

"NEW PHENOXYPROPANOLAMINE SALTS AND PHARMACEUTICAL
PREPARATIONS THEREOF"

Technical field

The present invention is related to new salts of the compound alprenolol which is a therapeutically active compound used in treatment of cardiac disorders such as hypertension, angina pectoris and arrhythmias. The pharmacological effect of alprenolol is exerted through blockade of beta receptors in the autonomic nerve system. In oral pharmaceutical preparations alprenolol is used as the hydrochloride. However, alprenolol hydrochloride has a strong local irritating effect. A number of ulcerations in the oesophagus of patients have been reported. Attempts to eliminate these side effects by using coated tablets have not yet been successful.

The object of the invention is to provide alprenolol in a form that avoids the side effects mentioned while maintaining a high absorption of the drug from the gastrointestinal system.

Background of the invention

Alprenolol, having the systematic name 1-(2-allylphenoxy)-3-isopropyl-amino-2-propanol, is described in SE-C-214 378, GB-C-1 140 508, DE-C-1 294 955 and FR-C-1 479 614. As salts were proposed the hydrochloride, lactate, sulfate and sulfamate. For other substituted phenoxypropanolamines salts of numerous acids have been proposed in generic and specific terms.

To reduce gastrointestinal side effects of locally irritating compounds slow-release preparations are used. Thus, potassium chloride is successfully used in preparations named Slow-K and Kalium Duretter[®]. Preparations of this kind containing alprenolol hydrochloride do however not reduce the risk of damage on the oesophagus. To the contrary, most of the damages reported are related to slow-release preparations.

Complex formation with carrageenan to reduce oesophageal damage of emepronium, doxycycline and propranolol has been proposed in EP-A1-0091409. Such complexes are difficultly soluble in water but release the drug in the acid environment of the stomach. The content of drug in these complexes is lower than in the original salts. This may cause problems in cases where high dosage tablets are desired.

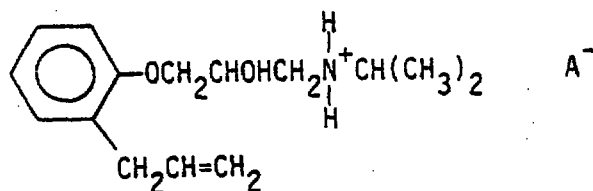
Description of the invention

10 The present invention provides as new salts the salts of alprenolol with benzoic acid or maleic acid. These salts are found to be very well tolerated and they are not causing damages on the oesophagus.

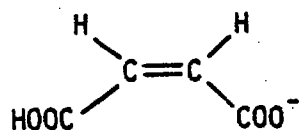
Further, the absorption of the new salts is about as high as for the hydrochloride.

Preferred salts are alprenolol benzoate and alprenolol hydrogenmaleate. Most preferred is alprenolol benzoate.

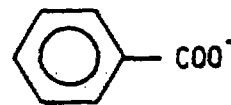
20 The preferred salts of the invention are represented by the formula



wherein A⁻ represents



or



The present invention also provides a pharmaceutical composition comprising a salt of alprenolol with benzoic acid or maleic acid, and a pharmaceutically acceptable adjuvant.

A pharmaceutical preparation for administration of alprenolol via the gastro-intestinal system where alprenolol is in the form of a salt with benzoic acid or maleic acid, is a further aspect of the invention.

Oral pharmaceutical preparations of the new alprenolol salts are found to provide the greatest advantages over previously known oral alprenolol preparations, and thus such oral preparations constitute a preferred embodiment of the invention. However, the new salts may advantageously
5 be used also in rectal pharmaceutical preparations.

The new salts of the invention may be formulated into pharmaceutical preparations in a manner known per se. They are suitable also for forming slow-release preparations, as they have a high content of
10 the active compound alprenolol. It is thus possible to produce both products which are rapidly absorbed and products with a prolonged duration.

In the preparation of pharmaceutical preparations containing a salt
15 of the present invention in the form of dosage units for oral administration the alprenolol salt may be mixed with suitable excipients such as lactose, saccharose, sorbitol, mannitol, starch such as potato starch, corn starch, amylopectin, cellulose derivatives or gelatine, as well as with a lubricating agent such as magnesium stearate, calcium
20 stearate, polyethyleneglycol, or the like, and be pressed into tablets. If coated tablets are wanted, the above prepared core may be coated with a concentrated solution of sugar, which solution may contain e.g. gum arabic, gelatine, talc, titanium dioxide or the like. Furthermore, the tablets may be film coated with a polymer in organic or aqueous
25 solution.

