PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 4 : A61K 47/00, 9/08, 9/16 A61K 9/20, 31/46, 31/47 A61K 31/245, 31/165	A1	(11) International Publication Number: WO 87/ 04077 (43) International Publication Date: 16 July 1987 (16.07.87)

(21) International Application Number: PCT/AU87/00003

(22) International Filing Date: 5 January 1987 (05.01.87)

(31) Priority Application Number: PH 4084

(32) Priority Date: 3 January 1986 (03.01.86)

(33) Priority Country: AU

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(81) Designated States: AT (European patent), AU, BE (European patent), BR, CH (European patent), DE (European patent), DK, FI, FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), NO, SE (European patent), US.

Published
With international search report.

(54) Title: GASTRO-OESOPHAGEAL REFLUX COMPOSITION

(57) Abstract

A pharmaceutical composition comprising a local anaesthetic adapted to inhibit relaxation of the lower oesophageal sphincter and a carrier therefor comprising a material adapted to float on gastrointestinal fluids contained in the stomach whereby to be more proximate to the gastric mucosa below said sphincter, than said fluids.

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GASTRO-OESOPHAGEAL REFLUX COMPOSITION

This invention relates to reflux.

In a particular aspect this invention relates to gastro-oesophageal reflux (commonly known as "heartburn").

In some humans, the lower oesophageal sphincter is prone to relaxing more frequently than in other humans. As a consequence gastrointestinal fluid can pass into the oesophagus at such times as the lower oesphageal sphincter is relaxed so causing the burning pain more commonly known as "heartburn".

Our research has shown that if a local anaesthetic is applied to gastric mucosa below the lower oesophageal sphincter the frequency of relaxation can be materially reduced.

However, a major delivery problem is to obtain contact of the local anaesthetic with the gastric mucosa below the lower oesophageal sphincter.

In this last respect, methods of delivery in which a local anaesthetic is dissolved or otherwise at least substantially uniformly distributed in gastrointestinal fluids have not been satisfactory as unacceptably high dosages of local anaesthetic would be necessary.

The present invention provides a pharmaceutical composition comprising a local anaesthetic adapted to inhibit relaxation of the lower oesophageal sphincter and a carrier therefor comprising a material adapted to float on gastrointestinal fluids contained in the stomach whereby to be more proximate to the gastric mucosa below said sphincter, than said fluids. Said carrier preferably includes a foam or a material adapted to form a foam in the presence of gastrointestinal fluids.

Said carrier may include a material adapted to form a foam cell wall and a blowing agent.

Suitable materials for forming foam cell walls include alginic acid and alginates and surface active agents.

Suitable blowing agents include those capable of being decomposed by gastrointestinal fluids to produce carbon dioxide.

A suitable carrier is Gaviscon produced by Reckitt &

Coleman. This carrier is described in U.S. Patent No. 4,140,760 and the whole of the subject matter thereof is incorporated hereto.

Said carrier may alternatively comprise a mucilage and a low density liquid adapted together to form a mucilage gel in the human stomach.

Another carrier is described in GB Patent Specification No. 2,008,408 and the whole of the subject matter thereof is incorporated hereinto.

Said carrier may be in the form of a liquid or solid.

The local anaesthetic may be any suitable anaesthetic but amongst them cocaine, oxethazine and benzocaine appear to be most effective. Suitable other alternatives include amethocaine, cinchocaine and lignocaine.

The present invention will be further illustrated by the following Example and the following Tests and Discussion.

Example 1

40 mgm of oxethazine was blended with 2,000 mgm Gaviscon and tabletted to form a dosage unit.

Gaviscon is a proprietary material produced by Reckitt & Coleman and containing $NaHCO_3$, $Al(OH)_3$, $Mg_2Si_3O_8$ and alginic acid. In gastrointestinal fluids the $NaHCO_3$ is decomposed to produce CO_2 which with the alginic acid or an alginate formed therefrom produces a foam which floats the mixture on top of gastrointestinal fluids.

Example 2

100 mgm of cocaine was blended with 2,000 mgm Gaviscon and tabletted to form a dosage unit.

