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(54) Title: USE OF BRADYCARDIAC SUBSTANCES IN THE TREATMENT OF MYOCARDIAL DISEASES ASSOCIATED WITH HYPERTROPHY AND NOVEL MEDICAMENT COMBINATIONS

(54) Bezeichnung: VERWENDUNG VON BRADYCARDICA BEI DER BEHANDLUNG VON MIT HYPERTROPHIE EINHERGEHENDEN MYOCARDERKRANKUNGEN UND NEUE ARZNEIMITTELKOMBINATIONEN

(57) Abstract: The invention relates to a novel use of bradycardiac substances such as a Ca^{++} channel blocker, beta-receptor blockers or i_f channel blockers, the i_f channel blockers being preferred. Said substances are optionally used in combination with a cardioactive substance for inducing the regression of myocardial diseases associated with hypertrophy, in particular for treating ideopathic hypertrophic cardiomyopathies (HCM) in humans and domestic animals.

(57) Zusammenfassung: Die vorliegende Erfindung betrifft die neue Verwendung von bradykarden Substanzen wie einen Ca^{++} Kanal Blocker, Beta-Rezeptorenblocker oder i_f-Kanalblocker, wobei die i_f-Kanalblocker bevorzugt sind, gegebenenfalls in Kombination mit einer herzwirksamen Substanz zur Induktion der Regression von mit Hypertrophie einhergehenden Myocarderkrankungen, insbesondere zur Behandlung von idiopathischen hypertrophischen Kardiomyopathien (HCM) bei Mensch und Haustier.

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Use of bradycardiac substances in the treatment of myocardial diseases associated with hypertrophy and novel medicament combinations

Background of the Invention

Elevated heart rate may be treated with bradycardiac substances, particularly Ca^{++} channel blockers such as diltiazem and verapamil or beta-receptor blockers such as atenolol, bisoprolol, carvedolol, metoprolol or propanolol and i_f channel blockers such as zatebradine [1-(7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-on-3-yl)-3-[N-methyl-N-(2-(3,4-dimethoxy-phenyl)-ethyl)-propane] (see EP-B-0 065 229), 3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-(7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one (see EP-B-0 224 794) and its enantiomers cilobradine [(+)-3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)-piperidin-3-(S)-yl)-methyl]-(7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one] or alinidine [2-(N-allyl-2,6-dichloro-anilino)-2-imidazolidine), cf. also US Patent No. 3,708,485], while zatebradine is also known to have a favourable activity in the treatment of cardiac insufficiency (see EP-B-0 471 388).

Moreover it is known that bradycardiac substances, particularly the abovementioned compounds, of which the i_f channel blockers such as zatebradine, cilobradine or alinidine, and in particular cilobradine, are preferred, can have a beneficial effect on the symptoms of myocardial diseases accompanied by hypertrophy, particularly for the treatment of idiopathic hypertrophic cardiomyopathies (HCM) such as hypertrophy of the remainder of the myocardium after myocardial infarction, ischaemic cardiomyopathy, hypertrophy of the myocardium in valve defects and myocarditis under toxic or iatrogenic influences.

Summary of the Invention

Surprisingly it has now been found that bradycardiac substances, of which the i_f channel blockers such as zatebradine, cilobradine or alinidine, and in particular cilobradine, are preferred, not only have a favourable effect on the clinical symptoms of hypertrophic cardiomyopathy, but will even induce regression of these serious heart diseases.

The present invention thus relates to the new use of bradycardiac substances, particularly the abovementioned compounds, of which the i_f channel blockers such as zatebradine, cilobradine or alinidine, and in particular cilobradine, are preferred, to induce the regression of myocardial diseases accompanied by hypertrophy, particularly for the treatment of idiopathic hypertrophic cardiomyopathies (HCM) in humans and domestic pets.

In one aspect of the present invention, there is provided a pharmaceutical composition for the treatment of myocardial diseases accompanied by hypertrophy, containing an i_f channel blocker and optionally a cardioactive compound.

In one embodiment, the pharmaceutical composition is characterised in that zatebradine, cilobradine or alinidine may be used as the i_f channel blocker.

In another embodiment, the pharmaceutical composition is characterised in that cilobradine may be used as the i_f channel blocker.

