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(54) Titre : COMPOSITION PHARMACEUTIQUE A USAGE LOCAL CONTENANT UN AGENT CHOLINERGIQUE OU UN
INHIBITEUR CALCIQUE
(54) Title: TOPICAL PHARMACEUTICAL COMPOSITION COMPRISING A CHOLINERGIC AGENT OR A CALCIUM
CHANNEL BLOCKER

(57) **Abrégé/Abstract:**

A cholinergic agent and/or a calcium channel blocker is administered locally to the anus for the treatment of benign anal disorders, in particular anal fissures and haemorrhoids. The agents induce a reduction in the mean and resting pressure, thereby assisting in the healing of the anal fissures and haemorrhoids. Particularly preferred active agents are bethanechol and diltiazem, more particularly a combination thereof.



ABSTRACT:

A cholinergic agent and/or a calcium channel blocker is administered locally to the anus for the treatment of benign anal disorders, in particular anal fissures and haemorrhoids. The agents induce a reduction in the mean and resting pressure, thereby assisting in the healing of the anal fissures and haemorrhoids. Particularly preferred active agents are bethanechol and diltiazem, more particularly a combination thereof.

TOPICAL PHARMACEUTICAL COMPOSITION COMPRISING A CHOLINERGIC AGENT OR A CALCIUM CHANNEL BLOCKER

5 This application is a division of copending Canadian Patent Application No. 2,281,755.

10 This invention relates to the use of nifedipine or a pharmaceutically acceptable salt thereof for the treatment of benign anal diseases where there is an associated anal sphincter spasm. The invention particularly relates to the treatment of anal fissures and painful haemorrhoidal conditions.

15 A fissure is a split in the skin of the distal anal canal. It is a common complaint in young adults with a roughly equal incidence in both sexes. Acute fissures are very common and most heal spontaneously, but a proportion progress to form a chronic linear ulcer in the anal canal and show great reluctance to heal without intervention.

20 Treatment has remained largely unchanged for over 150 years and the pathogenesis of anal fissure is not fully understood. The passage of a hard stool bolus has traditionally been thought to cause anal fissure. Thus for acute fissures the avoidance of constipation, such as involving a high bran diet, has been used as treatment for many years.

25 Anal dilators have also been involved in treatment. Typically a dilator of medium size was coated with anaesthetic jelly and inserted into the anal canal before the passage of stool to prevent exacerbation of the symptoms during defecation. The procedure was inconvenient and success rate was low. The most common treatment, for chronic anal fissures is a lateral internal sphincterotomy, which involves surgery to the internal anal sphincter. 30 This procedure, however, requires hospitalisation and leads in a sizeable number of patients to impairment of continence (British Journal of Surgery 1996, 83, 1334-1344). As yet there is no proven non-surgical treatment for chronic fissure, although local injection of botulinum A toxin shows early promise (Martindale, The Extra Pharmacopoeia 31st Edition p1516 and 35 1517).

A further potential non-surgical treatment that has recently been reported for anal fissures and haemorrhoids is the topical use of a nitric oxide donor, particularly glyceryl trinitrate. This reduces the internal anal resting pressure (British Journal of Surgery, 1994, 81, 1386-1389 and British Journal of Surgery, 1996, 83, 771-775 both by present inventors; Diseases of the Colon and Rectum, May 1995, p453-457, The New England Journal of Medicine Oct. 26, 1995, p1156 and 1157, WO 95/32715 and its equivalent US-A-5,504,117 - all by Gorfine; British Journal of Surgery 1996, 83, 776-777).

At a meeting of the Royal Society of Medicine Coloproctology Session on 27th November 1996, a paper entitled "The effect of alpha adrenoceptor blockade on the anal canal in patients with chronic anal fissure" was presented showing that indoramin reduced maximum resting pressures in the anal canal after 1 hour by 35.8% in patients with anal fissures. The author suggested a clinical trial to determine the efficacy of indoramin in the treatment of anal fissures.

