to the anorectal region while simultaneously stretching the sphincter muscles. To prevent the relapse or to treat a chronic condition, a rectal suppository or dermal patch containing one or more of the compounds described herein can be inserted to provide continuous delivery.

I. COMPOUNDS OF THE INVENTION


A. NO donors

[115] In preferred embodiments, the compounds of the present invention are NO donors. The nitric oxide donor can be any of a variety of NO donors including, for example, organic NO donors, inorganic NO donors and prodrug forms of NO donors. Additional suitable NO donors include compounds that can be metabolized in vivo into a compound which delivers nitric oxide (e.g., a prodrug form of a NO donor, or a binary NO generating system, such as acidified nitrates), or compounds that serve as physiological precursor of nitric oxide, such as L-arginine and salts of L-arginine. The NO donor may include at least one organic nitrate (including esters of nitric acid) and can be either a cyclic or acyclic compound. For example, suitable NO donors include nitroglycerin (NTG), isosorbide dinitrate (ISDN), isosorbide mononitrate (ISMN) which may include isosorbide-2-mononitrate (IS2N) and/or isosorbide-5-mononitrate (IS5N), erythritol tetranitrate (ETN), pentaerythritol tetranitrate (PETN), ethylene glycol dinitrate, isopropyl nitrate, glyceryl-l-monomonitrate, glyceryl-l,2-dinitrate, glyceryl-l,3-dinitrate, butane-l,2,4-triol trinitrate, and the like. Nitroglycerin and other organic nitrates including ISDN, ETN, and PETN, have been given regulatory approval for use in treatments in other fields of medicine on human subjects. Additional NO donors include sodium nitroprusside, N,O-diacetyl-N-hydroxy-4-
chlorobenzesulfonamide, N^2-hydroxy-L-arginine (NOHA), hydroxyguanidine sulfate, molsidomine, 3-morpholinosydnonimine (SIN-1), (±)-S-nitroso-N-acetylpenicillamine (SNAP), S-nitrosogluthathione (GSNO), (±)-(E)-ethyl-2-[(E)-hydroxyimino]-5-nitro-3-hexeneamide (FK409), (±)-N-{(E)-4-ethyl-3-[(Z)-hydroxyimino]-5-nitro-3-hexen-1-yl]-3-pyridinecarboxamide (FR144420), and 4-hydroxymethyl-3-furoxancarboxamide. In addition, compounds that interfere with the breakdown of NO in vivo may be administered.

B. Calcium Channel Blockers

[116] Ca^{2+} channel blockers are compounds that inhibit the entry of Ca^{2+} into the cell from the extracellular fluid. Suitable Ca^{2+} channel blockers for use with the methods of the present invention include, but are not limited to, nifedipine, nimodipine, felodipine, nicardipine, isradipine, amlodipine, diltiazem, bepridil, verapamil, etc. (see, e.g., WO 98/36733). L-type Ca^{2+} channel blockers are also available.

C. Cholinergic Modulators

[117] Other preferred compounds for use in the context of the present invention include cholinergic modulators (see, e.g., WO 98/36733). Cholinergic modulators suitable for use with the methods of the present invention include, but are not limited to, ambenonium, bethanechol, cisapride, edrophonium, neostigmine, physostigmine, pilocarpine, pyridostigmine, succinylcholine, tacrine, etc. Compounds (e.g., Botulinium Toxin) that can terminate the release of neurotransmitters (e.g., acetylcholine) are also suitable for use in the methods of the present invention. Acetylcholine storage blocking agents and acetylcholine vesicle transport blocking agents, such as vesamicol, are also preferred. Vesamicol prevents the storage of acetylcholine in the presynaptic storage vesicles as well as the release and transport of acetylcholine from these vesicles.

D. α-adrenergic Receptor Antagonists and β-adrenergic Receptor Agonists

[118] Additional preferred compounds for use in the context of the present invention include, e.g., α-adrenergic receptor antagonists and β-adrenergic receptor agonists. Suitable α-adrenergic receptor antagonists include, for example, α1-adrenergic receptor antagonists, α2-adrenergic receptor antagonists and other nonspecific α-adrenergic receptor antagonists. Preferred α1-adrenergic receptor antagonists include, but are not limited to, prazosin, doxazosin, phenoxybenzamine, phentolamine, terazosin, tolazoline, etc., and are
described in Goodman and Gilman, "The Pharmaceutical Basis of Therapeutics," 9th Edition, Hardman, et al. (ed.), McGraw-Hill (1996). Suitable $\alpha_2$-adrenergic receptor antagonists include, but are not limited to, yohimbine and are also described in Goodman and Gilman, "The Pharmaceutical Basis of Therapeutics," 9th Edition, Hardman, et al. (ed.), McGraw-Hill (1996). Other suitable antagonists are $\alpha_2$-adrenergic antagonists include, for example, post-synaptic $\alpha_2$-adrenergic antagonists. These post-synaptic $\alpha_2$-adrenergic antagonists include, but are not limited to, imiloxan, ARC 239 dihydrochloride and other pharmaceutically acceptable salts thereof. ARC 239 dihydrochloride is 2-[(4-(2-Methoxyphenyl)piperazin-1-yl)ethyl]-4,4-dimethyl-1,3-(2H,4H)-isoquinolindone dihydrochloride. Other suitable post-synaptic $\alpha_2$-adrenergic antagonists include, but are not limited to, idazoxan, rauwolscine, efaroxan, mianserin, and mirtazapine. Of these, mianserin and mirtazapine are particularly preferred.

[119] Suitable $\beta$-adrenergic receptor agonists for use with the methods of the present invention include, but are not limited to, $\beta_1$-adrenergic receptor agonists, $\beta_2$-adrenergic receptor agonists, $\beta_3$-adrenergic receptor agonists and other nonspecific $\beta$-adrenergic receptor agonists. In a preferred embodiment, the $\beta$-adrenergic receptor agonist is a $\beta_2$-adrenergic receptor agonist or a $\beta_3$-adrenergic receptor agonists. Examples of $\beta$-adrenergic receptor agonists suitable for use with the methods of the present invention include, but are not limited to, albuterol, bitolterol, salbutamol, terbutaline, metaproterenol, procterol, salmeterol, clenbuterol, isoproterenol, zinterol, BRL 37344, CL316243, CGP-12177A, GS 332, L-757793, L-760087, L-764646, and L-766892, etc. (see, e.g., Goodman and Gilman, supra).

E. Phosphodiesterase Inhibitors

[120] In another preferred embodiment, the compound is a phosphodiesterase inhibitor. Cyclic nucleotide second messengers (cAMP and cGMP) play a central role in signal transductions and regulation of physiologic responses. Their intracellular levels are controlled by the complex superfamily of cyclic nucleotide phosphodiesterases (PDE) enzymes. Inhibitors of phosphodiesterases (PDE) are agents that can either activate or suppress PDEs via allosteric interaction with the enzymes or binding to the active site of the enzymes. The PDE family includes at least 19 different genes and at least 11 PDE isozyme families, with over 50 isozymes having been identified thus far. The PDEs are distinguished by (a) substrate specificity, i.e., cGMP-specific, cAMP-specific or
non-specific PDEs, (b) tissue, cellular or even sub-cellular distribution, and (c) regulation by distinct allosteric activators or inhibitors. PDE inhibitors include both nonspecific PDE inhibitors and specific PDE inhibitors (those that inhibit a single type of phosphodiesterase with little, if any, effect on any other type of phosphodiesterase). Still other useful PDE inhibitors are the dual selective PDE inhibitors (e.g., PDE III/IV inhibitors or PDE II/IV inhibitors). Below is a table setting forth various PDE inhibitors that are useful in the methods of the present invention.

<table>
<thead>
<tr>
<th>Isozyme Family</th>
<th>Regulatory Characteristics</th>
<th>Selective Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Ca^{2+}, Calmodulin-regulated with different $K_m$ values for cG and cA hydrolysis</td>
<td>Vinpocetine</td>
</tr>
<tr>
<td>III</td>
<td>CG-inhibited cA hydrolysis; low $K_m$ for cA and cG</td>
<td>Milrinone, Amrinone, Pinobendan, Cilostamide, Enoximone, Peroximone, Vesarinone</td>
</tr>
<tr>
<td>IV</td>
<td>Low $K_m$ for cA hydrolysis</td>
<td>Rolipram; RO-20-1724</td>
</tr>
<tr>
<td>V</td>
<td>High and low $K_m$ isoforms for cG specific hydrolysis</td>
<td>Zaprinast; Dipyridamole</td>
</tr>
</tbody>
</table>

[121] In one embodiment, the PDE inhibitor is a PDE V inhibitor. Useful phosphodiesterase type V inhibitors include, e.g., cialis, tadalafil, zaprinast, MBCQ, MY-5445, dipyridamole and sildenafil. In another embodiment, the composition contains a phosphodiesterase type II (PDE II) inhibitor such as, e.g., EHNA. In yet another embodiment, the composition contains a phosphodiesterase type IV (PDE IV) inhibitor.

Suitable phosphodiesterase type IV inhibitors include, but are not limited to, roflumilast, ariflo (SB207499), RP73401, CDP840, rolipram, RO-20-1724, and LAS31025. In still another embodiment, the phosphodiesterase inhibitor is a dual selective phosphodiesterase inhibitor such as, e.g., a PDE III/IV inhibitor (e.g., zardaverine).

[122] In another embodiment, the PDE inhibitor is an inhibitor of the PDE IV isozyme family, or cAMP-specific and rolipram sensitive PDEs, which preferentially hydrolyze cAMP.
[123] In yet another embodiment, the composition contains an agent that is a nonspecific phosphodiesterase inhibitor. Suitable nonspecific phosphodiesterase inhibitors include, but are not limited to, theobromine, dyphyline, IBMX, theophylline, aminophylline, pentoxifylline, papaverine, caffeine and other methylxanthine derivatives.

F. cAMP-dependent Protein Kinase Activators

[124] In other preferred embodiments, the compound used to treat the disorders described herein is a cAMP-dependent protein kinase activator. Examples of cAMP-dependent protein kinase activators include cAMP mimetics or dual cGMP/cAMP-dependent protein kinase activators. Suitable cAMP mimetics or analogs include those compounds that are structurally similar to cAMP and that have similar functions e.g., activities, as cAMP. Examples of suitable cAMP mimetics include, but are not limited to, 8-bromo-cAMP, dibutyryl-cAMP, Rp-cAMPS, and Sp-cAMPS, and useful dual activators include compounds such as, e.g., Sp-8-pCPT-cGMPS, Sp-8-bromo-cGMPS and 8-CPT-cAMP.

G. Superoxide Scavengers

[125] In another aspect, the compound used in the compositions and methods of the present invention is a superoxide anion (O$_2^-$) scavenger. Superoxide can react with NO and dramatically reduce its biological effects. Accordingly, agents that scavenge superoxide anions can enhance the effects of NO. Examples of superoxide scavengers include, but are not limited to, exogenous Mn or Cu/Zn superoxide dismutase (SOD) or small molecule SOD mimetics such as, e.g., Mn(III) tetra(4-benzoic acid) porphyrin chloride (MnTBAP) and M40403 (see, e.g., Salvemini, et al., Science, 286(5438):304-306 (1999)).

H. Potassium Channel Activators

[126] In another aspect, the present invention provides pharmaceutical compositions comprising a potassium channel activator. In one embodiment, the potassium channel activator is an Potassium channel activator. Synthetic compounds that activate ATP-sensitive K channels are smooth muscle relaxants. Such compounds include, but are not limited to, minoxidil, minoxidil sulfate, pinocidil, diazoxide, levermokalim, cromokalim, etc. (see, e.g., White, et al., Eur. J. Pharmacol., 357:41-51 (1998)). Additional suitable ATP-sensitive K channel activators can be found in, e.g., Bristol, et al., "Annual Reports in
I. Estrogen-like Compounds

[127] In another aspect, the present invention provides pharmaceutical compositions comprising an estrogen-like compound. Estrogen-like compounds include those compounds that bind to the estrogen receptor and act as agonists thereof. Estrogen-like compounds include, but are not limited to, 17-β-estradiol, estrone, mestranol, estradiol valerate, estradiol dyponate, ethinyl estrodil, quinestrol, estrone sulfate, phytoestrogens such as flavones, isoflavones (e.g., genistein), resveratrol, coumestan derivatives, other synthetic estrogenic compounds including pesticides (e.g., p,p’-DDT), plasticizers (e.g., bisphenol A), and a variety of other industrial chemicals (e.g., polychlorinated biphenyls) (see, e.g., Goodman and Gilman, supra).

J. Testosterone-like Compounds

[128] In another aspect, the present invention provides pharmaceutical compositions comprising a testosterone-like compound. Testosterone-like compounds include those compounds that bind to the testosterone receptor and act as agonists thereof. Testosterone-like compounds include, but are not limited to, testosterone, testosterone propionate, testosterone enanthate, testosterone cypionate, testosterone undecenoate, dihydrotestosterone, danazol, fluoxymesterone, methyltestosterone, oxandrolone, DHEA and tibolone (see, e.g., Goodman and Gilman, supra).

K. Benzodiazepines

[129] In another aspect, the present invention provides pharmaceutical compositions comprising a benzodiazepine. Suitable benzodiazepines include, but are not limited to, alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, chlorazepate, demoxepam, diazepam, estazolam, flumazenil, flurazepam, halazepam, lorazepam, midazolam, nitrazepam, nordazepam, oxazepam, prazepam, quazepam, temazepam, and triazolam (see, e.g., Goodman and Gilman, supra).
L. Adrenergic Nerve Inhibitors

[130] In another aspect, the compounds of the present invention are compounds that inhibit adrenergic nerves. Adrenergic nerve inhibitors include compounds that destroy sympathetic nerve terminals, such as 6-hydroxydopamine and its analogs (see, e.g., Goodman and Gilman, supra). Adrenergic nerve inhibitors also include compounds that deplete norepinephrine storage, either by inhibiting norepinephrine biosynthesis or by depleting stores, and compounds that inhibit norepinephrine release. Compounds that inhibit norepinephrine biosynthesis include, but are not limited to, α-methyltyrosine. Compounds that deplete norepinephrine stores include, but are not limited to, reserpine, guanethidine and bretylium. Compounds that inhibit norepinephrine release include, but are not limited to, clonidine and other α₂-adrenergic receptor agonists. Examples of sympathetic nerve terminal destroyers include, but are not limited to, α₂-adrenergic receptor agonists.

M. Antidiarrheal Agents

[131] In another aspect, the compounds of the present invention are antidiarrheal agents. Examples of suitable antidiarrheal agents include, but are not limited to, diphenoxylate, loperamide, bismuth subsalicylate, octreotide, etc. (see, e.g., Goodman and Gilman, supra).

N. HMG-CoA Reductase Inhibitors

[132] In another aspect, the compounds of the present invention are HMG-CoA reductase inhibitors. Examples of HMG-CoA reductase inhibitors include, but are not limited to, mevastatin, lovastatin, simvastatin, pravastatin, cerivastatin, dalvastatin, atorvastatin, fluvastatin, etc. (see, e.g., Goodman and Gilman, supra).

O. Smooth Muscle Relaxants

[133] In other embodiments, the compounds of the present invention are smooth muscle relaxants such as, e.g., hydralazine, papaverine, tiropramide, cyclandelate, isoxsuprine and nylidrin.
P. Adenosine Receptor Modulators

[134] In another aspect, the present invention provides compositions for the treatment of urogenital tract disorders comprising adenosine receptor modulators, either alone or in combination with another agent. Methods for the use of these compositions are also provided. In one group of embodiments, adenosine receptor modulators are used alone. In another group of embodiments, the adenosine receptor modulators are combined with at least one other urogenital muscle-relaxing agent. In other embodiments, the compounds of the present invention are adenosine receptor modulators such as methylxanthines. Examples of adenosine receptor modulators include theophylline and diphyllyline. For other examples see, Goodman & Gilman, supra). Preferred agents are selected from those described with reference to the compositions of single agents or combinations above.

[135] Theophylline, a plant-derived methylxanthine, has been used for the treatment of bronchial asthma for decades. Theophylline relaxes smooth muscle, notably bronchial muscle, that has been contacted experimentally with a spasmogen, or clinically in asthma. Proposed mechanisms of methylxanthine-induced physiologic and pharmacological effects include: 1) inhibition of phosphodiesterases, thereby increasing intracellular cyclic AMP, 2) direct effects on intracellular calcium concentration, 3) indirect effects on intracellular calcium concentrations via cell membrane hyperpolarization, 4) uncoupling of intracellular calcium increases with muscle contractile elements, and 5) antagonism of adenosine receptors.

[136] A related compound, i.e., diphyllyline, is a preferred adenosine receptor modulator. This compound is not metabolized by the liver and is excreted unchanged by the kidneys, therefore its pharmacokinetics and plasma levels are independent of factors that effect liver enzymes such as smoking, age, congestive heart failure, or the use of other drugs that affect liver function.

Q. Adenylyl Cyclase Activators

[137] In another aspect, the present invention provides compositions comprising adenylyl cyclase activators, either alone or in combination with other compounds or agents described herein. The adenylyl cyclase activator forskolin is preferred. Other examples of adenylyl cyclase activators, include, but are not limited to, N6 N6, O2'-dibutyryl-cAMP, 8-chloro-cAMP, and Rp-diastereomers of adenosine 3', 5'-cyclic monophosphorothioate, and related analogs, such as Rp-8-bromo-adenosine 3', 5'-cyclic
monophosphorothioate, and derivatives of forskolin, including colforsin daropate hydrochloride.

R. Endothelin Receptor Antagonists

[138] In another aspect, the present invention provides compositions comprising endothelin receptor antagonist, either alone or in combination with other compounds disclosed herein. Examples of endothelin receptor antagonists include, but are not limited to, BE 1827B, JKC-301, JKC-302, BQ-610, W-7338A, IRL-1038, LRL-1620, bosetan, ABT 627, Ro 48-5695, Ro 61-1790, tesoventan (Ro 61-0612, ZD1611, BMS-187308, BMS-182874, BMS-193884, sitaxsentan (TBC 11251), TBC 2576, TBC 3214, TBC-10950, ABT-627, atrasentan, A-192621, A-308165, A-216546, CI-1020, EMD 122946, J-104132 (L753037), LU 127043, LU 135252, LU 302872, TAK-044 (69), SB 209670, SB 234551, SB 247083, ATZ1993, PABSA, L-749,329, RPR11723, RPR11801A, PD 164800, PD 180988 (CI1034), IRL 3630, IRL 2500, and their derivatives, etc. (see, Doherty, Annual Reports in Medicinal Chemistry, Volume 35, pp. 73-82, Academic Press, 2000). Other ethenesulfonamide derivatives, which are endothelin receptor antagonists and which are useful in the methods of the present invention, are disclosed by Harada, et al., Chem. Pharm. Bull., 49(12):1593-1603 (2001).

S. Bisphosphonates

[139] In another aspect, the present invention provides compositions comprising bisphosphonates, either alone or in combination with other agents. Suitable bisphosphonates suitable for use in the methods of the present invention include, but are not limited to, alendronate sodium (Fosamax), pamidronate disodium (Aredia), etidronate disodium (Ididronel) and the like.

T. cGMP-dependent Protein Kinase Activators

[140] In another aspect, the present invention provides cGMP-dependent protein kinase activators, either alone or in combination with other agents disclosed herein. Suitable cGMP-dependent protein kinase activators include, but are not limited to, cGMP mimetics or dual cGMP/cAMP-dependent protein kinase activators. Suitable cGMP mimetics or analogs include those compounds that are structurally similar to cGMP and that have similar functions, e.g., activities, as cGMP. Examples of suitable cGMP mimetics
include, but are not limited to, 8-bromo-cGMP, dibutyryl-cGMP, Rp-cGMPS, and Sp-cGMPS, and useful dual activators include compounds such as, e.g., Sp-8-pCPT-cGMPS, Sp-8-bromo-cGMPS and 8-CPT-cAMP.

