Abstract: Buspirone is useful in the treatment of a condition which is nausea, vomiting, retching or any combination thereof, in a human patient, when administered by a route which avoids first-pass metabolism.
THE TREATMENT OF NAUSEA AND VOMITING

Field of Invention

This invention relates to the treatment of nausea and vomiting.

Background of the Invention

Emesis is the act of vomiting and can be described as the forceful expulsion of gastrointestinal contents through the mouth brought about by the descent of the diaphragm and powerful contractions of the abdominal muscles. Emesis is usually, but not always, preceded by nausea. Retching or dry heaves involves the same physiological mechanisms as vomiting, but occurs against a closed glottis. Vomiting, nausea, retching or combinations thereof ("the symptoms") can be caused by a number of factors including but not limited to anaesthetics, certain types of surgery, radiation, cancer chemotherapeutic agents, toxic agents, medicines, for example serotonin reuptake inhibitors, analgesics such as morphine, antibiotics, pregnancy and motion. Conditions which are associated with vertigo, for example Meunier's disease, can also cause the symptoms. Headache, caused by for example migraine, increased intracranial pressure or cerebral vascular hemorrhage, can also result in the symptoms. Other maladies associated with the symptoms include cholecystitis, choledocholithiasis, intestinal obstruction, acute gastroenteritis, perforated viscus, dyspepsia resulting from, from example, gastroesophageal reflux disease, peptic ulcer disease, gastroparesis, gastric or oesophageal neoplasms, infiltrative gastric disorders (e.g. Menetrier’s syndrome, Crohn's disease, eosinophilic gastroenteritis, sarcoidosis and amyloidosis), gastric infections, parasites, chronic gastric volvulus, chronic intestinal ischaemia, altered gastric motility disorders and/or food intolerance or Zollinger-Ellson syndrome. In some cases of the symptoms, no etiology can be determined, as for example in Cyclic Vomiting Syndrome.

The symptoms may be defined as acute when they are present for less than a week. The causes of the symptoms of short duration can be separable from etiologies leading to more chronic symptoms. The symptoms may be defined as chronic when they are present for over a week; these can be continuous or intermittent and last for months or years.

Two areas of particular clinical relevance are nausea and vomiting resulting from the administration of general anaesthetics and/or surgery (post-operative nausea and vomiting, or PONV) or chemotherapeutic agents and
radiation therapy (chemotherapy-induced nausea and vomiting, or CINV). The symptoms caused by chemotherapeutic agents can be so severe that the patient refuses further treatment. Three types of emesis are associated with the use of chemotherapeutic agents. These are acute emesis, delayed emesis and anticipatory emesis. PONV is also an important problem. Despite the advances in surgical techniques and improved anaesthetic agents, one out of 3 patients still experiences PONV. Such conditions lead to patient dissatisfaction and lengthen hospital stays and prolong recovery. Children are twice as likely as adults to develop PONV. Factors have been considered which identify children at highest risk; these are where surgical procedures last more than 30 minutes, when children are 3 years of age or older, where there is a history of motion sickness or postoperative nausea and vomiting. Prolonged surgical operations, or those that use nitrous oxide as an agent of general anaesthesia, increase risk, as does the use of opioids to control pain after surgery. Women are more susceptible than men to certain emotogenic stimuli including motion, chemotherapy, inhalational anaesthetics and opioids, and are three times more likely to develop PONV than men. Types of surgery can be considered as risk factors, for example lengthy gynaecological surgery.

There are more than 35 million surgical procedures performed each year in the USA. More than 70% of all surgeries in the USA are performed as day cases, and the persistence of nausea and vomiting symptoms beyond discharge after surgery poses a great challenge to patients and their physicians.

There are a number of groups of agents that are used or have been considered for use clinically in the treatment of emesis. These include antihistamines, phenothiazines, metoclopramide, domperidone, 5-HT3 antagonists, dexamethasone, aprepitant and nabilone. See for example, Drugs used in nausea and vertigo, section 4.6 pages 210-217 British National Formulary edition 50 (September 2005); this reference is incorporated herein in its entirety. The entry on postoperative nausea and vomiting (p 211) states "The incidence of postoperative nausea and vomiting depends on many factors including the anaesthetic used, the type and duration of surgery and the patient's sex. The aim is to prevent postoperative nausea and vomiting from occurring. Drugs used include some phenothiazines (e.g. prochlorperazine), metoclopramide (but 10 mg dose has limited efficacy and higher parenteral doses associated with greater side effects), 5-HT3 antagonists, antihistamines
(such as cyclizine), and dexamethasone. A combination of two anti-emetic
drugs acting at different sites may be needed in resistant postoperative nausea
and vomiting. Droperidol has also been used to treat PONV but has recently
been linked to blockade of cardiac HERG channels.

