



THE REPUBLIC OF CYPRUS

Department of Registrar of Companies and Official Receiver

**ΚΥΠΡΙΑΚΟ ΓΡΑΦΕΙΟ ΔΙΠΛΩΜΑΤΩΝ
ΕΥΡΕΣΙΤΕΧΝΙΑΣ
THE PATENT OFFICE OF CYPRUS**

**ΑΡΙΘΜΟΣ ΔΗΜΟΣΙΕΥΣΗΣ
PUBLICATION NUMBER**

CY1457

ΑΡΙΘΜΟΣ ΔΗΜΟΣΙΕΥΣΗΣ
ΓΡΑΦΕΙΟΥ ΔΙΠΛΩΜΑΤΩΝ ΕΥΡΕΣΙΤΕΧΝΙΑΣ
ΗΝΩΜΕΝΟΥ ΒΑΣΙΛΕΙΟΥ
UK PATENT OFFICE
PUBLICATION NUMBER

GB2087234

Το έγγραφο που παρουσιάζεται πιο κάτω καταχωρήθηκε στο «Γραφείο Διπλωμάτων Ευρεσιτεχνίας» στην Αγγλία σύμφωνα με το Νόμο Κεφ. 266 πριν την 1^η Απριλίου 1998. Δημοσίευση έγινε μετέπειτα από το Γραφείο Διπλωμάτων Ευρεσιτεχνίας του Ηνωμένου Βασιλείου μόνο στην Αγγλική γλώσσα.

**The document provided hereafter was filed at "The Patent Office"
in England under the law CAP.266 before the 1st of April 1998.
It was published afterwards by the UK patent office only in English.**

(12) UK Patent Application (19) GB (11) 2 087 234 A

- (21) Application No **8133811**
(22) Date of filing **10 Nov 1981**
(30) Priority data
(31) **8391/80**
(32) **12 Nov 1980**
(33) **Switzerland (CH)**
(43) Application published
26 May 1982
(51) **INT CL³**
A61L 15/03
A61K 31/46
(52) Domestic classification
A5B 170 180 190 272 273
275 27Y 296 29Y 316 317
31X 31Y 380 385 38Y 392
393 39X 421 422 426 42Y
430 431 43Y 441 442 443
444 44Y 451 452 45X 45Y
482 483 48Y 501 503 50Y
541 542 54Y 550 551 55Y
565 566 56Y 575 576 57Y
586 58Y 595 596 59Y 616
61Y 641 644 64X 64Y 654
65Y 832 835 836 837 839 H
M N
(56) Documents cited
GB 1577259
GB 1511121
US 4262003A
US 4060084A
US 4031894A
US 3797494A
US 3598122A
US 2598123A
DE OS 2604718
The Extra
Pharmacopoeia,
Martindale, 27th
Edition Page 231, Re
Belladonna Root
(58) Field of search
A5B
(71) Applicants
Alza Corporation,
Palo Alto,
California 94304,
USA
(72) Inventors
Peter Bieck,
John William Fara,
Jane Elizabeth Shaw,
John Urquhart.
(74) Agents
Thomas Sharman,
Ciba-Geigy (UK) Limited,
Patent Dept.,
Tenax Road,
Trafford Park,
Manchester,
M17 1WT.

(54) **Anticholinergic drugs/
transdermal skin plasters**

(57) Anticholinergic drugs in the form of parenteral therapeutic systems which release these drugs continuously are used for the treatment of hyperacidity and peptic ulcers. The anticholinergic drug may be utropine, homatropine, scopolamine, benztropine, etybenztropine, oxyphenyclimine, glycopyrrolate, poldine, propantheline, isopropamide or clidinium. The therapeutic system is preferably a transdermal skin patch/plaster. Antacids and/or H₂-receptor-antagonists, e.g. cimetidine, ranitidine, metiamide, burimamide, tiotidine, metal salts, pepstatine, PGE₂ or 16,16-dimethyl PGE₂ can also be administered orally or the H₂-receptor-antagonists can be administered in combinations with the anticholinergic drugs.

