Title: USE OF PROGLUMIDE AND TRAMADOL IN THE TREATMENT OF PAIN

Abstract: A product comprises proglumide and tramadol as a combined preparation for simultaneous, separate or sequential use in the treatment of a pain condition.
USE OF PROGLUMIDE AND TRAMADOL
IN THE TREATMENT OF PAIN

Field of the Invention

The present invention relates to the treatment of pain.

Background of the Invention

Patients suffering from chronic benign pain and/or painful neuropathic disorders are often treated with either low dose full agonist opioids or low potency opioids. However, from time to time, the pain breaks through the analgesia that these drugs provide; as increasing the dose of opioid is not seen as good practice, patients are often not receiving full analgesia.

Proglumide is a drug which is licensed for the treatment of gastritis (stomach ulceration). However, it is no longer in widespread use as it has been superseded by the newer H₂ antagonists and proton pump inhibitors. The pharmacology of proglumide is known as a mixed CCKₐ (gastrin) and CCKₐ antagonist and its anti-ulceration action is via the inhibition of the CCKₐ receptor. However, there is the largely unexploited inhibitory action at the CCKₐ receptor, known to be involved in the development of tolerance to morphine analgesia (Watkins et al, Science; 1984).

It is known that opiate tolerance develops rapidly over a number of days following chronic administration of the commonly used full agonist opiates such as morphine (Sawe et al, British Journal of Clinical Pharmacology; 1983). CCK is widely recognised as having a role in the regulation of nociception, neuropathic pain and opiate tolerance (Wiesenfeld-Hallin and Xu; Regulatory Peptides; 1996). Moreover, CCK involvement in the development of opiate tolerance has been repeatedly demonstrated (Baber et al, Pain; 1989). However, the mechanism of tolerance development occurs by an unknown mechanism.

CCK receptor antagonists such as proglumide have been demonstrated to reverse tolerance to opiates, reducing the dose of opiate required to produce analgesia (Kellstein et al, Pain; 1991). Consequently, proglumide has been demonstrated to boost opiate analgesia, meaning that a markedly reduced dose of opioid is required to achieve the same analgesia. This has been to shown to occur, without any potentiation in respiratory depression (US-A-4576951) or any
effect on the development of opiate dependence (Paneria et al., Brain Research; 1987).

However, the pharmacokinetic profile of proglumide makes it non-ideal for the chronic boosting of opiate analgesia for either chronic or neuropathic pain. It has been demonstrated that proglumide has 3rd order kinetics on oral administration. The first phase of proglumide metabolism and clearance is very rapid, having a half-life of 2 hours, while the combined 2nd and 3rd order metabolic kinetics have a much longer half-life, of 24 hours, diminishing much more slowly at low plasma concentrations. This suggests that, after dosing, proglumide is either in the therapeutic window for only a short time (high therapeutic plasma levels), or is in the therapeutic window for a long time and for 2 hours plasma load is too high, with potential side-effects.

Tramadol is a SNRI, but it is not an opiate. A metabolite, i.e. (+)-tramadol, may have weak opiate activity.

**Summary of the Invention**

The present invention is based on a realisation that the use of proglumide and tramadol in combination may be of particular value, in the treatment of pain. The two active agents may be given simultaneously, sequentially, separately or in any combination. In one embodiment, they may be combined as a single novel entity, i.e. a proglumate salt of tramadol.

By means of this invention, the non-opiate drug tramadol can be used to treat moderate to severe pain (2-3 on the WHO scale), i.e. a higher level of pain than before. This allows the pain to be treated without the potential of addiction associated with opiates. Thus, for example, a patient can be treated at home, or under self-medication. Further, whereas opiates are not generally useful in the treatment of neuropathic pain, that is treatable according to this invention.

**Description of Preferred Embodiments**

More particularly, and by way of illustration, the present invention provides the use of proglumide for the treatment of chronic benign pain disorders and painful neuropathic disorders, when administered along with tramadol therapy. Each active agent may be used in the form of a salt, prodrug, active metabolite or enantiomer (or racemic or non-racemic mixture).
Chronic intractable benign pain disorders that may be treated include lower back and arthritic pain, amongst others. Neuropathic pain includes post-herpetic neuralgia, diabetic neuropathy, drug-induced neuropathy, sympathetic reflex dystrophy or causalgia, fibromyalgia, myofacial pain, entrapment neuropathy, phantom limb pain and trigeminal neuralgia. The invention is also of use in the treatment of central neuropathic pain related to stroke, multiple sclerosis, spinal cord injury, arachnoiditis, neoplasm, syringomyelia, Parkinson's disease or epilepsy.

Each active agent may be used in any suitable, e.g. known, formulation. For example, a controlled release formulation of proglumide may be used in this invention. Such formulations are known, or can be chosen by those skilled in the art. Dosages and routes of administration can similarly be chosen. By ensuring that the plasma load of proglumide does not reach a high level, the patient may be protected against toxicity and/or there may be improved efficacy; the drug may thus be used long term for chronic pain conditions.

