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(71) Applicant *(for all designated States except US)*: **ISIS INNOVATION LIMITED** [GB/GB]; Ewert House, Ewert Place, Summertown, Oxford, Oxfordshire OX2 7BZ (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **JONES, Oliver** [—/GB]; University of Oxford, Dept. of Pharmacology, Mansfield Road, Oxford OX1 3QT (GB). **BRADING, Alison, Frances** [—/GB]; University of Oxford, Dept. of Pharmacology, Mansfield Road, Oxford OX1 3QT (GB). **MORTENSEN, Neil, James, McCready** [—/GB]; John Radcliffe Hospital, Dept. of Colorectal Surgery, Headley Way, Oxford OX3 9DU (GB).

(74) Agent: **RUFFLES, Graham, Keith**; Marks & Clerk, 57-60 Lincoln's Inn Fields, London WC2A 3LS (GB).

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(54) Title: USE OF PHOSPHODIESTERASE INHIBITORS FOR THE TREATMENT OF ANORECTAL DISORDERS

(57) Abstract: The invention relates to a method for the treatment of an anorectal condition in a mammal, the method comprising administering to a subject in need of such treatment an effective amount of a phosphodiesterase inhibitor, and pharmaceutical preparations for use in this method.

USE OF PHOSPHODIESTERASE INHIBITORS FOR THE TREATMENT OF ANORECTAL DISORDERS

The present invention relates to treatment of anorectal disorders such as anal fissure.

Anal fissure can be an acute condition manifested as a longitudinal tear in the epithelium of the anal canal, or a chronic condition in which an acute tear does not heal and an ovoid ulcer forms. In the untreated condition the smooth muscle of the anus typically undergoes spasm, causing pain to the affected individual.

Historically, the condition has been treated by surgery to overcome the hypertonia either by manual dilation of the anus under general anaesthesia or by lateral internal sphincterotomy. The principal disadvantage of this procedure is a definite incidence of incontinence to flatus and faeces.

Improved understanding of the pharmacology of the anal sphincter [O'Kelly. Ann R Coll Surg Engl 1996 78: 31-8] has resulted in the development of drugs for the treatment of chronic fissures. Glyceryl trinitrate (GTN) paste has been used to treat this condition, [Lund JN, *et al.*, Br. J. Surg. 1996 83: 1335-1344.], but there are now concerns over long term relapse, headache and tachyphylaxis [Watson SJ, *et al.*, Br. J. Surg. 1996 83: 771-5.]. Moreover, as a topical preparation, it is difficult to regulate dosage, and some patients find the application distasteful which can affect compliance. A second class of drug, calcium channel blocking drugs, have the advantage that they may be give in oral or topical form. Healing rates are similar for those for GTN, but patients are similarly affected by headache [Cook TA, *et al* Br. J. Surg. 1999 86: 1269-73]. Finally, botulinum toxin injections have been used either into the internal sphincter [Maria G *et al*, N. Engl. J. Med. 1998 338: 217-20], the intersphincteric space [Minguez M *et al.*, Dis. Colon. Rectum. 1999 42: 1016-21.], or the external sphincter [Madalinski M *et al.*, Endoscopy 1999 31: S63.]. This treatment has resulted in higher healing rates in some studies [Brisinda G, *et al.*, N. Engl. J. Med. 1999 341: 65-9.], but is expensive and can

take time to administer. The alpha adrenoceptor antagonists have recently been proposed as an alternative therapy, but they remain incompletely evaluated both in terms of efficacy and side effects.

As such, there is still a need in the art for an effective treatment for anorectal disorders.

The present invention sets out to address this need.

In a first aspect, the present invention provides a method for the treatment of an anorectal condition in a mammal, the method comprising administering to a subject in need of such treatment an effective amount of a phosphodiesterase inhibitor.

We have now discovered that phosphodiesterase inhibitors (PDEI's) are able to cause a dose dependent reduction in the resting muscle tone of the smooth muscle of the anal sphincter which reduces muscle spasm. In this way the pain of anorectal disorders is reduced and healing of such disorders is promoted by the increased blood flow to the diseased area.

The present invention relates to any type of phosphodiesterase inhibitor. Such inhibitors act on phosphodiesterase enzymes, of which eleven families have been characterised to date. Inhibitors of all families tested so far [classes, 1,2,3,4,5,6,8,9,10 and 11] have proven effective in causing relaxation of the internal anal sphincter muscle. Accordingly, the present invention relates to the total range of phosphodiesterase inhibitors, which allows the treatment regime to be extremely flexible because the therapy of the present invention is not limited by the type of naturally occurring phosphodiesterase in the target cells or tissue. Moreover, the specificity of certain PDEI's can allow treatment to be given orally, for example, without generation of significant unwanted effects on other target tissues.