GB 2 087 234 A

SPECIFICATION

Use of anticholinergic drugs

- 5 The present invention relates to the use of anticholinergic drugs in the form of parenteral useable therapeutic systems which release these drugs continuously for the treatment of hyperacidity and peptic ulcers. 5
- It is known that anticholinergic drugs can be administered orally to treat hyperacidity and peptic ulcer conditions. In the newest edition of the textbook "The Pharmacological Basis of Therapeutics" by L.S. Goodman and A. Gilman (MacMillan Publ. Co. Inc., New York, 1980, 6th ed.), it is said that antimuscarinic 10 drugs of the atropine or scopolamine type that block at cholinergic receptors influence gastric secretion. It is pointed out, however, that only relatively large doses are effective. According to this current teaching, daily doses bordering on the subtoxic limit are necessary to inhibit gastric secretion. For example, when using scopolamine, doses of 1 mg and more are necessary to inhibit gastric secretion in humans. Such large 15 doses, however, almost always cause serious side effects, e.g. dry mouth, impaired vision, photophobia, tachycardia and difficulty in urination and urinary retention. In *Gastroenterology* 68, 154-166 (1975), K.J. Ivey comes to the same conclusion after a study of 400 publications on the use of anticholinergic drugs for treating peptic ulcers. The side effects are so intolerable that many patients are unable to endure the treatment over a prolonged period of time. 15
- 20 Investigations made by M. Feldman et al [N. Engl. J. Med 297, 1427-1430 (1977)] cast doubt on the view generally held up to now that gastric secretion can only be inhibited by administering very large doses of a parasympatholytic drug. These authors have found that a small dose (15 mg) of propantheline inhibits gastric secretion induced by intake of food in patients suffering from duodenal ulcer to the same extent as a subtoxic dose of 48 mg. It has also been found that this smaller dose of propantheline, administered in 25 combination with an H₂-receptor antagonist, e.g. cimetidine, inhibited acid secretion to a greater degree than did both drugs singly. Owing to the uncertain efficacy even in relatively large doses, this concept has not found widespread use in general. 20
- Surprisingly, it has now been found that the use of anticholinergic drugs in the form of parenteral useable therapeutic systems which release said drugs continuously, effectively inhibit gastric secretion while 30 reducing or totally eliminating unwelcome side effects. Suitable therapeutic systems which make possible a continuous release can be transdermal or intradermal, subcutaneous or intramuscular. 30
- The invention relates in particular to the use of anticholinergic drugs in the form of transdermal therapeutic systems, in the presence or absence of acid inhibiting medicaments, e.g. antacids and/or H₂-receptor antagonist, for inhibiting gastric secretion.
- 35 More particularly, the invention relates to the use of anticholinergic drugs of the atropine type in the form of transdermal therapeutic systems, in the presence or absence of acid inhibiting medicaments, e.g. antacids and/or H₂-receptor antagonists, for inhibiting gastric secretion. 35
- Very particularly, the invention relates to the use of scopolamine as anticholinergic drug in the form of a transdermal therapeutic system, in the presence or absence of antacids and/or H₂-receptor antagonists, for 40 inhibiting gastric secretion. 40
- Most particularly, the invention relates to the use of scopolamine base as anticholinergic drug in the form of a transdermal therapeutic system for inhibiting gastric secretion.
- Anticholinergic drugs, which are also termed parasympatholytic, antimuscarinic or cholinolytic drugs, belong to the class of neutropic or atropine-type spasmolytic drugs.
- 45 Anticholinergic drugs which are used, inter alia, for inhibiting gastric secretion using a therapeutic system which releases the drug continuously, are described by G. Erhardt and H. Ruschig, *Arzneimittel*, Vol 2, pp 75-79 (1972). However, particularly important drugs for inhibiting gastric secretion using a therapeutic 50 system for releasing medication continuously, are those of the atropine type, e.g. atropine, homatropine, scopolamine, benzatropine and etybenzatropine and the therapeutically useful salts thereof. 50
- 50 anticholinergic drugs of special importance which can be used are, e.g. oxyphencyclimine, glycopyrrolate, poldine, propantheline, isopropamide, and clidinium and the therapeutically useful salts thereof.
- The antacids and/or H₂-receptor-antagonists can be administered orally, or the H₂-receptor-antagonists can be administered in combination with the anticholinergic drugs.
- As H₂-receptor antagonists there may be used drugs which strongly inhibit histamine-induced gastric 55 secretion. Examples of suitable H₂-receptor antagonists are ranitidine, metiamide, burimamide, tiotidine and, in particular, cimetidine, and the therapeutically useful salts thereof. 55
- Suitable antacids which can be administered are e.g. the preparations described by B. and H.H. Helwig in "Moderne Arzneimittel", 5th edition, pp. 656-665, 1980. In particular, it is possible to use metal salts, e.g. alkali metal salts, alkaline earth metal salts and also salts of metals of Group III of the Periodic Table.
- 60 Examples of especially suitable salts are carbonates or bicarbonates of sodium, calcium or magnesium, or also aluminium silicate. Other complex double silicates which produce an aluminium hydroxide film by hydrolysis, e.g. sodium aluminium silicates, can also be used. As further gastric acid inhibiting agents pepstatine, and cytoprotective agents including various prostaglandins, such as PGE₂, and 16,16-dimethyl PGE₂ may be used. 60
- 65 The above mentioned parenteral useable therapeutic systems which can be used e.g. transdermally or 65