Example 3

Granules were prepared from a mixture containing in proportions by weight:-

1,000 alginic acid
50 magnesium trisilicate
200 aluminium hydroxide
380 sodium bicarbonate
40 oxethazine
3,000 sucrose

Example 4

Tablets were prepared from a mixture containing in proportions by weight:-

500 alginic acid
25 aluminium hydroxide
170 sodium bicarbonate
10 cocaine
640 sucrose

Example 5

A liquid composition was prepared and contained in proportions by weight:-

1,000 sodium alginate
320 calcium carbonate
530 sodium bicarbonate
500 water

Test 1

In humans and dogs most episodes of gastro-oesophageal reflux of gas and liquid occur as a result of distinctive, transient lower oesophageal sphincter relaxations (TLOSRs) which last from 3-35 seconds. In studies in 4 trained unsedated dogs we have examined the hypothesis that upper gastric sensory receptors trigger TLOSRs. A manometric sleeve side hole catheter, passed via a cervical oesophagostamy, monitored oesophageal motor function. The rates of occurrence of TLOSRs stimulated by gastric insufflation or air, 80ml/min, were determined initially for 1 hour and then for a second hour after treatment of a 5cm ring of gastric mucosa around the oesophageal opening with either 20ml water or 20ml of 1% cocaine solution, sprayed per-endoscopically via a gastric cannulum.

The cocaine treatment described above was associated with significant ($F=3.41$, $p<0.05$) reduction of TLOSR rate (see Table)

TABLE

TIME	1st Hour	2nd Hour	1st Hour	2nd Hour
TREATMENT	Cocaine	Water	Water	Water
TLOSR RATE	8.6	3.5	6.8	7.0

There was no detectable effect on TLOSR rate from application of cocaine 1%, either to the lowermost 5cm of oesophageal mucosa (5ml) or to a 1cm ring of gastric mucosa around the oesophageal opening (0.8-5 ml). Cocainization of the oesophageal mucosa did however block primary and secondary peristalsis of the distal oesophagus.

The inhibition of TLOSR rate by topical cocaine is more consistent with blockade of mucosal or deeper gastric sensory receptors than a central nervous action. This inhibition supports the concept that TLOSRs are triggered by gastric sensory receptors.

Discussion

The traditional concept is that gastro-oesophageal reflux occurs across a feeble lower oesophageal sphincter because of pressure differentials between stomach and oesophagus. Until 1976 it was not possible to achieve prolonged measurement of lower oesophageal sphincter pressure except in animals sedated by general anaethesia because of continual movement of the lower oesophageal sphincter, and consequently continual movement of side holes in relation to the point of maximal pressure in that sphincter; general anaethesia itself abolishes TLOSRs. This problem was successfully overcome by development of the sleeve sensor device (Dent 1976) which is now commonly termed the Dent sleeve. By use of this sleeve it was subsequently demonstrated that the majority of gastro-oesophageal reflux episodes in man occurred after periods of complete transient lower oesophageal sphincter relaxation

(TLOSRs). Such relaxations occurred most often without any prior pharyngeal or oesophageal body motor event, and were distinct from the normal swallow-induced LOS relaxation (Dent et al. 1980). The relaxation had an abrupt onset and usually lasted from 5 to 35 seconds. That time pattern was thought to be suggestive of a neural mediation. Subsequent to those initial studies on normal man (Dodds et al., 1982), demonstrated that the most common mechanism of gastro-oesophageal reflux in patients with peptic oesophagitis was also the TLOSR.

Other studies on TLOSRs in man have added to the understanding of this important phenomenon. Gastric gaseous distension has been shown to be a potent trigger of TLOSRs in normal subjects. Venting of gas from the stomach occurs only during TLOSRs and these appear to be under control of mechanisms which sense gastric distension. This phenomenon is suppressed by change from the erect to the supine posture - possibly indicating that there is overriding control of TLOSRs from higher centres, acting to limit acid reflux in the supine position, where venting of gas is likely to result in concomitant acid reflux due to the close proximity of acid to the LOS in that position. These data have confirmed that TLOSRs in man are at least in part triggered by gastric distension. It is relevant to the pursuit of the study of TLOSRs that gastric distension as occurs postprandially is a well-known and potent trigger of reflux in patients with pathological gastro-oesophageal reflux.

