USE OF COMT INHIBITORS FOR THE MANUFACTURE OF A MEDICAMENT FOR THE PREVENTION OF DIABETIC VASCULAR DYSFUNCTIONS

The invention relates to the use of catechol-O-methyl transferase (COMT) inhibitors in the prevention of diabetic vascular dysfunctions, preferably nephropathy, retinopathy and neuropathy.

There is a world-wide search for a therapy that can prevent the complications in type 1 and type 2 diabetes. Chronic exposure to diabetes leads to an increased incidence of microangiopathic complications which are associated with considerable morbidity and mortality. For example, disturbances in the microcirculation of the feet may leed to amputation of the legs which in turn can cause severe complications. In the case of diabetic nephropathy renal failure is usually the actual cause of death. Diabetes is also the most common cause of renal failure among young adults.

The factors that lead to diabetic nephropathy have been extensively studied but are still incompletely known. According to the general concept, early functional effects of diabetes, such as hyperfiltration, are contributing factors. Hyperfiltration is associated with increased glomerular pressure and increased albumin excretion rate (AER). Increased AER is considered to be an early sign of glomerular damage.

The presently most commonly used therapy, ACE inhibitors, will not prevent the development of diabetic nephropathy, but may postpone the development of terminal renal failure.

It has been disclosed that nitecapone, a COMT inhibitor has a natriuretic effect (Eklöf et al. J. Am. Soc. Nephrology 5 (3), 657, 1994, Holtbäck et al., J. Am. Soc. Nephrology, 7(9), 1633, 1996). However, the effect of COMT inhibitors on hyperfiltration and albuminuria has not been suggested earlier.

The object of the invention is to provide the use of COMT inhibitors, especially nitecapone (3-(3,4-dihydroxy-5-nitrophenyl)methylene-2,4-pentanedione) in the the prevention of diabetic vascular dysfunctions, such as nephropathy, retinopathy and neuropathy. The compounds of the invention may be used for the treatment of any type of diabetes.

Suitable COMT-inhibitors and methods for preparation thereof have been described, e.g. in GB 2200109, EP 237929 and PCT application PCT/FI96/00295.

Pharmaceutically acceptable salts and esters of these compounds, when applicable, may be prepared by known methods. All physiologically acceptable salts are useful as active medicaments, however, sodium, potassium, ammonium, calcium and magnesium salts and salts with hydrochloric, hydrobromic, phosphoric and sulfuric acids and with organic acids like oxalic, fumaric, tartaric, malonic, acetic and citric acids etc. are preferred.

The effective dose of the compound varies considerably depending on the efficacy of the COMT-inhibitor in question, the severity of the condition to be treated, and the route of administration. Most preferred are oral formulations. The effective dose for human beings is likely to be from about 20 to 2000 mg per day.

The compounds according to this invention are given to a patient as such or in combination with one or more other active ingredients and/or suitable pharmaceutical non-active additives. The latter group comprises solvents, gel forming agents, emulsifiers, stabilizers, colorants, preservatives, lubricants, glidants, fillers and other widely used excipients and formulation aids.

The compounds used in this invention are formulated into dosage forms using commonly known pharmaceutical manufacturing methods. The dosage forms can be e.g. tablets, capsules, granules, suppositories, emulsions, suspensions or solutions. Depending on the route fo administration and the galenic form, the concentration of the active compound in a formulation can typically vary between about 1 to 100 % (w/w).

Choosing the auxiliary ingredients for the formulation is routine for those of ordinary skill in the art. It is evident that suitable solvents, gel forming ingredients, dispersion forming ingredients, colors etc. are used in a normal way.

Results

The effect of nitecapone on renal function

The effect of nitecapone 3-(3,4-dihydroxy-5-nitrophenyl)methylene-2,4-pentanedione treatment (from 3 to 6 weeks) on renal function was tested in diabetic rats. Streptozocin (STZ) was injected into the tail vein of rats to induce diabetes. Blood glucose concentration was measured regularly. Hyperglycemia in diabetic rats to be included in the test had to be apparent 12 h after STZ injection and had to remain stable (16-25 mM glucose) throughout the whole observation time. STZ-administered rats with unfasting plasma glucose concentration < 16.5 mM at 48 h after injection were excluded.

