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Ottawa Hull K1A 0C9

(21) (A1) 2,173,208
(86) 1994/10/13
(43) 1995/04/20

(51) Int.Cl.[6] A61K 31/445

(19)(CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) Levobupivacaine Useful for Managing Chronic Pain

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(30) (GB) 9321061.5 1993/10/13

(57) 9 Claims

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/445 — A1

(11) International Publication Number: WO 95/10276

(43) International Publication Date: 20 April 1995 (20.04.95)

(21) International Application Number: PCT/GB94/02248

(22) International Filing Date: 13 October 1994 (13.10.94)

(30) Priority Data:
9321061.5 13 October 1993 (13.10.93) GB

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(81) Designated States: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ).

Published
With international search report.

(54) Title: LEVOBUPIVACAINE USEFUL FOR MANAGING CHRONIC PAIN

(57) Abstract

Levobupivacaine is useful for managing chronic pain.

2173208

LEVOBUPIVACAINE USEFUL FOR MANAGING CHRONIC PAIN

Field of the Invention

This invention relates to a new therapeutic use for a known analgesic agent, i.e. bupivacaine or 1-butyl-N-(2,6-dimethylphenyl)-2-piperidinecarboxamide.

Background of the Invention

Racemic bupivacaine, a long-acting local anaesthetic, is useful in chronic administration as an analgesic in some pain syndromes. However, racemic bupivacaine is cardiotoxic, having depressant electrophysiological and mechanical effects on the heart. It should therefore be used with caution in cardiac-compromised patients.

It is known that levobupivacaine is probably less cardiotoxic than dexbupivacaine and racemic bupivacaine. See, for example, Vanhoutte et al, Br. J. Pharmacol. 103:1275-1281 (1991), and Denson et al, Regional Anaesthesia, 17:311-316 (1992). Vanhoutte et al studied the effects of bupivacaine enantiomers on the electrophysiological properties of guinea pig isolated papillary muscle; this is based on their statement that "the cardiotoxicity of bupivacaine seems to be mainly of electrophysiological origin".

Berrisford et al, Br. J. Anaesthesia 70:201-204 (1993), disclose the administration of bupivacaine and its enantiomers during continuous extrapleural intercostal nerve block, as an analgesic for patients who have undergone thoracotomy. The infusion of bupivacaine was maintained until the morning of the fifth day after operation.

Du Pen et al, Pain 49:293-300 (1992), report the use of chronic epidural and opioid infusions in concentrations between 0.1 and 0.5% bupivacaine in intractable cancer pain. The median length of therapy was 60-120 days, with the longest infusion lasting 277 days. A progressive reduction in bupivacaine clearance was reported.

Cardiotoxicity is not usually a clinical problem at low single doses, e.g. by use in epidurals and nerve

blockade. However, for chronic administration, the myocardium may have to withstand the possible cumulative cardiotoxic side-effects of the local anaesthetic.

Pain has been classified, by the WHO Analgesic Ladder; see also the review by Ashburn and Lipman, "Management of Pain in the Cancer Patient". At the first step of the ladder, of mild to moderate pain, treatment with a non-opioid ± adjuvant is required. If pain persists or increases, treatment should be with an opioid for mild to moderate pain, plus non-opioid ± adjuvant. If pain persists or increases beyond this second step, an opioid for moderate to severe pain is required, with or without non-opioid and/or adjuvant. Cancer and post-operative pain is typically of this third step.

An individual can be at any step on this ladder of pain at any time. Patents with acute pain will tend to go down the ladder with time; patients with chronic pain or malignancy may "climb the ladder" with time, increasingly potent analgesics then being required to control the worsening pain associated with progression of the disease.

Summary of the Invention

It has now been found that there is less tissue uptake of levobupivacaine into ventricle and brain than dexbupivacaine. Levobupivacaine thus exhibits improved clearance. This, coupled with the evidence that levobupivacaine is less cardiotoxic than dexbupivacaine, supports the use of levobupivacaine as an improved, practical long-acting analgesic, i.e. for use in chronic pain management. This finding may be particularly beneficial for, but is not restricted to, human patients with compromised cardiac function and central nervous system damage or those predisposed to these conditions. In particular, cancer patients are a group likely to benefit from this agent.

The agent may be the single isomer, but is effectively free of dexbupivacaine, e.g. in at least 80%, more preferably at least 90%, and most preferably at least 99%,

enantiomeric excess. Any conventional salt, e.g. the hydrochloride, may be used.

Description of the Invention

For the purposes of the present invention, the management of chronic pain involves administration of levobupivacaine for a period of at least 2 days, preferably at least 30 days, e.g. up to 60 days or more. As indicated above, the chronic pain may be associated with cancer. Other suitable subjects are those suffering from post-operative pain, or from severe pain caused by other chronic medical conditions.

In use of the invention, levobupivacaine may be provided in solution, for administration by infusion. This may be done using conventional apparatus, e.g. including means for the patient to induce infusion as desired. concentration of levobupivacaine to be given for effective utility, is for example, 0.25%, 0.5% or 0.75%, depending on the procedure envisaged. Up to 60 ml in a single dose can be given. The usual routes of administration are infiltration, epidural, spinal and peripheral nerve block. It is also possible to provide continuous infusion of agent at lower concentration, for example 0.125%, with or without opioid, depending on anaesthetic practice.