It is known that certain activities of phosphodiesterase enzymes may be related to nervous signals generated by an individual, while others are independent of such host signals. Accordingly, treatments may be developed using appropriate inhibitors to

specific phosphodiesterase families which allow co-ordination of the PDEI treatment with the body's own natural nervous signals, or which are completely independent of such signals. By way of example, the treatment of anal fissure using PDEI's independent of such signals would be desirable to help reduce the resting tone of anal canal 24 hours a day, in order to promote wound healing. In contrast, in Hirschsprung's disease, a treatment whose effect is dependent upon the nervous signals of the patient would be desirable, to allow muscle relaxation and hence defecation when appropriate for the patient. Accordingly, the present invention also relates to a method for the treatment of an anorectal condition in a mammal as outlined above, wherein the PDEI facilitates an action such as defecation, whilst this action remains under voluntary or nervous control. Thus after administration, the patient is able to defer defecation, for example, until an appropriate time. We prefer that PDEI's which act on class 5 phosphodiesterases, such as sildenafil, are employed in treatments which have an element of voluntary control.

Preferred phosphodiesterase inhibitors are vinpocentine, erythro-9-(2-hydroxy-3-nonyl)adenine ('EHNA'), trequinsin, rolipram, zaprinast, dipyridamole, aminophylline, 4-(3-butoxy-4-methoxybenzyl)imidazolidin-2-one, caffeine, 1-(3-chlorophenylamino)-4-phenyl-phthalazine, cilostamide, 1,7 dimethylxanthine, etazolate, β-hydroxyethyltheophylline, 3-isobutyl-1-methylxanthine (IBMX), 8-methoxymethyl-3-isobutyl-1-methylxanthine sodium salt, milrinone, papaverine, pentoxifylline, propentofylline, quazinone, tetrahydropapaverine, theobromine, theophylline, trequinsin HCL, enoximone, sildenafil and zardaverine, although any suitable inhibitor may be used in the present invention. Moreover, combinations of PDEI's may also be used.

The anorectal disorders of the present invention include all disorders of the anus and rectum, and also encompass certain disorders of the lower gastrointestinal tract. In particular, it is preferred that the anorectal disorder is anal fissure, haemorrhoids, anismus or Hirschsprung's disease. In these cases there is failure of the internal anal sphincter to relax, which would then be beneficially treated by the phosphodiesterase inhibitors of the present invention.

The present invention also relates to pharmaceutical preparations comprising a phosphodiesterase inhibitor of the present invention in combination with a pharmaceutically acceptable carrier.

Examples of pharmaceutical compositions include any solid form (such as tablets, pills, capsule or granules), or liquid form (such as solutions, suspensions or emulsions). The pharmaceutical preparations may be delivered by any delivery means such as oral, topical or parenteral administration, and they may contain the pure phosphodiesterase inhibitor or inhibitor in combination with any carrier or any pharmacologically active compound. Preferably the patient is treated using either an oral dose of the phosphodiesterase inhibitor, a topical treatment such as a paste containing the inhibitor, a suppository, intravenously or by enema.

The correct dosage of the phosphodiesterase inhibitor will vary according to the particular formulation, mode of application, and the particular host being treated. Factors such as age, body weight, sex, diet, time of administration, rate of excretion, condition of the host, drug combinations, reaction sensitivities and severity of the disease are suitably to be taken into account.

The phosphodiesterase inhibitors and compositions of the present invention may be used with other drugs to provide combination therapies. The other drugs may form part of the same composition, or be provided as a separate composition for administration at the same time or a different time. The identity of the other drug is not particularly limited, and suitable candidates include drugs known to treat anorectal disorders at present such as glyceryl trinitrate (GTN), calcium channel blocking drugs, botulinum toxins and adrenocepter antagonists. In combination with PDEI's, levels of these other agents may be reduced such that their current problematic side effects are minimised or rendered clinically tolerable.

Without wishing to be constrained by theory, the use of phosphodiesterase inhibitors in the present invention may serve to improve anorectal disorders by preventing the breakdown of cGMP or cAMP by phosphodiesterase enzymes, thus increasing the level

of cGMP/cAMP in cells or tissues. Such an increase in cGMP/cAMP may then assist in smooth muscle relaxation. Accordingly, in addition to treatment of anorectal disorders using phosphodiesterase inhibitors, the present invention also relates to treatments comprising administering phosphodiesterase inhibitors in combination with an agent which increases or stabilises the cGMP or cAMP level in cells or tissues, and compositions comprising such combinations of agents. Suitable agents to increase cGMP or cAMP levels are stimulants of the cylase enzymes which produce these compounds, for example. Whilst this additional treatment is not necessary for the invention to be worked, increased cGMP/cAMP may enhance the therapeutic effect of the invention in certain cases.