II. PHARMACEUTICAL COMPOSITIONS AND ADMINISTRATION

[141] The present invention also provides pharmaceutical compositions for the administration of the herein-described compounds, e.g., the NO donors, calcium channel blockers, cholinergic modulators, α-adrenergic antagonists, β-adrenergic agonists, phosphodiesterase inhibitors, cAMP kinase activators, superoxide scavengers, Potassium channel activators, adrenergic nerve inhibitors, estrogen-like compounds, benzodiazepines, antidiarrheal agents, HMG-CoA reductase inhibitors, adenosine receptor modulators, and smooth muscle relaxants to a patient in need thereof. In the context of the present invention, the term “patient” refers to a subject to which the compounds of the invention can be administered. Preferably, a patient is a mammal, e.g., a rodent, a primate or a human. A patient may be affected with a disease, or may be free of detectable disease in which case the compounds and compositions of the present invention are administered prophylactically. The compositions of the present invention can be administered to patients with a anorectal disorder.

[142] One of skill in the art will appreciate that suitable formulations are dependent on the form of delivery to be employed, and all such forms are contemplated by the present invention. Additionally, in some embodiments, combinations of agents are employed in a single formulation, while in other embodiments, agents are formulated separately, but administered in combination, or sequentially. In the discussion below, compositions of single agents will be understood to also include compositions of two or more agents. Still further, different formulations can be used for those embodiments in which agents are administered separately or sequentially, by different routes of administration.

[143] The compounds of the present invention can be formulated to be administered using any of a variety of routes, including, e.g., oral, intravenous, intramuscular, subcutaneous, oral, pulmonary, transdermal, nasal, cervical, vaginal, buccal, anorectal for systemic or local delivery or, preferably, topical administration, such as, e.g., to anorectal area, for prophylactic and/or therapeutic treatment.

[144] The present compounds can be incorporated into a variety of compositions for therapeutic and/or prophylactic administration. A number of suitable
formulations for use in the present invention are found in Remington, *Pharmaceutical Sciences*, Mack Publishing Company, Philadelphia, PA, 17th ed. (1985); and in *Dermatological Formulations: Percutaneous absorption*, Barry (Ed.), Marcel Dekker Inc. (1983). Moreover, for a brief review of methods for drug delivery, see, Langer (1990) *Science* 249:1527-1533. The pharmaceutical compositions described herein can be manufactured in a manner that is known to those of skill in the art, *i.e.*, by means of conventional mixing, dissolving, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes. It will be appreciated that the present methods and excipients are merely exemplary and are in no way limiting.

A. **Topical Formulations**

[145] In view of the above, the present invention provides topical compositions useful for treating anorectal disorders and for treating spasms of mammals, including humans, which comprise an effective amount of a compound that reduces the contraction of the musculature of the anal sphincter and a pharmaceutically acceptable carrier. The compound for use in the topical compositions of the present invention include, but are not limited to, cAMP kinase activators, superoxide scavengers, Potassium channel activators, calcium channel blockers, cholineric modulators, α-adrenergic antagonists, β-adrenergic agonists, adrenergic nerve inhibitors, NO donors, phosphodiesterase inhibitors, estrogen-like compounds, benzodiazepines, antidiarrheal agents, HMG-CoA reductase inhibitors, and smooth muscle relaxants.

[146] In related embodiments, the present invention provides topical pharmaceutical compositions in unit dosage form comprising per unit dosage an amount of the compound or combination provided above, which is effective for treating a anorectal in a subject in need of such treatment. Typically the compounds are in combination with a pharmaceutically acceptable carrier. Such compositions are useful for treating or reducing pain associated with anorectal disorders and for treating the disorders themselves, including spasms of the sphincter muscles, in particular the internal and external anal sphincters. The topical compositions of the invention are also useful for treating conditions resulting from spasms of the musculature of the anal sphincter, including anal fissures, hemorrhoids, and the like. In addition, the topical compositions described herein are useful for relaxing the anal sphincter and reducing pain before, during and after proctologic and other examinations, including the insertion of instruments and procedures, such as surgery.
Dosage forms for the topical administration of the compounds of this invention include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches, suppositories and liposomal preparations. The dosage forms may be formulated with mucoadhesive polymers for sustained release of active ingredients at the anorectal area. The active compound may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants, which may be required. Topical preparations can be prepared by combining the compound of interest with conventional pharmaceutical diluents and carriers commonly used in topical dry, liquid, cream and aerosol formulations. Ointment and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Such bases may include water and/or an oil such as liquid paraffin or a vegetable oil such as peanut oil or castor oil. Thickening agents which may be used according to the nature of the base include soft paraffin, aluminum stearate, cetostearyl alcohol, propylene glycol, polyethylene glycols, woolfat, hydrogenated lanolin, beeswax, and the like. Lotions may be formulated with an aqueous or oily base and, in general, also include one or more of the following: stabilizing agents, emulsifying agents, dispersing agents, suspending agents, thickening agents, coloring agents, perfumes, and the like. Powders may be formed with the aid of any suitable powder base, e.g., talc, lactose, starch, and the like. Drops may be formulated with an aqueous base or non-aqueous base also comprising one or more dispersing agents, suspending agents, solubilizing agents, and the like.

The ointments, pastes, creams and gels also may contain excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof. Powders and sprays also can contain excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

Preferred formulations are either as solutions or semi-solid preparations (gel, ointment, suspension, lotion, cream, etc.). Suitable excipients, depending on the agent, include petrolatum, lanolin, methylcellulose, sodium carboxymethylcellulose, hydroxpropylcellulose, sodium alginate, carboxomers, glycerin, glycols, oils, glycerol, benzoates, parabens and surfactants. It will be apparent to those of skill in the art that the solubility of a particular compound will, in part, determine how the compound is formulated.
An aqueous gel formulation will is suitable for soluble compounds. Where a compound is insoluble at the concentrations required for activity, a cream or ointment preparation will typically be preferable. In this case, oil phase, aqueous/organic phase and surfactant may be required to prepare the formulations. Thus, based on the solubility and excipient-active interaction information, the dosage forms can be designed and excipients can be chosen to formulate the prototype preparations. Particularly preferred preparations include those in a suppository or sustained release format.

Representative compositions include topical compositions comprising one or more of the following first pharmacological compounds: a cAMP kinase activator, superoxide scavenger, Potassium channel activator, calcium channel blocker, cholinergic modulator, α-adrenergic antagonist, β-adrenergic agonist, adrenergic nerve inhibitor, NO donor, phosphodiesterase inhibitor, adenosine receptor modulators, estrogen-like compound, benzodiazepine, antidiarrheal agent, HMG-CoA reductase inhibitor, and smooth muscle relaxant in combination with a pharmaceutically acceptable carrier and at least one of the following second pharmacologic agents: a local anesthetic (e.g., lidocaine, prilocaine, etc.), local anti-inflammatory agent (e.g., naproxen, trimoxamic, etc.), corticosteroid (e.g., cortisone, hydrocortisone, etc.), anti-itch agent (e.g., loperamide, diphenoxylate, etc.), an agent that interferes with the activation of peripheral sensory neurons, including divalent and trivalent metal ions (e.g., manganese, calcium, strontium, nickel, lanthanum, cerium, zinc, etc.), analgesic agents, yeast-based product (e.g., lyophilized yeast, yeast extract, etc.), growth-promoting and/or wound healing-promoting agent known to promote re-epithelialization (e.g., platelet-derived growth factor (PDGF), interleukin-11 (IL-11), etc.), anti-microbial agent (e.g., neosporin, polymyxin B sulfate, bacitracin zinc, etc.), mucoadhesive agent (e.g., cellulose derivatives, etc.), cytoprotectant agent (e.g., colloidal bismuth, misoprostol, sucralfate, etc.) as defined in Goodman and Gilman, *The Pharmacological Basis of Therapeutics, supra*, or menthol. The at least one first pharmacological compound is typically present in the composition in unit dosage form effective for the treatment of a first medical condition(s), such as anorectal disorder or pain. The at least one second pharmacological compound is typically present in the composition in unit dosage effective for the treatment of a second medical condition(s), or a condition(s), symptom(s) or effect(s) associated with or resulting from the first medical condition(s).

The topical pharmaceutical compositions can also include one or more preservatives or bacteriostatic agents, e.g., methyl hydroxybenzoate, propyl hydroxybenzoate,
chlorocresol, benzalkonium chlorides, and the like. The topical pharmaceutical compositions also can contain other active ingredients such as antimicrobial agents, particularly antibiotics, anesthetics, analgesics, and antipruritic agents.

[152] One example of a topical formulation includes 75% (w/w) white petrolatum USP, 4% (w/w) paraffin wax USP/NF, lanolin 14% (w/w), 2% sorbitan sesquioleate NF, 4% propylene glycol USP, and 1% compound of the present invention.

[153] The dosage of a specific compound depends upon many factors that are well known to those skilled in the art, for example, the particular compound; the condition being treated; the age, weight, and clinical condition of the recipient patient; and the experience and judgment of the clinician or practitioner administering the therapy. An effective amount of the compound is that which provides either subjective relief of symptoms or an objectively identifiable improvement as noted by the clinician or other qualified observer. The dosing range varies with the compound used, the route of administration and the potency of the particular compound.

[154] In view of the above, the present invention provides topical compositions useful for treating anorectal disorders (including those related to hypertonicity and/or spasm of the internal anal sphincter muscle, e.g. hemorrhoidal pain) and for treating spasms of the mammal, including humans, which comprise an effective amount of an agent that reduces the contraction of anal sphincter muscle or maintains a reduced contraction of the anal sphincter muscle, and a pharmaceutically acceptable carrier. In one embodiment, the agent is an Potassium channel opener. In another embodiment, the agent is a phosphodiesterase inhibitor, a cyclic nucleotide mimetic, β-adrenergic agonist, an estrogen or estrogen like compound, an α1-adrenergic antagonist or a potassium channel opener.

[155] In related embodiments, the present invention provides topical pharmaceutical compositions in unit dosage form comprising per unit dosage an amount of the agent or combination provided above, which is effective for treating an anal disorder in a subject in need of such treatment. Typically the agents are in combination with a pharmaceutically acceptable carrier. Such compositions are useful in treating or reducing pain associated with anal disorders, such as hemorrhoidal pain, and for treating spasms and/or hypertonicity of the sphincters, including the internal anal sphincter, lower esophageal sphincter, pyloric sphincter, sphincter of Oddi, and the ileocolic sphincter. The topical composition is also useful in treating conditions resulting from spasms and/or hypertonicity of sphincters of the anorectal region including anal fissure, post-operative rectal pain, hypertrophic pyloric stenosis, and pancreatitis, as well as conditions resulting from general
spasm of the muscles of the GI tract including Zenkers diverticulum, achalasia, esophageal spasm (nutcracker esophagus), irritable bowel disease, and Hirschprungs disease (bowel obstruction). In addition, the topical compositions are useful for relaxing the anal sphincter, reducing anal sphincter pressure or maintaining reduced anal sphincter pressure and reducing pain and discomfort before, during and after examinations of the anus, rectum and lower gastrointestinal system, insertion of instruments, and procedures such as colonoscopy, cystoscopy and surgery.

B. Sustained or Controlled Delivery Formulations

[156] In yet other embodiments, the invention provides topical sustained and prolonged release pharmaceutical compositions comprising one or more pharmacological compounds described supra, and a pharmaceutically acceptable carrier, to treat anorectal disorders. Such compositions are useful in the treatment of such anorectal disorders and in controlling and reducing pain associated therewith. Such compositions may comprise a unit dosage of one or more particular active agent(s) (e.g., a NO donor, phosphodiesterase inhibitor, cAMP kinase activator, superoxide scavenger, Potassium channel activator, calcium channel blocker, cholinergic modulator, α-adrenergic antagonist, β-adrenergic agonist, adrenergic nerve inhibitor, estrogen-like compound, benzodiazepine, antidiarrheal agent, HMG-CoA reductase inhibitor, or smooth muscle relaxant) which is effective in treating anorectal disorders and in controlling and alleviating pain associated therewith.

Preferably, the compositions are administered in unit dosage form to a subject in need of such treatment. Topical sustained and prolonged release compositions are typically variants which include 1) an absorbent in a hydrophilic base; 2) an absorbent in a hydrophobic base; and 3) coated beads containing an absorbent matrix dispersed in a suitable vehicle. Also provided are methods of treating anorectal disorders comprising topically administering an effective amount of such compositions (e.g., in unit dosage form) to the appropriate anorectal area of the subject in need of such treatment.

[157] Such hydrophilic compositions and preparations of the invention comprise a compound of the invention and a polymer, such as cellulose (methyl cellulose, ethyl cellulose, hydroxy propyl cellulose, etc.), higher molecular weight polyethylene glycol, methacrylic-acrylic acid emulsion, hydrogel, carbopol, ethyl vinyl acetate copolymer, or polyester, etc., to bind the compound of interest to the polymer. The compound-polymer matrix is then dispersed in a hydrophilic vehicle to form a semi-solid. After administration of such hydrophilic composition into the appropriate anorectal area, the water in the semi-solid
preparation is adsorbed and the polymer matrix with the active ingredient \( i.e., \) the pharmaceutical compound) remains as a coating in the area to which it has been applied. The pharmaceutical compound is then slowly released from this coating.

[158] Hydrophobic compositions and preparations of the invention employ similar polymers as used in the hydrophilic preparations, but the polymer/compound matrix is dispersed into a vehicle, such as a plastibase, in the hydrophobic compositions and preparations. Plastibase is a mineral oil base that only partially dissolves the pharmaceutical compound. The semi-solid composition forms a thin coating on the anorectal region to which the composition has been applied \( i.e., \) the anorectal area and slowly releases the active compound. The prolonged action is controlled principally by the solubility of the active ingredient in the vehicle.

[159] The present invention also provides coated beads which are produced by first absorbing a compound of the present invention, or a combination of compounds, on a cellulosic material blended with polyethylene glycol, filler, binder and other excipients. The resulting matrix is then extruded and spheronized \( i.e., \) the process of making into spheres) to create small beads. The beads are then coated to an appropriate thickness with one or more of a suitable material, such as a methacrylic-acrylic polymer, polyurethane, ethyl vinyl acetate copolymer, polyester, silastic, etc. The coating on the beads acts as a rate controlling membrane that regulates the release of the compound from the core beads.

[160] In other embodiments, the invention provides pharmaceutical compositions suitable for oral administration which are provided in unit dosage form comprising per unit dosage a CAMP kinase activator, superoxide scavenger, Potassium channel activator, calcium channel blocker, cholinergic modulator, \( \alpha \)-adrenergic antagonist, \( \beta \)-adrenergic agonist, adrenergic nerve inhibitor, NO donor, phosphodiesterase inhibitor, estrogen-like compound, benzodiazepine, antidiarrheal agent, HMG-CoA reductase inhibitor or smooth muscle relaxant, and a pharmaceutically acceptable carrier. Such compositions are useful for treating anorectal disorders, including those disorders and conditions described above.

[161] For delivery to the buccal membranes, typically an oral formulation, such as a lozenge, tablet, or capsule is used. Methods of manufacture of these formulations are known in the art, including but not limited to, the addition of a pharmacological agent to a pre-manufactured tablet; cold compression of an inert filler, a binder, and either a pharmacological compound or a substance containing the compound \( i.e., \) as described in U.S.
Patent No. 4,806,356); and encapsulation. Another oral formulation is one that can be applied with an adhesive, such as the cellulose derivative, hydroxypropyl cellulose, to the oral mucosa, for example as described in U.S. Patent No. 4,940,587. This buccal adhesive formulation, when applied to the buccal mucosa, allows for controlled release of the pharmacological agent into the mouth and through the buccal mucosa. The compounds of the present invention can be incorporated into these formulations as well.

C. Aerosol Formulations

[162] For delivery to the nasal or bronchial membranes, typically an aerosol formulation is employed. The term “aerosol” includes any gas-borne suspended phase of the pharmacological agent that is capable of being inhaled into the bronchioles or nasal passages. Specifically, aerosol includes a gas-borne suspension of droplets of the compounds of the instant invention, as may be produced in a metered dose inhaler or nebulizer, or in a mist sprayer. Aerosol also includes a dry powder composition of a pharmacological compound of interest suspended in air or other carrier gas, which may be delivered by insufflation from an inhaler device, for example. For solutions used in making aerosols, the preferred range of concentration of the pharmacological agent is 0.1-100 mg/ml, more preferably 0.1-30 mg/ml, and most preferably, 1-10 mg/ml. Usually the solutions are buffered with a physiologically compatible buffer such as phosphate or bicarbonate. The usual pH range is 5 to 9, preferably 6.5 to 7.8, and more preferably 7.0 to 7.6. Typically, sodium chloride is added to adjust the osmolarity to the physiological range, preferably within 10% of isotonic. Formulation of such solutions for creating aerosol inhalants is discussed in Remington, *Pharmaceutical Sciences*, see also, Ganderton and Jones, *Drug Delivery to the Respiratory Tract*, Ellis Horwood (1987); Gonda (1990) *Critical Reviews in Therapeutic Drug Carrier Systems* 6:273-313; and Raeburn et al. (1992) *J. Pharmacol. Toxicol. Methods* 27:143-159.

[163] Solutions of the pharmacological agent may be converted into aerosols by any of the known means routinely used for making aerosol inhalant pharmaceuticals. In general, such methods comprise pressurizing or providing a means of pressurizing a container of the solution, usually with an inert carrier gas, and passing the pressurized gas through a small orifice, thereby pulling droplets of the solution into the mouth and trachea of the animal to which the drug is to be administered. Typically, a mouthpiece is fitted to the outlet of the orifice to facilitate delivery into the mouth and trachea.
D. Oral formulations

[164] In still another embodiment, the invention provides pharmaceutical compositions suitable for oral administration which are provided in unit dosage form comprising per unit dosage a phosphodiesterase inhibitor, cyclic nucleotide mimetic, or β-adrenergic agonist, and a pharmaceutically acceptable carrier. Such compositions are useful for treating anorectal disorders, including those disorders and conditions provided above.

[165] For delivery to the buccal membranes, typically an oral formulation, such as a lozenge, tablet, or capsule is used. The method of manufacture of these formulations are known in the art, including but not limited to, the addition of a pharmacological agent to a pre-manufactured tablet; cold compression of an inert filler, a binder, and either a pharmacological agent or a substance containing the agent (as described in U.S. Patent No. 4,806,356); and encapsulation. Another oral formulation is one that can be applied with an adhesive, such as the cellulose derivative, hydroxypropyl cellulose, to the oral mucosa, for example as described in U.S. Pat. No. 4,940,587. This buccal adhesive formulation, when applied to the buccal mucosa, allows for controlled release of the pharmacological agent into the mouth and through the buccal mucosa. The anti-inflammatory agents of the present invention can be incorporated into these formulations as well.