Buspirone is a drug which has beneficial actions in anxious patients. It is
administered orally for this purpose. The drug has a high affinity for serotonin
receptors of the 5-HT1A type; it is a partial agonist of these receptors (see
Goodman & Gilman's The Pharmacological Basis of Therapeutics 11th edition
Eds Brunton, Lazo and Parker, Published by McGraw-Hill Medical Publishing
Division including New York and London 2006, Section XII/ Dermatology,
Chapter 17/Drug therapy of depression and anxiety disorders Pharmacotherapy
of anxiety pp 452-453); this reference is incorporated herein in its entirety. It is
known that buspirone when given orally undergoes extensive first-pass
metabolism such that oral bioavailability in man is 4-5%.

A major metabolite of buspirone, i.e. 1-(2-pyrimidinyl)-piperazine (1-PP),
is known to be pharmacologically active as an adrenergic alpha 2 antagonist.
The human plasma levels of 1-PP were approximately 4-fold higher than for
buspirone after a 20 mg oral dose and elimination of 1-PP is slower than for
buspirone (see Raghavan et al, 2005 Drug Metab. Disposition 33(2):203-208).

The oral dose of buspirone for the treatment of anxiety as given in British
National Formulary (BNF, edition 50 September 2005 pp 180) is initially 5 mg 2-3
times per day, increased as necessary every 2-3 days, usual range 15-30 mg
daily in divided doses, maximum dose 45 mg/day. Pharmacokinetic data are
given for buspirone in Goodman & Gilman's The Pharmacological Basis of
Therapeutics 11th edition Eds Brunton, Lazo and Parker, Published by McGraw-
Hill Medical Publishing Division including New York and London 2006, Table A-
11-1 p 1803. The major side-effects for oral buspirone in man listed in the BNF
edition 50 include nausea, dizziness, lightheadedness and excitement.

Summary of the Invention

The invention relates to the use in man, when administered by routes
which avoid first-pass metabolism (thereby reducing systemic exposure to the 1-
PP metabolite) of buspirone for the treatment of nausea, vomiting, retching or
any combination thereof. When so administered, buspirone is unexpectedly
found to be effective against nausea, vomiting, retching or combinations thereof
in man and in particular against PONV.
Description of the Invention

The buspirone may be in the form of a salt, hydrate or solvate. Salts include pharmaceutically acceptable salts, for example acid addition salts derived from inorganic or organic acids, such as hydrochlorides, hydrobromides, p-toluenesulphonates, phosphates, sulphates, perchlorates, acetates, trifluoroacetates, propionates, citrates, malonates, succinates, lactates, oxalates, tartrates and benzoates.

Salts may also be formed with bases. Such salts include salts derived from inorganic or organic bases, for example alkali metal salts such as magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.

For the purpose of the present invention, buspirone is preferably administered by the intravenous, transdermal or rectal routes. In addition, the subcutaneous, inhalation, sublingual, buccal and nasal routes of administration may be employed, where passage of parent drug to the stomach (where appropriate) is limited.

A pharmaceutical composition containing the active ingredient may be in any suitable form, for example aqueous or non-aqueous solutions or suspensions, dispersible powders or granules, transdermal or transmucosal patches, creams, ointments or emulsions.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or non-aqueous (e.g. oleaginous) solution or suspension. The sterile injectable preparation may also be in a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, phosphate buffer solution, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed, including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables. Suspensions may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned elsewhere.

Aqueous suspensions contain the active ingredient in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose,
methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as a naturally occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such a polyoxyethylene with partial esters derived from fatty acids and hexitol anhydrides, for example polyoxyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl or n-propyl p-hydroxybenzoate, one or more colouring agents, one or more flavouring agents, and one or more sweetening agents, such as sucrose or saccharin.

Non-aqueous (i.e. oily) suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are known.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally occurring gums, for example gum acacia or gum tragacanth, naturally occurring phosphatides, for example soya bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate.

The active agent may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary
temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical delivery, transdermal and transmucosal patches, creams, ointments, jellies, solutions or suspensions may be employed. For purposes of this specification, topical application includes mouth washes and gargles.

For sub-lingual delivery, fast dissolving tablet formulations may be used, as well as a number of the presentations described above.

It may be advantageous to co-administer buspirone with other classes of drug which can add additional benefits of efficacy and/or, by titrating dosages downwards, result in fewer side-effects. These include, but are not limited to, 5-HT3 antagonists including granisetron, ondansetron, palonosetron, dolasetron, tropisetron, phenothiazines including prochlorperazine, perphenazine and trifluoperazine, other antipsychotics including haloperidol and levomepromazine, metoclopramide, domperidone, dexamethasone, aprepitant and other neurokinin-1 receptor antagonists, nabilone, droperidol and certain other drugs including tricyclic anti-depressants and noradrenaline reuptake inhibitors.

