S016646J.65

Use of Epinastine for the Treatment of Pain

The present invention relates to a new use of epinastine for the treatment and prophylaxis of pain, especially chronic or inflammation-induced pain and in particular migraine. Epinastine (3-amino-9,13b-dihydro-1H-dibenz[c,f]imidazo[5,1-a]azepine hydrochloride) was described by Fügner et al. [Arzneimittelforschung 38 (1988) 1446 - 1453]. The active principle can be used in the form of a racemate or in the form of pure enantiomers or as a mixture of different proportions of both enantiomers. Therapeutically, epinastine is used as the hydrochloride. The invention here described, however, is not limited to the hydrochloride but relates to every addition salt with a pharmacologically acceptable acid as well as the free base.

State of the art is the use of epinastine and its salts for the treatment of asthma. European patent EP-B-0 035 749 discloses that this substance is also suitable for therapy of allergic diseases such as allergic rhinitis, allergic conjunctivitis and allergic bronchitis.

Headache is a commonly occurring symptom. In most cases the headache is of short duration and can readily be controlled by weak analgesics such as aspirin, paracetamol or ibuprofen. Such headache is bothersome but does not lead to any significant impairment of health. By contrast, chronic recurring headaches such as migraine can lead to such serious adverse affects that a doctor has to be consulted. These serious types of headaches often cannot be treated satisfactorily with a weak analgesic.

On the other hand, there is no universally accepted system of classifying headache; chronic recurring pain in the sense of this invention refers predominantly to migraine and Bing-Horton syndrome. Migraine itself incorporates several sub-forms [see J. Olesen and R.B. Lipton, Neurology 44 (1994) p6-p10 for a classification]. Although migraine and tension headaches are two different forms, several scientists see them as a clinical continuum with migraine at one end and tension headache at the other other end of the spectrum [K.L. Kumar and T.G. Cooney: "Headaches" in "Medical Clinics of North America" Vol. 79 No. 2 (1995) p.261 to 286]. Therefore it seems reasonable to suppose that many patients with tension headache will also respond to a therapy for migraine. Several other diseases which are associated with chronic pain, such as neuralgia, muscle pains and inflammation pain (as for example after sunburn or in osteoarthritis or after sports injuries) have common features with chronic recurring pain [Dray, A. Urban L. and Dickenson, A. Trends in Pharmacological Sciences 1994; 15: 190-197].

Existing therapy for migraine includes the use of ergot alkaloids such as ergotamine and sumatriptan. Although many patients profit from these medicaments, by no means all patients respond. Further, there are numerous side effects such as dizziness and nausea. Drugs for prophylactic management of migraine include methysergide and pizotifen, beta-blockers such as propanolol, and calcium channel blockers such as flunarizine. Chronic administration of these drugs can have side effects that impair the patients' quality of life and the drugs usually only reduce the frequency of migraine attacks but do not abolish them [see Diener, H.C. Eur. Neurol. 1994; 34(Suppl 2): 18-25.]

It is for this reason the purpose of this invention to

provide a drug for the treatment of migraine which is not only effective but also free of significant side effects. A further purpose of this invention is to provide a medicament with a high degree of safety for particular patient groups such as children, and patients with reduced liver or kidney function, or cardiovascular disease.

It has now been found that, surprisingly, epinastine fulfils these requirements to an exceptional degree. This is shown by the following research results:

In laboratory animals, it is possible to induce inflammation in the dura mater by electrical stimulation of the trigeminal ganglion, which causes the release of neuropeptides such as substance P from sensory nerve endings. Plasma extravasation can be monitored by markers such as Evans blue. This animal model is widely used for testing for drugs useful in migraine. Surprisingly, epinastine shows exceptionally good activity in this model. For chronic inflammatory pain, a widely used model is that first described in principle by Randall and Selitto (Randall, L.O. and Selitto, J.J. Arch. Int. Pharmacodyn. 1957; 111: 409-419). Inflammation is induced in the paw of a rat by injection of yeast cells and the inflammation-induced hyperalgesia measured. Epinastine also showed surprisingly good activity in this model.

State of the art is that epinastine is known as an antihistamine. The interaction between a ligand (e.g. a drug) and a receptor can be quantified by means of an affinity constant (K_i). The smaller the value of the affinity constant, so the stronger is the binding between drug and receptor. Especial attention is paid to those compounds which show a K_i value that is smaller or in the same order of magnitude as the expected

concentration of drug in target tissues (or plasma). The $5HT_7$ receptor is a special subtype of 5-hydroxytryptamine binding receptor (for a classification see 'Trends in Pharmacological Sciences 1994 Receptor & Ion Channel Nomenclature Supplement'). Surprisingly, a good binding of epinastine to the $5HT_7$ receptor has been found. The K_i values for epinastine and two comparison antihistamines are listed in Table 1.