E. Transmucosal formulations.

[166] Transmucosal (i.e., sublingual, rectal, colonic, pulmonary, buccal and vaginal) drug delivery provides for an efficient entry of active substances to systemic circulation and reduces immediate metabolism by the liver and intestinal wall flora (See Chien Y.W., NOVEL DRUG DELIVERY SYSTEMS, Chapter 4 "Mucosal Drug Delivery," Marcel Dekker, Inc. (1992). Transmucosal drug dosage forms (e.g., tablet, suppository, ointment, gel, pessary, membrane, and powder) are typically held in contact with the mucosal membrane and disintegrate and/or dissolve rapidly to allow immediate local and systemic absorption. These formulations are used along with the anti-inflammatory agents of the present invention for reducing or eliminating inflammation of transmucosal membranes.

[167] In order to enhance transmucosal absorption efficiency and bioavailability of the active agents, selected mucosal adhesive polymers or dosages can be employed. For example, a selected potassium channel opener, e.g. minoxidil can be formulated in a liquid suppository in which mucoadhesive polymers such as polyvinylpyrrolidone (PVP, BASF, Germany), polycarbophil (Goodrich, USA), or sodium alginate (Hayashi Pure Chemicals, Tokyo, Japan), etc. are incorporated. This type of liquid

F. Parenteral formulations

[168] In yet another embodiment, the invention provides pharmaceutical compositions suitable for parental administration which are provided in unit dosage form comprising per unit dosage a phosphodiesterase inhibitor, cyclic nucleotide mimetic, or β-adrenergic agonist, and a pharmaceutically acceptable carrier. Such compositions are useful for treating anorectal disorders and conditions as described above.

G. Kits

[169] In yet another embodiment, the invention provides kits for the treatment of the anorectal disorders. The kits comprise an applicator, a container holding at least one unit dose of the pharmaceutical composition according to the invention, and instructions for applying the composition. In one embodiment, the composition is a topical composition and the instructions indicate the composition is to be applied to the anorectal region. In one embodiment, the applicator is disposable. In another embodiment the applicator provides an extension of at least from 1 inch, 2 inches, or 3 inches from where it is held to the tip of the applicator or to a point where the applicator contacts the skin in applying the composition. In another embodiment, the applicator dispenses unit dosages. In another embodiment, the kit provides one or more applicators and containers wherein the applicators and containers are integral and provide one unit dose.

III. METHODS OF TREATING ANORECTAL DISORDERS

[170] In another aspect, the present invention provides methods for treating anorectal disorders which comprise administering to or contacting an appropriate area or affected anorectal tissue (e.g., anus or rectum) of a subject in need of such treatment an effective amount of any of the compositions provided above. By use of such methods of the
invention, spasms of the musculature of the ano rectal area (e.g., anal sphincters) are relieved and signs and symptoms associated with ano rectal disorders, e.g., anal fissure, hemorrhoids, anal pain or anal itching or anal burning therewith are improved. The methods described herein are also applicable to the treatment of recurrent ano rectal diseases, and are also useful for relaxing the musculature of the ano rectal region and reducing pain during proctologic exams (in patients with and without disorders), particularly during procedures where instruments are inserted into the rectum.

[171] The present invention further provides methods of using the above-described compositions in combination with local anesthetic agents, such as, for example, lidocaine, prilocaine, etc. Each of the compositions will typically be in a pharmaceutically acceptable dosage form as an effective treatment for a ano rectal medical condition. These pharmaceutical preparations are also useful in treating conditions resulting from spasms of the musculature, including, but not limited to, levator spasm. In another aspect, the present invention provides methods for treating ano rectal disorders which comprise administering an effective amount of one a composition described herein along with a local anesthetic agent to a subject in need of such treatment. Such compositions can be administered orally, transdermally, transmucosally or parenterally.

[172] Similarly, the invention provides methods of using the above-described compositions in combination with local anti-inflammatory agents, for example, naproxen or piroxicam, in a pharmaceutically acceptable dosage form as an effective treatment for a ano rectal medical condition such as, e.g., anal fissure, hemorrhoids, levator spasm, ano rectal burning, itching or pain. These pharmaceutical preparations are also useful in treating conditions resulting from spasms of the sphincter muscle and the increased internal anal sphincter pressures associated therewith. In another aspect, the present invention provides methods for treating ano rectal disorders which comprise administering an effective amount of such composition along with a local anesthetic agent to a subject in need of such treatment. Such compositions can be administered orally, transdermally, transmucosally or parenterally.

[173] Additional methods provided by the present invention are those in which two or more agents selected from a cAMP kinase activator, superoxide scavenger, Potassium channel activator, calcium channel blocker, cholinergic modulator, α-adrenergic antagonist, β-adrenergic agonist, adrenergic nerve inhibitor, NO donor, phosphodiesterase inhibitor, estrogen-like compound, benzodiazepine, antidiarrheal agent, HMG-CoA reductase inhibitor and smooth muscle relaxant, are administered either in combination or sequentially
to provide an enhanced therapeutic benefit. The use of two compounds from those listed above can provide fewer and less severe side effects than equally effective doses of a single compound, if used alone. More particularly, the use of two compounds in combination allows for decreased amounts of each compound to be used to achieve the same benefit relative to a compound used alone, and provides significantly reduced occurrence and duration of side effects.

[174] In another aspect, the present invention provides methods for treating anorectal disorders which comprise administering to an appropriate anal area or affected anal tissue (e.g., external or internal anal tissue or anal canal) of a subject in need of such treatment an effective amount of any of the compositions provided above. By use of such methods of the invention, anorectal hypertonicity and/or spasms are relieved, anal sphincter pressure is reduced, reduced anal sphincter pressure is maintained, and signs and symptoms associated with anorectal disorders, e.g. anal fissures, anal ulcers and hemorrhoids, and pain are improved. The methods described herein are also applicable to the treatment of recurrent anal diseases, and are also useful for relaxing the anal sphincter and reducing pain during anorectal exams (in patients with and without disorders), particularly during procedures when instruments are inserted into the anus.

[175] The present invention further provides methods of using the compositions above in combination with local anesthetic agents, for example lidocaine, prilocaine, etc. Each of the compositions will typically be in a pharmaceutically acceptable dosage form as an effective treatment for a medical condition such as hemorrhoidal pain and for treating spasms and/or hypertonicity of the sphincters including the internal anal sphincter, lower esophageal sphincter, pyloric sphincter, sphincter of Oddi, and the ileocolic sphincter. These pharmaceutical preparations are also useful in treating conditions resulting from spasms and/or hypertonicity of sphincters of the anorectal region including anal fissure, post-operative rectal pain, hypertrophic pyloric stenosis, and pancreatitis, as well as conditions resulting from general spasm of the muscles of the GI tract including Zenker's diverticulum, achalasia, esophageal spasm (nutcracker esophagus), irritable bowel disease, and Hirschsprung’s disease (bowel obstruction). In another aspect, the present invention provides methods for treating anal disorders which comprise administering an effective amount of such composition along with a local anesthetic agent to a subject in need of such treatment. Such compositions can be administered orally, topically, or parenterally.

[176] Similarly, the invention provides methods of using the compositions above in combinations with local anti-inflammatory agents, for example, naproxen,
piroxicam, etc. in a pharmaceutically acceptable dosage form as an effective treatment for a medical condition such as hemorrhoidal pain and for treating hypertonicity and/or spasms of the sphincters including the internal anal sphincter, lower esophageal sphincter, pyloric sphincter, sphincter of Oddi, and the ileocolic sphincter. These pharmaceutical preparations are also useful in treating conditions resulting from spasms and/or hypertonicity of sphincters of the anorectal region including anal fissure, post-operative rectal pain, hypertrophic pyloric stenosis, and pancreatitis, as well as conditions resulting from general spasm of the muscles of the GI tract including Zenkers diverticulum, achalasia, esophageal spasm (nutcracker esophagus), irritable bowel disease, and Hirschsprung’s disease (bowel obstruction). In another aspect, the present invention provides methods for treating anal disorders which comprise administering an effective amount of such composition along with a local anesthetic agent to a subject in need of such treatment. Such compositions can be administered orally, topically, or parenterally.

[177] Additional methods provided by the present invention are those in which two or more agents selected from NO donors, phosphodiesterase type V (PDE V) inhibitor, a phosphodiesterase type II (PDE II) inhibitor, a nonspecific PDE inhibitor, a dual-selective PDE inhibitor, a β-adrenergic agonist, a cAMP-dependent protein kinase activator, an α₁-adrenergic antagonist, a superoxide anion (O₂⁻) scavenger, an ATP-sensitive K⁺ channel activator, an estrogen or estrogen-like compound, a adrenergic nerve inhibitor, an adenosine receptor modulator, or a smooth muscle relaxant, are administered either in combination or sequentially to provide an enhanced therapeutic benefit. In particular, the use of an NO donor and a second agent from those provided above can provide fewer and less severe side effects than equally effective doses of NO donors, if used alone. More particularly, the use of an NO donor in combination with a second agent allows for decreased amounts of the NO donor to be used to achieve the same benefit relative to use alone, while extending the period of reduction of anal sphincter pressure, and provides significantly reduced occurrence and duration of headaches.

GENERAL EXAMPLES

30  **NO Donors in Combination with a Second Agent**

[178] In one aspect, the present invention provides compositions for the treatment of anal disorders comprising a nitric oxide donor in combination with a second agent which modulates levels of cAMP or cGMP. In one group of embodiments the second
agent is a phosphodiesterase type V (PDE V) inhibitor. In another group of embodiments the second agent is a phosphodiesterase type IV (PDE IV) inhibitor. In another group of embodiments the second agent is a phosphodiesterase type II (PDE II) inhibitor. In another group of embodiments the second agent is a nonspecific PDE inhibitor. In still another group of embodiments the second agent is a superoxide anion \((O_2^-)\) scavenger. In yet another group of embodiments the second agent is a \(\beta\)-adrenergic agonist. In another group of embodiments, the second agent is a cAMP-dependent protein kinase activator. In another group of embodiments the second agent is an \(\alpha_1\)-adrenergic antagonist. In another group of embodiments the second agent is an estrogen, estrogen analog, or estrogenic compound. In another group of embodiments the second agent is an L-type \(Ca^{2+}\) channel blocker. In still another group of embodiments the second agent is an ATP-sensitive \(K^+\) channel activator.

The present invention further provides methods of using the compositions provided above. In a related aspect, the present invention provides compositions comprising a NO donor and a smooth muscle relaxant.

[179] In each of the above embodiments, the nitric oxide donor can be any of a variety of NO donors including, for example, organic NO donors, inorganic NO donors and prodrug forms of NO donors. Preferably, the NO donor includes at least one organic nitrate (including esters of nitric acid) and can be either a cyclic or acyclic compound. For example, suitable NO donors include nitroglycerin (NTG), L-arginine, isosorbide dinitrate (ISDN), isosorbide mononitrate (ISMN) which may include isosorbide-2-mononitrate (IS2MN) and/or isosorbide-5-mononitrate (IS5MN), erythrityl tetrinitrate (ETN), pentaerythrityl tetranitrate (PETN), ethylene glycol dinitrate, isopropyl nitrate, glycercyl-1-mononitrate, glycercyl-1,2-dinitrate, glycercyl-1,3-dinitrate, butane-1,2,4-triol trinitrate, and the like. More preferably, the NO donor is NTG. Nitroglycerin and other organic nitrates including ISDN, ETN, and PETN, have been given regulatory approval for use in treatments in other fields of medicine on human subjects. Additional NO donors include sodium nitroprusside, N,O-diacetyl-N-hydroxy-4-chlorobenzenesulfonamide, \(N^G\)-hydroxy-L-arginine (NOHA), hydroxyguanidine sulfate, molsidomine, 3-morpholinosydnonimine (SIN-1), \((\pm)\)-S-nitroso-N-acetylpenicillamine (SNAP), S-nitrosoglutathione (GSNO), \((\pm)-(E)-ethyl-2-[(E)-hydroxyimino]-5-nitro-3-hexeneamide (FK409), \((\pm)-N-[(E)-4-ethyl-3-[(Z)-hydroxyimino]-5-nitro-3-hexen-1-yl]-3-pyridinecarboxamide (FR144420), and 4-hydroxymethyl-3-furoxancarboxamide.
In general, the organic nitric oxide donor (e.g., the organic nitrate) is present in any amount less than that which is effective in the practice of the treatment of anal disease when used alone. In typical practice of the invention the organic nitric oxide donor can be present in a concentration from about 0.01 to about 10 percent by weight. All weight percentages herein are based on the total weight of the composition. For NTG, preferred concentrations are in the range of from about 0.01 to about 5 percent by weight.

In one group of embodiments, the composition contains an agent which is a phosphodiesterase (PDE) inhibitor. Inhibitors of phosphodiesterases (PDE), are agents which can block the breakdown of cAMP and cGMP in the tissue. PDE inhibitors include both non-specific PDE inhibitors and specific PDE inhibitors (those which inhibit a single type of phosphodiesterase with little, if any, effect on any other type of phosphodiesterase). Still other useful PDE inhibitors are the dual selective PDE inhibitors (e.g., PDE III/IV inhibitors).

In one group of embodiments, the PDE inhibitor is a PDE V inhibitor. Useful phosphodiesterase type V inhibitors include zaprinast, MBCQ, MY-5445, dipyridamole and sildenafil.

In another group of embodiments, the composition contains an agent which is a phosphodiesterase type II (PDE II) inhibitor. Suitable phosphodiesterase type II inhibitors include EHNA.

In yet another group of embodiments, the composition contains an agent which is a phosphodiesterase type IV (PDE IV) inhibitor. Suitable phosphodiesterase type IV inhibitors include ariflo (SB207499), RP73401, Ro-201724, CDP840, rolipram and LAS31025.

In still another group of embodiments, the composition contains an agent which is a dual selective phosphodiesterase inhibitor, preferably a PDE III/IV inhibitor such as, for example, zardaverine.

In yet another group of embodiments, the composition contains an agent which is a nonspecific phosphodiesterase (nonspecific PDE) inhibitor. Suitable nonspecific phosphodiesterase inhibitors include IBMX, theophylline, dyphylline theobromine, aminophylline, pentoxifylline, papaverine, caffeine and other methyl xanthine and non-xanthine derivatives (Goodman & Gilman’s “The Pharmacological Basis of Therapeutics” The McGraw-Hill Companies, 1996).

In still another group of embodiments, the composition contains an agent that is a superoxide anion (O₂⁻) scavenger. Superoxide can react with NO and
dramatically reduce its biological effects. Accordingly, agents that scavenge superoxide anion (e.g., exogenous Mn- or Cu/Zn superoxide dismutase (SOD) or small molecule SOD mimetics, e.g. Mn(III) tetra(4-benzoic acid) porphyrin chloride (MnTBAP) and M40403, see Salvemini, et al., Science 286(5438):304-306 (1999)) can enhance the effects of NO. SODs are relatively stable enzymes and can be used in topical formulations with NO donors such as, for example, NTG, to boost the local potency of NO generated from NTG. The nitric oxide formed from NTG acts only locally due to its short half-life. However, NTG itself is stable enough to exert systemic effects following mucosal absorption. By enhancing the local efficacy of NTG with SOD or a SOD mimetic, less NTG is required to produce the same degree of internal anal sphincter relaxation, and less NTG is absorbed, leading to a reduction in systemic side effects.

[188] In yet another group of embodiments, the composition contains an agent that is a β-adrenergic agonist, preferably a β2- or β3-adrenergic receptor agonist. A variety of β-adrenergic agonists have been described in the literature and are useful in the present invention. Suitable β3-adrenergic agonists are described in, for example, Bristol, et al., ANNUAL REPORTS IN MEDICINAL CHEMISTRY, VOL. 33, Chap. 19, pp 193-202, Academic Press (1998). Preferred β-adrenergic agonists include salbutamol, terbutaline, procaterol, clenbuterol, isoproterenol, zinterol, BRL 37344, CL316243, CGP-12177A, GS 332, L-757793, L-760087, L-764646, and L-766892.

[189] In another group of embodiments, the agent is a cAMP-dependent protein kinase activator. A variety of cyclic nucleotide-dependent protein kinase activators are useful in the present invention including, for example, cAMP mimetics and dual cGMP/cAMP-dependent protein kinase activators. cAMP mimetics are well known to those of skill in the art and include 8-bromo-cAMP, dibutyryl-cAMP, Rp-cAMPS, and Sp-cAMPS. Dual activators include Sp-8-pCPT-cGMPS, Sp-8-bromo-cGMPS and 8-CPT-cAMP.

[190] In yet another group of embodiments, the composition contains an agent that is an estrogen or estrogen analog or mimic. As used herein, the term “estrogens” is meant to include all forms of estrogen and estrogen-like compounds such as those compounds having estrogen like activity (e.g., those that bind to the estrogen receptor in a competitive binding assay). The estrogens can be either steroidal or nonsteroidal (see, for example, Bristol, et al., ANNUAL REPORTS IN MEDICINAL CHEMISTRY, VOL. 31, Chap. 19, pp 181-190, Academic Press (1996), and references cited therein). Estrogen-like compounds include but are not limited to 17-beta-estradiol, estrone, mestranol, estradiol valerate, estradiol dypionate, ethinyl estradiol, quinestrol, estrone sulfate, phytoestrogens such as
flavones, isoflavones (e.g. genistein), resveratrol, coumestan derivatives, other synthetic estrogenic compounds including pesticides (e.g., p,p'-DDT), plasticizers (e.g. bisphenol A), and a variety of other industrial chemicals (e.g. polychlorinated biphenyls).

[191] In yet another group of embodiments, the composition contains an agent that is an $\alpha_1$-adrenergic antagonist. The sympathetic neurotransmitter norepinephrine contracts sphincter smooth muscle via $\alpha_1$-adrenergic receptors. Pharmacological interference with norepinephrine release or binding to $\alpha_1$-adrenergic receptors by administering sympatholytic agents to the appropriate anal area of a subject can also lead to anal sphincter relaxation, reduction of anal sphincter pressure, maintenance of reduced anal sphincter pressure, and improvement of the signs and symptoms of anorectal disorders. Such sympatholytic agents include $\alpha_1$-adrenergic receptor antagonists (e.g. prazosin, doxazosin, phentolamine, tolazoline, and the like as described in Goodman & Gilman’s The Pharmacological Basis of Therapeutics, ninth edition, ed. JG Hardman, et al., McGraw-Hill 1996), $\alpha_2$-adrenergic agonists which block norepinephrine release (e.g. clonidine), nerve terminal norepinephrine depleting agents (e.g. guanethidine, bretlyium, reserpine), norepinephrine synthesis inhibitors (e.g. $\alpha$-methyl tyrosine), and agents which destroy sympathetic nerve terminals (e.g. 6-hydroxy dopamine). Accordingly, in a related embodiment, the composition contains an alternative sympatholytic agent, such as an $\alpha_2$-adrenergic receptor agonist, a nerve terminal norepinephrine depleting agent, a norepinephrine synthesis inhibitor or another agent which destroys sympathetic nerve terminals.

[192] In still another group of embodiments the agent is an ATP-sensitive K$^+$ channel activator. ATP, along with NO, is thought to serve as an inhibitory neurotransmitter released from the enteric non-adrenergic, non-cholinergic nerves that mediate adaptive relaxation of gastrointestinal smooth muscle (Burnstock, Pharmacol Rev. 24:509-81 (1972)). ATP appears to act primarily by opening ATP-sensitive potassium (K$_{ATP}$) channels which hyperpolarize the cell membrane, reducing intracellular calcium concentrations, leading to smooth muscle relaxation. Synthetic compounds that activate ATP-sensitive K$^+$ channels are smooth muscle relaxants, e.g. minoxidil, minoxidil sulfate, pinocidil, diazoxide, levromokalim, cromakalim, etc. (see White, et al., Eur. J. Pharmacol. 357(1):41-51 (1998)). ATP-sensitive potassium channels are expressed in GI smooth muscle (Koh, et al., Biophys. J. 75:1793-80 (1998)). Accordingly, specific potassium channel openers will be useful for relaxing internal anal sphincter smooth muscle, reducing anal sphincter pressure, maintaining
reduced anal sphincter pressure, and improving the signs and symptoms of anorectal disorders. It should be noted that other K⁺ channels can also influence smooth muscle tone, including apamin-sensitive low conductance calcium-activated K⁺ channels and charybdotoxin-sensitive high conductance calcium-activated K⁺ channels.