In addition, since CCK is a known anxiogenic agent, there is potential for proglumide to inhibit a phenomenon, which occurs in patients with chronic pain where they exhibit unusual personality traits, due to persistent exposure to pain (Hughes et al, Proceedings of the National Academy of Sciences USA; 1990). It is wholly reasonable to hypothesise that CCK may have a role in the development of these pain-related psychological disturbances, and that proglumide may have additional benefits alongside the potentiation of tramadol analgesia.

The present invention may be useful in the treatment of any pain condition, including those described above. It may also be useful in the treatment of breakthrough pain; see PCT/GB2004/004446.

For the treatment of pain conditions such as those highlighted 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.

A single dose of proglumide may be from 1 µg to 200 mg, preferably 1 µg to 20 mg, e.g. 0.1 to 5 mg. A single dose of tramadol may be 1 to 500 mg. The proglumide:tramadol ratio may be, for example below 1:10, 1:20 or 1:50, e.g., down to 1:200, 1:500, 1:1000, 1:2000 or even 1:5000 (w/w).

The following Example provides evidence on which the present invention is based. A single-centre, randomized, placebo-controlled, double-blind, crossover study in 35 healthy human male volunteers was performed to investigate three doses of proglumide, to obtain the analgesic response of laser pain thresholds in combination with a 100 mg fixed dose of tramadol. The pain model was a diode laser induced pain model (Kilminster et al, Br. J. Clin. Pharmacol. 2002 Jan;53(1), pages 43-47).

The volunteers were given oral capsules of tramadol + proglumide, placebo + tramadol or placebo + placebo and their pain threshold was measured at regular intervals post-dosing. The dose of tramadol was fixed at 100 mg and proglumide doses were 200 mg, 20 mg and 2 mg.

Tramadol and proglumide alone showed no analgesic effect in this model. The accompanying drawing is a graph of laser pain threshold values against time (hours), and illustrates the results obtained for the combination of 2 mg of proglumide and 100 mg of tramadol. The combination showed clear analgesic effect. This effect was not observed for the higher doses of proglumide indicating a bell-shaped dose response curve. Thus, it is evident proglumide (even at very low doses) in combination with tramadol can be of benefit in the treatment of pain.
CLAIMS

1. A product comprising proglumide and tramadol as a combined preparation for simultaneous, separate or sequential use in the treatment of a pain condition.

2. A product according to claim 1, wherein the proglumide is in a controlled release or enteric-coated formulation.

3. A product according to claim 1 or claim 2, wherein the condition is lower back or arthritic pain, post-herpetic neuralgia, diabetic neuropathy, drug-induced neuropathy, sympathetic reflex dystrophy or causalgia, fibromyalgia, myofacial pain, entrapment neuropathy, phantom limb pain, trigeminal neuralgia, central neuropathic pain related to stroke, multiple sclerosis, spinal cord injury, arachnoiditis, neoplasm, syringomyelia, Parkinson’s disease or epilepsy.

4. A product according to any preceding claim, which comprises a unit dosage of 0.1 to 20 mg proglumide.

5. A product according to any preceding claim, which comprises proglumide and tramadol in a weight ratio of 1:1000 to 1:10.

6. Use of proglumide for the manufacture of a medicament for the treatment of a pain condition in a subject receiving tramadol.

7. Use according to claim 6, wherein the proglumide is in a controlled release or enteric-coated formulation.

8. Use according to claim 6 or claim 7, wherein the condition is lower back or arthritic pain, post-herpetic neuralgia, diabetic neuropathy, drug-induced neuropathy, sympathetic reflex dystrophy or causalgia, fibromyalgia, myofacial pain, entrapment neuropathy, phantom limb pain, trigeminal neuralgia, central neuropathic pain related to stroke, multiple sclerosis, spinal cord injury, arachnoiditis, neoplasm, syringomyelia, Parkinson’s disease or epilepsy.

9. Use according to any of claims 6 to 8, wherein the medicament comprises a unit dosage of 0.1 to 20 mg proglumide.
Fig. 1
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC 7 A61K31/135 A61K31/167 A61P25/04

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 A61P

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

Electronic data bases consulted during the international search (name of database and, where practical, the search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, PASCAL

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<td>Y</td>
<td>US 4 576 951 A (ROVATI ET AL) 18 March 1986 (1966–03-18) column 1, line 1 – column 2, line 1 claims 1-8</td>
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Further documents are listed in the continuation of box C. Patent family members are listed in annex.

**Date of actual completion of the international search**

22 February 2005

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

10/03/2005

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Hilversum Tel. (+31–70) 540–2040, Tx. 31 651 epo nl, FAX (+31–70) 540–3016

Authorized officer

Albayrak, T
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<td>WO 03/086409 A (ML LABORATORIES PLC; JACKSON, KAREN) 23 October 2003 (2003-10-23) page 3, line 15 page 1, line 1 - page 2, line 6</td>
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From: PCT/GB/210 (patent family annex) (January 2004)