The invention here described will now be illustrated with examples. Other possibilities will be apparent to one skilled in the art from this description. It is specifically pointed out that the examples are intended only to illustrate and not to limit the present invention.

Examples:

Study of binding of epinastine of the $5HT_7$ receptor.

Binding of 2.0 nM [^{3}H] LSD (60-80 mCi/mmol) to a rat $5HT_7$ receptor expressed in CHO cells was measured for 60 minutes at 37°C in 50 mM Tris-HCl buffer, pH 7.4, containing 10 mM $MgCl_2$ and 0.5 mM EDTA. The reaction was terminated by rapid vacuum filtration onto glass fiber filters pretreated with 0.1% polyethyleneimine. Binding studies were made in duplicate in the absence of drug and in the presence of between 6 and 8 concentrations of epinastine between 3 nM and 10 μM. Radioactivity trapped on the filters in the presence of each drug concentration was measured and compared with control values in order to ascertain interaction of drug with the cloned 5-HT_7 receptor site. Non-specific binding was determined in the presence of 5-carboxamidotryptamine (5-CT). The IC_{50} for the displacement of radiolabelled ligand was determined by graphical extrapolation and K_i values were calculated after correction for the

radioligand occupancy shift by the Cheng and Prusoff equation (see Biochem. Pharmacol. 1973; 22: 3099-3108). Three experiments were carried out. In each experiment epinastine was found to bind the $5HT_7$ receptor surprisingly well. The mean K_i value for epinastine found was 33 nM, the mean K_i of the (+) enantiomer was 28 nM, of the (-) enantiomer 189 nM. The individual values for the K_i of epinastine and its enantiomers which were found in the three experiments carried out are listed in table 1, together with K_i values for two comparison antihistamines:

Table 1:

Binding of Epinastine (Racemate and Enantiomers) and two comparison antihistamines (ketotifen and mepyramine) to the $5HT_7$ receptor

Compound	Full chemical name	Measured K_i values, nM
Epinastine	3-Amino-9,13b-dihydro-1H-dibenz-[c,f]-imidazo[1,5a]azepine-hydrochloride (racemate)	27, 41, 30
Epinastine (+) Enantiomer	(+)-3-Amino-9,13b-dihydro-1H-dibenz-[c,f]-imidazo[1,5a]-azepine-hydrochloride	45, 18, 22
Epinastine (-) Enantiomer	(-)-3-Amino-9,13b-dihydro-1H-dibenz-[c,f]-imidazo[1,5a]-azepine-hydrochloride	155, 204, 207
Ketotifen		406, 572, 331
Mepyramine		2660, 747, 1330

Study of the effect of epinastine on the plasma extravasation in the dura mater induced by electrical stimulation of the trigeminal ganglion

Male Wistar rats weighing 175 - 190 g were anaesthetised with nembutal 50 mg/kg i.p. and the jugular vein was cannulated for injection of drugs. The animals were placed in a stereotaxic frame. Symmetrical boreholes were drilled 3.0 mm laterally and 3.2 mm posteriorly from bregma and the electrodes were lowered 9.5 mm from dura mater. The test compound epinastine or solvent were administered intravenously 10 min prior to electrical stimulation of the right trigeminal ganglion (5 min; 2.0 mA, 5 Hz, 5 ms duration and Evans blue (30 mg/kg i.v.), as a marker of plasma protein extravasation, was given 5 min prior to electrical stimulation. 15 minutes after the end of the stimulation period the animals were perfused with 50 ml saline via the left cardiac ventricle to remove intravascular Evans blue. The dura mater was removed, blotted dry and weighed. Tissue Evans blue was extracted in 0.3 ml formamide at 50°C for 24 h. Dye concentrations were measured with a spectrophotometer at 620 nm wavelength, interpolated on a standard curve and expressed as ng dye per mg tissue weight.

Calculation of data:

Extravasation was expressed as the quotient calculated by dividing the Evan's blue content of the stimulated side by the Evan's blue content of the unstimulated side. Results are expressed as means. The results are listed in table 2.