The PDEI's of the present invention are also suitable for use in combination with anti-inflammatory agents and analgesics, such as benzocaine, lignocaine, xylocaine, cinchocaine, hydrocortisone, prednisolone, prednisone, adrenalin or methylhydroxybenzoate, for example. Other suitable anti-inflammatory agents and analgesics are well known in the art.

The present invention also relates to the use of a phosphodiesterase inhibitor in the preparation of a medicament for the treatment of an anorectal disorder.

The present invention is now illustrated by the following figures and example, which serve to illustrate the present invention but are not limiting thereon, wherein:

Figure 1 illustrates a dose response curve for vinpocentine and the internal anal sphincter;
Figure 2 indicates the dose response curve for EHNA and the internal anal sphincter;
Figure 3 indicates the dose response curve for trequinsin and the internal anal sphincter;
Figure 4 illustrates the dose response curve for rolipram and the internal anal sphincter;
Figure 5 illustrates the dose response curve for zaprinast and the internal anal sphincter; and
Figure 6 illustrates the dose response curve for dipyridamole and the internal anal sphincter.

Example 1 Activity of Phosphodiesterase Inhibitors on internal anal sphincter muscle

Tissue was obtained from three patients (two male; age range 45-56) undergoing either abdominoperineal resection or proctectomy. The tissue was transferred immediately to Krebs solution at 4°C. The epithelium of the anal canal and mucosa of the rectum was removed along with the submucosa. Strips of internal anal sphincter were cut each measuring 1 x 1 x 7 mm, weighing 2 to 8 mg and containing parallel muscle bundles. Fine 5-0 silk ligatures were tied to each end and mounted for isometric tension recording in superfusion organ baths (capacity 0.2 ml). Strips were perfused continuously with Krebs solution (37°C) at a rate of 1 ml/min. Krebs solution contained 120 mM NaCl, 5.9 mM KCl, 15.4 mM Na HCO_3, 1.2 mM NaH_2PO_4, 2.5 mM $CaCl_2$, 1.2 mM $MgCl_2$ and 11.5 mM glucose. The Krebs solution was equilibrated with 97% oxygen and 3% carbon dioxide to maintain the pH at 7.4 ± 0.05. This apparatus allowed six strips to be studied simultaneously. The strips were initially loaded with 1 g tension and allowed to equilibrate for at least 90 minutes. Tension was measured by Pioden dynamometer UF1 transducers (Pioden Controls, Canterbury, UK) and recorded on a six channel Tekman 900 pen recorder (Tekman Electronics, Leamington Spa, UK).

The tension present in strips perfused with calcium free solution (CaCl2 replaced isosmotically with $MgCl_2$, and 0.5 mM ethylene glycol tetraacetic acid; Sigma Chemical Co, Poole, UK) was regarded as zero tension. This was subtracted from observed tension to give actual tension. Increasing concentrations of drugs were added for 15 minute periods. Drugs used were vinpocentine, EHNA hydrochloride, trequinsin, rolipram, zaprinast and dipyridamole; Sigma Chemical Co, Poole, UK.

Strips from the internal anal sphincter developed spontaneous tone and myogenic activity.

All phosphodiesterase inhibitors caused a dose dependent reduction in resting tone in strips from the internal anal sphincter. The maximum reduction in tone for each type of PDE inhibitor is shown in table 1.

	Selective for PDE type	Maximum percentage reduction in tone (±SE)	IC_{50} (μM)
Vinpocentine	1	44.1 (8.2)	4.9
EHNA hydrochloride	2	46.9 (5.8)	25
Trequinsin	3	56.9 (14.3)	0.0013
Rolipram	4	59.4 (6.3)	7.8
Zaprinast	5/6/9	73.9 (4.4)	0.64
Dipyridamole	5/6/8/10/11	76.1 (6.6)	5.2

Table 1: Maximum reduction in tone for PDE inhibitors with different subtype selectivity. The IC_{50} figure shown are those given in manufacturers data sheets and represent values from in vitro assays.

Dose response curves for the different PDE inhibitors on the internal anal sphincter are shown in Figures 1-6. All inhibitors caused profound reductions both in tone and spontaneous activity.

Claims

1 A method for the treatment of an anorectal condition in a mammal, the method comprising administering to a subject in need of such treatment an effective amount of a phosphodiesterase inhibitor.