intradermally, subcutaneously or intramuscularly, release continuously a drug at a certain rate and over a specific period of time. These therapeutic systems can also be employed in the practice of this invention for the continuous release of mixtures of drugs.

The transdermal therapeutic systems control the release of drug on the surface of intact skin. The rate of release is substantially below the maximum adsorption capacity of the skin. The drug diffuses through the epidermis and enters the circulation via the capillaries.

Intradermal systems are applied directly beneath the epidermis and subcutaneous systems beneath the dermis, e.g. as implantate in accordance with US patent No. 3 625 214, and they release the drug, controlled by biodegradation, continuously into the circulation.

Systems employing biodegradable polymers which control a continuous release of drug, for example as described in Belgian patent No. 837 935, can also be applied intramuscularly.

Preferably, however, therapeutic systems are used which are able to release continuously the drug transdermally.

Depending on the utility of the different suitable anticholinergic drugs, there may be employed as transdermal therapeutic systems, e.g. those described in US patents Nos. 3 598 122, 2 598 123, 3 797 494 and 4 060 084, but preferably the transdermal therapeutic system described in German Offenlegungsschrift No 2 604 718 or U.S. Patents Nos. 4 031 894 and 4 262 003. However, the utility of this invention is not restricted to the transdermal therapeutic systems disclosed in these publications. The system described in German Offenlegungsschrift No 2 604 718 or U.S. Patent 4,031,894 is a therapeutic drug delivery system in the form of plaster-type substrate which release an anticholinergic drug, e.g. scopolamine base, in the presence or absence of an H_2 -receptor antagonist, transdermally, firstly at an initial rate of 10 to 200 $\mu\text{g}/\text{cm}^2$ of skin, and thereby rapidly brings the concentration of drug in the plasma to a value at which it inhibits gastric secretion without the unpleasant side effects referred to previously, and then in an amount of 0.3 to 15 $\mu\text{g}/\text{hr}$, such that the content of drug in the plasma is kept approximately constant. In most instances the pulse will be in the range of 50 to 150 μg of an anticholinergic, e.g. scopolamine per cm^2 of skin of being treated.

The concentration of scopolamine in the plasma can be related to the concentration of free scopolamine in the urine if the glomerular filtration rate of the subject is known, and it is convenient to express the quantity of scopolamine in the plasma in terms of a urinary excretion rate. An average urinary excretion rate of about 0.5 μg free scopolamine per hr was found to generally correspond to a therapeutic plasma level. However, it was also found that this rate is subject to about a ± 5 fold biological variation. Therefore, the rate ranges between about 0.1 to 2.5 μg per hr depending on the individual.