[193] In still other embodiments, the compositions will comprise NO donors and smooth muscle relaxants. Preferred smooth muscle relaxants include, for example, hydralazine, papaverine, tiopronamide, cyclandelate, isoxsuprine or nylidrin.

[194] In yet other embodiments, the compositions will comprise NO donors and a second agent which is a methyl xanthine or adenosine receptor modulator. Preferred second agents include theophylline, dyphylline, aminophylline, caffeine, and theobromine.

[195] In a preferred embodiment, a second agent is a K⁺ATP channel opener, an adenosine receptor modulator, or a β2-adrenergic receptor agonist. In yet further embodiments, a second agent is preferably selected from the group consisting of theophylline, dyphylline, minoxidil, diazoxide, terbutaline, and salbutamol.

**Phosphodiesterase inhibitor compositions**

[196] In another aspect, the present invention provides compositions for the treatment of anorectal disorders comprising a phosphodiesterase inhibitor, preferably a PDE II inhibitor, a PDE IV inhibitor or a PDE V inhibitor, either alone or in combination with another agent selected from β-adrenergic receptor agonists, α₁-adrenergic antagonists, estrogens, L-type Ca²⁺ channel blockers, ATP-sensitive K⁺ channel activators, or smooth muscle relaxants, in combination with a pharmaceutically acceptable carrier. In other embodiments, the compositions will comprise a dual-selective PDE inhibitor (e.g., a PDE III/IV inhibitor such as zardaverine). The present invention also provides methods of using these compositions.

[197] Phosphodiesterase inhibitors (PDE inhibitors) are agents which can block the breakdown of cAMP and cGMP in the tissue. PDE inhibitors include non-specific PDE inhibitors and specific PDE inhibitors. A non-specific PDE inhibitor inhibits more than one type of phosphodiesterase, while a specific PDE inhibitor inhibits only one type of phosphodiesterase with little, if any, effect on any other type of phosphodiesterase. Specific inhibitors of five cyclic nucleotide PDE isozyme families have been characterized: 8-methoxymethyl-IBMX (isobutyl methylxanthine) or vinpocetine (Ca²⁺, calmodulin-dependent PDE type I); EHNA(erythro-9-(2-hydroxy-3-nonyl)adenine HCl) (cGMP-stimulated PDE type II); millrinone (cGMP-inhibited PDE type III); rolipram (cAMP-specific
PDE type IV); and zaprinast and DMPPO (1,3 dimethyl-6-(2-propoxy-5-methane sulphonylamidophenyl)-pyrazolo[3,4-d]pyrimidin-4-(5H)-one) (cGMP-specific PDE type V). Current knowledge suggests that there are at least nine classes of PDE isozymes with type 9A having been recently discovered (see, Fisher, et al., J Biol. Chem. 273(25):15559-15564 (1998)). Agents which are non-specific inhibitors of PDEs include, for example, IBMX, theophylline, aminophylline, theobromine, dyphylline caffeine, etc. (see, Venulapalli, et al., J Cardiovasc. Pharmacol 28(6):862-9 (1996)).

[198] Preferably, the compositions for treating anorectal disorders contain one or more compounds selected from the classes of PDE II, PDE IV and PDE V inhibitors, or a dual PDE III/IV inhibitor in a formulation suitable for local treatment. Members of each of these classes can be advantageously combined with a second agent selected from the group of β-adrenergic receptor agonists, preferably a β2- or β3-adrenergic receptor agonists, α1-adrenergic antagonists, L-type Ca^{2+} channel blockers, estrogens, ATP-sensitive K^{+} channel activators, adrenergic nerve inhibitors, adenosine receptor modulators, methylxanthines, or smooth muscle relaxants. Preferred members from each class of additional agent are those which have been described above for use with NO donors.

[199] In embodiments comprising a second active agent with a PDE, a second agent is preferably a K^{+} ATP channel opener, an adenosine receptor modulator, or a β2-adrenergic receptor agonist. In yet further embodiments, a preferred second agent is a compound selected from the group consisting of theophylline, dyphylline, minoxidil, diazoxide, terbutaline, and salbutamol.

β-adrenergic receptor agonist compositions

[200] In another aspect, the present invention provides pharmaceutical compositions for the treatment of anorectal disorders comprising a β-adrenergic receptor agonist, preferably a β2- or β3-adrenergic receptor agonist, either alone or in combination with another agent selected from cAMP-hydrolyzing PDE inhibitors (e.g., a PDE IV inhibitor), nonspecific PDE inhibitors, α1-adrenergic antagonists, estrogens, L-type Ca^{2+} channel blockers, ATP-sensitive K^{+} channel activators, or smooth muscle relaxants, and a pharmaceutically acceptable carrier. The present invention further provides methods of using those compositions.

[201] In this aspect of the invention, the β-adrenergic receptor agonist can be essentially any of the β-adrenergic receptor agonists provided above for use in combination with NO donors. Preferably, the β-adrenergic agonist, is a β2- or β3-adrenergic receptor

[202] Terbutaline and salbutamol (albuterol) are β2-adrenergic agonists commonly used for the long-term treatment of obstructive airway diseases and acute bronchospasm in asthma. Beta-adrenergic agents, like VIP, potently relax smooth muscle, including IAS smooth muscle by raising intracellular cyclic AMP levels (Parks et al., *Gut* 10(8): 674-7 (1969); Chakder, S. et al., *Amer J Physiol*. 264 (1 pt 1):G7-12, (1993); Chakder, S. et al., *Amer J Physiol*. 264 (4 pt 1): G702-7, (1993); O’Kelly, T.J. et al., *Gut* 34(5): 689-93, (1993)); O’Kelly, T.J. et al., *Br J Surg* 80(10): 1337-41, (1993)). Cyclic AMP induces smooth muscle relaxation through phosphorylation of smooth muscle regulatory proteins (e.g., myosin light chain kinase) and by decreasing intracellular calcium concentrations (e.g., via K⁺-ATP channel activation). Terbutaline and salbutamol have weaker cardiovascular effects than non-specific β-receptor agonists, e.g., isoproterenol, because they do not stimulate cardiac β₁-adrenergic receptors at therapeutic doses. They are commonly administered by inhalation (i.e., topically). Tolerance is a potential downside effect of β₂-adrenergic agonists. Long-term systemic administration of β-adrenergic agonists leads to down-regulation of β receptors in some tissues and decreased pharmacological responses, and has been demonstrated in patients with asthma¹.

[203] In one group of embodiments, the compositions comprise forskolin. Forskoline directly activates adenyl cyclase avoiding tolerance.

[204] In one group of embodiments, the composition contains a suitable β-adrenergic receptor agonist and a pharmaceutically acceptable carrier, preferably one formulated for local delivery to the site of the anorectal disease or disorder.

[205] In another group of embodiments, the composition contains another agent selected from cAMP-hydrolyzing PDE inhibitors (e.g., a PDE IV inhibitor), nonspecific PDE inhibitors, α₁-adrenergic antagonists, adenosine receptor modulators including methyl xanthises, estrogens, L-type Ca²⁺ channel blockers, ATP-sensitive K⁺ channel activators or smooth muscle relaxants.

[206] In one preferred group of embodiments, the agent is a cAMP-hydrolyzing PDE inhibitor, more preferably a phosphodiesterase type IV inhibitor. Preferred phosphodiesterase type IV (also referred to as PDE IV and PDE4) inhibitors are described in, for example, Bristol, et al., Annual Reports in Medicinal Chemistry, Vol. 33, Chap. 10, pp 91-109, Academic Press (1998). Most preferably, the PDE IV inhibitor is rolipram, Ro 20-1724 or Etazolate.

[207] In another group of preferred embodiments, the agent is a nonspecific PDE inhibitor such as, for example, IBMX, aminophylline, theophylline, pentoxifylline, theobromine, dyphylline, lisophylline and papaverine.

[208] In yet another group of preferred embodiments, the agent is an α₁-adrenergic antagonist. Suitable α₁-adrenergic receptor antagonists (e.g. prazosin, doxazosin, phentolamine, tolazoline, and the like) are described in Goodman & Gilman’s THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, ninth edition, ed. JG Hardman, et al., McGraw-Hill (1996). Preferred agents for use in these compositions are selected from prazosin, doxazosin, phentolamine, tolazoline and their derivatives.

[209] In still other preferred embodiments, the β-adrenergic receptor agonist is combined with an L-type Ca²⁺ channel blocker, such as, for example, nifedipine, nimodipine, felodipine, nicardipine, isradipine, amlodipine, diltiazem, mentol, pinavarium bromide (a gastrointestinal tract selective calcium channel blocker; Awad RA et al., Acta Gastroent. Latinoamer. 27:247-251, 1997) and verapamil.

[210] In yet other preferred embodiments, the β-adrenergic receptor agonist is combined with an ATP-sensitive K⁺ channel activator. Preferred agents within this group are the same as those that have been provided above for use with NO donors.

[211] Additional compositions are those in which a β-adrenergic receptor agonist is combined with an estrogen or estrogen like compound, or with a smooth muscle relaxant. Suitable compounds within each of these classes have been described above for use with NO donors.

[212] In embodiments comprising a second active agent with a β₂-adrenergic receptor agonist, a second agent is preferably a K⁺-ATP channel opener or an adenosine receptor modulator. In yet further embodiments, a preferred second agent is a compound selected from the group consisting of theophylline, dyphylline, minoxidil, and diazoxide.
Potassium channel activator compositions

In yet another aspect, the present invention provides compositions for the treatment of anorectal disorders comprising an ATP-sensitive K⁺ channel activator, either alone or in combination with another agent selected from cAMP-dependent protein kinase activators, estrogens, α₁-adrenergic antagonists, L-type Ca²⁺ channel blockers, adrenergic nerve inhibitors, or smooth muscle relaxants, and a pharmaceutically acceptable carrier. The present invention further provides methods of using those compositions.

In this aspect of the invention, the selected combinations are made from the components described in detail above for the NO donor compositions. Additional description of ATP-sensitive potassium ion channel activators can be found in, for example, Bristol, et al., ANNUAL REPORTS IN MEDICINAL CHEMISTRY, VOL. 29, Chap. 8, pp 73-82, Academic Press (1991). In preferred embodiments the potassium ion channel activator is diazoxide, minoxidil, PCO 400, pinocidil, levromokalin, or cromokalin.

In some embodiments, the composition comprises an additional agent which is a cAMP-dependent protein kinase activator, an estrogen or estrogen like compound, an α₁-adrenergic antagonist, an L-type Ca²⁺ channel blocker, a adrenergic nerve inhibitor, or a smooth muscle relaxant. Preferably, the cAMP-dependent protein kinase activator is a cAMP mimetic or a dual cGMP/cAMP-dependent protein kinase activator. More preferably, the cAMP mimetic is 8-bromo-cAMP, dibutryl-cAMP, Rp-cAMPS, or Sp-cAMPS, and the dual activator is selected from Sp-8-pCPT-cGMPS, Sp-8-bromo-cGMPS and 8-CPT-cAMP.

In one group of embodiments, an α₁-adrenergic antagonist is combined with an ATP-sensitive potassium ion channel activator. Preferably, the α₁-adrenergic antagonist is prazosin, phentolamine or tolazoline.

In another group of embodiments, an L-type Ca²⁺ channel blocker is combined with an ATP-sensitive potassium ion channel activator. Preferably, the L-type Ca²⁺ channel blocker is nifedipine, nimodipine, felodipine, nicardipine, isradipine, amlodipine, diltiazem, menthol, pinavarium bromide (a gastrointestinal tract selective calcium channel blocker; Awad RA et al., Acta Gastroent. Latinoamer. 27:247-251, 1997) or verapamil.

Diazoxide and minoxidil have been used for the treatment of hypertension. These drugs are vasodilators that hyperpolarize arterial smooth muscle cells by activating ATP-sensitive K⁺ channels (Meisher et al., J Pharmacol Exp Ther 245(3): 751-60 (1988); Standen et al., Science 245: 177-80 (1989)). Membrane hyperpolarization inactivates voltage-gated calcium channels, reduces intracellular calcium concentrations, and causes
muscle relaxation. ATP released by NANC nerve stimulation probably relaxes the IAS through this mechanism (Brookes J Gastroenterol Hepatol 8(6): 590-603 (1993); Rae et al., J Physiol (London) 493 (Pt 2): 517-27 (1996)). Baird and Muir (Baird et al., Br J Pharmacol 100(2)329-35 (1990)) demonstrated that cromakalim, a K⁺-ATP channel opener, inhibited spike discharge, hyperpolarized the membrane and relaxed the guinea pig IAS. In our studies, diazoxide and minoxidil relaxed the rat IAS in vivo. The adverse effects of these drugs are predictable and can be divided into three major categories: 1) fluid and salt retention, 2) cardiovascular effects, and 3) hypertrichosis. Topical minoxidil, inspired by the hypertrichosis side effect, is marketed for stimulating hair growth. This product has an excellent safety record and is now sold over the counter.

[219] In still another group of embodiments, a smooth muscle relaxant is combined with an ATP-sensitive potassium ion channel activator. Preferably, the smooth muscle relaxant is hydralazine, papaverine, tiropramide, cyclandelate, isoxsuprine or nylidrin.

[220] In embodiments comprising a second active agent with a K⁺-ATP channel opener, a second agent is preferably a K⁺-ATP channel opener, a β₂-adrenergic receptor agonist, or an adenosine receptor modulator. In yet further embodiments, a preferred second agent is a compound selected from the group consisting of theophylline, dipyridamole, terbutaline, and salbutamol.

α₁-Adrenergic antagonist compositions

[221] In still another aspect, the present invention provides compositions for the treatment of anorectal disorders comprising an α₁-adrenergic antagonist, either alone or in combination with another agent selected from cAMP-hydrolyzing PDE inhibitors (preferably a PDE IV inhibitor), estrogens, adrenergic nerve inhibitors, or smooth muscle relaxants, and a pharmaceutically acceptable carrier. The present invention further provides methods of using those compositions.

[222] α₁-Adrenergic antagonists which are useful in this aspect of the invention have been described above and can be found in, for example, Goodman & Gilman’s THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, ninth edition, ed. JG Hardman, et al., McGraw-Hill (1996). Preferred α₁-adrenergic antagonists are prazosin, phentolamine and tolazoline.

[223] For those embodiments in which an α₁-adrenergic antagonist is combined with a cAMP-hydrolyzing PDE inhibitor (preferably a PDE IV inhibitor), an estrogen or estrogen like compound, a adrenergic nerve inhibitor, or a smooth muscle
relaxant, the preferred members of each class are those which have been described above for use with NO donors.

[224] In embodiments comprising a second active agent with a $\alpha_1$-adrenergic antagonist, a second agent is preferably a $K^+$ ATP channel opener, a $\beta_2$-adrenergic receptor agonist or an adenosine receptor modulator. In yet further embodiments, a preferred second agent is a compound selected from the group consisting of theophylline, dypyrilline, minoxidil, diazoxide, terbutaline, and salbutamol.

**Cyclic nucleotide-dependent protein kinase activator compositions**

[225] In another aspect, the present invention provides pharmaceutical compositions for the treatment of anorectal disorders comprising cyclic nucleotide-dependent protein kinase activators, either alone or in combination with another agent. Methods for the use of these compositions are also provided. In one group of embodiments, cGMP-dependent protein kinase activators are used alone. In another group of embodiments, nonspecific cyclic nucleotide-dependent protein kinase activators are used alone. In yet another group of embodiments, nonspecific cyclic nucleotide-dependent protein kinase activators are used in combination with smooth muscle relaxants. In still another group of embodiments, cAMP-dependent protein kinase activators are provided in combination with L-type $Ca^{2+}$ channel blockers.

[226] In embodiments comprising a second active agent with the protein kinase activator, a second agent is preferably a $K^+$ ATP channel opener, a $\beta_2$-adrenergic receptor agonist or an adenosine receptor modulator. In yet further embodiments, a preferred second agent is a compound selected from the group consisting of theophylline, dypyrilline, terbutaline, minoxidil, diazoxide and salbutamol.

[227] In each instance, preferred members of the recited classes of compounds are those that have been described above for use alone or in other combinations.

**Estrogen and estrogen-like compositions**

[228] In another aspect, the present invention provides pharmaceutical compositions for the treatment of anorectal disorders comprising estrogen or an estrogen mimic, either alone or in combination with another agent from any of the classes of agents described above. Estrogen-like compounds include but are not limited to 17-beta-estradiol, estrone, mestranol, estradiol valerate, estradiol dypionate, ethinyl estradiol, quinestrol, estrone sulfate, phytoestrogens such as flavones, isoflavones (e.g. genistein), resveratrol,
coumestan derivatives, other synthetic estrogenic compounds including pesticides (e.g. p,p'-DDT), plasticizers (e.g. bisphenol A), and a variety of other industrial chemicals (e.g. polychlorinated biphenyls) (Goodman & Gilman’s THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, ninth edition, ed. JG Hardman, et al., McGraw-Hill (1996). Preferred agents are selected from those described with reference to the compositions of single agents or combinations above. Methods for the use of these compositions are also provided.

[229] In embodiments comprising a second active agent with the estrogenic agent, a second agent is preferably a K⁺ATP channel opener, a β₂-adrenergic receptor agonist or an adenosine receptor modulator. In yet further embodiments, a preferred second agent is a compound selected from the group consisting of theophylline, dyphylline, terbutaline, minoxidil, diazoxide and salbutamol.

Adrenergic nerve inhibitor compositions

[230] In another aspect, the present invention provides pharmaceutical compositions for the treatment of anorectal disorders comprising a adrenergic nerve inhibitor, either alone or in combination with another agent from any of the classes of agents described above. The adrenergic nerve inhibitor compounds include but are not limited to 6-hydroxydopamine and its analogs See, Goodman & Gilman’s THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, ninth edition, ed. JG Hardman, et al., McGraw-Hill (1996). Preferred agents are selected from those described with reference to the compositions of single agents or combinations above. Methods for the use of these compositions are also provided.

Adenosine receptor modulators/Methylxanthines

[231] In another aspect, the present invention provides pharmaceutical compositions for the treatment of anorectal disorders comprising a adenosine receptor modulator, either alone or in combination with another agent from any of the classes of agents described above. Examples of adenosine receptor modulators include theophylline and dyphylline. See, Goodman & Gilman’s THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, ninth edition, ed. JG Hardman, et al., McGraw-Hill (1996). Preferred agents are selected from those described with reference to the compositions of single agents or combinations above. Methods for the use of these compositions are also provided.

[232] Theophylline, a plant-derived methylxanthine, has been used for the treatment of bronchial asthma for decades. Theophylline relaxes smooth muscle, notably
bronchial muscle, that has been contracted experimentally with a spasmogen, or clinically in asthma. We found that theophylline relaxed the rat IAS when instilled into the distal anal canal. Proposed mechanisms of methylxanthine-induced physiologic and pharmacological effects include: 1) inhibition of phosphodiesterases, thereby increasing intracellular cyclic AMP, 2) direct effects on intracellular calcium concentration, 3) indirect effects on intracellular calcium concentrations via cell membrane hyperpolarization, 4) uncoupling of intracellular calcium increases with muscle contractile elements, and 5) antagonism of adenosine receptors. Adenosine receptor antagonism is thought to be the most important factor responsible for most of the pharmacological effects of methylxanthines in therapeutically administered doses².

