NEW USE OF LOCAL ANAESTHETICS AGAINST VASCULAR HEADACHES

Field of the invention

The present invention is directed to a new use of [(3-alkoxy-phenoxy)-ethyl]-dialkylamine derivatives. More particularly the invention is directed to the use of [(3-alkoxy-phenoxy)-ethyl]-dialkylamine derivatives as a medicament for use in the treatment of vascular headaches, and in particular as a medicament for the treatment of migraine.

Background and prior art

Migraine is a disorder that exhibits a spectrum of treatment responses in afflicted individuals. Some sufferers are fortunate and the therapy may be over-the-counter remedies or even non-drug regimens using behavior modification, acupuncture, and hypnosis as instruments of aborting the headache. Bed rest, a darkened room, and the use of cold packs applied to the temporal artery and its branches may modify the attack. Sleep also has a beneficial effect in ending an attack. Most patients, however, will require prescription drugs for relief from the migraine. The symptoms most in need of treatment are the head pain and gastrointestinal symptoms. To a lesser degree, photophobia and the aura warrant treatment; the latter may also be quite disturbing and require treatment although its duration is relatively brief. The oral absorption of agents is less than optimal during acute migraine because of the reduced gastrointestinal peristalsis. The more severe the attack, the greater is the absorption reduced. Furthermore, the presence of nausea and frequent vomiting will preclude oral administration of pharmacologic agents.

During most of the 20th century, ergot alkaloids have been the cornerstone of effective therapy. Still many patients do not respond to ergots. They find the response is incomplete, the side effects encountered are frequent and disturbing, and the contraindications preclude their use in many migraineurs.

The exact pathogenesis of migraine is still unknown. Many theories have been elaborated, but none can account for all the clinical features or for all the pathophysiological aspects demonstrated in recent years. The pendulum has been swinging between vascular (*Wolff 1963*) and neurogenic (*Sicuteri 1986*) theories, with brief peripheral blood excursions (*Hannington et al, 1981*). In recent years, however, a general consensus has been emerging that in migraine both vascular and neural components are relevant and most probably interrelated (*Lance et al, 1983; Welch 1987; Olesen 1991*).

Recent epidemicologic data suggest that 17.6 percent of adult females and 5.7 percent of adult males suffer from migraine (*Stewart et al, 1992*). The Center for Disease Control (1991) recently reported that over the last decade the prevalence of migraine has increased 60 percent. In addition, migraine is significantly under-diagnosed, with only 40 percent of adult females and 30 percent of adult males suffering from migraine being patient diagnosed (*Lipton et el, 1992*). Yet 80 percent of this population of undiagnosed migraineurs experience disability (*Stewart et al, 1992*), and most seek periodic medical care for other medical conditions.

Migraine is also under-treated. Only about 40 percent of females and 30 percent of males utilize prescription drugs (*Celentano et al, 1992*). However, many of these patients discontinue prescription medication and rely on the over-the-counter remedies.

The most common drugs which at present are used for the treatment of migraine and other forms of vascular headaches, are inter alia triptanes,ergotamine, aspirin, and NSAIDS.

One major problem with the just mentioned drugs, is that they often have an onset time of from 60 minutes and up to 4 hours, which is a disadvantage in therapy of vascular headache conditions such as migraine. Furthermore, these drugs are often in forms suitable for oral administration, which often causes problems for the patient since nausea and vomiting is common among patients suffering from migraine, or other forms of vascular headache conditions.

Headache, 1995; 35: pp. 83-84, reports a study of lidocaine (4%) administered intranasally via a spray bottle. The results from this study shows that only 27 % of the patients in the study experienced moderate relief, and none of the patients in the study experienced excellent relief.

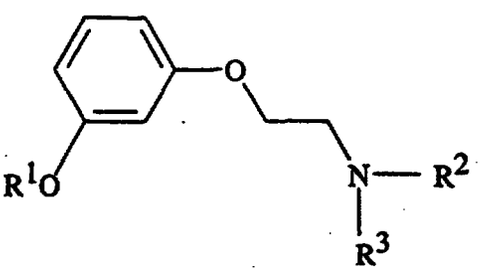
WO 98/38998 discloses the use of levobupivacaine and ropivacaine in the treatment of migraine. These local anaesthetics are however structurally distinct from the local anaesthetics used in accordance with the present invention.

In order to achieve satisfactory pain relief for patients suffering from vascular headache, the drug used to treat the vascular headache condition should preferably have a fast onset of action, and also as few side effects as possible.