The purpose of the substantially constant rate administration portion of the method is to supplement, if necessary, the pulse administration in delivering enough anticholinergic to reach the above-mentioned therapeutic level and to hold the level for as long as is necessary. It follows that the constant rate administration portion will proceed for as long as therapy is required. In this regard a total (including the pulse) of 0.1 to 2.5 mg anticholinergic administered in accordance with the above-described dosage program will provide a therapeutic effect for about 3 hours to 7 days. It also follows that the level of constant rate administration may vary depending on the body weight (plasma volume) of the patient. In this regard, in most instances the rate will be in the range of 1 to 15 μg per hr for adults and 0.5 to 15 μg per hr for children (measured as the steady rate of drug administration, i.e., after the initial 2 hr pulse administration).

The substrate can consist of a multi-layered laminate comprising the following four layers when viewed from above:

- a) a protective backing,
- b) a gel-like drug reservoir consisting of a mixture of mineral oil and polyisobutene and which is the source of the constant drug release,
- c) a semipermeable membrane which partly controls the constant rate of release, and
- d) a gel-like adhesive layer containing the drug in a mixture of mineral oil and polyisobutene and acting as the source of the initial dose, and also comprising adhesive materials with which the substrate is affixed to the skin.

For the covering layer a) it is preferred to use a laminate of polymer sheeting and a metal sheeting, e.g. aluminium foil. Exemplary polymers which may be used for this layer are polyethylene of high and low density, polypropylene, polyvinyl chloride and polyethylene terephthalate.

The scopolamine base contained in the drug reservoir b) is homogeneously dispersed - partly dissolved and partly undissolved - in the gel-like mixture of mineral oil having a viscosity of about 10 to 100 cP at 25°C and a polyisobutene. These mixtures of mineral oil and polyisobutene are excellent adhesives and serve in addition to hold the plaster-type substrate together. The mineral oil is used e.g. as carrier for the scopolamine base, which has limited solubility in the mineral oil (c. 2 mg/hl). The relative amounts in the reservoir are chosen such that the mineral oil is substantially saturated with the base during the entire release period of the substrate.

The next layer of the laminate is a semipermeable (microporous) layer c), the pores of which are filled with the mineral oil described above, which layer controls the rate at which the scopolamine base is released to the skin. The rate of flow of scopolamine through the semipermeable layer and the area covered by the membrane must be chosen such that the scopolamine is delivered to the skin from the reservoir layer substantially at a constant rate in the range from 0.3 to 15 $\mu\text{g}/\text{hr}$, after the transdermal therapeutic system has been applied to the skin. The semipermeable membrane is made of polymeric materials through which the

drug is able to penetrate by diffusion. Exemplary polymers which can be used for such membranes are polypropylene, polycarbonates, polyvinyl chloride, cellulose acetate, cellulose nitrate, polyacrylonitrile and organopolysiloxane rubber.

The adhesive layer d) of the laminate is composed substantially of the same constituents as the layer b) above, and it also contains the scopolamine base as drug and is responsible for the initial large dose at the commencement of treatment with the system. The plaster-type substrate is affixed to the skin with the aid of the strongly adhesive layer d) after the removable protective layer has been removed immediately before application.

The parenteral useable therapeutic systems described in this invention and which effect continuous release of anticholinergic drugs in the presence or absence of antacids and/or H₂-receptor antagonist, can be employed for inhibiting gastric secretion in acute gastritis or for treating peptic ulcers in the stomach or duodenum without the occurrence of unpleasant parasymphathological side effects, e.g. dry mouth, impaired vision, photophobia, tachycardia and difficulty in urination and urinary retention.