Table 2

Effect of epinastine in an animal mode of migraine

Group treated with 0.9% sodium chloride solution: 1 ml/kg i.v.

animal number	body weight	Dura mater of stimulated side			Dura mater of non-stimulated side			Quotient
		wet weight	EB-content	EB/wet weight	wet weight	EB-content	EB/wet weight	stimulated/non-stimulated side
		[mg]	[µg/ml]	[µg/mg]	[mg]	[µg/ml]	[µg/mg]	
1	180 g	4.24	0.85	0.060	5.58	0.73	0.039	1.54
2	185 g	5.34	0.76	0.043	5.13	0.60	0.035	1.23
3	185 g	5.06	0.47	0.028	4.60	0.38	0.025	1.12
4	190 g	6.05	1.33	0.066	6.23	1.03	0.050	1.32
5	185 g	4.22	0.72	0.051	5.77	0.67	0.035	1.46
6	185 g	4.81	0.57	0.036	5.03	0.54	0.032	1.13
7	185 g	7.62	1.35	0.053	6.53	1.22	0.056	0.95

EB=Evans blue

mean 1.25

Group treated with epinastine 10 µg/kg i.v. dissolved in saline 1 ml/kg

animal number	body weight	Dura mater of stimulated side			Dura mater of non-stimulated side			Quotient
		wet weight	EB-content	EB/wet weight	wet weight	EB-content	EB/wet weight	stimulated/non-stimulated side
		[mg]	[µg/ml]	[µg/mg]	[mg]	[µg/ml]	[µg/mg]	
1	175 g	6.63	1.20	0.054	6.01	1.28	0.064	0.84
2	175 g	4.96	0.74	0.046	4.78	0.80	0.050	0.92
3	170 g	4.63	0.53	0.034	7.68	1.01	0.039	0.87
4	165 g	6.52	0.54	0.025	6.29	0.53	0.025	1.00
5	190 g	7.97	1.23	0.046	9.32	1.39	0.045	1.02
6	190 g	6.24	0.70	0.034	6.52	0.83	0.038	0.89
7	190 g	6.87	0.60	0.026	7.29	0.48	0.020	1.30

mean 0.98

Table 2 shows that in the animal model for migraine the treatment with epinastine significantly reduced the Evans blue extravasation induced by electrical stimulation of the trigeminal ganglion.

Study of the effect of epinastine on yeast-induced hyperalgesia in the rat paw

The method of Randall and Selitto was modified through use of the Analgesia meter by Basile of Milan.
Groups of 10 fasted rats of the strain Chbb:THOM (weight 110-140 g, 5 male 5 female) were dosed orally with 1% Natrosol 250 HX, 1 ml/100 g body weight, containing 0, 0.3, 1.0, 3.0 or 10 mg/kg epinastine (racemic mixture). 1 hour later the rats were injected subplantar with a suspension of yeast cells in a volume 0.1 ml into the right hind paw. 3 hours after injection of the yeast suspension, the pain threshold was determined in that the pressure on the inflamed paw was increased until a sign of pain was produced. From the pain threshold measured after the different doses of the epinastine, linear regression analysis was used to determine an ED_{50}. As Table 3 shows, epinastine increased the pain threshold in this model. The dose of epinastine required to increase the pain threshold by 50% was calculated as 1.1 mg/kg.

Table 3: Effect of epinastine on pain threshold in inflamed rat paw.

Substance	Dose mg/kg p.o.	Number of rats	Mean value of pain threshold g/hind paw	Standard deviation	% Increase
Control	0.0	10	150.4	30.4	
Epinastine	0.3	10	164.8	41.8	9.6
Epinastine	1.0	10	235.2	51.5	56.4
Epinastine	3.0	10	259.4	60.7	72.5
Epinastine	10.0	10	272.8	60.9	81.4

Table 4:
Test on the analgesic activity according to Randall Selitto

Type of animal: male/female rats
Weight: 110 to 140 g
Feeding: fasting
Application: 1.0 ml/100 g by oral route
Carrier: Natrosol 1%
Results after 90 minutes

Substance	Dosage	N	Mean	Effect in %	SD	VK in %
Control	0/0	10	150		46.188	30.792
Epinastine/Ibuprofen	0/3.0	10	153	2.00	20.028	13.090
Epinastine/Ibuprofen	0/10.0	10	202.00	34.67	29.740	14.723
Epinastine/Ibuprofen	0.3/0	10	216.00	44.00	44.020	20.380
Epinastine/Ibuprofen	0.3/3.0	10	252.00	68.00	57.116	22.665
Epinastine/Ibuprofen	0.3/10.0	10	277.00	84.67	81.792	29.528
Epinastine/Ibuprofen	1.0/0	10	232.00	54.67	57.889	24.952
Epinastine/Ibuprofen	1.0/3.0	10	295.00	96.67	70.593	23.930
Epinastine/Ibuprofen	1.0/10.0	10	369.00	146.00	107.233	29.060

Epinastine or its enantiomers may be given for the treatment of pain as an aqueous solution for injection by a suitable route such as intravenous, intramuscular or subcutaneous, as a tablet, as a suppository, as a cream, as a plaster for transdermal application, as an aerosol for inhalative administration to the lung, or as a nasal spray.