Thus, the problem underlying the present invention is to find a new way of therapy for vascular headache conditions, and in particular migraine. A further problem underlying the present invention, is to find a new way of therapy providing a fast onset of action, i.e. a fast pain relief as well as relief of other symptoms associated a vascular headache condition, to the patient suffering from the vascular headache condition.

Outline of the invention

The present invention is directed to the use of a compound of the formula I



I

wherein

R^1 represents C_{3-5} alkyl; and

R^2 and R^3 independently represent C_{1-3} alkyl; or a pharmaceutically acceptable salt thereof ;

for the manufacture of a medicament for use in the treatment of a vascular headache condition.

A further aspect of the present invention is the use of a compound of the formula I above, for the manufacture of a medicament for use in the treatment of migraine.

Still a further aspect of the present invention is a method for the treatment of vascular headache conditions, in particular migraine, comprising administering to a subject suffering from said vascular headache condition, an effective amount of a medicament comprising a compound of the formula I as active agent.

A person skilled in the art will appreciate the various kinds of headache conditions falling under the definition vascular headache. However, the following brief explanations may be given.

The wording "vascular headache" is intended to include any kind of vascular headaches, in particular migraine, cluster headache, post-traumatic headache, tension headache, muscular headache and headaches due to vascular diseases.

The wording "migraine" should be interpreted according to *The International Classsification of Migraine, Headache Classification Committee 1988.* However, the specified vascular headache conditions are not to be considered as limiting the invention in any way.

"Cluster headache" is most typically defined as the temporal clustering of attacks during periods usually lasting between 2 weeks and 3 months, separated by remissions of at least 14 days, but usually several months - this type of cluster headache is also called "episodic cluster headache". "Chronic cluster headache" is characterised by absence of remissions of at least 14 days for more than one year (*Textbook of pain, p.504*, 3rd edition, 1994).

"Post-traumatic headache" is headache caused as a result of some head trauma (*Textbook of pain, p.504*, 3rd edition, 1994).

"Tension headache" and "muscular headache" belong to the group of headaches formerly described as "muscle contraction", "psychogenic", "stress" or "essential" (*Textbook of pain, p. 502, 3rd edition 1994).*

The compounds according to formula I above, may also preferably be used for surgery in the nasal area.

By the wording "fast onset of action" is intended that a therapeutic or prophylactic effect shall preferably have been achieved within 15 minutes from the time of administration.

Patients suffering from vascular headache conditions such as migraine, often get a feeling that an attack of headache is approaching. In accordance with the present invention, when a patient starts to feel that an attack of a vascular headache condition is going to afflict him or her, this patient may administer, preferably intranasally, a dosage of a compound of the formula I . Since the active agent of the formula I has a fast onset of action, the attack of approaching headache will be blocked before it has developed into a painful, vascular headache condition.

The use in accordance with the present invention also encompasses the administration of a compound of the formula I as an acute rescue medicine. This means that the use of a compound of the formula I is also effective for therapy of fully developed vascular headache conditions such as migraine.

Thus, the present invention is intended not only to encompass therapeutic treatment of vascular headache conditions, but also prophylactic treatment of vascular headache conditions.

The medicament comprising a compound of the formula I above as the active agent may be administered in form of a pharmaceutical formulation, further comprising pharmaceutically acceptable carriers, diluents or adjuvants.

The compound according to formula I above may be administered nasally or intravenously. Preferably the medicament is administered nasally in form of a spray. The wording "spray" will be appreciated by a person skilled in the art, but includes a solution which is distributed such as to increase the contact area with the nasal mucosa. Administration of the medicament in form of drops and powders is a further useful alternative.

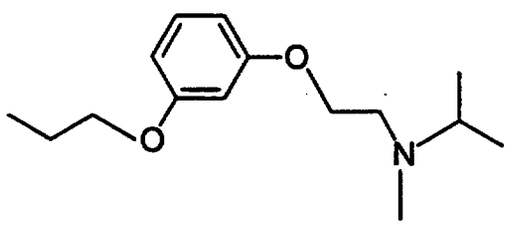
The dose of the active agent of the formula I above will vary depending on the formulation used, as well as on the severity of the vascular headache condition to be treated.
A preferred dose is 0.01-200 mg active agent/kg body weight, more preferably 0.1-2 mg active agent/kg body weight. Similar ranges apply if a compound of the formula I is used for prophylactic treatment.