For gastric acid inhibiting purposes and especially anti-ulcer therapy comprising administering orally a H₂-receptor antagonist, the dosage unit will contain from about 25 mg to 250 mg of the drug. Generally, the dosage form containing the antagonists will be administered orally from one to six times a day, and the daily dosage will be from about 25 mg to 1500 mg of the H₂-receptor antagonists. For therapeutic use, the dosage form comprising a PGE₂ will contain about 0.1 mg to 3 mg of prostaglandin, and the daily dose generally will be from about 0.1 mg to 10 mg administered 1 to 3 times a day. For antacids, the dosage form will contain from about 25 mg to 500 mg of an antacid administered orally from 1 to 6 times a day. A representative dosage form for a H₂-receptor antagonist comprises 150 mg of cimetidine and 100 mg of lactose filled into a hard gelatine capsule, for a prostaglandin 1 mg of PGE₂, 27 mg of sucrose, 25 mg of starch, 5 mg of talc and 2 mg of magnesium stearate compressed into a tablet, and for an antacid 300 mg of aluminium magnesium antacid and 15 mg of magnesium stearate compressed into a tablet.

When used in conjunction with transdermal administration, the dosage may gradually be decreased as the patient responds to the transdermal administration of scopolamine. The transdermal dosages of scopolamine found useful are in the range of 0.05 to 25 µg/hr when used in conjunction with oral or parenteral administration of another anti-ulcer agent.

Bandages for the transdermal use are prepared as follows:

a) A solution of 29.2 parts molecular weight polyisobutene (sold under the designation Vistanex MML-100, 1,200,000 viscosity average molecular weight), 36.5 parts low molecular weight polyisobutene (sold under the designation Vistanex LM-MS, 35,000 viscosity average molecular weight), 58.4 parts mineral oil (10 cp at 25°C), 15.7 parts scopolamine base and 860.2 parts chloroform is solvent cast onto an approximately 64 micron thick backing film of aluminized polyethylene terephthalate (sold under the designation MEDPAR) to form a scopolamine base reservoir layer approximately 50 microns thick. A contact adhesive layer-strippable coating combination is similarly prepared by solvent casting onto a 200 micron thick siliconized, aluminized, polyethylene-backed polyethylene terephthalate film a solution of 31.8 parts of said high molecular weight polyisobutene, 39.8 parts of said low molecular weight polyisobutene, 63.6 parts of said mineral oil, 4.6 parts of scopolamine base and 860.2 parts chloroform. The resulting contact adhesive layer is approximately 50 microns thick.

The above-described backing-reservoir layer combination is then laminated to one face of a 25 micron thick microporous polypropylene membrane (sold under the designation Celgard 2400) saturated with said mineral oil and the above-described contact adhesive layer-strippable coating combination is laminated to the opposite face of the membrane. One cm² circular, disc-shaped bandages are punch cut from the resulting 5-layer laminate. Each bandage is designed to release an initial 150 µg/cm² pulse of scopolamine followed by an essentially constant dosage of 3 to 3.5 µg/cm²/hr.

b) A solution of 22.3 parts of the high molecular weight polyisobutene described in Example 1, 28.0 parts of the low molecular weight polyisobutene described in Example 1, 44.9 parts mineral oil (66 cp at 25°C), 12.8 parts scopolamine base, 8.8 parts dimethyl lauramide and 883.2 parts of chloroform is solvent cast onto the backing film described in a) to form a scopolamine base reservoir layer approximately 50 microns thick. A contact adhesive layer-strippable coating combination is similarly prepared by solvent casting onto the siliconized polyethylene terephthalate film described in a) a solution of 23.5 parts of said high molecular weight polyisobutene, 29.5 parts of said low molecular weight polyisobutene, 47.6 parts mineral oil (66 cp at 25°C), 7.8 parts scopolamine base, 9.0 parts dimethyl lauramide and 882.6 parts chloroform. The resulting contact layer is approximately 50 microns thick.