Administration of the active agent may be directly into the spine or epidural space. The agent is thus provided in the desired locus. By contrast with a conventional drug that is required to pass the blood-brain barrier, active agent acts, and then passes into the blood, for clearance. Accumulation is to be avoided; the present invention relies on the known activity of bupivacaine and the surprising discovery that levobupivacaine does not accumulate in the heart and brain as such as the other component (dexbupivacaine) of racemic bupivacaine. Clinicians can thus utilise the present invention without the likelihood of incurring long-term problems associated with the dexbupivacaine content of racemic bupivacaine. The treatment of the present invention, i.e. to mitigate

the effect of chronic pain, is to be distinguished from the use of bupivacaine as a local anaesthetic, i.e. to avoid the effect of induced pain.

The term "chronic pain" is used herein to indicate a longer pain state than is currently associated with the use of racemic bupivacaine as a local anaesthetic. Thus the invention includes the treatment of patients who are suffering from what a skilled clinician might call "acute pain". The reduced toxicity risk associated with the use of levobupivacaine justifies both long-term administration and the use of higher concentrations, leading to a significant therapeutic benefit.

Categories of pain are given in Table 1.

Table 1

Pain Type	Acute	Chronic (non-malignant)	Chronic (malignant)
Duration	Hours to days	Months to years	Unpredictable
Associated pathology	Present	Often none	Usually present
Prognosis	Predictable	Unpredictable	Increasing pain with possibility of disfigurement and fear of dying
Associated problems	Uncommon	Depression, anxiety	Many, especially fear
Nerve conduction	Rapid	Slow	Slow
Autonomic nervous system	Present	Generally absent	Present or absent
Biological social effects	High minimal	Low or absent	Variable, usually marked
Treatment	Primary analgesics	Multimodal: often largely behavioural, drugs play a minor role	Multimodal: drugs usually play a major role

Levobupivacaine may be effectively used as an adjuvant to opioids in the treatment of severe pain for the following reasons:

1) Breakthrough pain is possible despite the use of opioids, and neuropathic pain affecting the central or afferent nerve ways often responds poorly to these agents.

2) Most cancer patients have pain of more than one aetiology and each must be treated separately.

3) In the treatment of advanced pain, drugs such as morphine have a ceiling effect above which additional analgesia does not occur but side-effects increase and tolerance is sometimes seen.

4) Although most patients are treated by the oral route, 60% will require drug administration by additional or alternative routes during the last four weeks of life.

The use of levobupivacaine in post-operative pain control may be a simpler proposition. Bupivacaine has been demonstrated to be effective in the control of post-operative pain, and to reduce the opioid requirements of patients recovering from herniorrhaphy. In this study, the surgical wound was infiltrated with anaesthetic before closure. A low concentration of 0.25% was used; with levobupivacaine, higher levels could result in improved clinical benefit.

The evidence for the selective tissue uptake is as follows:

Four sheep weighing 39-49 kg (mean 44, SD 4 kg) were given increasing bolus doses (from 40 mg) of *rac*-bupivacaine HCl. These were administered at least 1 day apart via a PVC cannula until a fatal outcome resulted. The heart and brain were removed within 20 min of death to be analysed for bupivacaine concentration. The heart was removed by transection through the great vessels approximately 20 mm above the level of the aortic valve, and 20 mm below the caudal border of the right atrium. Blood was immediately expressed from the cardiac chambers, and representative samples of the left and right atrium and ventricle were obtained, blotted and stored frozen (-20°C) until assay. The brain was removed by transection at the

level of the lower border of the pons, blotted and stored frozen as for the heart tissue.

Tissue concentrations of the bupivacaine enantiomers are presented in Table 2. The variability in the fatal doses (80-200 mg) was reflected in the tissue concentrations measured post-mortem. Larger differences in the concentrations of both bupivacaine enantiomers in the atrium and ventricle were apparent. Significant differences in the concentrations of the bupivacaine enantiomers in the ventricle and brain (both $P = 0.03$ by the Students paired t test) were evident, more (+)-(R)- than (-)-(S)-bupivacaine being taken up by these tissues. This was not so for the atrium.

Table 2

Sheep No.	Fatal dose (mg)	Enantiomer	Tissue concentration (µg/g)		
			Atrium	Ventricle	Brain
1	80	R-	5.70	9.93	6.91
		S-	6.22	8.44	6.53
		R:S	0.92	1.18	1.06
2	80	R-	3.94	7.70	4.97
		S-	3.65	7.36	4.59
		R:S	1.08	1.05	1.08
3	200	R-	17.9	45.6	12.7
		S-	18.0	44.1	11.7
		R:S	0.99	1.03	1.09
4	200	R-	21.5	34.1	17.2
		S-	21.2	33.3	16.3
		R:S	1.02	1.03	1.08

An additional benefit of levobupivacaine over racemic bupivacaine is its reduced cardiodepressant effect. It is therefore particularly suitable for use in treated cardiac-compromised patients. This is described more fully in the other International Patent Application filed today by Chiroscience Limited et al, with the same title, the contents of which are incorporated herein by reference.

CLAIMS

1. Use of levobupivacaine or a salt thereof, substantially free of dexbupivacaine, for the manufacture of a medicament for use in managing chronic pain in a human patient.

2. Use according to claim 1, wherein the patient has cancer.

3. Use according to claim 1 or claim 2, wherein the pain is on step 3 of the WHO ladder.

4. Use according to any preceding claim, wherein the patient is concomitantly treated with an opioid.

5. Use according to any preceding claim, wherein the patient is cardiac-compromised, e.g. suffering heart failure at level 2, 3 or 4 of the New York Heart Association Index.

6. Use according to any preceding claim, wherein the pain is of more than 2 days duration.

7. Use according to claim 6, wherein the duration is at least 30 days.

8. Use according to claim 6, wherein the duration is at least 30 days.

9. Use according to any preceding claim, wherein the levobupivacaine is in at least 90% enantiomeric excess with respect to dexbupivacaine.