The effect of nitecapone on glomerular filtration rate (GFR) is given in Table 1. The rats were studied with conventional clearance techniques using inulin as an indicator of GFR. Values are given for age-matched control rats. The nontreated diabetic rats had a characteristic hyperfiltration, which was abolished by nitecapone treatment. GFR in diabetic nitecapone treated rats and control rats was not different.

Table 1 Effect of daily treatment with nitecapone (30 mg/kg bw BID) on GFR in rats with streptozotocin-indiced diabetes (3 weeks)

	GFR ml/min
Diabetic rats without nitecapone	2.25 +/– 0.26*
Diabetic rats with nitecapone	1.28 +/- 0.26
Non-diabetic rats	1.59 +/- 0.12

n=7-8 in each group

* significantly different from other 2 group (ANOVA)

The effect of daily treatment with nitecapone on albumin excretion rate (AER) in diabetic rats is given in Table 2. The untreated diabetic rats had increased AER. Nitecapone treatment caused a pronounced attenuation of this diabetic complication. Almost 50 % of the nitecapone treated rats had a very low (i.e. normal) AER.

Table 2 Effect of daily treatment with nitecapone (30 mg/kg bw BID) on albumin excretion rate (AER)

	AER, mg/ml GFR
3 weeks without nitecapone	6.18 +/- 1.53
3 weeks with nitecapone	1.20+/- 1.39*
6 weeks without nitecapone	10.9 +/- 2.33
6 weeks with nitecapone	2.33 +/- 2.91*

* significantly lower than in nontreated rats

In addition to the above identified results it was consistently observed that intestinal edema, which characteristically occurs in diabetic rats, was not present in the nitecapone treated animals.

It is also surprising how low doses of nitecapone are needed to obtain the desirable effect. This fact is shown by the results represented in Table 3. Nitecapone in drinking water (25 µg/ml water = 9.7 mg/kg/day) was administered to Sprague Dawley rats with streptozotocin-induced diabetes for 10 days. The glomerular filtration rate was determined on day 10. The blood samples were taken on day 7 at 10 a.m

Table 3. Effect of daily treatment with nitecapone (9.7 mg/kg in drinking water) on GFR in rats with streptozotocin-induced diabetes (10 days)

Rat Nr	Treatm.	BW g	Water intake ml/day	GFR ml/min	NC in plasma ng/ml
84A	CON	281	140	3.36	-
84B	CON	276	140	2.34	-
84C	CON	276	140	3.31	-
85A	CON	272	180	3.55	-
85B	CON	256	180	3.87	-
		m 272 ± 4	m 156 ± 10	m 3.29 ± 0.3	
92A	NC	273	100	2.38	64
92B	NC	289	100	2.42	58
92C	NC	279	100	ND	65
93A	NC	256	110	2.38	43
93B	NC	269	110	2.87	29
93C	NC	265	110	2.44	70
		m 272 ± 4	m 105 ± 5	m 2.50 ± 0.1	m 55 ± 6

ND = not determined.
m = mean
± = se

The effect of nitecapone on retinopathy

The ability of nitecapone to attenuate the biochemical markers associated with diabetic retinopathy was tested in cultured porcine retina pigment epithelium cells (RPE). The content of protein kinase C (PKC) was measured in the cells exposed to normal (5 mM) or high (20 or 50 mM) glucose concentrations with or without nitecapone. At the tested concentrations (10 to 40 µM) nitecapone abolished the glucose-induced increase in the PKC content in RPE cells. This suggests that nitecapone has an antiretinopathic effect.

CLAIMS

1. Use of COMT inhibitors or their pharmaceutically acceptable salts or esters in the manufacture of a medicament for use in the prevention of diabetic vascular dysfunctions.

2. The use of claim 1, wherein said prevention is related to microangiopathy.

3. The use of claim 2, wherein said prevention is related to nephropathy and / or retinopathy.

4. The use of claim 3, wherein said prevention is related to attenuation of albuminuria.

5. The use according to any of claims 1 to 4, wherein the COMT inhibitor is nitecapone.

6. A method for the prevention of diabetic vascular dysfunctions by administering to a mammal in need of such prevention an effective amount of a COMT inhibitor or its pharmaceutically acceptable salt or ester to prevent said dysfunctions.

7. The method according to claim 6, wherein said prevention is related to microangiopathy.

8. The method according to claim 7, wherein said prevention is related to nephropathy and / or retinopathy.

9. The method according to any of claims 6 to 8, wherein said COMT inhibitor is nitecapone

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