The above described backing-reservoir layer combination is then laminated to one face of a 25 micron thick microporous polypropylene membrane (sold under the designation Celgard 2400) adhesive layer-strippable coating combination is laminated to the opposite face of the membrane. Four cm² circular, disc-shaped bandages are punch cut from the resulting 5-layer laminate. Each bandage is designed to release an initial 125 µg/cm² pulse of scopolamine followed by an essentially constant dosage of 2 µg/cm²/hr.

c) Bandages were made according to the procedure of a) except that: the strippable coating was 127 microns thick siliconized polyethylene terephthalate film and the bandages were each 2.5 cm² in area. *In vitro* tests of these bandages showed they released an initial pulse of approximately 200 µg in the first two hours of use and an average of approximately 10 µg/hr thereafter through 72 hrs.

The invention is illustrated in more detail by the following nonlimitative Example, in which parts are by

weight unless otherwise stated.

Example 1: Young, healthy test persons are given a physical examination and tested for somatic condition, haematology, blood chemistry and urine. In order not to falsify the results of the examination, the test persons may not taken any other medication for one week before and during the period of the examination. The normal manner of living may not be altered during the study and excesses of any kind are avoided. A transdermal therapeutic system as described herein under a) b) and c) above and in the description part for the delivery of scopolamine is applied behind the ear to 8 healthy volunteer test persons over a period of 48 hours. Before the start of the assay, and on the 2nd and 4th day of the actual study, the acid secretion (HCl and volume) is measured basally by the method of Lindenschmid et al., Zschr. Gastroenterologie 17, 820-826 (1979).

The gastric secretion is collected at 10 minute intervals by continuous suction. The amount of hydrochloric acid secreted is determined by titration of a 5 ml sample against 0.1N aqueous sodium hydroxide.

Side effects on the test persons are entered daily on a 100 mm scale. Blood pressure, pulse, and diameter of the pupil are entered on day 0, 2 and 4 of the study.

The following table shows that acid secretion decreases substantially using scopolamine in the form of a transdermal therapeutic system.

TABLE I

Action of scopolamine in the form of a transdermal therapeutic system on basal gastric secretion

time period of study	HCl (mval/l) $\bar{x} \pm s$	test-versus ¹⁾ prevalue
before TTS-scopolamine use	53 $\pm$ 13	
on day 2 during TTS-scopolamine use	31 $\pm$ 15	**
2 days after TTS-scopolamine use	22 $\pm$ 20	*

1) paired t-test; n = 8 test persons

* = p < 0.05

** = p < 0.01

Example 2: Bandages were fastened to the post-auricular skin of five adult male duodenal ulcer patients ranging in age from 21 to 40 years after removing the strippable coating layer. A study was conducted over a period of 48 hours using placebo and scopolamine containing bandages on alternate nights. The placebo bandage was the same as the scopolamine-containing bandage except that it contained no scopolamine.

At mid-day before each study commenced the left post-auricular area was cleaned and either a placebo or a scopolamine bandage was applied to the skin. One hour later a standard meal was eaten. Four hours later the patients were intubated with a sump tube and one hour after that another standard meal was consumed. From then until the next morning no food, only water, was taken. Five hours after the last meal the stomach contents were aspirated and discarded. Gastric secretion was collected hourly by pump suction for the next nine hours.

Five ml aliquots of each hourly collection were used for measurement of pH and titration with 0.1 N sodium hydroxide to pH 7.00 using an automatic titrator. pH electrodes were calibrated between each determination with standard buffers.

Results after testing for two consecutive nights were expressed in terms of mean hourly acid output in millimoles per hour and mean hourly hydrogen ion concentration in millimoles per liter. Wilcoxon's signed rank test and students' t-test for paired samples were used for statistical analysis.

The mean hourly acid output was found to decrease from a mean of 6.8 $\pm$ 1.8 mmol/hr on the placebo night to 1.7 $\pm$ 0.4 mmol/hr when the scopolamine-containing bandage was used. The results were statistically significant (p 0.001).

The hydrogen ion concentration was unaffected (79.1 $\pm$ 6.4 mmol/l on placebo; 68.2 $\pm$ 3.5 mmol/l on scopolamine-containing bandage).

Four of the patients had a dry mouth after overnight scopolamine administration. One of the patients had a dry mouth soon after application of the scopolamine-containing bandage to the skin. There were no other reported side effects.