In the preparation of soft gelatine capsules (pearl-shaped, closed capsules), which consist of gelatine and e.g. glycerine or in the preparation of similar closed capsules the alprenolol salt is mixed
30 with a vegetable oil. Hard gelatine capsules may contain the active compound in combination with suitable excipients such as lactose, saccharose, sorbitol, mannitol, starch (such as e.g. potato starch, corn starch or amylopectin), cellulose derivatives or magnesium stearate.

Dosage units for rectal administration may be prepared in the form of suppositories, which contain the active substance in a mixture with a neutral fat base, or they may be prepared in the form of gelatine-rectal capsules which contain the active substance in a mixture with a vegetable oil or paraffin oil.

The alprenolol salts of the invention may be administered in equal molar amounts as recommended for alprenolol hydrochloride. Thus, suitable daily dosages of the new salts would be from 0.1 to 1.5 g.

Dosage units may suitably contain amounts corresponding to 50 to 200 mg alprenolol hydrochloride.

The salts of the invention may be prepared in a manner known per se by reacting alprenolol base with maleic acid and benzoic acid, respectively.

The invention is further illustrated by the following examples.

Example 1

31.2 g of a 40% solution of alprenolol base (50.1 mmol) in acetone was evaporated and 35 ml isopropyl alcohol was added. After evaporation the residue was dissolved in 18.7 g of isopropyl alcohol and heated to 50°C. 5.8 g (50.1 mmol) of maleic acid was dissolved in 60 ml isopropyl alcohol with stirring. The maleic acid solution was mixed with the alprenolol solution at 50°C. 15.3 g of alprenolol hydrogenmaleate (1:1 salt) was obtained as a white crystalline powder after crystallization and drying. Yield 83.6%. M.p. 111°C.

Example 2

31.2 g of a 40% solution of alprenolol base (50.1 mmol) in acetone and 25 ml of acetone was heated to 50°C. 6.1 g (50.1 mmol) of benzoic acid was dissolved in 70 ml acetone. The benzoic acid solution was added to the alprenolol solution and heated to 50°C. 16.7 g of

alprenolol benzoate was obtained as big white crystals after crystallization and drying. Yield 89.8%. M.p. 119°C.

Example 3

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Alprenolol hydrogenmaleate (128 g, corresponding to 100 g of alprenolol hydrochloride) was mixed with anhydrous lactose (136 g), microcrystalline cellulose (90.7 g) and magnesium stearate (3.3 g). The mixture was compressed into tablets with 10 mm diameter weighing 358 mg. The tablets disintegrated in 37°C water in 3 min. (test according to USP XX)

Example 4

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Alprenolol benzoate (130 g, corresponding to 100 g alprenolol hydrochloride) was mixed with anhydrous lactose, microcrystalline cellulose and magnesium stearate according to Example 3. Tablet weight 360 mg. Disintegration time according to USP XX 3.5 min.

20 Example 5

Tablets were prepared in a manner analogous to Example 3 of a mixture of alprenolol benzoate (260 g), anhydrous lactose (142 g), microcrystalline cellulose (181 g), crosslinked polyvinylpyrrolidone (29 g) and magnesium stearate (6 g). The tablet weight was 309 mg and the time of disintegration 20 s.

Example 6

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Slow release tablets were prepared by mixing alprenolol benzoate (260 g) with magnesium stearate (26 g). The mixture was moistened with a

solution of 12.6 g ethyl cellulose 10 cps in 71 g of ethanol 95%. The moist mass was dried and milled through a 1.0 mm sieve. Anhydrous lactose (115 g), microcrystalline cellulose (90 g) and magnesium stearate (4.9 g) were added. Tablets weighing 510 mg were made with 12 mm punches. The tablets disintegrated very slowly. The dissolution properties in artificial gastric juice were compared with commercial slow-release tablets of alprenolol hydrochloride (Aptin[®] Durules[®], AB Hässle). The test was carried out with a paddle method at 50 rpm according to USP XX.

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	1	2	4	6 hours
Tablets, Example 6	40	58	77	88 %
Aptin [®] Durules [®]	45	63	83	94 %

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Example 7

Alprenolol hydrogenmaleate (64 g) was granulated with ethanol (17 g). After drying the granules were sieved through a 0.7 mm sieve and mixed with anhydrous lactose (136 g), microcrystalline cellulose (91 g), crosslinked polyvinylpyrrolidone (14.5 g) and magnesium stearate (3 g). The mixture was compressed into tablets with 10 mm diameter weighing 308 mg. The disintegration time was about 10 s and the dissolution in artificial gastric juice was complete in 10 min.

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Example 8

A slow release preparation based on a large number of individually coated small pellets was prepared in the following manner.