On the basis of the observations summarised above, it appears that the TLOSR is a normal physiological response which allows venting of the stomach. It follows therefore, that pathological gastro-oesophageal reflux results from defective control of this lower oesophageal sphincter response. The following hypotheses have been constructed by us about normal control of TLOSRs:-

1. Gastric stretch receptors are an important trigger of TLOSRs and afferent fibres from these receptors travel up the vagus to the hind brain, or possibly by local intra-

mural pathways to the lower oesophageal sphincter;

2. Signals from afferent fibres are integrated either in the CNS or in the myenteric plexus and lead to stimulation of non-cholinergic, non-adrenergic neural elements which inhibit the lower oesophageal sphincter;

3. TLOSRs are suppressed by inputs from other sensory receptors (eg. gastric mucosal and receptors which sense posture).

The concepts of triggering and control of TLOSRs contained in the hypotheses stated above suggest the possibility of new approaches to the management of pathological gastro-oesophageal reflux. Current surgical methods for treatment of gastro-oesophageal reflux depend on fashioning of a mechanical substitute for the lower oesophageal sphincter, an approach which has significant morbidity and failure rate, particularly in the hands of surgeons who perform anti-reflux surgery infrequently. Definition of sensory and motor neural pathways that produce TLOSRs may allow adjustment of the threshold for the production of relaxations by selective nerve sectioning, an approach which may prove more durable, less morbid and technically simpler than current anti-reflux operations. Identification of the pharmacological mechanisms responsible for TLOSRs would allow a specification of the type of pharmacological agent which would need to be developed to treat disordered gastro-oesophageal incompetence effectively.

Ethical constraints make it impossible to pursue rigorously in man the hypotheses stated above. Accordingly, we worked on establishing a method to identify and subsequently characterise TLOSRs in animals. Because TLOSRs do not occur during stable sleep in man, nor during anaesthesia in animals, we chose to study the unsedated trained dog. Oesophageal motor function was studied with manometric methods based on those used for the initial studies of TLOSRs in man (Dent et al. 1980; Dodds et al.1982). A manometric sleeve catheter assembly, passed via a Komarov cervical oesophagostomy, monitored gastric, lower oesophageal sphincter, and oesophageal body pressures.

A separate catheter was passed orad into the pharynx to monitor swallowing. A miniature glass pH electrode was positioned 5cm. above the lower oesophageal sphincter. Thus equipped, it proved possible to monitor motility and occurrence of reflux episodes for several hours, during fasting and after food. These studies have demonstrated that gastro-oesophageal reflux occurs during TLOSRs in dogs as well as in man. As with man the reflux producing LOS relaxation in the dog was usually unrelated to swallowing.

Spontaneous gastro-oesophageal episodes and TLOSRs occurred infrequently in our dogs (less than 1/hour). In order to study the mechanisms and control of TLOSRs, it was necessary to devise a stimulus which would trigger these relaxations at a higher frequency. Experience in man suggested that gastric gaseous distension would be effective for this purpose in dogs. This has proved to be the case. Continuous gastric insufflation with air at a rate of 80 ml./min. resulted in stimulation of 10.3 TLOSRs/hour. These TLOSRs were associated with audible belching and were identical to those associated with gastro-oesophageal reflux.