[233] We have found the related compound, dyphylline, to also reduce IASP in tests. Dyphylline is not metabolized by the liver and is excreted unchanged by the kidneys, therefore its pharmacokinetics and plasma levels are independent of factors that effect liver enzymes such as smoking, age, congestive heart failure, or the use of other drugs that affect liver function.

[234] In embodiments comprising a second active agent with the adenosine receptor modulator, a second agent is preferably a K⁺ATP channel opener or a β₂-adrenergic receptor agonist. In yet further embodiments, a preferred second agent is a compound selected from the group consisting of terbutaline, minoxidil, diazoxide and salbutamol.

Formulations for the Treatment of Anorectal Disorders

[235] Many of the individual components of the compositions provided herein have been described for use in a variety of disease states. However, certain classes and combinations of classes have now been found to be useful for the treatment of anorectal diseases and can be provided in formulations best suited for delivery to an appropriate anal area. Preferred formulations are those in which the components are combined in a topical formulation for local application to the external or internal anus, the external or internal anal sphincter, anal sphincter muscle, the external or internal anal canal and the lower rectum proximate to the internal anal sphincter.

Accordingly, each of the compositions provided above will typically be presented in an appropriate pharmaceutical formulation comprising an effective amount of the noted agents (e.g., NO donors, β2- or β3-adrenergic receptor agonists, cAMP-hydrolyzing PDE inhibitors, nonspecific PDE inhibitors, α1-adrenergic antagonists, L-type Ca2+ channel blockers, ATP-sensitive K+ channel activators, adenosine receptor modulators, and the like).

One of skill in the art will appreciate that suitable formulations are dependent on the form of delivery to be employed, and all such forms are contemplated by the present invention. Additionally, in some embodiments, combinations of agents are employed in a single formulation, while in other embodiments, agents are formulated separately, but administered in combination, or sequentially. In the discussion below, compositions of single agents will be understood to also include compositions of two or more agents. Still further, different formulations can be used for those embodiments in which agents are administered separately or sequentially, by different routes of administration.

Example 1

This example illustrates the effect of cGMP mimetics, alone and in combination with a NO donor in a rat internal anal sphincter (IAS) relaxation model.

Male Sprague-Dawley rats (300-400 gm) were anesthetized with ketamine (90 mg/kg), xylazine (9 mg/kg) given intramuscularly and supplemented as needed with 1/3rd dose. Rats were gently restrained on their backs on a heated surgical table (Harvard Apparatus) for the duration of the experiments. The diuretic effects of anesthesia was offset by rehydration with saline through an intraperitoneal implanted 24 gauge angiocatheter (VWR, San Francisco, CA). The constriction/relaxation measurement assembly included a Millar catheter/transducer (1.67mm diameter.) connected to a Digi-Med Low Pressure Analyzer (Micro-Med) accurate for pressure measurements between -50 and 150 mmHg. The data were integrated and converted to waveforms with the Digi-Med System Integrator software. Blood pressure changes were monitored using an arterial catheter/transducer and a Digi-Med Blood Pressure Analyzer with the DMSI software. Drug delivery was accomplished through two Hamilton syringes with no dead space using PE 10 tubing adjacent to the catheter sensor. Drugs, typically were applied soon after stable baseline readings are recorded. Although unanesthetized restrained rats had been used in other studies, no differences have been observed in resting anal pressures after anesthesia; therefore, these studies were carried out with anesthetized rats to avoid undue distress to the animals.
Typical resting mean internal anal sphincter pressures (IASP) varied between 30 and 60 mmHg in this model. The Millar catheter sensor allowed for accurate, isolated recordings of the IAS. Figure 1 represents a typical waveform pattern for resting IASP in a rat under conditions of a control experiment. The first 10 minutes after treatment with nitroglycerin is shown in Figure 2.

Using the same experimental protocol, the effect of a cGMP mimetic, dibutyryl-cGMP was studied. Figure 3 shows that 20 μl of a 10% solution of dibutyryl-cGMP in saline applied to the anal canal reduced the mean IASP by 45% over 2.5 hours following treatment. The average IASP over the last hour prior to terminating the experiment had dropped 60%.

The IASP was still reduced 34% by the following morning indicating a potential long-term effect of the drug. A subsequent dose of 1% nitroglycerin dropped the IASP by 24% for 30 minutes and 71% for the first 10 minutes following treatment. After IASP returned to pre-treatment levels, a further dose of dibutyryl-cGMP was administered and found to lower IASP 15% over the ensuing 3 hours and 10 minutes.

These results support the effect of cGMP mimetics in relaxing anal sphincter muscle tone, and more importantly, suggest a potential benefit of using a combination of NO donor and cGMP mimetic due to the quick onset of action of the NO donor and the more prolonged duration of relaxation produced by the cGMP mimetics.

Example 2

This example illustrates the effect of phosphodiesterase inhibitors in a rat internal anal sphincter relaxation model.

Using the same experimental protocol described above, an application of 20μL of a 5% zaprinast solution in 1-methyl-2-pyrrolidinone reduced mean IASP by 21% over 32 minutes compared with vehicle treatment alone. The effect of phosphodiesterase inhibitors could be further enhanced by minimal concentrations of NO donors, such as nitroglycerin that produced a quicker onset and sustained sphincter relaxation without headache and other adverse reactions observed with high dose of NO donors alone (see figure 4).
Example 3

[246] This example illustrates the effect of a potassium channel opener (minoxidil) in a rat internal anal sphincter constriction/relaxation model.

[247] Following the same experimental protocol as described above, a single 20 µl dose of a 4% solution of minoxidil in 62.5% propylene glycol resulted in a 64% reduction of the IASP over 2.5 hours following treatment. The vehicle alone had little effect on IASP (see Figure 5).

Example 4

[248] This example illustrates the use of a variety of compositions of the invention for the relaxation of the IAS.

[249] In this example, male Sprague-Dawley rats (250-300 g each) from Charles River were used. The rats were anesthetized intramuscularly with ketamine (90 mg/kg) and xylazine (9 mg/kg) and kept warm on a heated surgical table. All internal anal sphincter pressures (IASP) were measured with Millar catheter/transducers (MPC-500 micro-tip; Millar Instruments, Houston) on low pressure analyzers and blood pressure analyzers and recorded by DMSI software provided by Micro-Med (Louisville). Rats were provided with saline i.p. for rehydration due to the diuretic effects of the anesthesia and re-anesthetized as needed with approximately 1/3 the original dosage. In most experiments, the IASP was allowed to reach a stable baseline level prior to drug delivery. Drugs were delivered to the anal sphincter mainly via PE 20 tubing attached to the catheter(s) near the sensor(s) from 100 µl or 250 µl Hamilton syringes either manually or by infusion with a programmable Harvard automatic infusion pump.

Example 5

[250] This example illustrates the effect of repeated or prolonged dosing of a nitric oxide donor (NTG) on the responsiveness of the rat IAS.

[251] One issue with chronic or subchronic therapy with nitric oxide or nitric oxide donors such as NTG is the extent of any tachyphylaxis or tolerance to the relaxant effect of nitric oxide. Clinical studies have shown that the human cardiovascular system develops tolerance to nitric oxide donors. We have found that in the rat model, cardiovascular tolerance, as measured in vivo by the mean arterial blood pressure, also develops with repeated dosing of NTG. At the biochemical level, using in vitro assays, we have shown that NTG-induced increases in cGMP levels were attenuated dramatically in
vascular smooth muscle. Thus, it seemed likely that the IAS would also develop tolerance to the effects of nitric oxide upon repeated or prolonged dosing.

[252] In Fig. 6, 0.1% NTG in 5% dextrose/water with 1% propylene glycol was administered in bolus doses directly to the IAS via a Hamilton syringe attached to a Harvard automatic infusion pump at 20 μg/min every 30 minutes. Each successive dose represented by asterisks produced a dramatic drop in resting IASP followed by a complete recovery to resting levels; a slight decline in resting pressures is observed over time, for most experiments, possibly due to the effects of anesthesia. Since each NTG administration was able to provide similar level and duration of pressure reduction, no nitrate related pressure tolerance was noted with repeated NTG administration.

[253] Fig. 7 demonstrates that a continuous infusion of NTG at 20 μg/hour produced a steady and sustained decline in resting IASP with no evidence of recovery in IASP during the entire treatment period, ruling out the incidence of tolerance, even after 4 hours of perfusion; asterisks indicate hours following initiation of NTG infusion. Similar results were obtained using a ten-fold higher dose of NTG. Since there was no rebound of pressure reduction with continuous NTG administration, no nitrate related pressure tolerance was noted with continuous NTG administration.

[254] Surprisingly, we have found that tachyphylaxis to the relaxant effect of NTG on the IAS does not develop with repeated or prolonged dosing in vivo. Our in vitro studies have also found that NTG-induced increases in cGMP levels in the muscle of the IAS which were not as attenuated as those in vascular smooth muscle.

**Example 6**

[255] This example illustrates the use of cyclic nucleotide analogs to affect IASP in the rat model.

[256] 8-bromo cAMP (0.1% in saline) was infused to the IAS at 20μg/hour for 3 hours. Minimal pressure reduction was noted; this could due to the poor absorption of the 8-bromo cAMP from saline to the sphincter tissue during the study duration (see Figure 8).

[257] Dibutyryl cAMP (0.1% in saline) was infused to the IAS at 20μg/hour for 3 hours. A minor depression in IASP was noted (see Figure 9). cGMP analogs also elicited very little depression of IASP, possibly due to the poor bioavailability through the in vivo topical dosage form.
[258] Since increasing levels of cGMP and cAMP in the IAS with NTG or ISO resulted in an expected decrease in IASP, introduction of the aqueous-soluble 8-bromo and dibutyryl analogues of cGMP and cAMP were fully expected to also lower resting IASP in the rat model. Surprisingly, the cGMP analogs provided almost no effect on IASP (data not shown), whereas dibutyryl cAMP proved to be more efficacious in the rat model than the 8-bromo derivative as demonstrated in the figures. These results may reflect differences in bioavailability of the analogs and/or direct effects of the butyrate moiety on smooth muscle relaxation.

Example 7

[259] This example illustrates the varying ability of superoxide scavengers to potentiate the effect of nitric oxide/nitric oxide donors in vivo.

[260] The ability of superoxide scavenger superoxide dismutase (SOD) to potentiate the relaxing effects of NTG by prolonging the half-life of nitric oxide (NO) was examined using the rat model. NO, produced from the enzymatic degradation of NTG within cells, has a half-life of only a few seconds before it is acted upon by oxygen radicals such as the superoxide anion to form peroxynitrite (Weller, 1997). Perfusion of the anal sphincter with SOD prior to NTG treatment, theoretically should remove superoxide from the equation, providing a longer half-life for NO in the tissue and resulting in more sustained cGMP levels, potentiating the NTG-induced relaxation of the IAS.

[261] Vehicle (20 μl of 5% dextrose/water with 10% propylene glycol) was delivered to the IAS followed in 30 minutes by a 200 μg bolus delivery of superoxide dismutase (SOD) in vehicle, followed 15 minutes later with a bolus dose of 200 μg NTG in the same vehicle. A significant potentiation of NTG effect, e.g. increasing the duration of action on reducing anal sphincter was observed (see Figure 10). This result indicates that the activity of the NO donor in the presence of a superoxide anion scavenger is enhanced.

[262] Vehicle (20 μl of 5% dextrose/water with 10% propylene glycol) was delivered to the IAS followed in 30 minutes by a 200 μg bolus delivery of NTG in vehicle, followed 15 minutes later with a bolus dose of 20 μg SOD. No significant potentiation of NTG was observed suggesting that the potentiation effect of SOD is most pronounced when administered prior to NTG (see Figure 11). This result suggests that the NTG-derived NO has already dissipated from the tissue.
Surprisingly, the synthetic superoxide scavenger Mn (III) tetrakis (4-benzoic acid) porphyrin chloride (MnTBAP), did not demonstrate significant NO enhancing activity in this model.

Further, as Figures 10 and 11 demonstrate, SOD alone has little effect on IASP since the resting IAS has low endogenous levels of NO to act upon by superoxide anion.

Example 8

This example illustrates the potentiation of NTG in the rat model by PDE V inhibitor blockage of the cGMP-specific PDE activity.

Zaprinast:

The vehicle, 1-methyl 2-pyrollidinone (1M2P) was injected intra-peritoneal (i.p.). (100 µl), 30 minutes prior to bolus doses of NTG (20µg/min every 30 minutes). The duration of depression of IASP due to NTG was constant with each dose (see Figure 12).

Zaprinast (10 mg in 100 µl 1M2P) was injected i.p. 30 minutes prior to bolus doses of NTG (20 µg/min every 30 minutes). There was an increasing duration of IASP depression with consecutive doses of NTG demonstrating potentiation of NTG by a selective PDE V inhibitor (see Figure 13).

The vehicle, 1-methyl 2-pyrollidinone (1M2P) was injected intra-peritoneal (i.p.). (100µl), followed after 2.75 hours by the first dose of NTG (20µg/min every 30 minutes). The duration of depression of IASP was consistent with each NTG dose (see Figure 14).

Zaprinast (10 mg in 100µl 1M2P) was injected i.p. 2.75 hours prior to bolus doses of NTG (20 µg/min every 30 minutes). The duration of depression of IASP continued to increase with each NTG dose and peaked at around 3.5-4 hours and decreased with additional doses of NTG. This study suggests that an i.p. dose of zaprinast reaches maximal levels in the IAS between 3.5-4 hours and causes potentiation with NTG (see Figure 15).

These results show that potentiation of NTG activity can be achieved by agents protecting from PDE degradation the cGMP formed through NO activation of guanylyl cyclase.
Dipyridamole:

[271] The vehicle, 1-methyl 2-pyrolidinone (1M2P) was injected i.p. (100 μl), 50 minutes prior to bolus doses of NTG (20 μg/min every 30 minutes). The duration of depression of IASP due to NTG was constant with each dose (see Figure 16).

[272] Dipyridamole (10 mg in 100 μl 1M2P) was injected i.p. 50 minutes prior to bolus doses of NTG (20 μg/min every 30 minutes). The duration of depression of IASP due to NTG was constant with each dose and approximately twice that for the vehicle-treated rat (see Figure 17).

MBCQ:

[273] MBCQ (10 mg in 100μl 1M2P) was injected i.p. 30 minutes prior to bolus doses of NTG (20μg/min every 30 minutes). No noticeable potentiation of NTG was observed with this PDE V inhibitor in this experiment (see Figure 18). Bioavailability of MBCQ could be the cause of the minimal effect seen with this compound.

[274] Whereas dipyridamole demonstrated less striking potentiation with NTG, the most potent of the PDE V inhibitors under in vitro conditions, MBCQ, did not demonstrate significant activity, potentially due to diminished bioavailability of this drug in the in vivo model (data not shown).

Example 9

[275] This example illustrates the effect of non-selective β-adrenergic agonists using isoproterenol. These agonists activate adenyl cyclase, thereby increasing cAMP levels, and act on the IASP through the direct smooth muscle relaxing activity of cAMP.

[276] A bolus dose of 200 μg isoproterenol produced a dramatic drop in IASP eliminating significant pressure readings by the catheter/transducer in fact, isoproterenol proved to be a very potent IAS relaxant and had to be titrated down, in another study, to a continuous dose of 0.2 μg/hour in order to avoid significant drops in IASP (see Figure 19).

Example 10

[277] This example illustrates the effect of β2-agonists on the IASP.

[278] The β2-agonist, terbutaline (in saline) was infused continuously at 20 μg/hour. A steady and sustained decline in IASP over the 3 plus hours of infusion (fig. 4n, 68
20) resulted. The significant drop in IASP throughout the experiment reached a plateau between 1.5 and 2 hours post initiation of treatment.

[279] This sustained, however moderate, drop in IASP is considered desirable for prolonging the increased blood flow to the anoderm necessary for healing anal fissures, without inducing a complete relaxation of the IAS which might result in temporary incontinence.

[280] The $\beta_2$-agonist, salbutamol (in saline) was infused continuously at 20 $\mu$g/hour and demonstrated a significant drop in IASP throughout the experiment similar to terbutaline (see Figure 21).

**Example 11**

[281] This example illustrates the effects of cAMP levels on the IASP and the effects of PDE IV inhibitor blockage of the cAMP-specific PDE activity in the rat model.

**Effects of Rolipram:**

[282] The PDE IV inhibitor rolipram, in 5% DMSO/Acetone:Olive oil 1:1 was continuously infused at 20 $\mu$g/hour rate. A pattern including significant drops in IASP followed by shorter recovery phases occurred prior to 1 hour after initiating the drug infusion (see Figure 22).

**Etazolate potentiation of salbutamol:**

[283] Delivery of 200$\mu$g of salbutamol in saline to the IAS produced no short-term effects on the IASP; however a subsequent treatment with salbutamol plus the PDE IV inhibitor etazolate, also at 200$\mu$g in saline, produced a dramatic and sustained drop in IASP, suggesting a potentiation effect of a $\beta_2$-agonist with a PDE IV inhibitor on anal sphincter pressure reduction (see Figure 23).

[284] This experiment is similar to that described above for Figure 23, however the order of the delivery of the drugs was reversed. The results were similar (see Figure 24).

[285] Smooth muscle relaxation is caused by agents that elevate cAMP levels via phosphorylation of myosin light chain kinase by cAMP-dependent protein kinase (PKA). PDE type IV inhibitors prevent degradation of cAMP by cAMP-specific PDE. As seen with the above PDE IV inhibitor etazolate potentiation of the effects of the $\beta_2$-adrenergic
agonist, salbutamol, potentiation of agents which activate adenylyl cyclase, can be achieved with PDE type IV inhibitors.

Effects of RO-20-1724:

[286] The PDE IV inhibitor RO-20-1724 was infused at 20 μg/hour in the vehicle 5% DMSO/Acetone:Olive oil 1:1. The drop in IASP was minimal suggesting either lack of bioavailability of the drug from the current route of administration (see Figure 25).

Effects of Forskolin

[287] The specific adenylyl cyclase activator forskolin, was infused at 20 μg/hour in the vehicle 5% DMSO/Acetone:Olive oil 1:1. A significant and sustained drop in IASP was observed (see Figures 26 (control) and 27). This experiment clearly demonstrates the contribution of cAMP in inducing relaxation of the internal anal sphincter.

Example 12

[288] This example illustrates the use of α-adrenergic antagonists to reduce IASP in the rat model.

[289] The α₁-blocker, prazosin in 5% DMSO/Acetone:Olive oil 1:1 was infused at 20 μg/hour. A significant and sustained drop in IASP that plateaued after 1 hour was observed suggesting that the increase of cAMP level leads to relaxation of internal anal sphincter pressure (see Figure 28).

Example 13

[290] This example illustrates the effect of non-selective PDE Inhibitors on IASP in the rat model.

[291] Isobutyl methylxanthine (IBMX) in 5% DMSO/Acetone:Olive oil 1:1 was infused at 200μg/hour. A significant and sustained drop in IASP that leveled off at 1 hour after initiation of the infusion was observed (see Figure 29).

[292] Isobutyl methylxanthine (IBMX) in 5% DMSO/Acetone:Olive oil 1:1 was infused at a lower dose, i.e. 20μg/hour. The results were similar as for the experiment described in Figure 29 (see Figure 30).

