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(71) Applicant *(for all designated States except US)*: **ARAKIS LTD.** [GB/GB]; Chesterford Research Park, Little Chesterford, Saffron Walden, Essex CB10 1XL (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BANNISTER, Robin, Mark** [GB/GB]; Arakis Ltd., Chesterford Research Park, Little Chesterford, Saffron Walden, Essex CB10 1XL (GB). **ROTHAUL, Alan** [GB/GB]; Arakis Ltd., Chesterford Research Park, Little Chesterford, Saffron Walden, Essex CB10 1XL (GB).

(74) Agent: **GILL JENNINGS & EVERY**; Broadgate House, 7 Eldon Street, London EC2M 7LH (GB).

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(54) Title: THE USE OF PROGLUMIDE FOR THE TREATMENT OF EMESIS

(57) Abstract: Proglumide is useful for the treatment of a condition selected from nausea, dizziness, blurred vision and emesis. Such a condition may be druginduced.

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# THE USE OF PROGLUMIDE FOR THE TREATMENT OF EMESIS

## Field of the Invention

The present invention relates to the treatment of emesis.

## Background to the Invention

Nausea (the urge to vomit) and emesis (the act of forcibly ejecting the stomach contents through the oesophagus and out of the mouth) are common conditions. They can be caused by a number of factors, including medications, viral and bacterial infections, motion sickness, migraine headaches, food poisoning and allergies, chemotherapy, radiotherapy, bulimia, alcoholism, pyloric stenosis, intestinal obstruction, renal calculi, pancreatitis and pregnancy.

A number of studies have linked nausea and emesis to an increase of arginine vasopressin (AVP). These include animal studies on motion sickness (Kohl, J. Clin. Pharm. 1991), and studies in patients receiving chemotherapy (Barreca *et al*, Biomed. Pharmacotherap. 1996), a study in patients receiving the emetogen ipecacuanha (Page *et al*, Clinical Endocrinology 1990) and a study in human volunteers that had received a range of emetogenic insults including water loading, apomorphine and ethanol. In addition, a number of studies indicate that cholescystokinin (CCK) is a potent stimulus for the release of AVP (Calegro *et al*, Neuroendocrinology 1993, and Abelson, Neuropsychopharmacology 2001).

Proglumide, i.e. 4-(benzoylamino)-5-(dipropylamino)-5-oxopentanoic acid, is a cholecystokin antagonist which is licensed for the treatment of gastritis (stomach ulceration). However, it is no longer in widespread use as it has been superseded by $H_2$ antagonists and proton pump inhibitors. The pharmacology of proglumide is known as a mixed $CCK_A$ (gastrin) and $CCK_B$ antagonist and its anti-ulceration action is via the inhibition of the $CCK_A$ receptor.

## Summary of the Invention

The present invention is based on the discovery that proglumide possesses anti-nausea and antiemetic activity. This discovery makes it possible to treat nausea and emesis with a drug that is recognised as a less potent CCK antagonist, providing efficacy while minimising or avoiding side-effects commonly associated with the more potent and selective agents.

According to another aspect of the invention, a product comprises proglumide and a proemetic drug as a combined product for simultaneous, separate or sequential use in therapy associated with the intended use of the proemetic drug.

Description of the Invention

Proglumide has an asymmetrically substituted carbon atom. The presence of this asymmetric centre gives rise to stereoisomers, and the invention is to be understood to extend to all such stereoisomers, including enantiomers (R or S, substantially free of the other) and diastereoisomers, and mixtures including racemic mixtures thereof.

The active agent may be in free or salt form, or given as a prodrug or metabolite. Salts of compounds according to the invention 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 benzoate.

Proglumide is useful to treat emesis caused by the administration of another, proemetic drug. In one aspect of the invention, proglumide is used when emesis is observed. In another it is administered prophylactically, in combination with a proemetic drug. Thus, by way of example only, it may be combined with a dopamine agent such as apomorphine which is under development for the treatment of erectile dysfunction. It may also be combined with an opiate or an anti-depressant.

According to one aspect of the invention, the active agent is used in therapy, for the treatment (including prevention) of nausea, dizziness, blurred vision or emesis, including, but not limited to, acute, delayed, post-operative, last-phase and anticipatory emesis. This condition may be associated with (or caused by) various pain conditions such as dysmenorrhoea, migraine, cancer or pancreatitis. This condition may be induced by, for example, chemotherapy, radiation, toxins, pregnancy, alcohol withdrawal, nicotine withdrawal, drug withdrawal, vestibular disorder, motion, post-operative sickness, surgery,

gastrointestinal obstruction, reduced gastrointestinal motility, dysmenorrhoea, visceral pain, migraine, increased or decreased intracranial pressure, depression or opioid analgesics.