Using this model, we have examined the question of whether TLOSRs are mediated via vagal nerve fibres or by local intra-mural nerve pathways. For that purpose, trained dogs were prepared with cervical vago-sympathetic trunks isolated in bridges of cervical skin, so that reversible vago-sympathetic blockade could be produced by cooling. Blockade was confirmed by the development of tachycardia greater than 150/minute, slow deep respiration, failure of oesophageal peristalsis in response to swallowing and bilateral Horner's syndrome. In a series of experiments oesophageal manometry was performed for 30 minutes before, followed by 30 minutes during and then 30 minutes after vagal blockade. In all four dogs studied, complete vagal blockade during gastric insufflation abolished without exception TLOSRs and belching, despite reduction of lower oesophageal sphincter pressure from 18.5 $\pm$ 5.9 mmHg, to 9.3 $\pm$ 6.0 mmHg (S.E.). Within one to four

minutes of cessation of cooling, TLOSRs and belching returned. Administration of two doses of atropine (50 and 200 microgram/kg. iv) did not block TLOSRs or gas reflux. We interpreted these findings as follows:-

1. TLOSRs are produced by neural pathways;
2. Either sensory and/or motor pathways that trigger TLOSRs travel within the vagus;
3. TLOSRs produced by gastric distension are not triggered by local intra-mural fibres that pass directly from the stomach to the lower oesophageal sphincter;
4. Muscarinic mechanisms are not primarily involved in the mediation of TLOSRs. The results of these initial studies have recently been published (Martin et al, 1986).

On the basis of these experiments we proposed as a working model that TLOSRs triggered by gaseous distension arose from mechanoreceptors situated in the fundus of the stomach, travelled up afferent pathways which were probably vagal, were integrated in the hind brain, and then returned down vagal inhibitory non-cholinergic and non-adrenergic pathways to produce lower oesophageal sphincter relaxation.

We have sought to study the sensory arm of this arc. We have performed selective nerve division studies of the fundus of the stomach, and we have attempted to inhibit the occurrence of transient lower oesophageal sphincter relaxations pharmacologically. Of particular relevance are our pharmacological studies. We have demonstrated in the dog that transient lower oesophageal sphincter relaxations produced by gastric insufflation are inhibited by topical application of local anaesthetic to the fundic mucosa.

Amongst the agents that have been tested so far are cocaine, lignocaine bupivicaine, benzocaine and oxethazaine. We were unable to demonstrate significant reductions of TLOSRs by topical application of lignocaine or bupivicaine to upper gastric mucosa. We therefore examined the effect of topical benzocaine which because of its low pKa (3.5) might be expected to be better absorbed across the gastric mucosa, a lipid membrane. An effect of similar magnitude to that observed with cocaine was recorded, however, the

concentrations of benzocaine required to produce this effect were high, thereby limiting the pharmacological usefulness of this agent in humans. Some special properties of the local anaesthetic agent oxethazaine made it particularly useful in the acidic gastric environment. As a weak base it is relatively unionized in acid solution giving it the same theoretical advantageous adsorbtive properties of benzocaine. Furthermore the high fat solubility of the derivative oxethazaine HCl make penetrations of lipid membranes of the gastric mucosa and the myelin sheaths of gastric nerves by the salt derivative likely.

In paired studies suing 100 mg of oxethazaine sprayed onto the upper 5 cm area of gastric mucosa, just distal to the lower oesophageal sphincter we found that by comparison with control that oxethazaine reduced the incidence of TLOSRs produced by gastric insufflation in 4 of 5 dogs. Increase of the dose applied to 400 mg, inhibited the TLOSR response in all 4 dogs tested. In further studies in 7 dogs in which 40 mg of oxethazaine was incorporated into 20 ml of liquid gaviscon and then mixed with canned meat, a 35% reduction in gastro-oesophageal venting of gastric contents was observed in the 2 hour postprandial period.

Accordingly, using a pharmaceutical carrier which will result in a local anaesthetic being brought to being specifically proximate to the fundic mucosa will have significant effect in reducing TLOSRs.

The claims defining the invention are as follows:

1. A pharmaceutical composition comprising a local anaesthetic adapted to inhibit relaxation of the lower oesophageal sphincter and a carrier therefor comprising a material adapted to float on gastrointestinal fluids contained in the stomach whereby to be more proximate to the gastric mucosa below said sphincter, than said fluids.

2. A pharmaceutical composition as claimed in claim 1, wherein said carrier includes a foam or a material adapted to form a foam in the presence of gastrointestinal fluids.

3. A pharmaceutical composition as claimed in claim 2, wherein said carrier includes a material adapted to form a foam cell wall and a blowing agent.