2 A method according to claim 1, wherein the phosphodiesterase inhibitor is selected from the list consisting of vinpocentine, EHMA, trequinsin, rolipram, zaprinast and dipyridamole, vinpocentine, erythro-9-(2-hydroxy-3-nonyl)adenine ['EHNA'], trequinsin, rolipram, zaprinast, dipyridamole, aminophylline, 4-(3-butoxy-4-methoxybenzyl)imidazolidin-2-one, caffeine, 1-(3-chlorophenylamino)-4-phenyl-phthalazine, cilostamide, 1,7 dimethylxanthine, etazolate, β-hydroxyethyltheophylline, 3-isobutyl-1-methylxanthine [IBMX], 8-methoxymethyl-3-isobutyl-1-methylxanthine sodium salt, milrinone, papaverine, pentoxifylline, propentofylline, quazinone, tetrahydropapaverine, theobromine, theophylline, trequinsin HCL, enoximone, sildenafil and zardaverine.

3 A method according to claim 1 or 2, wherein the anorectal disorder of the present invention is anal fissure, haemorrhoids, anismus or Hirschsprung's disease.

4 A method according to any preceding claim, wherein more than one phosphodiesterase inhibitor is administered.

5 A method according to any preceding claim, additionally comprising administration of one or more of glyceryl trinitrate (GTN), a calcium channel blocking drug, botulinum toxin or an adrenocepter antagonist.

6 A method according to any preceding claim, additionally comprising administration of an agent which increases or stabilises the cGMP or cAMP level in cells or tissues of the subject.

7 A method according to any preceding claim additionally comprising administration of an anti-inflammatory agent or analgesic.

8 A method according to any preceding claim, wherein the administration is by oral or topical delivery, intravenously, by suppository or enema.

9 A method according to any preceding claim, wherein the phosphodiesterase inhibitor facilitates an effect on smooth muscle, the effect being under voluntary or nervous control of the subject.

10 A method according to claim 9, wherein the phosphodiesterase inhibitor is an inhibitor of class 5 phosphodiesterases.

11 A pharmaceutical preparation for use in the method of any preceding claim comprising a phosphodiesterase inhibitor in combination with a pharmaceutically acceptable carrier.

12 A pharmaceutical preparation according to claim 11 comprising more than one phosphodiesterase inhibitor.

13 A pharmaceutical preparation according to claim 11 or 12 additionally comprising glyceryl trinitrate (GTN), a calcium channel blocking drug, botulinum toxin or an adrenocepter antagonist.

14 A pharmaceutical preparation according to claim 11, 12 or 13 additionally comprising an agent which increases or stabilises the cGMP or cAMP level in cells or tissues of the subject.

15 A pharmaceutical preparation according to any of claims 11-14 additionally comprising an anti-inflammatory agent or analgesic.

16 Use of a phosphodiesterase inhibitor in the preparation of a medicament for the treatment of an anorectal disorder.

Fig.1

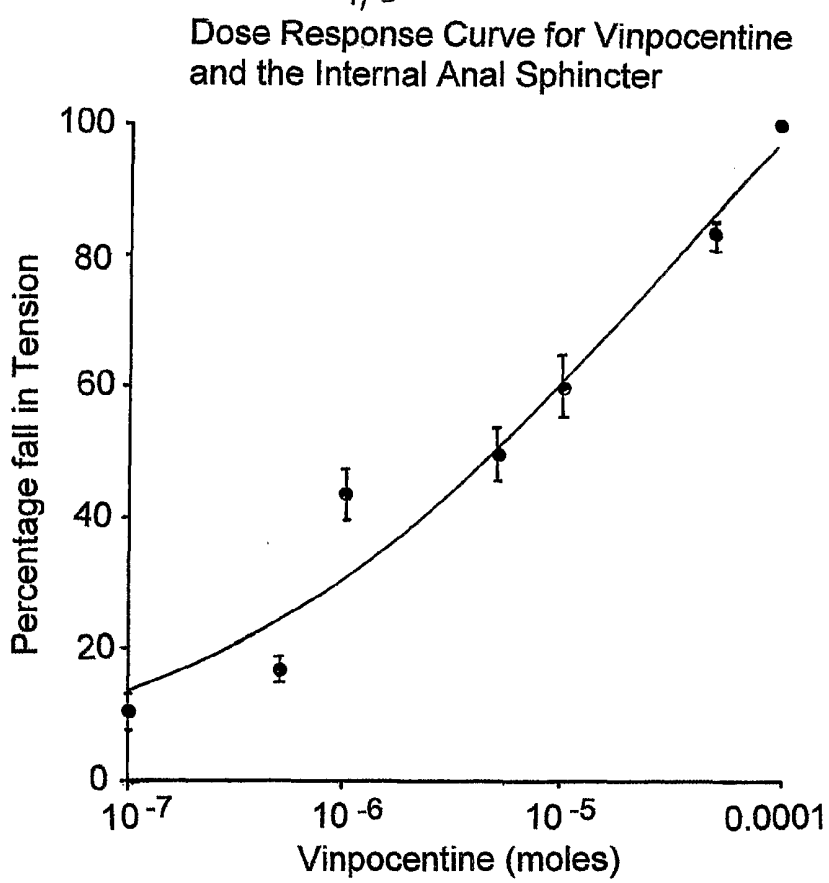

Dose Response Curve for Vinpocentine and the Internal Anal Sphincter
Percentage fall in Tension
100
80
60
40
20
0
10 -7
10 -6
10 -5
0.0001
Vinpocentine (moles)