[293] The non-selective PDE inhibitor, IBMX is thought to act on smooth muscle by a number of potential mechanisms including: 1) PDE inhibition and increasing
cAMP levels; 2) effects on intracellular calcium concentration; 3) effects on membrane hyperpolarization; 4) uncoupling of increased calcium levels with muscle contractility; and 5) adenosine receptor antagonism (Goodman & Gilman's "The Pharmacological Basis of Therapeutics" 9th edition. Section IV-Autoxidants; Drug Therapy of Inflammation).

Example 14

[294] This example illustrates the use of K⁺-ATP Channel Openers to relax the IAS.

[295] The K⁺-ATP channel openers, minoxidil and diazoxide, induce hyperpolarization of the cell membranes of smooth muscle, and thereby inactivate voltage-gated Ca²⁺ channels.

[296] Minoxidil (830μg in 20 μl 62.5% propylene glycol/water) was delivered to the IAS. A significant and sustained drop in IASP was observed shortly after delivery of the drug (see Figure 31).

[297] Diazoxide in 5% DMSO/Acetone:Olive oil 1:1 was infused at 20 μg/hour. A dramatic drop in IASP was observed for the duration of the experiment (see Figure 32).

Example 15

[298] This example illustrates the use of Ca²⁺-channel blockers

[299] Diltiazem in saline was infused at 20μg/hour. The drug produced a dramatic and sustained drop in IASP for the duration of the experiment (see Figure 33).

[300] Verapamil in saline was infused at 20μg/hour. The drug produced a dramatic and sustained drop in IASP for the duration of the experiment (see Figure 34).

Example 16

[301] This example illustrates the use of adrenergic nerve inhibitors to achieve a long term reduction in IASP in the rat model following a short term administration of the active agent.

Recent clinical trials using one of the most potent toxins known, botulinum toxin, produced by Clostridium botulinum, have demonstrated success in healing anal fissures after multiple injections of the toxin directly into the IAS. Botulinum toxin presumably relaxes the IAS through its action of blocking acetylcholine (ACH) release from cholinergic pre-synaptic fibers (Kao, I., et al., Science 193, 1256-8 (1976)). However, cholinergic innervation of the IAS is not thought to contribute significantly to IAS tone. We decided to use a drug that can be applied topically to the IAS, and that destroys adrenergic nerve terminals, thereby blocking the actions of norepinephrine in maintaining sphincter tone.

[303] 6-hydroxydopamine in saline was delivered to the IAS in bolus doses of 200 µg to a rat each day for 5 days. The IASP was measured over three weeks. A continuous drop in IASP was noted through day 16, 11 days after termination of the treatment. By day 19 a partial recovery in IASP was observed, and by day 22 the average IASP was 36% below the original baseline pressure (see Figure 35).

[304] Thus, treatment with 6-hydroxydopamine (6-OHDA) resulted in a prolonged reduction in IASP over at least a 3 week period following 5 daily topical doses of 200 µg in saline to the rat IAS.

Example 17

[305] This example illustrates the effects of a PDE III/IV inhibitor on IASP under a variety of experimental conditions.

[306] This experiment serves as a control for the experiment described in Figure 37. An i.p. injection of 100µl 1M2P was followed in 30 minutes by a continuous infusion of isoproterenol in saline at 0.2µg/hour. This sub-threshold dose of isoproterenol had no significant effect on lowering IASP (see Figure 36).

[307] The PDE III/IV inhibitor, zardaverine (10 mg in 100µl 1M2P) was injected i.p. followed in 30 minutes by a continuous infusion of isoproterenol in saline at 0.2µg/hour. A rapid drop in IASP was noted immediately after the i.p. injection of zardaverine, and a sustained decrease in average IASP followed isoproterenol infusion. A continuous slow wave pattern of decreasing and increasing IASP was observed after isoproterenol infusion (see Figure 37).

[308] The PDE III/IV inhibitor, zardaverine (7.5 mg in 100µl 1M2P) was injected i.p. followed in 30 minutes by a continuous infusion of 5% dextrose at 20µl/hour. The zardaverine injection produced a rapid but transient drop in IASP that soon returned to
normal baseline levels. The subsequent infusion of 5% dextrose had no effect on lowering the IASP (see Figure 38).

309 The PDE III/IV inhibitor, zardaverine (7.5 mg in 100μl 1M2P) was injected i.p. followed in 30 minutes by a continuous infusion of isoproterenol in saline at 0.2μg/hour. Zardaverine, again induced a rapid and transient decrease in IASP. The isoproterenol infusion further reduced the IASP to almost zero mmHg (see Figure 39). These experiments (Figures 36-39) suggest a potentiation of subthreshold levels of isoproterenol by zardaverine.

Example 18

310 This example illustrates the use of adenosine antagonists to relax the IAS in the rat model.

Theophylline:

311 Theophylline, an adenosine antagonist, was continuously infused at 200μg/hour in 5% dextrose. A dramatic and sustained drop in IASP was observed throughout the 4 hour duration of the experiment (see Figure 40).

312 Theophylline was continuously infused at 20μg/hour in 5% dextrose. A moderate drop in average IASP was observed throughout the 3 hour duration of the experiment (see Figure 41).

313 Theophylline was continuously infused at a lower dose, i.e. 2μg/hour in 5% dextrose. A minimal drop in average IASP was observed throughout the 3 hour duration of the experiment (see Figure 42).

Dyphylline:

314 Figure 43 shows the IAS relaxing effects of a 20 μg/hr continuous dose of dyphylline [7-(2,3-dihydroxypropyl) theophylline], a theophylline derivative that is not metabolized by the liver and is excreted unchanged by the kidneys, providing this drug with a low toxicity potential.

Example 19

315 This example illustrates a method for treating anal disorders in an individual using phosphodiesterase inhibitors and other agents to reduce pain associated with the disorders, including acute and chronic anal fissures.
[316] Patients with severe anal pain especially during and after bowel movement can be treated with the following therapies: zaprinast, zaprinast and nitroglycerin, minoxidil, nitroglycerin and cGMP mimetics, isoproterenol, or sildenafil, either one to three times daily or as required to effectively reduce anorectal pain. Pain reduction (indicated by a reduction in the average pain and/or the defecation pain) will be evaluated and the time to pain reduction will also be evaluated. Therapy that is effective in relieving anal pain will eventually lead to effective resolution of these anorectal disorders. Additionally, drugs that can effectively reduce anal sphincter pressure, maintain reduced anal sphincter pressure, or prevent recurrence of the diseases and yet cause minimal or no adverse reactions such as headache, dizziness, and hypotension will be of great therapeutic benefit.

Example 20

[317] This example illustrates a method for treating anal disorders in an individual using phosphodiesterase inhibitors and other agents to promote healing in acute and chronic anal fissures.

[318] Patients with anal fissures can be treated with the following therapies: zaprinast, zaprinast and nitroglycerin, minoxidil, nitroglycerin and cGMP mimetics, isoproterenol, or sildenafil, either one to three times daily or as required to effectively promote healing. Healing is indicated by improving re-epithelization of the observed fissure and can be evaluated along with the time needed to complete healing. Therapy that is effective in healing anal fissures eventually leads to complete resolution of these anorectal disorders. Furthermore, drugs that can effectively reduce anal sphincter pressure, maintain reduced anal sphincter pressure, or prevent recurrence of the diseases and yet cause minimal or no adverse reactions such as headache will provide significant medical benefit.

Example 21

[319] This example illustrates a method to reduce bleeding in patients with hemorrhoidal symptoms or diseases.

[320] Patients with hemorrhoidal symptoms or diseases can be treated with the following therapies: zaprinast, zaprinast and nitroglycerin, minoxidil, nitroglycerin and cGMP mimetics, isoproterenol, or sildenafil, either one to three times daily or as required to effectively reduce bleeding and promote healing. Disease resolution indicated by reduction in bleeding and or pain can be evaluated along with the time to healing. Therapy that is effective in improving hemorrhoidal symptoms will eventually lead to complete resolution of
these anorectal disorders. Furthermore, drugs that can effectively reduce anal sphincter pressure, maintain reduced anal sphincter pressure, or prevent recurrence of the diseases while causing minimal or no adverse reactions such as headache are of significant medical benefit.

Example 22

[321] A composition of a base gel comprising 1.0 gm of salbutamol, 0.6 gm of carbopol 1342 USP, 35.44 gm of propylene glycol, 15.16 gm of dehydrated ethanol USP, 15.16 gm of isopropyl alcohol USP, 2.5 % oleic acid, triethanolamine HCl 1N to adjust the pH from 6.0 to 7.0, 0.05 gm of butylated hydroxytoluene NF, and 29.72 gm of purified water USP. Other concentrations of salbutamol can be added in the same gel base to achieve the therapeutically effective dose; this can also be achieved by adjusting the concentration of other β-agonists with gel base excipients such as oleic acid.

Example 23

[322] One example of a topical composition comprises 0.05 to 1% sildenafil, 75% (w/w) white petrolatum USP, 4% (w/w) paraffin wax USP/NF, lanolin 14% (w/w), 2% sorbitan sesquioleate NF, and 4% propylene glycol USP at the therapeutic effective dose to the anorectal area. Typically, the 50 mg to 600 mg of sildenafil ointment can be applied to the anorectal area in order to reduce the signs and/or symptoms associated with anorectal disorders, for example, anal fissure, anal ulcers, and hemorrhoidal diseases. The concentration of sildenafil, or other phosphodiesterase inhibitors can be varied by adjusting the ratio between the sildenafil with excipients facilitate either the attachment of sildenafil to the local tissue, or agents enhance absorption to the afflicted tissue.

[323] Yet another example of a topical composition comprises nitroglycerin at 0.1% concentration and sildenafil at 0.1% concentration can be incorporated in the same ointment base as mentioned above. This composition can be applied topically from a metered dosing device where a 50 mg to 1.5 gm dose of the composition is administered to the afflicted anorectal tissue to achieve the desired therapeutic effects.

[324] Another therapeutic regimen is to provide patients afflicted with the anorectal disorders with both oral sildenafil tablets and topical nitroglycerin ointment. These two dosage forms can be used in combinations which provide the best efficacy and compliance among these patients.
Example 24

[325] A composition of aminophylline topical spray composition comprises 0.1 to 5.0% (w/w) of aminophylline, acetylated lanolin alcohol, aloe vera, butane, cetyl acetate, hydrofluorocarbon, methyl paraben, PEG-8 laurate and polysorbate 80 in a 2 oz. pump spray bottle. The concentration of aminophylline or other non-specific phosphodiesterase inhibitor can vary between 0.5% to 5%. Other non-hydrofluorocarbon propellant can also be used instead of hydrofluorocarbon in the current composition. This composition can be sprayed directly onto the afflicted tissue once to four times daily to achieve the desired relief of signs and/or symptoms associated with anorectal disorders. This composition can also include menthol and benzocaine to provide the immediate local pain relief and soothing sensation whereas aminophylline provides the longer lasting relaxation of anal sphincter pressure.

Example 25

[326] A base cream composition comprises 2 gm prazosin hydrochloride (2.0 % w/w), 54.3 gm of purified water USP, 2 gm of Sepigel 305, 4.5 gm of Crodamol, 5.0 gm of glycerin, 6.0 gm sesame oil, 15.0 gm of white petrolatum USP, 2.0 gm of lanolin USP, 7.0 gm of 1,3-butyleneglycol, 0.2 gm of methylparaben and 2.0 gm of silicon HL88.

[327] A base cream can be prepared by first separate mixings of aqueous versus non-aqueous, i.e. oil phase, components of the cream. Once the aqueous phase containing the prazosin hydrochloride is well mixed, the melted oil phase is gently stirred into the aqueous phase to form a uniform cream base.

Example 26

[328] Sildenafil, a specific inhibitor of type V phosphodiesterase, can be given orally via a tablet, parenterally or can be applied topically to patients diagnosed with anal fissures, either acute or chronic anal fissures, or other anorectal disorders. Sildenafil can be given one to three times daily for 8 weeks, especially in the case of patients afflicted with chronic anal fissure to cause the reduction of signs and symptoms associated with anorectal disorders.

[329] For topical application, an approximate 50 mg to 900 mg dose of the cream measured by a metered dosing device, containing sildenafil, at the concentration from 0.02% to 5%, can be applied to the afflicted anorectal region using an applicator or by finger,
one to four times daily to achieve the desirable therapeutic effects. Alternatively, the oral and topical treatment can be used in a defined regimen to achieve the best therapeutic effects.

**Example 27**

[330] A phosphodiesterase inhibitor, for example aminophylline, can be given either orally via a tablet, parenterally or can be applied to patients diagnosed with anal fissures or other anorectal disorders, either acute or chronic anal fissures from a topical dosage form, e.g. a cream. For topical application, an approximate 50 mg to 900 mg of the cream measured by a metered dose device, can be applied to the afflicted anorectal region using an applicator or by finger, one to four times daily to achieve the desirable therapeutic effects.

**Example 28**

[331] A β-adrenergic agonist, for example salbutamol, can be given from a suppository dosage form to patients diagnosed with anal fissures or other anorectal disorders, either acute or chronic anal fissures from a topical dosage form, e.g. a cream. For suppository application, an approximate 300 mg to 3 gm of the suppository unit can be applied to the afflicted anorectal region using an applicator or by finger, one to four times daily. Once the suppository melts in the anal cavity, the salbutamol released from the dosage form is available to achieve the desirable therapeutic effects.

**Example 29**

[332] An α-adrenergic antagonist, *i.e.* prazosin can be applied from a topical spray to patients diagnosed with hemorrhoidal disorders, alone or in combination with a local anesthetic, for example, lidocaine, or in combination with a mixed β2- and β2-adrenergic agonist, for example salbutamol, or in combination with a PDE IV inhibitor, for example, ariflo (SB207499), RP73401, CDP840, rolipram and LAS31025. Prazosin can be applied directly to the afflicted area with the propellant from the spray and can be used as needed to relieve the local pain and anal sphincter hypertonicity. Eventually, the application of prazosin leads to healing of the hemorrhoidal disorders.

**Example 30**

[333] This example illustrates the preparation of a theophylline topical formulation from theophylline oral tablets.
[334] Five Theo-24 tablets (400 mg of theophylline per tablet; UCB Pharmaceuticals, Inc.) were combined and ground into a fine powder. To this powder, 50 ml of ethanol was added and the solution was stirred at room temperature for 15 minutes. Next, 48 ml of propylene glycol and 100 ml of distilled water were added to the ethanol mixture while stirring. This mixture was stirred for 15 minutes, at which time the powder was completely dissolved. A solution of carbopol in distilled water was then added to the mixture while stirring, forming a 1% topical theophylline gel. The resulting gel was then stirred for another 15 minutes.

Example 31

[335] A methylxanthine derivative, for example diphylamine or theophylline, can be given either orally via a tablet, parenterally or can be applied to patients diagnosed with anal fissures or other anorectal disorders, either acute or chronic anal fissures from a topical dosage form, e.g. a cream or a rectal suppository.

[336] For topical application, an approximate 50 mg to 900 mg of the cream measured by a metered dose device, can be applied to the afflicted anorectal region using an applicator or by finger, one to four times daily to achieve the desirable therapeutic effects.

Example 32

[337] Patients are first diagnosed with anal fissure, and a baseline severity score is established for each patient at baseline. Objective and subjective signs and symptoms may be scored. Nitroglycerin ointment is applied to the outer anorectal area, once to four times daily to relax the internal anal sphincter. Nitroglycerin ointment can also be applied as frequently as needed to achieve the desired effect. Alternatively, nitroglycerin ointment can be applied 5 to 15 minutes before a bowel movement to relax the sphincter muscles; thus allowing for successful effort. The nitroglycerin ointment concentration varies between 2.0% (w/v) to 0.05%, more preferably, between 0.1% to 0.6% to achieve the desired effect. The desired effects include, but are not limited to, immediate pain relief, local tissue relaxation, and increase in blood flow. Patients may also use commercially available Nitrobid®, Percutol® or Rectogesic® ointments as is or by diluting to the appropriate concentration.

Example 33

[338] Patients are first diagnosed with hemorrhoids and the severity of the disorder is scored at baseline. Objective and subjective signs and symptoms may be
scored. Under physician assistance, a suppository containing diltiazem, a calcium channel blocker, is inserted into the patient's rectum. The controlled and continuous release of diltiazem from the suppository allows for relaxation of the internal anal sphincter and thus, a decreased intra-anal pressure. If desired, patients using a diltiazem suppository can also apply nitroglycerin ointment to maximize the relaxation.

**Example 34**

[339] Patients are first diagnosed with levator spasm and the intensity of the spasm symptoms are scored for each patient at baseline. Objective and subjective signs and symptoms may be scored. If patients do not have other cardiovascular disease complication, oral nifedipine or other calcium channel blocker tablets (or caplets, capsules, etc.) can be administered, approximately 45 minutes to 4 hours before coitus to produce the desired effects. Alternatively, patients can take the calcium channel blocker orally once to three times daily and apply nitroglycerin ointment or topical diltiazem cream as needed to maximize the desired effects. The desired effects can include immediate pain relief, local tissue relaxation, and increased blood flow.

**Example 35**

[340] Patients are first diagnosed with anal fissure and the severity score for each patient is recorded at baseline. Objective and subjective signs and symptoms may be scored. Topical aminophylline cream is applied either externally to the anorectal area or internally to achieve pain relief, muscle relaxation, and increased blood flow. Alternatively, rectal suppositories or tablets containing aminophylline are inserted once daily or as needed to achieve the desired effects.

**Example 36**

[341] Patients are first diagnosed with anal fissures. Loperamide solution is applied to the site to prevent pain, 1-4 times daily for several consecutive days for relief of pain. Pain prevention or relief is further improved by using either nitroglycerin ointment or a diltiazem cream in conjunction with or sequentially with the loperamide solution. The concentration of diltiazem cream is 4.0% (w/v) to 0.5%; more preferably, the diltiazem cream concentration is 3-1%, depending upon the efficacy.

**Example 37**

[342] Patients diagnosed with anal fissures are treated with nifedipine ointment topically to anorectal area once or multiple times each day until the symptoms are reduced. Alternatively, patients can take anti-inflammatory agents, such as glucocorticoids or NSAIDS, as recommended by the physician. Subsequently, topical calcium channel blocker
cream, e.g., diltiazem cream, is applied to further decrease the internal pressure at the internal anal sphincter or to relax the sphincter.

**Example 38**

[343] Patients suffering from anal ulcers. In order to mitigate the symptoms associated with the ulcer, a continuous source of lovastatin is provided to greatly facilitate the relief of the debilitating symptoms. Alternatively, patients can take anti-inflammatory agents, such as glucocorticoids or NSAIDS, orally at the frequency recommended by the physician while the lovastatin is being applied. Another approach is to take oral antibiotic while patients are using the lovastatin suppository or dermal patch is being applied to further expedite the relief of symptoms.

**Example 39**

[344] Patients with anal fissures are given 0.2% nitroglycerin (NTG) ointment for use on an as needed basis. Patients are instructed to apply an effective amount of the nitroglycerin ointment to the affected area. Following the 0.2% NTG treatment, all patients are evaluated for improvement in pain reduction and ability conduct normal activity after the therapy. Signs of symptomatic relief, such as pain reduction, are assessed.

**Example 40**

[345] Patients are first diagnosed with anal fissures and scored at baseline as above. Yohimbine gel is applied to the anorectal region once to four times daily to relax the anal sphincter. Yohimbine gel can also be applied to the region as frequently as needed to achieve the desired effect. Alternatively, yohimbine gel can be applied as needed for relief of symptoms of pain, itching, or burning. The yohimbine gel concentration varies between 2.0% (w/v) to 0.05%, preferably, between 0.05% to 0.1%. or 0.1% to 0.5%, to achieve the desired effect. The desired effects include, but are not limited to, immediate pain relief, local tissue relaxation, and increase in blood flow.