Preferred compounds for use as active agents in accordance with the present invention, are compounds of the formula I selected from anyone of

isopropyl-methyl-[2-(3-n-propoxy-phenoxy)-ethyl]-amine;
ethyl-isopropyl-[2-(3-n-propoxy-phenoxy)-ethyl]-amine;
diisopropyl-[2-(3-n-propoxy-phenoxy)-ethyl]-amine;
diethyl-[2-(3-n-propoxy-phenoxy)-ethyl]-amine;
isopropyl-methyl-[2-(3-n-butoxy-phenoxy)-ethyl]-amine;
ethyl-isopropyl-[2-(3-n-butoxy-phenoxy)-ethyl]-amine;
diisopropyl-[2-(3-n-butoxy-phenoxy)-ethyl]-amine;
ethyl-isopropyl-[2-(3-n-pentoxy-phenoxy)-ethyl]-amine; and
diisopropyl-[2-(3-n-pentoxy-phenoxy)-ethyl]-amine.

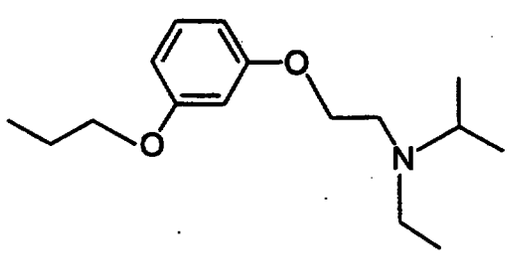
Particularly preferred compounds of the formula I for use in accordance with the present invention are

(i) isopropyl-methyl-[2-(3-n-propoxy-phenoxy)-ethyl]-amine, which is a compound of the formula II



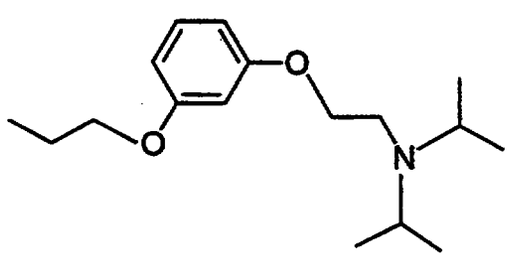
II ;

(ii) ethyl-isopropyl-[2-(3-n-propoxy-phenoxy)-ethyl]-amine, which is a compound of the formula III



III ; and

(iii) diisopropyl-[2-(3-n-propoxy-phenoxy)-ethyl]-amine, which is a compound of the formula IV



IV

Biological evaluation

Neurogenic inflammation within cephalic tissue, involving vasodilation and plasma protein extravasation, has been proposed as a mechanism in headache pathogenesis (*Michael A. Moscowitz, Neurology 43, (Suppl 3), June 1993*).

I. In order to determine the ability of the compounds of the formula I above at inhibiting neurogenic inflammation, the following test model was used.

The effect of isopropyl-methyl-[2-(3-n-propoxy-phenoxy)-ethyl]-amine on neurogenic inflammation was examined in the hindpaws of rats.

Animal preparation

Six male Sprague Dawley rats (260 - 290 g) were anesthetized with 2 % isoflurane in a nitrous oxide/oxygen mixture (2/3 - 1/3) and artificially ventilated after insertion of a tracheal cannula. The jugular vein was cannulated and the animals were paralyzed by an i.v. injcetion of 0.06 mg/kg pancuronium bromide (Pavulon®). The levels of isoflurane, O_2, N_2O and the end-tidal CO_2 (3.5 - 4.5 %) were monitored during the entire experimental period. Core temperature was maintained at 38 ± 0.5 °C with a homeothermic blanket system.

The animals were prepared to enable electrical stimulations (3 mA, 2ms, 2 Hz for 5 min) of the sciatic nerve of both legs. 10 - 20 µl of isopropyl-methyl-[2-(3-n-propoxy-phenoxy)-ethyl]-amine (2 %) in a gel formulation (batch TARO-83-2) or, when needed, the vehicle (batch 106-10-2) were applied on the sciatic nerve distal to the stimulation electrodes 10 min prior to stimulation. The nerves were then sectioned proximal to the electrodes, and Evans blue dye (10 mg/ml, kg) was given intravenously 2 min prior to stimulation.

Assessment of neurogenic inflammation

The neurogenic inflammation was assessed 5 min after the end of the stimulation by rating the localized extravasation of Evans Blue in the skin area of the hindpaw innervated by the sciatic nerve, using a 4-point scale as shown in Table 1 below. In a preliminary experiment the inability of the vehicle to block the development of the neurogenic inflammation was checked.