Example 3: Scopolamine may be used according to this invention to supplement conventional peptic ulcer therapy employing histamine H₂-receptor antagonists, cytoprotective agents and traditional neutralizing

antacids, for example. Bandages according to a), b) or c) may be used in conjunction with other anti-peptic ulcer treatments by applying such bandage each day to the mastoidal area of a patient suffering from peptic ulcer while administering the conventional peptic ulcer therapy as shown in Table II.

5		TABLE II	5
	<i>Drug</i>	<i>Dosage</i>	
10	<i>Histamine H₂ Receptor</i>		10
	<i>Antagonist</i>		
15	Cimetidine	1 g per day with meals for 6 weeks followed by reduction to 400 mg per day for maintenance	15
	<i>Cyto-protective Agent</i>		
20	PGE ₂	3 mg PGE ₂ 3 times a day with meals reduced to 2 mg, 3 times per day with meals after 1 week for maintenance	20
25	<i>Antacids</i>		25
	Al-Mg Salts	250 mg 3 times a day with meals followed by 100 mg 3 times a day with meals after 1 week for maintenance	30

Example 4: A transdermal therapeutic system bandage (TTS) designed to release scopolamine at a constant rate of 4 µg/cm²/hr and deliver 0.5 mg of scopolamine at a steady rate over 3 days was worn by the subjects of this example in the post-auricular area. Overnight acid output was measured during two consecutive nights in 6 male duodenal ulcer patients in remission (age range 21-40, average age 31.2 years) admitted to a special ward for 48 hr. At mid-day before each study the left post-auricular area was cleaned and placebo (first study), or scopolamine-loaded (second study) TTS applied to the skin. At 17.00 hr the subjects were incubated with 10 G Salen Sump tube (Argyle Medical). Standard meals were eaten by the subjects on both study days at 13.00 and 18.00 hr. with only water allowed thereafter. Stomach contents were aspirated and discarded at 23.00 hr and gastric secretion was then collected in hourly samples until 08.00 hr by pump suction, aided when required by syringe aspirin. 5 ml aliquots of each hourly collection were used for measurement of pH and titration with 0.1 N NaOH to pH 7.000, using an automatic titrator (Radiometer, Copenhagen). pH electrodes were calibrated between each determination with standard buffers.

All subjects were questioned about unwanted effects on each morning. Results were expressed in terms of mean hourly acid output in mmol h⁻¹ and in mean hourly hydrogen ion [H⁺] concentrations in mmol l⁻¹. Wilcoxon's signed rank test and student's t-test for paired samples were used for statistical analysis.

50 Results

Placebo TTS gastric aspirates were technically unsatisfactory in one subject and he was excluded from analysis. In the remaining five patients the mean hourly (23.00-08.00 hr) acid output decreased from a mean of 6.8 ± SEM 1.8 mmol hr⁻¹ on the placebo night to 1.7 ± 0.4 mmol hr⁻¹ when scopolamine filled TTS was used. This 75 percent inhibition of acid secretion was significant (p 0.001). All the subjects responded to scopolamine administered via the TTS. The [H⁺] concentration was unaffected (79.1 ± 6.4 mmol l⁻¹ on placebo, 68.2 ± 3.5 mmol l⁻¹ on scopolamine). Some patients do not respond to H₂ blockade and one of the patients in this study was a cimetidine non-responder. His overnight acid output was decreased by 88 percent with TTS-scopolamine. While acid output decreased, the pH was unaffected so that gastric bacterial colonisation should not be a problem. Gastric juice collections were remarkable by the absence of mucus, in contrast to the appearance of gastric juice collected during H₂-histamine blockade. Cholinergic agents stimulate mucus secretion in the human alimentary tract, so that this observation should be further evaluated if TTS-scopolamine is used for prolonged periods.

The results of this study indicate that transdermal delivery of scopolamine at the rate of 5 µg hr⁻¹ using the TTS significantly inhibits nocturnal acid secretion in patients with DU. The TTS-scopolamine delivered the drug at a steady rate over 72 hr.