4. A pharmaceutical composition as claimed in claim 3, wherein said material adapted to form a foam cell wall is selected from alginic acid and alginates.

5. A pharmaceutical composition as claimed in claim 3 or claim 4, wherein said blowing agent is one capable of being decomposed by gastrointestinal fluids to produce carbon dioxide.

6. A pharmaceutical composition as claimed in any preceding claim, wherein the local anaesthetic is selected from cocaine, oxethazine, benzocaine, amethocaine, cinchocaine and lignocaine.

7. A pharmaceutical composition as claimed in any preceding claim, wherein the carrier is Gaviscon.

8. A pharmaceutical composition as claimed in any preceding claim, wherein the local anaesthetic is present in said composition in an amount of 1 - 10% by weight.

9. A pharmaceutical composition substantially as hereinbefore described with reference to any one of the Examples.

10. The articles, things, parts, elements, steps, features, methods, processes, compounds and compositions referred to or indicated in the specification and/or claims of the application individually or collectively, and any and all combinations of any two or more of such.

INTERNATIONAL SEARCH REPORT

International Application No PCT/AU 87/00003

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int. Cl.[4] A61K 47/00, 9/08, 9/16, 9/20, 31/46, 31/47, 31/245, 31/165

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC	A61K 47/00, 9/08, 9/20, 9/16
US Cl.	514/53

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

AU : IPC as above; Australian Classification 87.16

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	US,A, 3944660 (GOTTFRIED) 16 March 1976 (16.03.76)	
X	US,A, 4172120 (TODD et al) 23 October 1979 (23.10.79)	
P,X	JOURNAL OF CONTROLLED RELEASE Volume 3(No's 2-3) pages 167-175 1986, Elsevier Science Publishers, Amsterdam, The Netherlands "In Vitro Evaluation of Alginate Gel Systems as Sustained Release Drug Delivery Systems" (Stockwell, A.F. et al)	
P,X	EP,A, 0188040 (ABBOTT LABORATORIES LIMITED) 23 July 1986 (23.07.86)	
X	GB,A, 2008408 (ROUSSEL LABORATORIES LIMITED) 6 June 1979 (06.06.79) See especially page 2 lines 65-69	
X	GB,B, 1355985 (PHARMA-CHEMIE BETEILIGUNGS GMBH) 12 June 1974 (12.06.74)	
A	US,A, 4140760 (WITHINGTON) 20 February 1979 (20.02.79)	
A	JP,A, 57-106611 (SANWA KAGAKU KENKYUSHO K.K.) 2 July 1982 (02.07.82) (JAPATIC English Language Abstract)	

Continued

* Special categories of cited documents: [10]

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

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"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

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
10 April 1987 (10.04.87)	23.4.87 (23 APRIL 1987)
International Searching Authority	**Signature of Authorized Officer**
Australian Patent Office	J.P. PULVIRENTI

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

P,A	JP,A, 61-30516 (NICHIBAN CO. LTD) 12 February 1986 (12.02.86) (JAPATIC English Language Abstract)	

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers....., because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim numbers....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON
INTERNATIONAL APPLICATION NO. PCT/AU 87/00003

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report	Patent Family Members		
US 3944660	AU 63126/73	BE 802700	CA 1006091
	DE 2360918	FR 2210399	GB 1390683
	HK 410/78	IL 42313	KE 2853
	NL 7317238	ZA 7302438	
US 4172120	AU 33969/78	BE 864726	CA 1087986
	CH 647949	DE 2810250	FR 2382893
	GB 1566609	JP 53113007	NL 7802588
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GB 2008408	AU 41815/78	DE 2850791	FR 2409759
	NL 7811542	SE 7811798	ZA 7806132
GB 1355985	BE 447728	CH 580965	DE 2062715
	FR 2118492	IT 979653	NL 7115390
US 4140760	AU 28306/77	BE 858003	CA 1083964
	CY 1131	DE 2738014	FR 2369843
	GB 1524740	HK 596/81	JP 53059016
	KE 3175	NL 7709307	NZ 184931
	ZA 7704920		

END OF ANNEX