Table 1

Score	Extravasation of Evans Blue
0	No evidence of blue spots on the skin
1	< 25 % of the sciatic nerve innervation area tintedin blue
2	25 - 75 % of the sciatic nerve innervation area tinted in blue
3	> 75 % of the sciatic nerve innervation area tinted in blue

Protocol

The following gel formulation was used in the tests performed below.

Ingredient	Quantity [mg/g]
isopropyl-methyl-[2-(3-n-propoxy-phenoxy)-ethyl]-amine	20
Hydroxypropylmethylcellulose 4000 cps	20
Hydrochloric acid 2 M	44
Sodium hydroxide 2 M, to pH 4.0-5.5	q.s.
Water, purified to 1.00 g	q.s.

The gel was prepared by mixing isopropyl-methyl-[2-(3-n-propoxy-phenoxy)-ethyl]-amine and the hydrochloric acid, whereafter a major part of the water was added. The mixture was stirred until all of the isopropyl-methyl-[2-(3-n-propoxy-phenoxy)-ethyl]-amine had dissolved. pH was adjusted to about 4 and the rest of the water was added. The obtained

solution was heated to 70 °C, whereafter the hydroxypropylmethylcellulose was added while vigorous stirring. The jelly was finally cooled while stirring, pH was measured and, if necessary, adjusted to 4.0 - 5.5.

Three rats received a 2 %gel formulation as described above on the sciatic nerve on one side and the vehicle on the other side. Both sciatic nerves were stimulated simultaneously by the same constant-current stimulator. The vehicle-treated side received isopropyl-methyl-[2-(3-n-propoxy-phenoxy)-ethyl]-amine (2 %) in a gel formulation gel and the stimulating procedure, while the other side was neither treated nor stimulated and then served as a sham control (no neurogenic inflammation). As is shown in Table 2 below, isopropyl-methyl-[2-(3-n-propoxy-phenoxy)-ethyl]-amine (2 %) applied topically on the sciatic nerve, blocked the development of the neurogenic inflammation in the rat as asessed by the extravasation of Evans Blue.

Table 2

Treatment	**Score:**	**0**	**1**	**2**	**3**
isopropyl-methyl-[2-(3-n-propoxy-phenoxy)-ethyl]-amine (n=6)		5	1		
Vehicle (n=3)					
Sham (n=3)		3			

II. Clinical model

A compound of the formula I above is administered to migraine patients having moderate to severe pain according to the 4 point verbal rating scale (VRS): none, mild, moderate and severe respectively. The route of administration is two different types of nasal administration, one anterior application and one dorsonasal application. Each type of administration is having its own placebo control. The patient´s visual analogue scale (VAS) score is recorded at baseline.

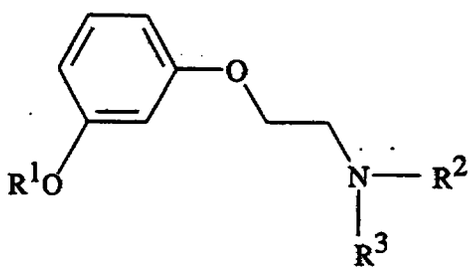
Each patient receives 1 puff in each nostril every 2 minutes for a 10 minute period. Thus, each patient receives a total of 10 puffs (5 puffs in each nostril) of a compound of the formula I above

After administration of the first puffs (1 per nostril), patient satisfaction is recorded every 5 minutes up to 2 hours. Migraine pain according to the 4 point VRS and VAS scales is recorded every 15 minutes up to 2 hours, and thereafter every hour up to 24 hours following the initial does. Other symptoms such as nausea, vomiting, photophobia and phonophobia, are recorded to the same schedule as theat for VRS and VAS.

Adverse events are monitored throughout the treatment period as well as at a follow-up visit after administration of the study drug.

Claims

1. Use of a compound of the general formula I



I

wherein

R^1 represents C_{3-5} alkyl; and

R^2 and R^3 independently represent C_{1-3} alkyl; or a pharmaceutically acceptable salt thereof ;

for the manufacture of a medicament for use in the treatment of a vascular headache condition.

2. Use according to claim 1, wherein the vascular headache condition is anyone of migraine, cluster headache, post-traumatic headache, tension headache, muscular headache or headache due to vascular diseases.

