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(54) Title: ANALGESIC AGENT AND ITS USE

(57) Abstract

Levobupivacaine is useful as an anaesthetic in a human patient having or disposed to depressed myocardial contractility.

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ANALGESIC AGENT AND ITS USE

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 is an effective long-acting local anaesthetic, and may be given as an epidural. 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".

Many patients who require analgesics are undergoing concomitant therapy with other drugs, e.g. anti-hypertensive agents. Many such drugs are cardio-depressant. In particular, it has recently been reported that cardio-depressant effects are observed in isolated organs, following administrations of bupivacaine and Ca^{2+} channel inhibitors such as verapamil.

Summary of the Invention

Surprisingly, it has been found that the effect of levobupivacaine on the heart is reduced, in respect not simply of electrophysiological properties, but also mechanical properties. Although racemic bupivacaine may have both electrophysiological and mechanical depressant effects on the heart, there is no evidence to suggest that these effects are linked.

In particular, it has now been found that levobupivacaine in man has less effect on stroke, cardiac and acceleration indices than racemic bupivacaine. As these are indices of myocardial contractility, this finding indicates that levobupivacaine is less cardio-depressant than racemic bupivacaine. This finding supports the use of levobupivacaine as a safer long-acting local anaesthetic for use in patients having or disposed to depressed myocardial contractility, i.e. a class of cardiac-compromised patients and also patients undergoing concomitant therapy with medicines having a cardio-depressant effect or with cytotoxic drugs. For the same reasons, levobupivacaine may also have beneficial therapeutic effects after certain kinds of surgery when sympathetic blockade is required with minimal cardio-depressant effects.

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, "depressed myocardial contractility" indicates that the patient is suffering from, or disposed to, heart failure at level 2, 3 or 4 of the New York Heart Association Scale. There are various therapeutic indications associated with reduced force of contraction of the heart, where the use of bupivacaine or its isomers, on the basis of prior knowledge, would have been contra-indicated. In certain populations, reduced mechanical effectiveness of the heart is a major problem.

Specific indications to which the present invention relates, and for which the use of levobupivacaine as an analgesic is thus appropriate, include hypertension, renal disease, viral illness, alcohol-dependence or effects, major ischaemia and diabetes. The invention is also

applicable for providing anaesthesia in the old and frail, for stable post-infarct, shock, following cardiac surgery or multiple organ failure, and others at risk from post-myocardial infarcts.

The 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. This is common during labour and is distinct from the treatment of chronic pain when infusions can continue for days rather than hours.

An additional benefit of levobupivacaine over racemic bupivacaine is its reduced uptake into heart and brain. It is therefore particularly suitable for use in treating chronic paid. 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.

The following provides the evidence that is the basis of the present invention.

The cardiovascular and central nervous effects of levobupivacaine were compared with racemate (Marcaine) in healthy male volunteers. Drugs were administered by intravenous administration in a double-blind crossover manner. The infusion rate was 10 mg/min for each drug and infusion was continued up to a maximum of 150 mg or stopped following the first detection of CNS effects (including tinnitus, numb tongue or lips and dry mouth). Volunteers were previously conditioned to the CNS effects of local anaesthetics by administration of a test dose of lignocaine. A range of cardiovascular parameters were measured, including systolic and diastolic blood pressures, ECG, and, using the transthoracic electrical bioimpedance

technique (with a BoMed NCCOM3-R7), aortic blood flow, allowing measurements of cardiac index and stroke index. Based on results from a previous study in which racemic bupivacaine was infused it was anticipated that the major cardiovascular changes observed following bupivacaine administration would be related to myocardial contractility. Therefore, an acceleration index, representing the initial maximum acceleration of blood flow during the onset of ejection, was measured to estimate myocardial contractility in this new study.