It may also be advantageous to co-administer buspirone with drugs which are associated with emesis in man, for examples certain opioids including morphine. Buspirone, at an appropriate concentration determined by one of skill, can be formulated with the drug in question, for example morphine, in a dosing system such as an infusion bag or other appropriate dosage form.

The dose of buspirone will depend upon the route of administration, the age and condition of the patient and other factors known to those skilled in the art. A typical dosage, e.g. for intravenous administration, is from 0.1 to 100 mg, preferably 0.5 to 30 mg, more preferably 1.0 to 20 mg. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular condition undergoing therapy.

The following Study provides evidence on which the invention is based. The evidence involves assessment of antiemetic activity in ferrets.

**Study**

The method used to test antiemetic activity follows that described by

Sixty minutes before administration of the test substance, ferrets were placed in individual stainless steel cages (40 x 50 x 34 cm) with a grid floor. Then, the animals were challenged with apomorphine (0.25 mg/kg s.c.) or morphine (0.4 mg/kg i.p.), and immediately observed over a 2-hour period. Parameters recorded included: number of ferrets showing retches and vomits; latency to first retching; latency to first vomiting; number of retches; vomiting (number of vomits); number of emesis periods and mean duration of emesis periods.

Retching is defined as a rhythmic respiratory movement against a closed glottis, while vomiting is defined as a forced expulsion of upper gastrointestinal contents.

Where apomorphine was used as the emetogen, buspirone (or vehicle) was administered subcutaneously (s.c. 30 minutes before administration of apomorphine. Animals (6 per group) were treated with vehicle or buspirone at 0.1 mg/kg, 0.5 mg/kg or 2.5 mg/kg given s.c. For these experiments, domperidone at 0.1 mg/kg s.c. was used as a comparison substance.

Where morphine was used as the emetogen, buspirone (n=6 per group) or vehicle (n=12) was administered 30 minutes before administration of morphine. Animals were treated with vehicle or buspirone at 0.5 mg/kg, 2.5 mg/kg, 7.5 mg/kg or 12.5 mg/kg given s.c. For these experiments, droperidol given at 3 mg/kg s.c. was used as a comparison substance.

Apomorphine in the vehicle control group induced emesis in all ferrets over the 2 hour observation period (36.0 ± 8.1 retches, 2.8 ± 0.9 vomits, 6.8 ± 1.4 emesis periods). Retches and vomits occurred 248 ± 82 and 437 ± 116 seconds after administration respectively. Buspirone dose-dependently decreased the emetic effects induced by apomorphine as compared with the vehicle control group. The numbers of emesis periods for buspirone at 0.1, 0.5 and 2.5 mg/kg were 2.8 ± 1.2 ('), 1.7 ± 1.1 ('') and 0.0 ± 0.0 ('''') versus 6.8 ± 1.4 in the vehicle control group (' p<0.05: '' p<0.01 versus control group). From these data an effective dose (ED50, dose causing 50% inhibition of emesis periods) was calculated by extrapolation; this was 0.04 mg/kg. No animals had
emesis when treated with the dopamine D2 antagonist domperidone.

Morphine in the vehicle control group induced emesis in all ferrets over the 2 hour observation period (45.8 ± 9.3 retches, 2.2 ± 0.62 vomits and 9.1 ± 1.9 emesis periods). Retches and vomits occurred 247.5 ± 32 and 343.6 ± 52 seconds after administration respectively. Buspirone-dose dependently decreased the emetic effects induced by morphine as compared with the vehicle control group. The numbers of emesis periods for buspirone at 0.5, 2.5, 7.5 and 12.5 mg/kg were 8.5 ± 1.9, 6.5 ± 1.5, 2.7 ± 1.4 (') and 0 ± 0 ("') versus 9.1 ± 1.9 in the vehicle control group. The ED50 for buspirone against morphine emesis was calculated to be 5.6 mg/kg. The reference substance droperidol administered 30 minutes before morphine slightly decreased the emesis compared with the buspirone vehicle group with 7.0 ± 1.8 emesis periods (n=6).

In a further test using the same method, and sixty minutes before administration of the test compound which, in this case, was 1-(2-pyrimidyl)piperazine (1-PP), ferrets were placed in individual stainless steel cages (40 x 50 x 34 cm) with a grid floor. Then, the animals were then dosed orally with 1-PP and immediately observed over a 2-hour period. Parameters recorded included: number of ferrets showing retches and vomits; latency to first retching; latency to first vomiting; number of retches; vomiting (number of vomits); number of emesis periods and mean duration of emesis periods.

1-PP induced the occurrence of retches and vomits at 1 mg/kg, 3 mg/kg and 10 mg/kg in 1/5, 3/5 and 3/5 animals respectively. The corresponding emesis periods were 0.6±0.6, 3.0±1.8 and 4.4±3.0. The mean times to first retches and vomits were between 30 minutes and 1 hour after drug administration.