In addition, proglumide may be used to treat emesis caused by certain pro-emetic drugs such as antidepressants (examples including amitriptyline, imipramine, desipramine, venlafaxine, citalopram, trazadone, paroxetine, nefazodone, nefopam, fluoxetine and (S)-citalopram), anticonvulsants (examples including lamotrigine, gabapentin and carbamezepine), antipsychotics (examples including clozapine, chlorpromazine, fluphenazine, haloperidol and loxapine), anxiolytics (examples including buspirone and lorazepam), anti-Parkinson's agents (examples including apomorphine, pergolide, levodopa, dopamine, naxagolide, bromocriptine and amantadine), CNS stimulants (examples including dexamphetamine and methylphenidate), opioids (examples including morphine, fentanyl, buprenorphine, codeine, methadone, oxycodone, tramadol, phenacozine and diamorphine), anticancer agents (examples including cisplatin, aldesleukin, altretamine, carboplatin, carmustine, cyclophosphamide, cytarabine, decarbazine, dactinomycin, daunorubicin, docetaxel, doxorubicin, epirubicin, fluorouracil, idarubicin, ifosfamide, irotecan, lomustine, mechlorethamine, melphalan, methotrexate, mitoxantrone, pentostatin, procarbazine and streptozocin), and anti-HIV drugs (examples including amdoxovir, litomeglovir, tomeglovir, valacyclovir, acyclovir, buciclovir, desciclovir, rociclovir, penciclovir, valganciclovir, ganciclovir, famciclovir, detiviciclovir, tiviciclovir, valomaciclovir, omaciclovir, valaciclovir, aciclovir, tenofovir, cidofovir, adefovir, denotivir, amitivir, celgosivir, oseltamivir, peramivir, zanamivir, ritonavir, droxinavir, saquinavir, lasinavir, lopinavir, telinavir, palinavir, nelfinavir, indinavir, mozenavir, fosamprenavir, amprenavir, atazanavir, tipranavir, pirodavir, lobucavir, entecavir, abacavir, maribavir, edoxudine, epervudine, alovudine, zidovudine, fozivudine, netivudine, sorivudine, brivudine, lamivudine, clevudine, stavudine, azithromycin, clarithromycin, rifabutin, dapsone, foscarnet, fluconazole, delavirdine, efavirenz and nevirapine. Such a proemetic agent and progumide may be administered simultaneously, sequentially or separately, e.g. in combination.

The active agent may also be used according to the invention when the patient is also being given another anti-emetic agent. Such agents include phenothiazines, 5HT3 receptor antagonists, dopamine antagonists, anticholinergic agents, anti-histamines, histamine analogues, cannabinoids, corticosteroids, GABA receptor antagonists, NK1 receptor antagonists, $\alpha_2$ and $\alpha_3$ adrenoceptor antagonists, and SNRis. Specific examples of these types of compounds are cyclizine, dolasetron, granisetron, ondansetron, tropisetron, nabilone, scopolenine, cinnerizine, promethazine, betahistine, dexamethasome, methylprednisolone, metoclopramide, chlorpromazine, perphenazine, prochlorperazine, thiethylperazine, droperidol, domperidone and haloperidol. Such an agent and proglumide may be administered simultaneously, sequentially or separately, e.g. in combination.

For the treatment of nausea and vomiting conditions such as those given above, the active agent may be administered orally, topically, parenterally, by inhalation or nasal spray or rectally in dosage unit formulations containing non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The composition may be in controlled release form or have an enteric coating. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats etc, the compounds of the invention are effective in the treatment of humans.

The dose of the active agent will depend on the nature and degree of the condition, the age and condition of the patient, and other factors known to those skilled in the art. A typical dosage for a human patient is 1 to 200, e.g. 10 to 100, mg given one to three times per day.

A Study illustrating the invention will now be described. The Study investigated the anti-emetic effect of proglumide against cisplatin-induced emesis in piglets.

Study

Details of the animal preparation have been described previously (Grélot *et al.*, 1996 ; Grélot *et al.*, 1998 ; Girod *et al.*, 2002). The series of investigations

was performed on weaned purebred (Pietrain, Hampshire) or crossbred (Pietrain X Hampshire) piglets (40-70 days old), of either sex, weighing approximately 7-11 kg.

Animals were surgically prepared under ketamine (500 mg/kg) and isoflurane anaesthesia (i.e. 1 to 2.5 % in a mixture of oxygen and room air) with a catheter (Tygon S50-HL) implanted in the left jugular vein for subsequent administration of cisplatin. The catheter was tunnelled subcutaneously and fixed with screws and dental cement on the top of the head. To prevent the development of any infection, the surgery was conducted using aseptic techniques. In addition, all animals were treated just after the induction of anesthesia with a broad spectrum antibiotic (i.e. 20 mg/kg of oxytetracycline) and, after suturing, with an anti-inflammatory agent (betamethasone) with local effects. Piglets, isolated in individual boxes (0.7 $m^3$), were then allowed 3-4 days recovery before commencement of vomiting experiments, and were fed daily with 400-500 g of a solid commercial diet (9500 kJ/kg; Sofetac, Cenord) and water *ad libitum*.