Levobupivacaine, like racemate, was well tolerated. The mean total doses administered of levobupivacaine and racemate were 54.0 and 45.6 mg respectively and plasma concentrations at the end of infusion were 2.384 μg/ml and 1.87 μg/ml respectively (n=12). Despite the mean total dose and plasma concentration being higher with levobupivacaine, this produced much smaller mean changes in cardiac variables than the racemate. The myocardial contractility index was significantly reduced by bupivacaine from a value of 1.36 S^{-2} to 1.18 S^{-2}, a decrease of 0.18 S^{-2} or 13%. For levobupivacaine the pre-dose value was 1.34 S^{-2} and this only decreased to 1.28 S^{-2} at the end of infusion, a decrease of 0.06 S^{-2} or 4.5%. The difference between drug treatments was highly significant ($p < 0.02$, n=12). The results were similar for stroke index, a parameter likely to reflect changes in myocardial contractility. Bupivacaine reduced this from 55.3 ml/M^2 to 44.4 ml/M^2, a decrease of 10.9 ml/M^2 or 20%. For levobupivacaine the pre-dose value was 52.4 ml/M^2 and 49.1 ml/M^2 at the end of infusion, a decrease of 3.3 ml/M^2 or 6%. Again the difference between drug treatments was statistically highly significant ($p < 0.01$, n=12). Small changes in other variables occurred including heart rate and mean blood pressure (increases) and ejection fraction and cardiac index (decreases). As with acceleration index and stroke index the changes tended to be greater with bupivacaine.

A second study has been carried out, to compare the efficacy of levobupivacaine against bupivacaine using the ulnar block technique. Concentrations of 0.125%, 0.25% and 0.5% levobupivacaine were compared with 0.25% bupivacaine (all volumes 5 mls) in a double-blind study in 20 volunteers. A preliminary analysis of the data suggests that in terms of sensory block, levobupivacaine has comparable efficacy to bupivacaine, with the duration of sensory block to 0.25% bupivacaine being similar to that seen with levobupivacaine 0.25%.

These results with levobupivacaine have provided evidence that this local anaesthetic, in comparison with the currently clinically-used racemate, has a lower potential to cause cardiotoxicity in man. This, along with evidence that levobupivacaine has a similar anaesthetic potency to the racemate, suggests that levobupivacaine will be a safer local anaesthetic in the clinic. This would be of particular importance for obstetrics use and large plexus blocks where accidental intravenous injection of the racemate can have grave consequences. In addition, the lower propensity to cause myocardial depression would be beneficial in patients with compromised cardiac function.

Based on preclinical results obtained with separated enantiomers, the reduced cardiotoxicity of levobupivacaine in man is likely due to reduced direct actions on the heart. However additional factors may contribute to the reduced cardiotoxicity. Recently, others have reported stereoselective plasma binding of bupivacaine enantiomers in man, with the plasma binding of levobupivacaine being about 50% higher than binding for dexbupivacaine. This higher binding would reduce the consequences of accidental intravascular administration.

CLAIMS

1. Use of levobupivacaine or a salt thereof, for the manufacture of a medicament for use as an anaesthetic in a human patient having or disposed to depressed myocardial contractility.

2. Use according to claim 1, wherein the patient is suffering from hypertension, renal disease, a post-myocardial infarct, ischaemia, diabetes, a virus or alcohol-dependence.

3. Use according to claim 1, wherein the patient has undergone cardiac surgery, multiple organ failure or a valve replacement, or has been fitted with a pacemaker.

4. Use according to any preceding claim, wherein the patient is undergoing concomitant therapy with a cardio-depressant drug.

5. Use according to any preceding claim, wherein the patient is undergoing concomitant anti-hypertension therapy, by the administrations of a Ca^{2+} channel blocker such as verapamil.

6. Use according to any preceding claim, wherein the patient is undergoing concomitant therapy with a cytotoxic drug.

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

INTERNATIONAL SEARCH REPORT

Interna .l Application No
PCT/GB 94/02249

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/445

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 6 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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BR.J.PHARMACOL., vol.103, no.1, May 1991 pages 1275 - 1281 F.VANHOUTTE ET AL. 'Stereoselective effects of the enantiomers of bupivacaine on the electrophysiological properties of the guinea-pig papillary muscle' ---	1-7
X	REG. ANESTH., vol.17, no.6, November 1992 pages 311 - 316 D.D.DENSON ET AL. 'Enantiomer-Specific Effects of an Intravenously Administered Arrhythmogenic Dose of Bupivacaine on Neurons of the Nucleus Tractus Solitarius and the Cardiovascular System in the Anesthetized Rat' see the whole document --- -/--	1-7