In conclusion, 1-PP administered orally in the ferret exhibited dose-dependent emetic properties, including retches and vomits over the 2 hour observation period.
CLAIMS

1. Buspirone for use in the treatment of a condition which is nausea, vomiting, retching or any combination thereof, in a human patient, wherein the medicament is to be administered by a route which avoids first-pass metabolism.

2. Buspirone according to claim 1, wherein the route is intravenous.

3. Buspirone according to claim 1, wherein the route is transdermal.

4. Buspirone according to claim 1, wherein the route is subcutaneous.

5. Buspirone according to claim 1, wherein the route is rectal.

6. Buspirone according to any preceding claim, wherein the condition is post-operative nausea and vomiting.

7. Buspirone according to any of claims 1 to 5, wherein the condition is chemotherapy or radioactivity-induced emesis.

8. Buspirone according to any preceding claim, wherein the patient is also undergoing treatment with an emetic drug such as morphine.

9. Buspirone according to any preceding claim, wherein the patient exhibits acute symptoms.

10. Buspirone according to any preceding claim, wherein the buspirone is in the form of an acceptable pharmaceutical salt.

11. Buspirone according to claim 10, wherein the salt is the hydrochloride salt.

12. Buspirone according to any preceding claim, used in combination with another anti-emetic drug.
13 (new), Buspirone according to claim 1, wherein the route is intravenous, rectal, subcutaneous, by inhalation, sublingual, buccal or nasal, and the dosage is from 0.1 to 100 mg buspirone.

14 (new). Buspirone according to claim 13, wherein the dosage is 0.5 to 30 mg.

15 (new). Buspirone according to claim 13, wherein the dosage is 1.0 to 20 mg.

1B (new). Buspirone according to any of claims 13 to 15, wherein the route is intravenous.

17 (new). Buspirone according to any of claims 13 to 15, wherein the route is subcutaneous.

18 (new). Buspirone according to any of claims 13 to 15, wherein the route is rectal.

19 (new). Buspirone according to any of claims 13 to 1S1 wherein the condition is post-operative nausea and vomiting.

20 (new). Buspirone according to any of claims 13 to 18, wherein the condition is chemotherapy or radioactivity-Induced emesis.

21 (new). Buspirone according to any of claims 13 to 20, wherein the patient is also undergoing treatment with an anti-emetic drug such as morphine.

22 (new). Buspirone according to any of claims 13 to 21, wherein the patient exhibits acute symptoms.

23 (new). Buspirone according to any of claims 13 to 22, wherein the buspirone is in the form of an acceptable pharmaceutical salt.

24 (new). Buspirone according to claim 23, wherein the salt is the hydrochloride salt.

25 (new). Buspirone according to any of claims 13 to 24, used in combination with another anti-emetic drug.
Statement under Article 19(1), PCT

Basis for the routes defined in new claim 13 may be found at page 4 lines 13-14, and basis for the dosage at page 6 line 25. Basis for new claims 14 and 15 may be found at page 6 line 26. New claims 10 to 25 correspond respectively to claims 2 and 4 to 12, but are presented in the context of new claim 13.

In a human patient (as defined in claim 1), a dosage of 100 mg (the maximum defined in new claim 13) is equivalent to little more than 1 mg/kg. It is surprising that such a low dose is effective. The fact that still lower doses, as defined in new claims 14 and 15, are effective, as evidenced in the specification, is yet more surprising.

The available evidence is that transdermal patches containing buspirone are largely ineffective. Accordingly, the utility via different routes, as defined in new claim 13, is surprising.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

| INV. | A61K31/506 | A61P1/08 |

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) | A61K | A61P |

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

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of ciled documents:

- **A** document defining the general state of the art which is not considered to be of particular relevance.
- **E1** earlier document but published on or after the international filing date.
- **L** document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another invention.
- **O** document referred to in an oral disclosure, use, exhibition or other means.
- **P** document published prior to the international filing date but later than the priority date claimed.
- **T** later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention.
- **X** document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone.
- **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**

9 September 2008

**Date of mailing of the international search report**

15/09/2008

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

Hornich-Paraf, E

Form POT/ISA/21.0 (second sheet) (April 2005)
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<td>GAMMANS R E ET AL: &quot;METABOLISM AND DISPOSITION OF BUSPIRONE&quot; AMERICAN JOURNAL OF MEDICINE, XX, XX, vol. 80, no. SUPPL. 03B, 31 March 1996 (1996-03-31), pages 41-51 XP002939962 ISSN: 0002-9343 abstract 'Plasma levels of buspirone and metabolites' page 43, left-hand column paragraph [0001]</td>
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### INTERNATIONAL SEARCH REPORT

**Information on patent family members**

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International application No
PCT/GB2008/001803

Form PCT/ISA/210 (patent family annex) (April 2005)