Fig.2

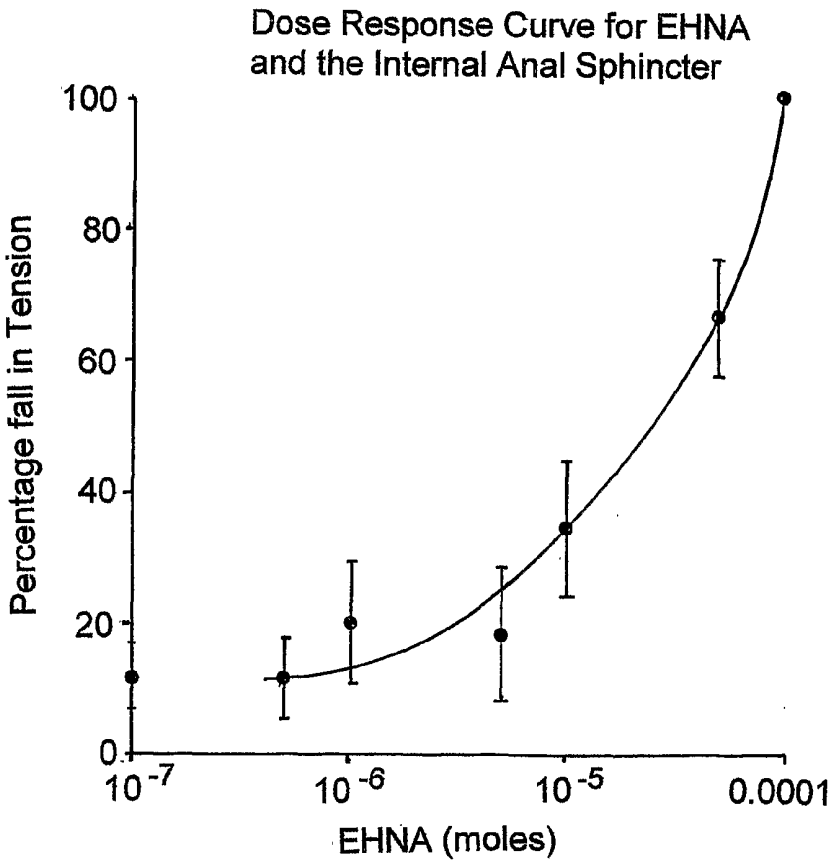

Dose Response Curve for EHNA and the Internal Anal Sphincter
Percentage fall in Tension
100
80
60
40
20
0
10 -7
10 -6
10 -5
0.0001
EHNA (moles)