In Dis Colon Rectum, February 1996, vol 2, no.2, p212-216 nifedipine was reported as reducing the activity of the internal anal sphincter in patients with high anal resting pressure, and was proposed for use in relieving symptoms in patients with haemorrhoids or anal fissures.

Haemorrhoids ('piles') are venous swellings of the tissues around the anus. Those above the dentate line (the point where the modified skin of the outer anal canal becomes gut epithelium), which usually protrude into the anal canal, are termed internal haemorrhoids, while those below this point are called external haemorrhoids. Due to internal pressure, internal haemorrhoids tend to congest, bleed and eventually prolapse; with external haemorrhoids painful thrombosis may develop.

Initial treatment of internal haemorrhoids involves a high-fibre diet and avoidance of straining at stool, so bulk laxatives and faecal softeners may be indicated. Small bleeding haemorrhoids may be injected with a sclerosing agent such as oily phenol injection, or they may be ligated with rubber bands.

More severe and prolonged prolapse generally requires surgery. Surgical excision to remove the clot is used for thrombosed external haemorrhoids.

5 A range of mainly topical drug treatments is available for symptomatic relief, but in many cases their value is at best unproven. Local anaesthetics may be included to relieve pain, and corticosteroids may be used when infection is not present. Preparations containing either group of drugs are intended only for short-term use. Some preparations include heparinoids and other agents frequently included for their soothing properties include various
10 bismuth salts, zinc oxide, hamamelis, resorcinol and peru balsam.

In British Journal of Surgery 1994, 81, 946-954, Loder *et al* reviewed the possible pathology, pathophysiology and aetiology of haemorrhoids but came to no firm conclusions. The authors speculate that the anal cushions
15 surround the anal canal act as a seal to prevent minor leakage from the anus and these cushions distend as a consequence of haemorrhoidal disease. The authors also explored whether haemorrhoids is more prevalent in certain racial groups, whether it is a function of diet, habits or body habitus, whether it is a genetic disorder or whether it is associated with other conditions such as
20 hernia. No firm conclusions were, however, reached as to the aetiology of haemorrhoids or how to treat it effectively.

Diltiazem (a calcium channel blocker) is indicated orally for the treatment of angina pectoris and hypertension, and may be given
25 intravenously in the treatment of arterial fibrillation or flutter and paroxysmal supraventricular tachycardia. Bethanechol (a cholinergic agent) is used as an alternative to catheterisation in the treatment of urinary retention, gastric atony and retention, abdominal distension following surgery, congenital megacolon, and oesophageal reflux. It is given in doses of 5mg subcutaneously or 10 to
30 50mg by mouth (Martindale, The Extra Pharmacopoeia, 31st Edition, p857 and p1417).

In a letter to the Lancet June 28, 1986 at p1493 and March 28, 1987 at p754 diltiazem given orally at 60mg was found to reduce internal anal resting
35 pressure and to treat proctalgia fugax. There was, however, no suggestion of diltiazem being used to treat anal fissure or haemorrhoids.

The present invention is directed towards the provision of a non-surgical treatment for anal fissures and/or haemorrhoids, or other benign anal disorders.

5 The inventors have now found that anal fissures and haemorrhoids and other benign anal disorders can be treated by local application to the anus of the calcium channel blocker nifedipine or a pharmaceutically acceptable salt thereof. Other benign anal disorders would be those conditions associated with a high anal pressure or where there is an associated anal sphincter
10 spasm.

Accordingly in a first aspect of the invention, there is provided use of nifedipine or a pharmaceutically acceptable salt thereof. in the preparation of a medicament for local application to the anus for the treatment or prophylaxis
15 of benign anal disorders.

A second aspect of the invention provides a composition adapted for local application to the anus nifedipine or a pharmaceutically acceptable salt thereof. together with a pharmaceutically acceptable carrier.
20

By local application to the anus we mean to include local injection into the anal sphincter, and administration in and around the anal canal, preferably by topical application such as spreading a topical composition in and around the anal canal.
25

Without being bound by theory, it is believed that nifedipine or a pharmaceutically acceptable salt thereof is at least partially effective (and there may be other mechanisms of action) by lowering the anal resting pressure of the patient. This helps the fissures to heal. This reduction in anal
30 pressure should also allow better venous drainage which will allow the haemorrhoidal vascular cushions to heal.