In other embodiments, the pharmaceutical compositions disclosed above are characterised in that they may contain as a further cardioactive compound a cardioglycoside, a vasodilator, an ACE-inhibitor or an angiotensin-II antagonist.

In another aspect of the present invention, there is provided a use of an i_f channel blocker and optionally a further cardioactive compound as defined above for preparing a pharmaceutical composition which is suitable for the treatment of myocardial diseases accompanied by hypertrophy.

Detailed Description of the Invention

In order to achieve the effect according to the invention it is expedient to use the dosage known from the literature for the treatment of elevated heart rate for the individual bradycardiac substances. For example the single dose

for cilobradine is 0.1 to 0.5 mg/kg per os, preferably 0.2 to 0.4 mg/kg, 1 to 3 x daily,

for zatebradine it is 0.2 to 1 mg/kg 2 x daily and

for alinidine it is 0.5 to 5 mg/kg 2 x daily.

The new use of the bradycardiac substances according to the invention was investigated with the i_f channel blocker cilobradine by way of example, using the following method:

A cat with severe hypertrophic cardiomyopathy (heart rate about 200 beats/minute), ECG with ST accentuations as a sign of myocardial ischaemia, increased creatinine kinase activity in the plasma and in the ultrasound image, massive compression of the ventricular wall with a reduction in the ventricular

volume and the ejection fraction, exhibited a significant improvement in clinical symptoms after treatment with the i_f channel blocker cilobradine (0.3 mg/kg per os, 2 x daily) (relief from pain, normal ECG, return of normal physiological activity pattern).

Follow-up investigations after one year and after about 2 years' treatment surprisingly showed a regression in myocardial hypertrophy while the improvement in symptoms was maintained.

The hypertrophic cardiomyopathy in the cat serves as a model for the corresponding disease in humans (Kittleson et al., Circulation 91, 3172-3180 (1999)).

Treatment with the i_f channel blocker cilobradine thus leads not only to an improvement in symptoms but also to regression of the disease.

The present invention also relates to drug combinations, containing at least one bradycardiac substance, particularly one of the abovementioned compounds, preferably an i_f channel blocker, and at least one cardioactive substance such as

a cardioglycoside, e.g. methyldigoxin or digitoxin,

a vasodilator, e.g. nitroglycerine,

an ACE inhibitor, e.g. captopril or enalapril,

an angiotensin-II antagonist, e.g. losartan or telmisartan,

which are also suitable for treating myocardial diseases accompanied by hypertrophy, particularly for the treatment of idiopathic hypertrophic cardiomyopathies (HCM), if a rise in heart rate can be prevented by combining them with a bradycardiac substance.

To achieve the effect according to the invention it is convenient to use the dosages known from the literature for the individual bradycardiac substances for the treatment of elevated heart rate and the dosages known from the literature for the cardioactive compound used.

For this purpose the bradycardiac substances, either on their own or combined with other cardioactive compounds, are formulated with one or more conventional inert carriers and/or diluents, e.g. with maize starch, lactose, glucose, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethyleneglycol, propyleneglycol, stearyl alcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof, to produce conventional Galenic preparations such as plain or coated tablets, capsules, powders, suspensions, solutions, sprays or suppositories.

Thus, for example, the combination consisting of cilobradine and a cardioactive compound conveniently contains 0.1 to 0.5 mg/kg, preferably 0.2 to 0.4 mg/kg of cilobradine per os

plus 0.01 to 1 mg of methyldigoxin, 1 to 2 x daily,
0.01 to 1 mg of digoxin, 1 x daily,
0.1 to 2 mg of nitroglycerine, 2 to 3 x daily,
10 to 100 mg of captopril, 1 to 2 x daily,
2 to 20 mg of enalapril, 1 x daily,
10 to 200 mg of losartan, 2 x daily, or
20 to 80 mg of telmisartan, 1 x daily.

As the partners for the i_f channel blockers in the drug combination additionally act on an independent biological system and i_f channel blockers inhibit reflex increases in heart rate, which may occur in connection with the above combination partner, these have a synergistic activity.

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The Examples that follow are intended to illustrate the invention without restricting it:

Example 1

Capsules containing 1.25 mg of cilobradine

Composition:
1 capsule contains:

lactose monohydrate	82.75 mg
maize starch	55.3 mg

Method of preparation

The active substance, lactose monohydrate and maize starch are mixed and packed into size 4 capsules.