Fig.3

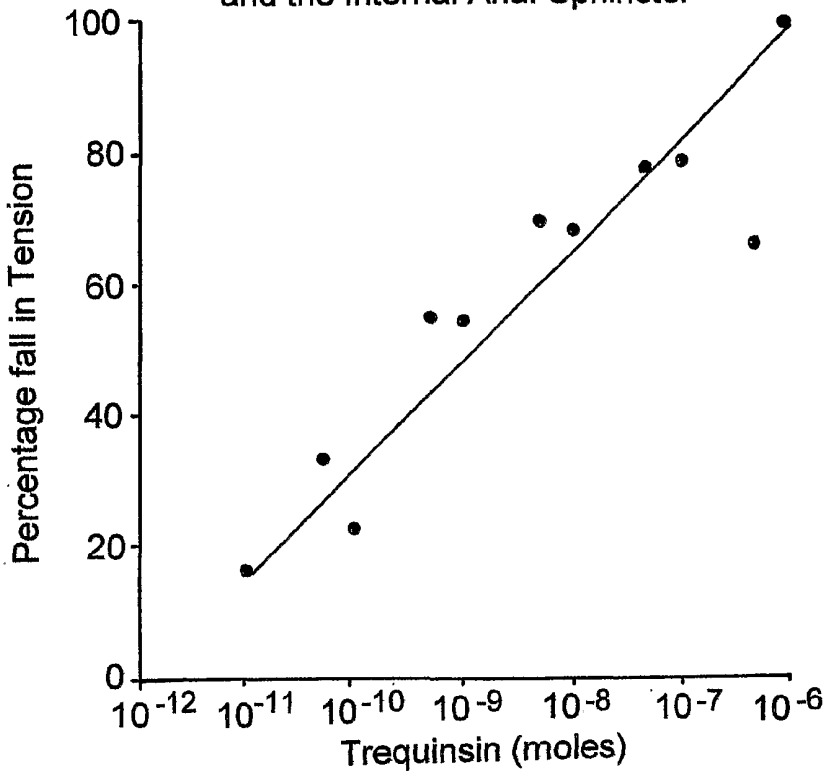

Dose Response Curve for Trequinsin and the Internal Anal Sphincter
Percentage fall in Tension
100
80
60
40
20
0
10-12
10-11
10-10
10-9
10-8
10-7
10-6
Trequinsin (moles)

Fig.4

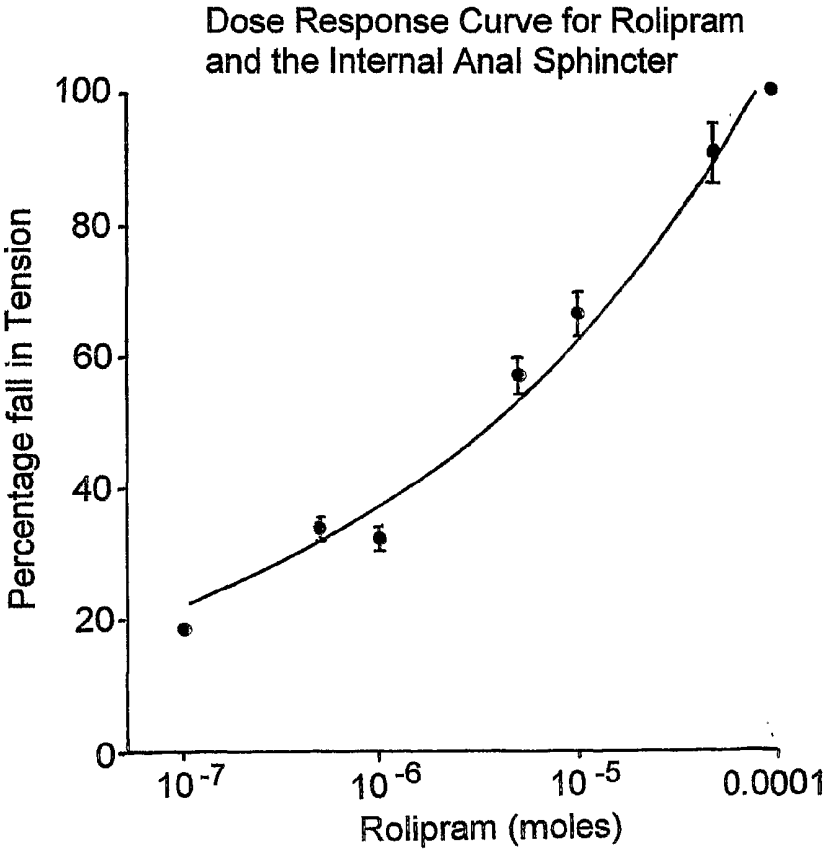

Dose Response Curve for Rolipram and the Internal Anal Sphincter
Percentage fall in Tension
100
80
60
40
20
0
10-7
10-6
10-5
0.0001
Rolipram (moles)