In any case the clinical results to date suggest the inventors have made a major advance in the field by providing a safe and efficacious non-surgical treatment for anal fissures and haemorrhoids.
35

By anal fissures we mean to include both acute and chronic fissures or ulcers. Any patient with persistent symptoms for more than two weeks is taken to have a chronic fissure in accordance with the invention.
40

By haemorrhoids we mean to include both internal and external haemorrhoids and acute thrombosis of external haemorrhoid (TEM).

Pharmaceutically acceptable salts include those formed with both organic and inorganic acids. Such acid addition salts will normally be pharmaceutically acceptable although salts of non-pharmaceutically acceptable salts may be of utility in the preparation and purification of the compound in question. Thus, preferred salts include those formed from hydrochloric, hydrobromic, sulphuric, citric, tartaric, phosphoric, lactic, pyruvic, acetic, succinic, oxalic, fumaric, maleic, oxaloacetic, methanesulphonic, ethanesulphonic, benzenesulphonic, and isethionic acids. Salts of the compounds of formula (1) can be made by reacting the appropriate compound in the form of the free base with the appropriate acid. Salts of halides are also suitable.

A suitable proportion of nifedipine in a topical or local composition for a beneficial effect is at least 0.5% w/w, such as 0.5% to 10% w/w, preferably 0.5% to 5% w/w, more preferably still 1% to 5% w/w, still more preferably 1% to 3%, and most preferably about 2% w/w. Preliminary dose ranging studies suggest that the maximum effect of the invention is obtained at about 2% and thereafter higher concentrations will not produce a substantial additional effect.

Pharmaceutical compositions adapted for topical administration in and/or around the anal canal may be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, foam, oils, aerosols, suppositories or enemas.

The topical compositions used in the invention can comprise emulsifiers, preservatives, buffering agents and anti-oxidants. Preferably the compositions also comprise steroids (e.g. present at 0.1 to 5% w/w) such as prednisolone, busenonide or hydrocortisone, locally acting anaesthetics such as lignocaine (e.g. at 0.1 to 5% w/w), and soothants. Typical components used in existing fissure or haemorrhoidal treatments which can also be used in topical compositions of the invention include: zinc oxide, benzyl benzoate, bismuth oxide, bismuth subgallate and Peru balsam.

In accordance with the invention, nifedipine can be administered in combination with trinitroglycerine or any other nitric oxide donor, isoprenaline, histamine, prostaglandin E₂, adenosine triphosphate, nictotine, DMPP, bradykinin, caerulein, glucagon, and phentolamine.

5

The topical composition may comprise skin penetrating agents, particularly the sulphoxides, such as dimethyl sulphoxide (DMSO) preferably at 25% to 50% w/w. Amides, (DMA, DMF) pyrrolidones, organic solvents, laurocapram (AZONE) and calcium thioglycollate are suitable alternative
10 penetrants. The composition may also optionally contains a polyacrylic acid derivative, more particularly a carbomer. This would both act as a skin hydrating agent to aid penetration of the drug, but also an emulsifying agent. The carbomer will help emulsify the DMSO, thereby mitigating skin irritation and providing enhanced skin hydration. Propylene glycol may also be present
15 in the composition to soften the skin, increase thermodynamic potential and aid skin penetration by the DMSO and thus the drug. The final pH of the composition is advantageously pH 3.5 to 4.5.

The following are examples of analogous compositions containing a
20 calcium channel blocker and/or a cholinergic agent and intended for use in the treatment of benign anal disorders.

Composition Example 1

25 A composition of base gel had the following composition: carmellose sodium 6g, polyethylene glycol 30ml, methylhydroxybenzoate 150mg, propylhydroxybenzoate 15mg, made up to volume with distilled water (pH6-7).