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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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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Name and mailing address of the ISA	Authorized officer
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BR.J.ANAESTH., vol.67, no.3, September 1991 pages 247 - 256 A.J.RUTTEN ET AL. 'CARDIOVASCULAR EFFECTS AND REGIONAL CLEARANCES OF I.V. BUPIVACAINE IN SHEEP: ENANTIOMERIC ANALYSIS' see page 247 ---	1-7
X	ACTA PHARMACOL. TOXICOL., vol.31, no.4, 1972 pages 273 - 286 G.ABERG 'Toxicological and Local Anaesthetic Effects of Optically Active Isomers of Two Local Anaesthetic Compounds' see abstract ---	1-7
X	ARCH.INT.PHARMACODYN.THER., vol.200, no.2, December 1972 pages 359 - 369 F.P.LUDUENA ET AL. 'Optical Isomers of Mepivacaine and Bupivacaine' see page 368, last paragraph ---	1-7
X	CHIRALITY, vol.5, no.7, 1993 pages 485 - 491 A.J.RUTTEN ET AL. 'Tissue Distribution of Bupivacaine Enantiomers in Sheep' see the whole document ---	1-7
X	ANESTH.ANALG., vol.77, no.3, September 1993 pages 477 - 482 J.X.MAZOIT ET AL. 'Myocardial Uptake of Bupivacaine: II. Pharmacokinetics and Pharmacodynamics of Bupivacaine Enantiomers in the Isolated Perfused Rabbit Heart' see the whole document ---	1-7
A	ANESTHESIOLOGY, vol.77, no.2, August 1992 pages 324 - 335 S.LEE-SON ET AL. 'Stereoselective Inhibition of Neuronal Sodium Channels by Local Anesthetics' see abstract ---	1-7
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	J.GEN.PHYSIOL., vol.100, no.6, December 1992 pages 1003 - 1020 G.K.WANG ET AL. 'Altered Stereoselectivity of Cocaine and Bupivacaine Isomers in Normal and Batrachotoxin-modified Na+ Channels' see abstract ---	1-7
X	BR.J.CLIN.PHARMACOL., vol.6, no.1, July 1978 pages 63 - 68 C.APS ET AL. 'AN INTRADERMAL STUDY OF THE LOCAL ANAESTHETIC AND VASCULAR EFFECTS OF THE ISOMERS OF BUPIVACAINE' see abstract ---	1-7
X	CHEMICAL ABSTRACTS, vol. 73, no. 5, 3 August 1970, Columbus, Ohio, US; abstract no. 25314a, see abstract & ZA,A,6 802 611 (STERLING DRUG INC.) 12 December 1968 ---	1-7
X	J.PHARM.PHARMACOL., vol.44, no.4, April 1992 pages 355 - 358 A.J.RUTTEN ET AL. 'Postoperative course of plasma protein binding of lignocaine, ropivacaine and bupivacaine in sheep' see abstract ---	1-7
X	J.CHROMATOG., vol.553, 1991 pages 383 - 390 B.J.CLARK ET AL. 'Reversed-phase and chiral high-performance liquid chromatographic assay of bupivacaine and its enantiomers in clinical samples after continuous extrapleural infusion' see page 390 ---	1-7
A	US,A,4 695 576 (AF EKENSTAM ET AL.) 22 September 1987 see the whole document ---	1-7
T	EXPERT OPIN. INVEST.DRUGS, vol.3, no.11, November 1994 pages 1209 - 1212 R.GRISTWOOD ET AL. 'Reduced cardiotoxicity of levobupivacaine compared with racemic bupivacaine (Marcaine): new clinical evidence' see the whole document ---	1-7

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PHARMACEUTISCH WEEKBLAD, vol.125, no.2, 1 June 1990 pages 552 - 554 E.J.ARIËNS 'Racemische therapeutica probleemmiddelen' see the whole document	1-7
X	SCHWEIZ.MED.WOCHENSCHR., vol.120, no.5, 3 February 1990 pages 131 - 134 E.J.ARIËNS 'Stereoselectivity in pharmacodynamics and pharmacokinetics' see the whole document	1-7
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X	CHIRALITY, vol.2, 1990 pages 129 - 133 B.TESTA ET AL. 'Racemates Versus Enantiomers in Drug Development: Dogmatism or Pragmatism?' see the whole document	1-7

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat. Application No
PCT/GB 94/02249

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
ZA-A-6802611		NONE	
US-A-4695576	22-09-87	NONE	