Example 2

Capsules containing 10 mg of cilobradine

Composition:
1 capsule contains:

lactose monohydrate	77.6 mg
maize starch	51.7 mg

Method of preparation

The active substance, lactose monohydrate and maize starch are mixed and packed into size 4 capsules.

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Example 3

Tablets containing 7.5 mg of cilobradine

Composition:

1 tablet contains:

active substance	7.5 mg
maize starch	59.5 mg
lactose	48.0 mg
polyvinylpyrrolidone	4.0 mg
magnesium stearate	1.0 mg
	120.0 mg

Method of preparation

The active substance, maize starch, lactose and polyvinylpyrrolidone are mixed and moistened with water. The moist mixture is forced through a sieve with a 1.5 mm mesh and dried at 45°C. The dry granules are passed through a sieve with a 1.0 mm mesh and mixed with magnesium stearate. The finished mixture is compressed in a tablet press with punches 7 mm in diameter provided with a dividing notch, to form tablets.

Weight of tablet: 120 mg

Example 4

Coated tablets containing 5 mg of cilobradine

1 tablet core contains:

active substance	5.0 mg
maize starch	41.5 mg
lactose	30.0 mg
polyvinylpyrrolidone	3.0 mg
magnesium stearate	0.5 mg
	80.0 mg

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Method of preparation

The active substance, maize starch, lactose and polyvinylpyrrolidone are mixed thoroughly and moistened with water. The moist mass is forced through a sieve with a 1.0 mm mesh and dried at 45°C, then the granules are passed through the same sieve. After mixing with magnesium stearate, convex tablet cores with a diameter of 6 mm are compressed in a tablet-making machine. The tablet cores thus produced are coated in known manner with a coated consisting essentially of sugar and talc. The finished coated tablets are polished with wax.
Weight of coated tablet: 130 mg

Example 5

Ampoules containing 5 mg of cilobradine

1 ampoule contains:

active substance	5.0 mg
sorbitol	50.0 mg
water for injections ad	2.0 mg

Method of preparation

In a suitable mixing vessel the active substance is dissolved in water for injections and the solution is made isotonic with sorbitol.

After filtration through a diaphragm filter, the solution is transferred into purified and sterilised ampoules under N_2 and autoclaved for 20 minutes in a stream of water vapour.

Example 6

Suppositories containing 10 mg of cilobradine

1 suppository contains:

active substance	0.010 g
hard fat (e.g. Witepsol H 19 and W 45)	1.690 g
	1.700 g

Method of preparation

The hard fat is melted. At 38°C the ground active substance is homogeneously dispersed in the melt. This is cooled to 35°C and poured into slightly chilled suppository moulds.

Example 7

Drops solution containing 10 mg of cilobradine

100 ml of solution contain:

active substance	0.2	g
hydroxyethylcellulose	0.15	g
tartaric acid	0.1	g
sorbitol solution, 70 % dry matter	30.0	g
glycerol	10.0	g
benzoic acid	0.15	g
dist. water ad	100	ml

Method of preparation

The distilled water is heated to 70°C. The hydroxyethylcellulose, benzoic acid and tartaric acid are dissolved therein with stirring. The solution is cooled to ambient temperature and the glycerol and the sorbitol solution are added with stirring. At ambient temperature the active substance is added and the mixture is stirred to dissolve it completely. It is then evacuated with stirring to eliminate air from the syrup.

Patent Claims

1. Pharmaceutical composition for the treatment of myocardial diseases accompanied by hypertrophy, containing an i_f channel blocker and optionally a further cardioactive compound.

2. Pharmaceutical composition according to claim 1, characterised in that zatebradine, cilobradine or alinidine is used as the i_f channel blocker.

3. Pharmaceutical composition according to claim 1, characterised in that cilobradine is used as the i_f channel blocker.

4. Pharmaceutical composition according to claims 1 to 3, characterised in that it contains as a further cardioactive compound a cardioglycoside, a vasodilator, an ACE-inhibitor or an angiotensin-II antagonist.

5. Use of an i_f channel blocker and optionally a further cardioactive compound as defined in claims 1 to 4 for preparing a pharmaceutical composition which is suitable for the treatment of myocardial diseases accompanied by hypertrophy.