3. Use according to claim 2, wherein the vascular headache condition is migraine.

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4. Use according to any of the preceding claims, wherein the active agent is a compound of the formula I selected from anyone of

isopropyl-methyl-[2-(3-n-propoxy-phenoxy)-ethyl]-amine;
ethyl-isopropyl-[2-(3-n-propoxy-phenoxy)-ethyl]-amine;
diisopropyl-[2-(3-n-propoxy-phenoxy)-ethyl]-amine;
diethyl-[2-(3-n-propoxy-phenoxy)-ethyl]-amine;
isopropyl-methyl-[2-(3-n-butoxy-phenoxy)-ethyl]-amine;
ethyl-isopropyl-[2-(3-n-butoxy-phenoxy)-ethyl]-amine;
diisopropyl-[2-(3-n-butoxy-phenoxy)-ethyl]-amine;
ethyl-isopropyl-[2-(3-n-pentoxy-phenoxy)-ethyl]-amine; and
diisopropyl-[2-(3-n-pentoxy-phenoxy)-ethyl]-amine.

5. Use according to claim 4, wherein the active agent is anyone selected from

isopropyl-methyl-[2-(3-n-propoxy-phenoxy)-ethyl]-amine;
ethyl-isopropyl-[2-(3-n-propoxy-phenoxy)-ethyl]-amine; and
diisopropyl-[2-(3-n-propoxy-phenoxy)-ethyl]-amine.

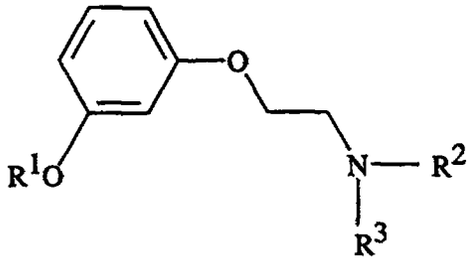
6. Use according to anyone of the preceding claims, wherein the use is suitable for intranasal administration.

7. Use according to anyone of the preceding claims, wherein the use is suitable for intravenous administration.

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8. A method for the treatment of a vascular headache condition, comprising administering to a patient suffering from said vascular headache condition, an effective amount of a compound of the general formula I



I

wherein

R^1 represents C_{3-5} alkyl; and

R^2 and R^3 independently represent C_{1-3} alkyl; or a pharmaceutically acceptable salt thereof .

9. A method according to claim 8, wherein the vascular headache condition is migraine.

10. A method according to claim 8 or 9, whereby the active agent is selected from anyone of

isopropyl-methyl-[2-(3-n-propoxy-phenoxy)-ethyl]-amine;
ethyl-isopropyl-[2-(3-n-propoxy-phenoxy)-ethyl]-amine;
diisopropyl-[2-(3-n-propoxy-phenoxy)-ethyl]-amine;
diethyl-[2-(3-n-propoxy-phenoxy)-ethyl]-amine;
isopropyl-methyl-[2-(3-n-butoxy-phenoxy)-ethyl]-amine;
ethyl-isopropyl-[2-(3-n-butoxy-phenoxy)-ethyl]-amine;
diisopropyl-[2-(3-n-butoxy-phenoxy)-ethyl]-amine;
ethyl-isopropyl-[2-(3-n-pentoxy-phenoxy)-ethyl]-amine; and
diisopropyl-[2-(3-n-pentoxy-phenoxy)-ethyl]-amine.

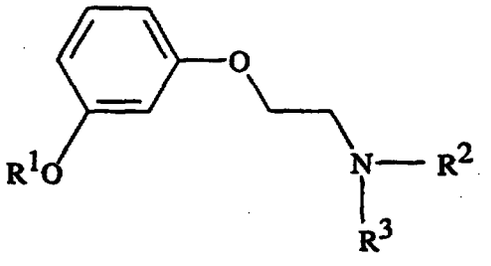
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11. A method according to claim 10, wherein the active agent is selected from anyone of

isopropyl-methyl-[2-(3-n-propoxy-phenoxy)-ethyl]-amine;
ethyl-isopropyl-[2-(3-n-propoxy-phenoxy)-ethyl]-amine; and
diisopropyl-[2-(3-n-propoxy-phenoxy)-ethyl]-amine.

12. A pharmaceutical composition suitable for use in the treatment of a vascular headache condition, comprising a compound of the formula I



I

wherein
R^1 represents C_{3-5} alkyl; and
R^2 and R^3 independently represent C_{1-3} alkyl; or a pharmaceutically acceptable salt thereof, as active ingredient, and optionally anyone of pharmaceutically acceptable carriers, diluents or adjuvants.

13. A pharmaceutical composition according to claim 12, wherein the vascular headache condition is migraine.

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