When dosed as a tablet or suppository the single dose for adults lies between 5 and 200 mg, with the preferred dose between 10 and 50 mg. For inhalation single doses between 0.05 and 20 mg, preferably between 0.2 and 5 mg

are administered. For parenteral injection the single dose lies between 0.1 and 50 mg with a preferred dose between 0.5 and 20 mg. The cited doses may if necessary be given several times in a day. Particularly advantageous could be the combination with other therapeutic principles, for example aspirin, paracetamol, non-steroidal anti-inflammatory drugs such as ibuprofen, meloxicam, indomethacin or naproxen; $5HT_{1D}$ agonists such as sumatriptan, MK-462, naratriptan or 311C; CP-122,288; UK 116,044; dopamine D_2 receptor antagonists such as metoclopramide; ergot alkaloids such as ergotamine, dihydroergotamine or metergoline; clonidine; methysergide; dotarizine; lisuride; pizotifen; valproic acid; aminotryptiline; beta blockers such as propanolol or metoprolol; calcium channel antagonists such as flunarizine or lomerizine, or neurokinin antagonists.

The following are examples of pharmaceutical formulations containing the active principle:

Tablets:
Epinastine 20 mg
Magnesium stearate 1 mg
Maize starch 62 mg
Lactose 83 mg
Polyvinylpyrrolidone 1.6 mg

Injectable solution:
Epinastine 0.3 g
Sodium chloride 0.9 g
Water for injection to 100 ml.

The solution may be sterilised using standard methods.

Solution for nasal or inhalative administration:
Epinastine 0.3 g

Sodium chloride 0.9 g
Benzalkonium chloride 0.01 mg
Purified water to 100 ml.

The solution described above is suitable for nasal administration as a spray, or in combination with a device which is able to produce an aerosol of particle size with preferred size distribution 2 to 6 μM, for administration to the lung.

Capsules for inhalation:
Epinastine is applied in a micronised form (particle size between 2 and 6 μM) usually with addition of micronised carrier substance such as lactose and filled into a capsule of hard gelatine. For inhalation, the usual devices for administering powders to the lung can be applied. In every capsule is between 0.2 and 20 mg epinastine and 0 and 40 mg lactose.

Inhalation aerosol
Epinastine 1 part
Soya lecithin 0.2 parts
Propellant gas mixture to 100 parts.
The mixture is preferably filled into an aerosol canister with a metering valve, the individual puff being so measured that a dose of 0.5 mg is administered. For other doses in the suggested dose ranges the appropriate preparation with a larger or smaller amount of active principle is used.

Cream

Composition	g/100 g cream
Epinastine	2
Concentrated hydrochloric acid	0.011
Sodium pyrosulphite	0.050
Mixture of equal parts of cetyl alcohol and stearyl alcohol	20
White vaseline	5
Synthetic bergamot oil	0.075
Distilled water to	100

The components are mixed in the usual way for preparation of a cream.

Claims

1. Use of epinastine in the form of its enantiomers, a mixture of the enantiomers, or as the racemate for the treatment of pain.

2. Use of epinastine, according to claim 1, for the treatment of migraine, Bing-Horton syndrome, tension headaches, muscular pains, inflammatory pains or neuralgias.

3. Use of epinastine as the racemate or in the form of its enantiomers present as free base or as an addition salt with a pharmacologically acceptable acid for the production of a medicament for the therapeutic treatment of pain.

4. Use of epinastine according to claim 3 as the racemate or in the form of its enantiomers present as free base or as an addition salt with a pharmacologically acceptable acid for the production of a medicament for the therapeutic treatment of migraine, Bing-Horton syndrome, tension headaches, muscular pains, inflammatory pains or neuralgias.

5. Use of epinastine in the form of its racemate or its enantiomers according to claim 1 or 2 in combination with another analgesic.

6. Use of epinastine in the form of its racemate or its enantiomers according to claim 5, characterised in that the pain-relieving drug used with it is an NSAID, a $5HT_{1D}$-agonist, a dopamine D_2 receptor antagonist, an ergot alkaloid, a beta blocker, a calcium channel blocker or a neurokinin antagonist.

7. Use according to claim 6, characterised in that the

NSAID is ibuprofen, meloxicam, indomethacin or naproxen.

8. Use according to claim 6, characterised in that the $5HT_{1D}$ agonist is sumatriptan, MK-462, naratriptan or 311C.

9. Use according to claim 6, characterised in that the dopamine D_2 receptor antagonist is metoclopramide.

10. Use according to claim 6, characterised in that the ergot alkaloid is ergotamine, dihydroergotamine or metergoline.

11. Use according to claim 6, characterised in that the beta-blocker is propanolol or metoprolol.

12. Use according to claim 6, characterised in that the calcium channel blocker is flunarizine or lomerizine.

13. Use according to claim 6, characterised in that the pain-relieving drug that is combined is aspirin, paracetamol, clonidine, methysergide, dotarizine, lisuride, pizotifen, valproic acid, aminotryptiline, CP-122,288 or UK 116,044.