**Example 41**

[346] Patients are first diagnosed with anal fissure and evaluated at baseline as above. Yohimbine tablets (10 mg) are taken orally, once to four times daily to relax the anal sphincter muscles. Additionally, yohimbine gel can be applied to the anorectal area as frequently as needed to achieve the desired effect. Alternatively, in addition to administration of yohimbine tablets, yohimbine gel can be applied to relax the anal sphincter muscle. The yohimbine gel concentration varies between 2.0% (w/v) to 0.05%, preferably, between 0.05% to 0.1%. or 0.1% to 0.5%, to achieve the desired effect. The desired effects
include, but are not limited to, immediate pain relief, local tissue relaxation, and increase in blood flow.

**Example 42**

[B347] Benzodiazepines can be useful in achieving anal sphincter relaxation. For instance, patients may be first diagnosed with levator spasm or anal fissure and the baseline severity of the symptoms and disorders scored. Diazepam (a benzodiazepine) ointment is applied derrmally to the anorectal region, once to four times daily to relax the sphincter. The diazepam ointment can also be applied to the external anorectal area as frequently as needed to achieve the desired effect. The diazepam ointment concentration varies between 2.0% (w/v) to 0.05%, preferably, between 0.05% to 0.1%. or 0.1% to 0.5%, to achieve the desired effect. The desired effects include, but are not limited to, immediate pain relief, local tissue relaxation, and increase in blood flow.

**Example 43**

[B348] Patients are first diagnosed with anal fissures. A topical vesamicol solution or ointment is applied to the site to prevent pain, 1-4 times daily for several consecutive days for relief of pain. Pain prevention or relief may be further improved by using either nitroglycerin ointment or a diltiazem cream in conjunction with or sequentially with the vesamicol. The concentration of diltiazem cream is 4.0% (w/v) to 0.5%; more preferably, the diltiazem cream concentration is 3-1%, depending upon the efficacy.

**Example 44**

[B349] An $\alpha_2$-adrenergic receptor antagonist can be useful in the treatment of patients in need of relaxation of the internal anal sphincter. For instance, patients may be first diagnosed with anal fissure or hemorrhoids. Depending on the site of disease manifestation, a topical $\alpha_2$-adrenergic receptor antagonist (e.g. yohimbine) solution is applied to the site, 1-4 times daily for several consecutive days for relief of pain. Pain prevention or relief may be further improved by using either nitroglycerin ointment or a diltiazem cream in conjunction with or sequentially with the yohimbine. The concentration of diltiazem cream is 4.0% (w/v) to 0.5%; more preferably, the diltiazem cream concentration is 3-1%, depending upon the efficacy.

[B350] In the case of yohimbine, this compound can be formulated in an aqueous formulation of up to 0.8% in sterile water. Yohimbine may also be formulated as
topical composition comprising an aqueous or slightly alcoholic gel or in a cream or lotion for direct application to the anorectal region.

Example 45

[351] Acetylcholine storage blockers may be useful in patients in need of internal anal sphincter relaxation. An acetylcholine storage blocker (e.g., vesamicol) ointment is applied to the skin of the anorectal region, once to four times daily to relax the anal sphincter. The ointment can also be applied to the anorectal area as frequently as needed to achieve the desired effect. When the acetylcholine storage blocker is vesamicol, the vesamicol ointment concentration varies between 2.0% (w/v) to 0.05%, preferably, between 0.05% to 0.1%, or 0.1% to 0.5%, to achieve the desired effect. The desired effects include, but are not limited to, immediate pain relief, local tissue relaxation, and increase in blood flow. Vesamicol can be applied in an aqueous gel or lotion type of formulation.

Example 46

[352] Adenosine receptor modulators, may be useful in patients in need of relaxation of the internal anal sphincter. An adenosine receptor modulator (e.g., theophylline or dyphylline) ointment is applied topically to the anorectal region, once to four times daily to relax the sphincter muscle. The ointment can also be applied topically as frequently as needed to achieve the desired effect. Alternatively, the ointment can be applied by suppository. The adenosine receptor modulator ointment concentration varies between 2.0% (w/v) to 0.05%, preferably, between 0.05% to 0.1%. or 0.1% to 0.5%, to achieve the desired effect. The desired effects include, but are not limited to, immediate pain relief, local tissue relaxation, and increase in blood flow.

Example 47

[353] An adenosine receptor modulator may be useful in the treatment of patients in need of relaxation of the internal anal sphincter or suffering from elevated intraanal pressures. For instance, patients may be first diagnosed with levator spasm or anal fissures. Depending on the site of disease manifestation, a topical adenosine receptor modulator (e.g. theophylline or dyphylline) ointment is applied to the anorectal area to prevent pain and promote healing, 1-4 times daily for several consecutive days for relief of pain. Pain prevention or relief may be further improved by using either nitroglycerin ointment or a diltiazem cream in conjunction with or sequentially with the yohimbine. The concentration of diltiazem cream is 4.0% (w/v) to 0.5%; more preferably, the diltiazem cream concentration is 3-1%, depending upon the efficacy.
Example 48

[354] Patients complaining of recurrent pain, itching or burning of the anorectal region will be evaluated for signs of inflammation and infection, previous history of surgery, and any other signs of pathology. If they are found to be free of any of these medical conditions and yet still have ongoing pain, itching or burning of the anorectal area, topical treatment with nitroglycerin will be prescribed. A 0.2% topical nitroglycerin ointment will be applied to the affected area, either once daily or as frequent as needed to achieve efficacy, depending on the severity of the symptoms. The efficacy of relief can be evaluated based on a visual analog scale of 10 cm or on the patients’ self-assessment. If the patients are diagnosed with minor infection, topical nitroglycerin ointment can be used in conjunction with antibiotic treatment to facilitate faster relief of symptoms.

Example 49

[355] In another embodiment, the anorectal disorder is a colostomy. Smooth muscle relaxing agents may be used in the treatment of colostomy patients, particularly during irrigation of the colostomy, to improve their quality of life. Colostomy irrigation improves the quality of life of colostomy patients by reducing episodes of fecal incontinence. However, such irrigation is often time consuming. Administration of smooth muscle relaxing agents including particularly, for example, potassium channel openers can improve the effectiveness and efficiency of the irrigation process saving time and effort and thereby enhancing the acceptability of irrigation among colostomy patients. A more thorough cleansing reduces the likelihood of later leakage. A more efficient process saves time. Without being wed to theory, it is thought that the smooth muscle relaxants expedite the irrigation by reducing the internal pressure which would otherwise offer more resistance to the inflow of the cleansing irrigation fluid. Particularly preferred, potassium channel openers for administration during the irrigation of a colostomy include minoxidil, minoxidil sulfate, pinocidil, diazoxide, levromokalim, cromokalim, and PCO-400. The potassium channel opener may be administered about or during the time period of the irrigation and may preferably be administered by being formulated with or as the irrigation fluid. The amount of potassium channel opener or other smooth muscle relaxing agent will be sufficient to improve the time or extent of the colostomy irrigation. The amounts may generally range from 0.01% to 0.2%.
Example 50

[356] In another embodiment, the anorectal disorder is chronic idiopathic anal pain. Smooth muscle relaxants, including particularly NO donors, are used to treat chronic idiopathic anal or perineal pain, including proctalgia fugax and coccygodynia. The patients may have no objective abnormalities on clinical examination. The smooth muscle relaxant or NO donor can be administered as a topical ointment or suppository. Concentrations of the NO donor in an ointment formulation may range from 0.01% to 2%, and more preferably range from 0.1% to 0.4%, and more particularly, may be 0.2%. The NO donor may be administered to the anorectal region as needed to relieve or prevent pain. The NO donor may be co-administered or formulated with an analgesic. A preferred NO donor is glycerol trinitrate.

Example 51

[357] Patients are first diagnosed with anal fissure and evaluated at baseline as above, mianserin is administered orally, once to four times daily in an amount sufficient to relax the anal sphincter muscles. Additionally or alternatively, mianserin gel can be applied to the anorectal area as frequently as needed to achieve the desired effect. Mianserin gel can be applied to relax the anal sphincter muscle. The mianserin gel concentration varies between 2.0% (w/v) to 0.05%, preferably, between 0.05% to 0.1%. or 0.1% to 0.5%, to achieve the desired effect. The desired effects include, but are not limited to, immediate pain relief, local tissue relaxation, and increase in blood flow.

Example 52

[358] Patients are first diagnosed with anal fissure and evaluated at baseline as above. mirtazapine is administered orally, once to four times daily in an amount sufficient to relax the anal sphincter muscles. Additionally or alternatively, mirtazapine gel can be applied to the anorectal area as frequently as needed to achieve the desired effect. mirtazapine ointment can be applied to relax the anal sphincter muscle. The mirtazapine gel concentration varies between 2.0% (w/v) to 0.05%, preferably, between 0.05% to 0.1%. or 0.1% to 0.5%, to achieve the desired effect. The desired effects include, but are not limited to, immediate pain relief, local tissue relaxation, and increase in blood flow.
EXAMPLE 53

[359] Patients are first diagnosed with an anorectal disorder, such as anal pain and/or anal fissure or hemorrhoids, and evaluated at baseline as above. A compound or agent having a mixture of pharmacological properties comprising $\alpha_2$-adrenergic receptor antagonism, $\alpha_1$-adrenergic receptor antagonism, serotonin receptor agonist activity, $H_1$ antagonist activity, and optionally muscarinic antagonism is administered. In a preferred embodiment, the agent is mianserin or mirtazapine. The agent is administered orally, once to four times daily in an amount sufficient to relax the anal sphincter muscles. Additionally or alternatively, a gel containing the agent can be applied to the anorectal area as frequently as needed to achieve the desired effect. The gel can be applied to relax the anal sphincter muscle. Agent concentrations will generally vary between 2.0% (w/v) to 0.05%, preferably, between 0.05% to 0.1%, or 0.1% to 0.5%, to achieve the desired effect. The desired effects include, but are not limited to, immediate pain relief, local tissue relaxation, and increase in blood flow.

Example 54

[360] The effect of vesamicol on the IASP was investigated in a rat model using the following procedure: Male Sprague-Dawley rats (300-400 gm) were anesthetized with ketamine (90 mg/kg), xylazine (9 mg/kg) given intramuscularly and supplemented as needed with 1/3rd dose. Rats were gently restrained on their backs on a heated surgical table (Harvard Apparatus) for the duration of the experiments. The diuretic effects of anesthesia was offset by rehydration with saline through an intraperitoneal implanted 24 gauge angiocatheter (VWR, San Francisco, CA). The constriction/relaxation measurement assembly included a Millar catheter/transducer (1.67mm diameter) connected to a Digi-Med Low Pressure Analyzer (Micro-Med) accurate for pressure measurements between -50 and 150 mmHg. The data were integrated and converted to waveforms with the Digi-Med System Integrator software. Blood pressure changes were monitored using an arterial catheter/transducer and a Digi-Med Blood Pressure Analyzer with the DMSI software.

[361] The anodermal blood flow in the rat can be measured non-invasively by laser Doppler velocimetry. In the laser Doppler technique, low power laser light is transmitted via an optic fiber to the tissue. The light is scattered by moving red blood cells and its frequency shifted according to the Doppler effect; the average Doppler frequency shift being proportional to the average speed of the blood cells. The scattered light is photodetected and the photocurrent signal electronically processed to produce the Doppler flux signal.
For instance, blood flow measurements were accomplished using a DRT4 laser Doppler monitor (Moor Instruments) which is interfaced with both channels of Digi-Med Analog System Analyzer (ASA) via BCN connectors and an ANO2 analog interface unit (Moor Instruments). The DRT4/ASA data was recorded using the DMSI software provided by Digi-Med. In this manner blood flow measurements (FLUX) can be analyzed and graphed along with IAS pressure as well as blood pressure as desired, using the LPA and BPA analyzers. For simplicity, changes in blood flow are measured in volts. The greater the volts, the greater the blood flow. Flexible side delivery probes were inserted through the anal opening just past the optic sensor to rest adjacent to the IAS. The probes were adjusted so that the sensors were in line with the anterior anal mucosa of the IAS. Drug delivery was accomplished through two Hamilton syringes with no dead space using PE 10 tubing adjacent to the catheter sensor. Drugs typically were applied soon after stable baseline readings are recorded.

As shown in Figure 44, when infused at a rate of 100 ul/hr to the anorectal region vesamicol (0.1% in saline) dramatically lowered IASP in the rat model. In other experiments (not shown), a dose-response effect was demonstrated upon infusing concentration of 0.05% and 0.01% vesamicol in saline at a rate of 100 ul/hr. Concentrations of 0.2% were also effective in lowering IASP (results not shown).

It is also possible in this animal model to measure the effect of the administered treatment on blood flow.

The ability of yohimbine to lower IASP and increase blood flow was assessed in the rat model as described in Example 54. Infusion to the anorectal region of yohimbine (0.1% or 0.2% in water) at a rate of 100 ul/hour lowered IASP faster and to a comparable large maximum effect of a clonidine infusion (0.1% in water) at the same rate. Infusion of a 0.1%, a 0.05%, a 0.01%, and a 0.005% yohimbine gel at rate of 100 ul per hour also lowered IASP in a dose response fashion (Fig. 45) as opposed to a gel control lacking the yohimbine.

Anodermal blood flow can be measured in the rat using a 2-channel DRT4 laser Doppler and temperature monitor (Moor Instruments, Wilmington DE) equipped with an endoscopic side view probe. In this system, low-energy laser light (780 nm, 1.0 mW, Class I) is delivered at a right angle via a 100-µm fiber optic within 2-5 mm of the probe tip (e.g., DP6ds endoscopic side view probe, flexible nylon sleeve, 1.34 mm OD, Moor
Instruments, Wilmington DE). After introduction into the anal canal, the probe sensor can be aligned with the IAS and maintained in place by taping to the tail of the rat as described before. At a collection rate of 2 data points per seconds, the DRT4 system can store over 8 hours of data, which can accommodates the duration of many experiments. Faster collection rates (up to 40 data points per seconds) can be used for shorter protocols. The DRT4 system also allows for simultaneous temperature monitoring providing the proper probes are used.

**Example 56**

[367] The ability of diazepam to lower the IASP was also evaluated in the rat under similar conditions to those described above. In these experiments, 1%, 0.1% and 0.01% diazepam in 5% DMSO/acetone:olive oil (1:1) were infused at a rate of 20 ul/hour. A dose-response relationship was observed with substantial and measurable effects at each dose level (i.e. 2, 20, or 200 ug/hour). See Figures 46-47.

**Example 57**

[368] Increased blood flow in the anorectal region can increase healing and can reduce pain, particularly ischemic pain. The ability of anal sphincter relaxing agents to increase blood flow in the anorectal region may be evaluated according to the method provided in Example 54. Preferred anal sphincter relaxing agents also increase blood flow in the anorectal region. For instance, an infusion to the anorectal region of an anal sphincter relaxing agent (0.01% to 2.0%) in water or other suitable vehicle at a rate of 100 ul/hour can be administered to increase blood flow in the anorectal region. Infusion of a 0.2%, 0.1%, 0.05% and 0.01% of the anal sphincter relaxing agent at rate of 100 ul per hour allows the dose response effect of the anal sphincter relaxing agent on increasing blood flow in the anorectal region to be assessed.

[369] Such anal sphincter relaxing agents include cAMP kinase activators, superoxide scavengers, ATP-sensitive potassium channel activators, calcium channel blockers, cholinergic modulators, α-adrenergic antagonists, β-adrenergic agonists, adrenergic nerve inhibitors, NO donors, phosphodiesterase inhibitors, estrogen-like compounds, testosterone-like compounds, benzodiazepines, antiarrheal agents, HMG-CoA reductase inhibitors, adenosine receptor modulators, and smooth muscle relaxants.

[370] Preferred anal sphincter relaxing agents for this purpose include the NO donors, benzodiazepines (e.g., diazepam), the alpha-adrenergic antagonists, potassium channel activators, calcium channel blockers, and particularly yohimbine and vesamicol.
Example 58

[371] Increased blood flow in the anorectal region can increase healing and can reduce pain, particularly ischemic pain. The ability of anal sphincter relaxing agents to increase blood flow in the anorectal region may be evaluated according to the method provided in Example 54. For instance, an infusion to the anorectal region of yohimbine (0.01% to 2.0%) in water or other suitable vehicle at a rate of 100 ul/hour can be administered to increase blood flow in the anorectal region. Infusion of a 0.2%, 0.1%, 0.05% and 0.01% of this anal sphincter relaxing agent at rate of 100 ul per hour allows the dose response effect of this agent on increasing blood flow in the anorectal region to be assessed.

Example 59

[372] Increased blood flow in the anorectal region can increase healing and can reduce pain, particularly ischemic pain. The ability of anal sphincter relaxing agents to increase blood flow in the anorectal region may be evaluated according to the method provided in Example 54. For instance, an infusion to the anorectal region of vesamicol (0.01% to 2.0%) in water or other suitable vehicle at a rate of 100 ul/hour can be administered to increase blood flow in the anorectal region. Infusion of a 0.2%, 0.1%, 0.05% and 0.01% of this anal sphincter relaxing agent at rate of 100 ul per hour allows the dose response effect of this agent on increasing blood flow in the anorectal region to be assessed.

Example 60

[373] In one embodiment of the invention, therefore, preferred anal sphincter relaxing agents are those compounds which increase blood flow and especially preferred agents are those which increase blood flow while reducing IASP. Anodermal blood flow in the subject (e.g., human, rat) can be measured non-invasively by laser Doppler velocimetry. In the laser Doppler technique, low power laser light is transmitted via an optic fiber to the tissue. The light is scattered by moving red blood cells and its frequency shifted according to the Doppler effect; the average Doppler frequency shift being proportional to the average speed of the blood cells. The scattered light is photodetected and the photocurrent signal electronically processed to produce the Doppler flux signal. Schouten et al. (Schouten WR, Briel JW and Auwerda JJ (1994) Dis Colon Rectum 37(7): 664-9.) have successfully used this technique to assess anodermal blood flow in patients with colorectal disorders (including anal fissures and hemorrhoids) as well as in healthy volunteers. In healthy patients, they found that the anodermal blood flow at the posterior commissure is significantly lower than for other segments of the anoderm. In anal fissure patients, blood flow at the posterior
midline was significantly lower than in healthy patients and correlated strongly with the maximum anal resting pressure. In another study (Schouten WR, Briel JW, Auwerda JJ and Boerma MO (1996) Scand J Gastroenterol Suppl 218: 78-81.), patients with chronic anal fissures received intra-anal application of the nitric oxide donor, isosorbide dinitrate for 6 or 12 weeks. The investigators monitored IAS pressure and anodermal blood flow and showed that the former was significantly reduced while the latter was significantly increased following 12 weeks of treatment. This dual effect was accompanied with an 88% healing rate. Following sphincterotomy (Schouten et al. 1996) in patients with anal fissures, healing (89%) was accompanied by a 35% decrease in pressure and a 65% increase in blood flow at the original fissure site. While these findings provide evidence for an ischaemic contribution in the pathology of anal fissure, it has yet to be demonstrated whether blood flow and pressure are always inversely correlated when different treatments are used.