Fig.5

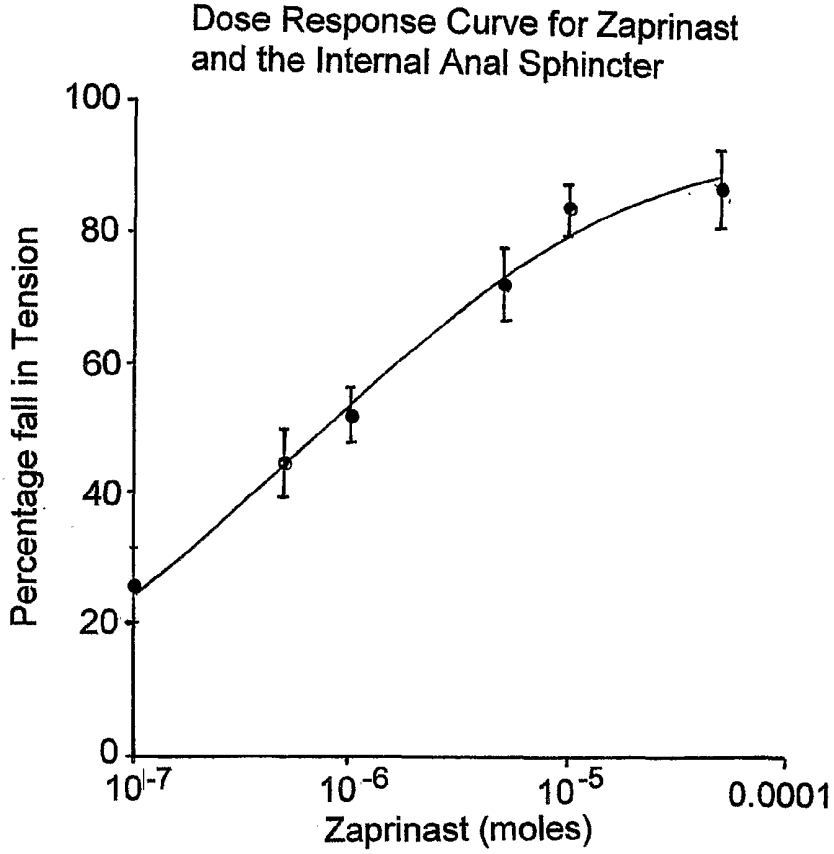
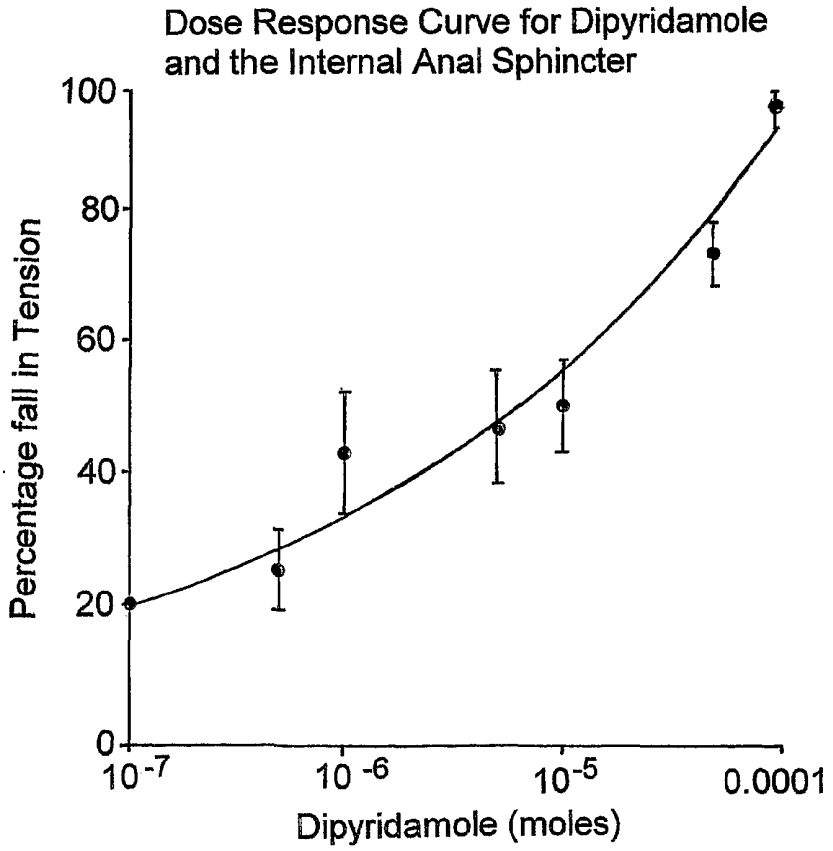

Dose Response Curve for Zaprinast and the Internal Anal Sphincter
Percentage fall in Tension
100
80
60
40
20
0
10-7
10-6
10-5
0.0001
Zaprinast (moles)

Fig.6


Dose Response Curve for Dipyridamole and the Internal Anal Sphincter
Percentage fall in Tension
100
80
60
40
20
0
10-7
10-6
10-5
0.0001
Dipyridamole (moles)

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/505 A61K31/52 A61K31/522 A61K31/4015 A61K31/519
A61P17/02 A61K31/00 A61P1/00 A61K31/4375 A61K45/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BIOSIS, MEDLINE, SCISEARCH, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 35434 A (CELLEGY PHARMA INC) 22 June 2000 (2000-06-22) abstract page 1, line 17 - line 27 page 4, line 8 - line 25 figure 4 page 8, line 29 -page 9, line 2 page 11, line 19 - line 28 page 12, line 11 - line 28 page 13, line 17 - line 23 page 15, line 3 -page 16, line 6 page 20, line 12 - line 15 page 21, line 25 - line 27 page 23, line 11 - line 20 page 26, line 5 - line 10 page 27, line 16 - line 22 page 28, line 3 -page 29, line 16 examples 4-6,8,9,11,12 claims 1,3,4,8-10,23,26,27 -/--	1-16

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 July 2001	20/07/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Cielen, E

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.