Various modifications of the above-described methods will be apparent to persons skilled in the medical, chemical and/or pharmaceutical arts and may be made without departing from the scope of the invention which is limited only the by following claims wherein:

5 CLAIMS

5

1. Use of an anticholinergic drug in the form of a parenteral useable therapeutic system which releases said drug continuously for inhibiting gastric secretion.
2. Use according to claim 1, wherein the anticholinergic drug is used in the form of a therapeutic system
10 which can be applied transdermally or intradermally, subcutaneously or intramuscularly, which system releases the drug continuously, in the presence or absence of an antacid or H₂-receptor antagonist, for inhibiting gastric secretion. 10
3. Use according to claim 1, wherein an anticholinergic drug is used in the form of a transdermal therapeutic system which releases said drug continuously, in the presence or absence of an antacid and/or
15 H₂-receptor antagonist, for inhibiting gastric secretion. 15
4. Use according to claim 1, wherein an anticholinergic drug of the atropine type is used in the form of a transdermal therapeutic system which releases said drug continuously, in the presence or absence of an antacid and/or H₂-receptor antagonist, for inhibiting gastric secretion.
5. Use according to claim 1, wherein scopolamine is used as anticholinergic drug in the form of a
20 transdermal therapeutic system which releases scopolamine continuously, in the presence or absence of an antacid and/or H₂-receptor antagonist, for inhibiting gastric secretion. 20
6. Use according to claim 1, wherein scopolamine is used as anticholinergic drug in the form of a transdermal therapeutic system which releases scopolamine continuously for inhibiting gastric secretion.
7. Use according to claim 1, wherein scopolamine is used as anticholinergic drug in form of a
25 transdermal therapeutic system, which releases scopolamine continuously in an amount of 0.3 to 15 µg/hr for inhibiting gastric secretion. 25
8. Use according to claim 1, wherein scopolamine is used as anticholinergic drug in the form of a transdermal therapeutic system, which releases scopolamine in an initial pulse, of 10 to 200 µg/cm² of skin and thereafter continuously in an amount of 0.3 to 15 µg/hr for inhibiting gastric secretion.
9. A method of treating hyperacidity and peptic ulcers by inhibiting gastric secretion, which method
30 comprises administering an anticholinergic drug in the form of a therapeutic system which can be applied transdermally or intradermally, subcutaneously or intramuscularly and which releases said drug continuously, in the presence or absence of an antacid and/or H₂-receptor blocker. 30
10. A method according to claim 9 for treating hyperacidity and peptic ulcers by inhibiting gastric
35 secretion, which method comprises administering an anticholinergic drug in the form of a transdermal therapeutic system which releases said drug continuously, in the presence or absence of an antacid and/or H₂-receptor blocker. 35
11. A method according to either of claims 9 or 10 for treating hyperacidity and peptic ulcers by inhibiting gastric secretion, which method comprises administering scopolamine as anticholinergic drug in the form of
40 a transdermal therapeutic system which releases scopolamine continuously, in the presence of an antacid and/or H₂-receptor blocker. 40
12. A method according to any one of claim 9 to 10 for treating hyperacidity and peptic ulcers by inhibiting gastric secretion, which method comprises administering scopolamine as anticholinergic drug in the form of a transdermal therapeutic system which releases scopolamine continuously.
13. A method according to any one of claims 9 to 12 for treating hyperacidity and peptic ulcers by
45 inhibiting gastric secretion, which method comprises administering scopolamine as anticholinergic drug in the form of a transdermal therapeutic system which releases scopolamine continuously in an amount of 0.3 to 15 µg/hr. 45
14. A transdermal therapeutic system which continuously releases an anticholinergic drug for inhibiting
50 gastric secretion. 50
15. A transdermal therapeutic system as claimed in claim 14 wherein the anticholinergic drug is scopolamine.
16. A transdermal therapeutic system as claimed in claim 14 or 15 which also contains an antacid or H₂-receptor antagonist.