30 Various amounts of diltiazem and bethanechol were added in the amounts shown in examples 4 and 6 to form various compositions for dose ranging studies.

Composition Example 2

A base cream of the invention had the following composition:

Diltiazem hydrochloride (2% w/w)	10g
Dimethyl sulphoxide	250g
Carbomer 974P	5g
White soft paraffin	15g
Cetomacrogol emulsifying ointment*	115g
Propylene glycol	23g
Methylhydroxybenzoate (preservative soln)	to 500g

5

*composition: white soft paraffin 50g, liquid paraffin 20g, cetomacrogol emulsifying wax 30g (cetosteryl alcohol 24g and cetomacrogol 1000, 6g).

10 A base cream was formed by firstly separate mixing of the aqueous and non-aqueous components of the cream. Weighed quantities of propylene glycol and a proportion of the preservative solution were placed in a beaker to which the weight quantity of carbomer powder was added using an impeller type mixer to form a colloidal suspension of the carbomer. Thereafter, the weighed quantity of DMSO was added and rapid stirring continued at room
15 temperature until a translucent uniform gel had been formed.

In the meantime, the weighed quantities of white soft paraffin and the cetomacrogol emulsifying ointment were placed in a separate beaker, heated to melting point and gently stirred to give a uniform base.

20

The drug is then added to the remainder of the preservative solution, which in turn was then added to the gel and whilst vigorously stirring, the uniform base (above) was added to form a cream. The carbomer acted as a dual neutralisation agent and primary emulsifier (of the oil and aqueous
25 phases) to form the uniform cream base.

Composition Example 3

A bethanechol cream composition was made up as above, but using
30 0.5g of bethanechol (0.1% w/w) instead of diltiazem.

Local application to the anus of nifedipine provides an efficacious treatment for benign anal disorder, particularly anal fissures and haemorrhoids. Furthermore since efficacy can be obtained at surprisingly low doses, the treatment of the invention is also substantially free of side effects normally associated with the active agents.

The embodiment of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A composition adapted for topical application in and around the anal
5 canal for the treatment or prophylaxis of benign anal disorders associated with high anal pressure or anal sphincter spasm comprising nifedipine or a pharmaceutically acceptable salt thereof and a locally acting anaesthetic together with a pharmaceutically acceptable carrier.
- 10 2. A composition as claimed in Claim 1, wherein nifedipine is present in an amount of 0.5% to 10% w/w.
3. A composition as claimed in Claim 1 or Claim 2 wherein the locally acting anaesthetic is lignocaine.
- 15 4. A composition as claimed in any one of claims 1 to 3, wherein the locally acting anaesthetic is present in an amount of 0.1 to 5% w/w.
5. A composition as claimed in any one of claims 1 to 4 in the form of a
20 gel, ointment, or cream.
6. Use of nifedipine or a pharmaceutically acceptable salt thereof in the preparation of a medicament for topical application in and around the anal canal for the treatment or prophylaxis of benign anal disorders associated
25 with high anal pressure or anal sphincter spasm.
7. A use as claimed in Claim 6, wherein the medicament contains nifedipine in an amount of 0.5% to 10% w/w.
- 30 8. A use as claimed in Claim 6 or Claim 7, wherein the medicament contains nifedipine or salt thereof as the sole active component.
9. A use as claimed in any one of Claims 6 to 8, wherein the medicament also comprises a locally acting anaesthetic.
- 35 10. A use as claimed in Claim 9 wherein the locally acting anaesthetic is lignocaine.

11. A use as claimed in Claim 9 or Claim 10 wherein the locally acting anaesthetic is present in an amount of 0.1 to 5% w/w.

5 12. A use as claimed in any one of Claims 6 to 11, wherein the medicament is for application to the internal anal sphincter.

13. A use as claimed in any one of Claims 6 to 12, wherein the benign anal disorder to be treated is haemorrhoids.

10

14. A use as claimed in any one of Claims 6 to 12, wherein the benign anal disorder to be treated is anal fissures.