The experimental procedures were carried out in accordance with European Council Directive 86/609/EEC. Every effort was made to minimize the animals' suffering and to reduce the number of animals used in the experiments. Piglets included in these experiments were naive to previous administration of cytotoxic, anti-emetic drugs and of any other emetic challenges. All animals were killed by administering an overdose of sodium pentobarbitone (Nembutal®, Sanofi, 60 mg/kg, i.v.) immediately after the end of the experiment.

The antineoplastic agent cisplatin (5.5 mg/kg in 25 ml saline, i.e. approximately 100-125 mg/$m^2$) was infused via the jugular cannula over approximatively 15 min at rate of 1.7 ml/min. The animals were then observed continuously throughout the following 4 hours to quantify the production of episodes of both nausea and vomiting. Episodes of vomiting are characterized by a series of retchings culminating in a bolus expulsion. The animals were treated with vehicle (NaCl 0.9%) or proglumide (0,3 , 3 or 30 mg/kg dissolved in NaCl 0.9%). Both treatments were administered 10 minutes before cisplatin treatment administered *per os*.

The protocol of drug administration, including the numbers of piglets given each treatment, are given in the following table.

| Groups | N | Cisplatin (mg/kg) | Proglumide in NaCl 0.9 %mg/kg, p.o. | NaCl 0.9% (vehicle) |
|---|---|---|---|---|
| 1 | 8 | 5.5 | 0 | Yes |
| 2 | 8 | 5.5 | 0.3 | No |
| 3 | 8 | 5.5 | 3 | No |
| 4 | 8 | 5.5 | 30 | No |

At 3 mg/kg, two criteria, i.e. latency to the first nausea-like and emetic episode, and the number of episodes, were advantageously affected by the administration of proglumide.

CLAIMS

1. Use of proglumide in the manufacture of a medicament for the treatment of a condition selected from nausea, dizziness, blurred vision and emesis.

2. Use according to claim 1, wherein the condition is nausea or emesis.

3. Use according to claim 1, wherein the condition is selected from acute, delayed, post-operative, late-phase and anticipatory emesis.

4. Use according to any preceding claim, wherein the condition is associated with pain.

5. Use according to claim 4, wherein the condition is associated with dysmenorrhoea, migraine, cancer or pancreatitis.

6. Use according to any preceding claim, wherein the condition is induced by one or more of radiation, toxins, pregnancy, alcohol withdrawal, nicotine withdrawal, drug withdrawal, vestibular disorder, motion, post-operative sickness, surgery, gastrointestinal obstruction, reduced gastrointestinal mobility, visceral pain or increased or decreased intracranial pressure.

7. Use according to any preceding claim, wherein the condition is drug-induced.

8. Use according to claim 7, wherein the condition is induced by chemotherapy.

9. Use according to claim 7, wherein the condition is induced by an opioid analgesic.

10. Use according to any preceding claim, wherein the patient is also administered another agent that has anti-emetic properties.

11. Use according to claim 10, wherein said another agent is selected from phenothiazines, 5HT3 receptor antagonists, dopamine antagonists, anticholinergic agents, anti-histamines, histamine analogues, cannabinoids, corticosteroids, GABA receptor antagonists, NK1 receptor antagonists, and $\alpha_2$ and $\alpha_3$ adrenoceptor antagonists.

12. Use according to claim 10, wherein said another agent is a SNRi (serotonin-noradrenaline-reuptake inhibitor).

13. Use according to claim 10, wherein said another agent is selected from cyclizine, dolasetron, granisetron, ondansetron, tropisetron, nabilone,

scopolenine, cinnerizine, promethazine, betahistine, dexamethasome, methylpredrisolone, metoclopramide, chlorpromazine, perphenazine, prochlorperazine, thiethylperazine, droperidol, domperidone and haloperidol.

14. Use according to any of claims 10 to 13, wherein the proglumide and said another agent are provided in combination.

15. A product comprising proglumide and a proemetic drug as a combined product for simultaneous, separate or sequential use in therapy associated with the intended use of the proemetic drug.

16. A product according to claim 15, wherein the proemetic drug is selected from antidepressants, anticonvulsants, antipsychotics, anxiolytics, anti-Parkinson's agents, CNS stimulants, opoids, anticancer agents and anti-HIV agents.

17. A product according to claim 15, wherein the proemetic drug is tramadol.

# INTERNATIONAL SEARCH REPORT

PCT/GB2004/003169

**A. CLASSIFICATION OF SUBJECT MATTER**
IPC 7 A61K31/195 A61P1/08 A61K31/137 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, BIOSIS, EMBASE, SCISEARCH, CHEM ABS Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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[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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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
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