EXAMPLE 61

[374] In order to determine dose response and the time course of the anodermal blood flow response of a human to an administered anal sphincter relaxing agent, blood flow can be measured non-invasively by laser Doppler velocimetry. In the laser Doppler technique, low power laser light is transmitted via an optic fiber to the tissue. The light is scattered by moving red blood cells and its frequency shifted according to the Doppler effect; the average Doppler frequency shift being proportional to the average speed of the blood cells. The scattered light is photodetected and the photocurrent signal electronically processed to produce the Doppler flux signal. Schouten et al. (Schouten WR, Briel JW and Auwerda JJ (1994) Dis Colon Rectum 37(7): 664-9.) have successfully used this technique to assess anodermal blood flow in patients with colorectal disorders (including anal fissures and hemorrhoids) as well as in healthy volunteers. In healthy patients, they found that the anodermal blood flow at the posterior commissure is significantly lower than for other segments of the anoderm. In anal fissure patients, blood flow at the posterior midline was significantly lower than in healthy patients and correlated strongly with the maximum anal resting pressure. In another study (Schouten WR, Briel JW, Auwerda JJ and Boerma MO (1996) Scand J Gastroenterol Suppl 218: 78-81.), patients with chronic anal fissures received intra-anal application of the nitric oxide donor, isosorbide dinitrate for 6 or 12 weeks. The investigators monitored IAS pressure and anodermal blood flow and showed that the former was significantly reduced while the latter was significantly increased following 12 weeks of treatment. This dual effect was accompanied with an 88% healing rate. Following sphincterotomy (Schouten et al. 1996) in patients with anal fissures, healing (89%) was
accompanied by a 35% decrease in pressure and a 65% increase in blood flow at the original fissure site. While these findings provide evidence for the ischaemic nature of the anal fissure, it has yet to be demonstrated whether blood flow and pressure are always inversely correlated when different treatments are used.

**EXAMPLE 62**

[375] Effects of α₂-adrenergic postsynaptic antagonists on IASP was studied with respect to several species of this class. The effects of mianserin (0.01%, 0.05%); mirtazapine ARC (0.1%), imiloxan (0.05%, 100 ul/hr), idazoxan (0.05%, 50 ul/30 min.); efaroxan (0.05%, 100 ul/hr) and rauwolscine (0.05%, 100 ul/hr) were studied in the above described rat IASP model. Infusion of the above amounts and concentrations of mianserin, mirtazpine, imiloxan, idazoxan, efaroxan, and rauwolscine each caused the rat IASP to decrease (data not shown).

[376] All publications, patents and patent applications cited in this specification are herein incorporated by reference in their entirety to the extent not inconsistent with the present disclosure and for all purposes.

[377] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to one of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.
WHAT IS CLAIMED IS:

1. A method for treating or preventing an anorectal disorder in a patient, said method comprising administering to said patient a compound selected from the group consisting of cAMP-dependent protein kinase activators, superoxide scavengers, benzodiazepines, calcium channel blockers, adenosine receptor modulators, antidiarrheal agents, HMG-CoA reductase inhibitors, testosterone-like compounds, α2-adrenergic receptor antagonists, and β-adrenergic agonists, and adrenergic nerve inhibitors in a therapeutically effective amount.

2. The method of claim 1, wherein said anorectal disorder is a hemorrhoid or associated with a hemorrhoidal ligation.

3. The method of claim 1, wherein the anorectal disorder is selected from the group consisting of constipation, acute or chronic anal fissure, chronic idiopathic anal pain, abnormally increased resting anal pressures, and hypertonicity of the anal sphincters.

4. The method of claim 1, wherein said compound is a cAMP-dependent protein kinase activator.

5. The method of claim 1, wherein said compound is a benzodiazepine.

6. The method of claim 1, wherein said compound is an adenosine receptor modulator.

7. The method of claim 1, wherein said compound is a HMG-CoA reductase inhibitor.

8. The method of claim 1, wherein said compound is a testosterone-like compound.

9. The method of claim 1, wherein said compound is a superoxide scavenger.

10. The method of claim 1, wherein said compound is an antidiarrheal agent.
11. The method of claim 1, wherein said compound is an $\alpha_2$-adrenergic receptor antagonist.

12. The method of claim 1, wherein said compound is a $\beta$-adrenergic agonist.

13. The method of claim 1, wherein said compound is an adrenergic nerve inhibitor.

14. The method of claim 1, wherein said compound is a calcium channel blocker.

15. The method of claim 1, wherein said method further comprises administering to said patient a second compound selected from the group consisting of cAMP-dependent protein kinase activators, superoxide scavengers, benzodiazepines, adenosine receptor modulators, antidiarrheal agents, HMG-CoA reductase inhibitors, testosterone-like compounds and Potassium channel activators.

16. The method of claim 1, wherein said method comprises administering to said patient a second compound selected from the group consisting of calcium channel blockers, cholinergic modulators, acetylcholine storage blocking agents, $\alpha$-adrenergic receptor antagonists, $\beta$-adrenergic agonists, adrenergic nerve inhibitors, NO donors, phosphodiesterase inhibitors, estrogen-like compounds, testosterone-like compounds, and smooth muscle relaxants.

17. The method of claim 1, wherein said compound is administered orally.

18. The method of claim 1, wherein said compound is administered parenterally.

19. The method of claim 1, wherein said compound is administered topically to the anorectal region.

20. The method of claim 19, wherein said compound is in a form selected from the group consisting of gel, ointment, cream, lotion, powder, solution, suspension, spray, paste, oil, suppository, and foam.
21. The method of claim 1, wherein said compound is delivered continuously.

22. The method of claim 21, wherein said compound is administered by a rectal suppository.

23. A method for treating or preventing an anal fissure in a patient, the method comprising administering to said patient in need thereof a compound selected from the group consisting of calcium channel blockers, $\alpha_2$-adrenergic receptor antagonists, and $\beta$-adrenergic agonists.

24. The method of claim 23, wherein said method further comprises administering to said patient a second compound selected from the group consisting of calcium channel blockers, $\alpha_1$-adrenergic receptor antagonists, $\alpha_2$-adrenergic receptor antagonists, and $\beta$-adrenergic agonists.

25. The method of claim 23, wherein said method comprises administering to said patient a second compound selected from the group consisting of cAMP-dependent protein kinase activators, superoxide scavengers, benzodiazepines, adenosine receptor modulators, antidiarrheal agents, HMG-CoA reductase inhibitors, Potassium channel activators, cholinergic modulators, acetylcholine storage blocking agents, $\alpha$-adrenergic receptor antagonists, adrenergic nerve inhibitors, NO donors, phosphodiesterase inhibitors, estrogen-like compounds, testosterone-like compounds, and smooth muscle relaxants.

26. The method of claim 23, wherein said compound is administered orally.

27. The method of claim 23, wherein said compound is administered parenterally.

28. The method of claim 23, wherein said compound is administered topically.

29. The method of claim 28, wherein said compound is in a form selected from the group consisting of gel, ointment, cream, lotion, powder, solution, suspension, spray, paste, oil, suppository, and foam.
30. The method of claim 23, wherein said compound is delivered continuously.

31. The method of claim 30, wherein an rectal suppository is used to administer said compound.

32. A method for treating or preventing anal fissures or hemorrhoids in a patient, the method comprising administering to said patient an $\alpha_2$-adrenergic receptor antagonist.

33. A method according to claim 84, wherein the $\alpha_2$ adrenergic antagonist is selected from the group consisting of yohimbine, mianserin, mirtazapine, imiloxan, ARC, idazoxan, rauwolscine, and efaroxan.

34. The method of claim 32, wherein said method further comprises administering to said patient a second compound selected from the group consisting of cAMP-dependent protein kinase activators, superoxide scavengers, $\alpha_1$-adrenergic receptor antagonists and $\beta$-adrenergic agonists, benzodiazepines, adenosine receptor modulators, antidiarrheal agents, HMG-CoA reductase inhibitors, potassium channel activators, calcium channel blockers, cholinergic modulators, acetylcholine storage blocking agents, $\alpha$-adrenergic receptor antagonists, adrenergic nerve inhibitors, NO donors, phosphodiesterase inhibitors, estrogen-like compounds, and testosterone-like compounds.

35. The method of claim 32, further comprising administering to said patient a smooth muscle relaxant.

36. The method of claim 32, wherein said compound is administered orally.

37. The method of claim 32, wherein said compound is administered parenterally.

38. The method of claim 32, wherein said compound is administered topically.
39. The method of claim 38, wherein said compound is in a form selected from the group consisting of gel, ointment, cream, lotion, powder, solution, suspension, spray, paste, oil, suppository, and foam.

40. The method of claim 32, wherein said compound is delivered continuously.

41. The method of claim 40, wherein a rectal suppository is used to administer said compound.

42. A method for treating or preventing levator spasm in a patient, the method comprising administering to said patient a compound selected from the group consisting of β-adrenergic agonists, adenosine receptor modulators and benzodiazepines.

43. The method of claim 42, wherein said method further comprises administering to said patient a second compound selected from the group consisting of NO donors, phosphodiesterase inhibitors, adrenergic receptor antagonists, benzodiazepines, and ATPase sensitive potassium channel activators.

44. The method of claim 42, wherein said method further comprises administering to said patient a second compound selected from the group consisting of cAMP-dependent protein kinase activators, superoxide scavengers, antidiarrheal agents, HMG-CoA reductase inhibitors, calcium channel blockers, cholinergic modulators, acetylcholine storage blocking agents, adrenergic nerve inhibitors, NO donors and phosphodiesterase inhibitors and smooth muscle relaxants.

45. The method of claim 42, wherein said method further comprises administering to said patient a second compound selected from the group consisting of estrogen-like compounds and testosterone-like compounds.

46. The method of claim 42, wherein said compound is administered orally.

47. The method of claim 42, wherein said compound is administered parenterally.
48. The method of claim 42, wherein said compound is administered topically.

49. The method of claim 48, wherein said compound is in a form selected from the group consisting of gel, ointment, cream, lotion, powder, solution, suspension, spray, paste, oil, suppository, and foam.

50. The method of claim 42, wherein said compound is delivered continuously.

51. The method of claim 50, wherein a rectal suppository is used to administer said compound.

52. A method for treating levator spasm, the method comprising administering to a patient in need thereof an $\alpha_2$-adrenergic receptor antagonist.

53. The method of claim 52, wherein said method further comprises administering to said patient a second compound selected from the group consisting of NO donors, calcium channel blockers, cholinergic modulators, acetylcholine storage blocking agents, $\alpha_1$-adrenergic receptor antagonists, $\alpha_1$-adrenergic receptor antagonists, $\beta$-adrenergic agonists, phosphodiesterase inhibitors, adrenergic nerve inhibitors, and estrogen-like compounds.

54. The method of claim 52, wherein said method comprises administering to said patient a second compound selected from the group consisting of cAMP-dependent protein kinase activators, superoxide scavengers, benzodiazepines, adenosine receptor modulators, antidiarrheal agents, HMG-CoA reductase inhibitors, Potassium channel activators, calcium channel blockers, cholinergic modulators, acetylcholine storage blocking agents, $\alpha_1$-adrenergic receptor antagonists, $\beta$-adrenergic agonists, adrenergic nerve inhibitors, NO donors, phosphodiesterase inhibitors, estrogen-like compounds, testosterone-like compounds, and smooth muscle relaxants.

55. The method of claim 52, wherein said compound is administered orally.
56. The method of claim 52, wherein said compound is administered parenterally.

57. The method of claim 52, wherein said compound is administered topically.

58. The method of claim 52, wherein said compound is in a form selected from the group consisting of gel, ointment, cream, lotion, powder, solution, suspension, spray, paste, oil, suppository, and foam.

59. The method of claim 52, wherein said compound is delivered continuously.

60. The method of claim 59, wherein a rectal suppository is used to administer said compound.

61. A method for treating or preventing non-specific pain and/or burning of the anorectal region in a patient, the method comprising administering to said patient a compound selected from the group consisting of NO donors, superoxide scavengers, benzodiazepines, adenosine receptor modulators, HMG-CoA reductase inhibitors, calcium channel blockers, cholinergic modulators, acetylcholine storage blocking agents, α₁-adrenergic receptor antagonists, α₂-adrenergic receptor antagonists, β-adrenergic agonists, phosphodiesterase inhibitors, adrenergic nerve inhibitors, estrogen-like compounds, testosterone-like compounds and smooth muscle relaxants.

62. The method of claim 61, wherein said method further comprises administering to said patient a second compound selected from the group consisting of NO donors, calcium channel blockers, cholinergic modulators, acetylcholine storage blocking agents, α₁-adrenergic receptor antagonists, α₂-adrenergic receptor antagonists, β-adrenergic agonists, phosphodiesterase inhibitors, adrenergic nerve inhibitors, estrogen-like compounds.

63. The method of claim 61, wherein said method further comprises administering to said patient a second compound selected from the group consisting of cAMP-dependent protein kinase activators, superoxide scavengers, benzodiazepines, adenosine receptor modulators, antidiarrheal agents, HMG-CoA reductase inhibitors,
Potassium channel activators, \( \alpha \)-adrenergic receptor antagonists, and testosterone-like compounds and smooth muscle relaxants.

64. The method of claim 61, wherein said compound is administered orally.

65. The method of claim 61, wherein said compound is administered parenterally.

66. The method of claim 47, wherein said compound is administered topically.

67. The method of claim 66, wherein said compound is in a form selected from the group consisting of gel, ointment, cream, lotion, powder, solution, suspension, spray, paste, oil, suppository, and foam.

68. The method of claim 61, wherein said compound is delivered continuously.

69. The method of claim 68, wherein a rectal suppository is used to administer said compound.

70. A method for treating or preventing an anorectal disorder in a patient, the method comprising administering to said patient a compound selected from the group consisting of cholinergic modulators, NO donors, phosphodiesterase inhibitors, \( \alpha_1 \)-adrenergic receptor antagonists, non-specific adrenergic receptor antagonists, Potassium channel activators, acetylcholine storage blocking agents, and smooth muscle relaxants.

71. The method of claim 70, wherein said method comprises administering to said patient a second compound selected from the group consisting cAMP-dependent protein kinase activators, superoxide scavengers, benzodiazepines, adenosine receptor modulators, antidiarrheal agents, HMG-CoA reductase inhibitors, Potassium channel activators, calcium channel blockers, cholinergic modulators, \( \beta \)-adrenergic agonists, adrenergic nerve inhibitors, NO donors, phosphodiesterase inhibitors, \( \alpha_1 \)-adrenergic receptor antagonists, \( \alpha_2 \)-adrenergic receptor antagonists, acetylcholine storage blocking agents, and smooth muscle relaxants.
72. The method of claim 70, wherein said method further comprises administering to said patient a second compound selected from the group consisting of estrogen-like compounds and testosterone-like compounds.

73. The method of claim 71, wherein said compound is administered orally.

74. The method of claim 71, wherein said compound is administered parenterally.

75. The method of claim 71, wherein said compound is administered topically.

76. The method of claim 75, wherein said compound is in a form selected from the group consisting of gel, ointment, cream, lotion, powder, solution, suspension, spray, paste, oil, suppository, and foam.

77. The method of claim 71, wherein said compound is delivered continuously.

78. The method of claim 77, wherein a rectal suppository is used to administer said compound.

79. A topical composition for the treatment of an anorectal disorder, and for controlling the pain associated therewith, said composition comprising an agent selected from the group consisting of superoxide scavengers, benzodiazepines, β-adrenergic agonists, cAMP-dependent protein kinase activators, estrogen-like compounds, testosterone-like compounds, α2-adrenergic receptor antagonists, and adenosine receptor modulators, with a pharmaceutically acceptable topical carrier.

80. A composition in accordance with claim 79, wherein said composition comprises a second agent which is selected from the group consisting of the NO donors nitroglycerin, L-arginine, SNAP, GSNO and SIN-1, adrenergic receptor antagonists, phosphodiesterase inhibitors, and ATPase sensitive potassium channel activators.
81. A method of treating a colotomy patient, the method comprising
administering to said patient a therapeutically effective amount of a composition comprising
at least one agent selected from the group consisting of NO donors, phosphodiesterase type II
inhibitors, phosphodiesterase type IV inhibitors, phosphodiesterase type V inhibitors,
nonspecific phosphodiesterase inhibitors, superoxide scavengers, β-adrenergic agonists,
calcium channel blockers, L-type Ca\(^2+\) channel blockers, cAMP-dependent protein kinase
activators, α\(_1\)-adrenergic antagonists, α\(_2\) adrenergic antagonists, estrogen-like compounds, K\(^+\)
channel activators, adenosine receptor modulators, benzodiazepines, and smooth muscle
relaxants.

82. A method according to claim 81, wherein the agent is an α\(_2\) adrenergic
antagonist.

83. A method according to claim 82, wherein the α\(_2\) adrenergic antagonist
is selected from the group consisting of yohimbine, mianserin, mirtazapine, imiloxan, ARC,
idazoxan, rauwolscine, and efaroxan.

84. A method according to claim 81, wherein the agent is administered via
the colostomy irrigation fluid.

85. A composition for improved irrigation of a colostomy, said
composition comprising said composition comprising at least one agent selected from the
group consisting of NO donors, phosphodiesterase type II inhibitors, phosphodiesterase type
IV inhibitors, phosphodiesterase type V inhibitors, nonspecific phosphodiesterase inhibitors,
superoxoide scavengers, β-adrenergic agonists, calcium channel blockers, cAMP-dependent
protein kinase activators, α\(_1\)-adrenergic antagonists, α\(_2\) adrenergic antagonists, estrogen-like
compounds, K\(^+\) channel activators, adenosine receptor modulators, benzodiazepines, and
smooth muscle relaxants, with a pharmaceutically acceptable carrier.

86. A colostomy irrigation fluid comprising a composition according to
claim 85.

87. A fluid of claim 86 comprising a β-adrenergic agonist, an α-adrenergic
antagonist, an potassium channel activator, or a phosphodiesterase inhibitor.
88. A fluid of claim 87, wherein the β-adrenergic agonist comprises albuterol, bitoterol, salbutamol, terbutaline, metaproterenol, procaterol, salmeterol, clenbuterol, isoproterenol, zinterol, BRL 37344, CL316243, CGP-12177A, GS 332, L-757793, L-760087, L-764646, or L-766892.
FIGURE 1
Baseline IASP

FIGURE 2
IASP after NTG

FIGURE 3
IASP after dibutyryl-cGMP
FIGURE 6

* NTG (20mg/min every 30 minutes)

FIGURE 7

NTG (20mg/hr for 4 hours)

* hours post-NTG
FIGURE 8

FIGURE 9
FIGURE 12

FIGURE 13
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**FIGURE 16**

**FIGURE 17**
FIGURE 18

FIGURE 19
FIGURE 23

FIGURE 24
FIGURE 25

FIGURE 26

FIGURE 27

SUBSTITUTE SHEET (RULE 26)
FIGURE 28

FIGURE 29

FIGURE 30

SUBSTITUTE SHEET (RULE 26)
**FIGURE 33**

Diltiazem (20mg/hr for 3 hours)

**FIGURE 34**

Verapamil (20mg/hr for 3 hours)
FIGURE 35
FIGURE 36

vehicle (100ml i.p.)

isoproterenol (0.2mg/hr)

mmHg

1  3352  6703  10054  13405  16756  20107  23458  26809  30160

(n) hours post-isoproterenol

Seconds (x 2)

FIGURE 37

zardaverine (10mg i.p.)

isoproterenol (0.2mg/hr)

mmHg

1  3370  6739  10108  13477  16846  20215  23584  26953  30322

(n) hours post-isoproterenol

Seconds (x 2)
FIGURE 38

FIGURE 39
FIGURE 40

FIGURE 41
FIGURE 45A

FIGURE 45B
FIGURE 46