

Aktiebolaget DRACO
Lund/SWEDEN

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Inventors: Carl-Axel Bauer
Leif-Åke Svensson

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ML/ÅW

New use

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New useField of the invention

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The present invention is related to the use of a pharmaceutically acceptable salt of the bis-dimethyl carbamate pro drug of terbutaline, namely 5-[2-(tert-butylamino)-1-hydroxyethyl]-m-phenylene-
10 bis(dimethylcarbamate), called bambuterol or a pharmaceutically acceptable salt thereof in the manufacture of pharmaceutical preparations with lipid lowering effects.

15 Background of the invention

Bambuterol, which is described in the European patent EP 43807 is a pro drug of a beta-2-adrenergic agonist (terbutaline) and can be used in the treatment of
20 asthmatic patients, no effect on the lipoprotein metabolism has been reported earlier.

A positive correlation between high risk for coronary heart disease and increased concentrations of low-density
25 lipoprotein (LDL) has been well documented, Castelli WP, Doyle JT, Gordon T, et al. HDL Cholesterol and other lipids in coronary heart disease. The Cooperative Lipoprotein Phenotyping Study. Circulation 55, 767-772 (1977). In contrast, it has been suggested that an
30 increased concentration of high-density lipoprotein (HDL) may confer a low risk for heart disease. A more recent study, Gordon T, Castelli WP, Hjortland MC, et al. High density lipoprotein as a protective factor against coronary heart disease. The Framingham Study. Am J Med 62,
35 707-714 (1977), however, suggests that the ratio between LDL cholesterol and HDL Cholesterol is a better indicator of risk rather than either of them alone, on the premise that LDL transports the cholesterol produced in the liver



to the extra-hepatic tissues and HDL brings it back into the liver for further metabolism.

Different kinds of cholesterol are present in the blood,
5 and the most important forms are HDL = High Density Lipoprotein, and LDL = Low Density Lipoprotein.

Prior art

10 In an earlier study the beta-2-adrenoreceptor agonist terbutaline was found to significantly increase the HDL-cholesterol levels in healthy nonobese man. Cf Hooper P.L et al N.Engl.J.Med 305, p.1455, 1981. Furthermore, it is known from Jain R et al.Clin. Chem 29, p.1031, 1983 that
15 there might be an interrelationship between plasma cholinesterase inhibition and lipoprotein metabolism, resulting in a decrease in LDL cholesterol. There is, however, always a risk with plasma cholinesterase inhibition, namely if the effect is not selective towards
20 the plasma cholinesterase. An unselective inhibitor gives toxic effects depending on the inhibition of acetylcholinesterase. Thus in order to obtain an effective lipid lowering effect, the combination of a HDL-cholesterol increasing effect and a plasma cholinesterase
25 inhibiting effect, which will lower LDL, is wanted.

Outline of the invention

With the background above it was decided to test the lipid
30 lowering effect of bambuterol, which is a specific inhibitor of plasma cholinesterase, which generates the beta-2-adrenoreceptor agonist terbutaline, which gives a significantly prolonged effect duration 24 h versus 8 h for conventional terbutaline tablets or 12 h for
35 terbutaline slow release tablets (compared to terbutaline). The lipid lowering preparation contains between 5-30 mg of bambuterol, preferably 10-20 mg. It is especially preferred to use the hydrochloride of



bambuterol. The pharmaceutical preparations are preferably in the form of tablets, but it is also possible to use other kinds of preparations such as capsules, oral solutions or injection solutions.

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Conventional pharmaceutical preparations can be used.

Biological test

10 In a study on the effects of bambuterol and terbutaline
slow release on lipoprotein metabolism in healthy
volunteers with normal lipoprotein status both bambuterol
and terbutaline induced favourable changes in lipoprotein
metabolism, and atherogenic index (s-LDL/s-HDL),
15 statistically significant and clinically relevant
elevations were seen in HDL cholesterol and Apo A1
concentrations (in Apo A1 the major protein component is
HDL), while plasma triglycerides levels decreased. In
parallel the activity of lipoprotein lipase, increased,
20 suggesting that the alterations in plasma lipoprotein
concentrations were mediated via an increase in the rate
of turnover of triglyceride-rich
lipoproteins. No effect on LDL cholesterol could be
demonstrated with any of the drugs.

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On the other hand, in a second placebo controlled study in
16 patients with diabetes mellitus with moderately
impaired lipoprotein status, bambuterol 20 mg once daily
for 5 weeks was found to significantly rise S-HDL-
30 cholesterol levels and to lower S-LDL-cholesterol levels
compared to placebo. This was accompanied by a significant
decrease in both S-cholesterol and S-triglyceride levels.
Cf. Table 1.

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Table 1. Effects of bambuterol on lipoprotein metabolism markers in 16 diabetes mellitus patients.

	Before treatment	After 3 weeks	After 6 weeks	
N = 16				
<u>S-HDL-Cholesterol</u> (mmol/L)	1.06 ± 0.31	P: 1.12 ± 0.34 B: 1.29 ± 0.35	1.18 ± 0.33 1.26 ± 0.35	p=0.0001
<u>S-LDL-Cholesterol</u> (mmol/L)	4.04 ± 0.92	P: 4.11 ± 0.89 B: 3.85 ± 0.98	4.11 ± 0.93 3.90 ± 0.97	p=0.004
<u>S-Cholesterol</u> (mmol/L)	5.92 ± 1.08	P: 6.02 ± 0.93 B: 5.76 ± 1.14	6.00 ± 0.89 5.78 ± 1.05	p=0.029
<u>S-Triglyceride</u> (mmol/L)	1.86 ± 1.62	P: 1.69 ± 1.10 B: 1.38 ± 0.86	1.58 ± 0.98 1.36 ± 0.86	p=0.026

P = Placebo

B = Bambuterol

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Conclusion

From the results given in table 1, it can be concluded
5 that bambuterol gives beneficial effects on the
lipoprotein metabolism in patients with moderately
impaired lipoprotein status. The effect of bambuterol is
persistent and highly significant and of the same order as
seen with other well known lipid lowering drugs.
10 Bambuterol thus offers a new, convenient lipid lowering
therapy, since bambuterol is dosed only once daily.

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Claims

1. Use of 5-[2-(tert-butylamino)-1-hydroxyethyl]-m-phenylene-bis(dimethylcarbamate), bambuterol, or a
5 pharmaceutically acceptable salt thereof, in the
manufacture of a pharmaceutical preparation with
lipid lowering effects.
2. Use according to claim 1, wherein bambuterol is in
10 the form of its hydrochloride.
3. A method for obtaining of lipid lowering effect
whereby a lipid lowering effective amount of
bambuterol or a pharmaceutically acceptable salt
15 thereof is used.
4. A method according to claim 3 wherein the
hydrochloride of bambuterol is used.
- 20 5. A pharmaceutical preparation for use as in lowering
the lipid content of the blood, wherein the active
ingredient is bambuterol or a pharmaceutically
acceptable salt thereof.
- 25 6. A preparation according to claim 5 wherein the active
ingredient is the hydrochloride of bambuterol.

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