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Alprenolol benzoate (74 g), microcrystalline cellulose (16 g), di-sodium hydrophosphate (10 g) were mixed in an intensive mixer. The mixture was moistened with about 35 g of water and was worked until round granules were formed. These were dried and granules greater than 1.0 mm and smaller than 0.5 mm were sieved off.

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The granules were coated in a fluid-bed coating equipment with a solution consisting of 10 g ethyl cellulose, 2.5 g hydroxypropyl cellulose and 2.5 kg ethanol. After drying the granules were filled into hard gelatine capsules in an amount corresponding to 200 mg of alprenolol hydrochloride.

The capsules thus prepared disintegrate after ingestion and then release the dosage as a large number of small granules each contained within a coating which causes slow release of the drug. By these means further safety against local damage in the digestive channel is achieved.

Release of the drug from this product tested in artificial gastric juice (USP XX) with equipment II according to (USP XX) was as follows

0.5	1	2	3	4 hours
21	41	72	85	90 %

Biological tests

Oesophageal irritating effect

Tablets prepared according to Examples 3 and 4 were compared on oesophagus-irritating effect with tablets containing 100 mg alprenolol hydrochloride (Aptin[®], AB Hässle) and tablets containing di-alprenolol fumarate in an amount corresponding to 100 g of the hydrochloride, said tablets being prepared in analogy with Example 3. The test was carried out in the anaesthetized pig by lowering the tablets into the oesophagus and fixing with a silk thread according to Olofsson et al., Acta Pharmacol. et Toxicol. 53, 385-391 (1983). After 5 hours the tablets were taken up and the oesophagus was rinsed with 50 ml of water. The mucous membrane was photographed through fibre optic. The results appear in the table below.

Preparation	Pig no.	Reaction in the oesophagus
Tablet, example 3	1	no reaction
	2	" "
Tablet, example 4	3	erythema
	4	no reaction
Alprenolol hydrochloride } tablet)	5	severe ulceration
	6	ulceration
Alprenolol fumarate tablet	7	no reaction
	8	ulceration

- 10 Thus, tablets containing the alprenolol salts of maleic acid and benzoic acid produced substantially less harmful effects than did the marketed alprenolol hydrochloride product.

In vivo absorption

- 15 Absorption of tablets prepared according to Example 5 and alprenol hydrochloride (Aptin[®]) tablets 100 mg was studied in 6 healthy test persons after one night of fasting. Plasma samples were taken during 25 h and alprenolol content was determined by gas chromatography. In the
- 20 accompanying drawing, Figure 1 shows the absorption of an alprenolol benzoate tablet compared with an alprenolol hydrochloride tablet, wherein ⊙ represents alprenolol HCl (Aptin[®] tabl) 100 mg (n=6) and □ represents alprenolol benzoate tabl 130 mg (n=6); the absorption from the
- 25 benzoate tablet was as fast and complete as from the reference tablet.

- Absorption of alprenolol from tablets prepared according to Example 7 was studied and compared with tablets containing 50 mg alprenolol hydrochloride (Aptin[®] 50 mg) by
- 30 administering orally on different occasions two tablets to a fasting dog. Blood samples were taken repeatedly during five hours. Plasma concentrations appear from the table below.

	Time (h)	Alprenolol hydro- chloride tablet (nmol/l)	Tablet Example 7 (nmol/l)
5	0.25	27	<5
	0.5	221	54
	0.75	401	457
	1	590	690
	1.5	432	398
10	2	367	315
	3	164	206
	4	62	126
	5	19	64

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Both tablets were rapidly absorbed to about the same degree.

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- 10 -

CLAIMS

1. A salt of alprenolol with benzoic acid or maleic acid.

2. A salt according to claim 1 which is alprenolol benzoate or alprenolol hydrogenmaleate.

5 3. Alprenolol benzoate.

4. A compound according to claim 1 substantially as herein described with reference to any one of the Examples.

5. A pharmaceutical composition comprising a
10 compound as defined in any one of claims 1 to 4 and a pharmaceutically acceptable adjuvant.

6. A pharmaceutical composition according to claim 5 which is suitable for oral administration.

7. A pharmaceutical composition according to
15 claim 5 substantially as herein described with reference to any one of Examples 3 to 8.

8. A process for preparing an alprenolol salt as defined in any one of claims 1 to 4 wherein an alprenolol base is reacted with benzoic acid or maleic
20 acid.

9. A process according to claim 8 substantially as herein described with reference to Example 1 or 2.

10. A compound according to any one of claims
25 1 to 4 or a composition according to any one of claims



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5 to 7 for use in a method of treatment of the human or animal body by surgery or therapy or of diagnosis practised on the human or animal body.

11. A compound according to any one of 5 claims 1 to 4 or a composition according to any one of claims 5 to 7 for use in the treatment of cardiac disorders.