X	WO 00 24745 A (BUNNAGE MARK EDWARD ;MATHIAS JOHN PAUL (GB); STREET STEPHEN DEREK) 4 May 2000 (2000-05-04) abstract page 1, line 5 -page 2, line 3 page 38, line 18 -page 39, line 25 page 40, line 7 - line 21 page 41, line 21 - line 24 page 43, line 15 - line 20 claims 12-14	1,3, 8-11,16

X	WO 98 41232 A (BASF AG ;CARTER ADAM (US); SEKUT LES (US); GHAYUR TARIQ (US); TRAC) 24 September 1998 (1998-09-24) abstract page 2, line 11 - line 21 page 6, line 28 -page 7, line 2 page 69, line 30 - line 37 page 71, line 28 - line 37 page 74, line 28 -page 75, line 25 page 78, line 17 - line 22 page 80, line 22 - line 29 example 3 claims 1,6,8-10,17,19,23,43,46,52	1,2,7-9, 11,15,16

X	WO 98 19672 A (SAENZ DE TEJADA INIGO ;GARVEY DAVID S (US); NITROMED INC (US)) 14 May 1998 (1998-05-14) abstract page 4, paragraph 2 page 6, paragraph 1 - paragraph 3 page 7, paragraph 4 - paragraph 5 page 15, paragraph 6 page 55, paragraph 2 - paragraph 3 claims 1,24,7	1-3, 9-11,16

X	WO 00 42018 A (BYK GULDEN LOMBERG CHEM FAB ;GUTTERER BEATE (DE)) 20 July 2000 (2000-07-20) page 21, paragraph 1 - paragraph 2 page 22, paragraph 7 page 23, paragraph 4	1,11,16

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; IONESCU, MIOARA ET AL: "Formulation of antispastic and cicatrizant suppositories" retrieved from STN Database accession no. 121:263690 XP002170195 abstract & RO 103 863 B (INTREPRINDEREA DE MEDICAMENTE, ROM.) 2 December 1991 (1991-12-02) ---	1-3, 8-10,12, 16
X	DE 38 00 301 A (LEITZ RUDOLF) 20 July 1989 (1989-07-20) the whole document ---	1-3,8,9
X	US 4 486 436 A (SUNSHINE ABRAHAM ET AL) 4 December 1984 (1984-12-04) abstract column 1, line 21 - line 29 column 6, line 44 - line 55 column 7, line 1 - line 12 column 7, line 60 - line 65 column 9, line 10 - line 15 column 10, line 30 - line 33 column 11, line 12 - line 14 column 12, line 40 - line 50 column 15, line 62 - line 67 column 21, line 54 -column 23, line 64 claims ---	11,15
X	DATABASE WPI Week 200051 Derwent Publications Ltd., London, GB; AN 2000-557073 XP002170196 KOZYREV V.A.: "Method of nocturnal enuresis treatment" & RU 2 144 354 A (KOZYREV V.A.), 20 January 2000 (2000-01-20) abstract ---	11,15
X	WO 99 30697 A (WYLLIE MICHAEL GRANT ;PFIZER PROD INC (US)) 24 June 1999 (1999-06-24) abstract page 1, line 1 - line 7 page 1, line 27 - line 28 page 3, line 9 - line 23 page 4, line 1 - line 33 page 9, line 23 -page 12, line 12 page 14, line 14 - line 30 claims 1,2,4,7-9,31-39,81,82,84-89 --- -/--	11,13

INTERNATIONAL SEARCH REPORT

ıtional Application No
PCT/GB 00/03510

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 552 267 A (KOGA SHIN ET AL) 3 September 1996 (1996-09-03) abstract page 2, line 42 - line 49 column 10, line 11 - line 25 column 11, line 51 -column 12, line 47 claims 1,2,4,15-19	11,13,14
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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1, 3-16 relate to compounds which actually are not well-defined. The use of the definitions "a phosphodiesterase inhibitor", "a calcium channel blocking drug", "an adrenoceptor antagonist", "an agent which increases or stabilises the cGMP or cAMP level in cells or tissues of the subject", "an anti-inflammatory agent", "an analgesic", "wherein the phosphodiesterase inhibitor facilitates an effect on smooth muscle", "a class 5 phosphodiesterase" in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. The lack of clarity is such as to render a meaningful complete search impossible.
Moreover, claims 1-2, 4-10, 16 relate to a therapeutic application which actually is not well-defined. The use of the definitions "an anorectal condition" and "an anorectal disorder" in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. The lack of clarity is such as to render a meaningful complete search impossible.
Consequently, the search has been restricted to the phosphodiesterase inhibitors specifically mentioned in claim 2 and the diseases specifically mentioned in claim 3.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

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