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

VERWENDUNG VON COMT INHIBITOREN ZUR HERSTELLUNG EINES ARZNEIMITTELS ZUR VORBEUGUNG VON DIABETISCHEN VASKULÄREN FUNKTIONSSTÖRUNGEN

UTILISATION D'INHIBITEURS DE LA COMT POUR FABRIQUER UN MEDICAMENT POUR LA PREVENTION DES DYSFONCTIONS VASCULAIRES DIABETIQUES

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(56) References cited:
• SEPPO KAAKKOLA ET AL.: “General properties and clinical possibilities of new selective inhibitors of catechol O-methyltransferase” GEN.PHARMAC., vol. 25, no. 5, 1994, pages 813-824, XP0002056721

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**Description**

[0001] 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.

[0002] 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 lead 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.

[0003] 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.

[0004] 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.

[0005] 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.

[0006] 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 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.

[0007] Suitable COMT-inhibitors and methods for preparation thereof have been described, e.g. in GB 2200109, EP 237929 and PCT application PCT/FI96/00295.

[0008] 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.

[0009] 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.

[0010] 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.

[0011] 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 of administration and the galenic form, the concentration of the active compound in a formulation can typically vary between about 1 to 100 % (w/w).

[0012] 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**

[0013] 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.

[0014] 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.
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.

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.

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### Table 1

<table>
<thead>
<tr>
<th>Effect of daily treatment with nitecapone (30 mg/kg bw BID) on GFR in rats with streptozotocin-induced diabetes (3 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic rats without nitecapone</td>
</tr>
<tr>
<td>Diabetic rats with nitecapone</td>
</tr>
<tr>
<td>Non-diabetic rats</td>
</tr>
</tbody>
</table>

n=7-8 in each group
* significantly different from other 2 group (ANOVA)

### Table 2

<table>
<thead>
<tr>
<th>Effect of daily treatment with nitecapone (30 mg/kg bw BID) on albumin excretion rate (AER)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AER, mg/ml GFR</td>
</tr>
<tr>
<td>3 weeks without nitecapone</td>
</tr>
<tr>
<td>3 weeks with nitecapone</td>
</tr>
<tr>
<td>6 weeks without nitecapone</td>
</tr>
<tr>
<td>6 weeks with nitecapone</td>
</tr>
</tbody>
</table>

* significantly lower than in nontreated rats

### Table 3

<table>
<thead>
<tr>
<th>Effect of daily treatment with nitecapone (9.7 mg/kg in drinking water) on GFR in rats with streptozotocin-induced diabetes (10 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat Nr</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>84A</td>
</tr>
<tr>
<td>84B</td>
</tr>
<tr>
<td>84C</td>
</tr>
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<td>85A</td>
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<tr>
<td>92C</td>
</tr>
<tr>
<td>93A</td>
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</tbody>
</table>
The effect of nitecapone on retinopathy

[0018] 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. The use of claim 1 wherein said prevention is related to neuropathy.

7. The use according to any of claims 6, wherein the COMT inhibitor is nitecapone.

### Patentansprüche


2. Verwendung nach Anspruch 1, wobei sich die Vorbeugung auf Mikroangiopathy bezieht.

3. Verwendung nach Anspruch 2, wobei sich die Vorbeugung auf Nephropathie und/oder Retinopathie bezieht.

4. Verwendung nach Anspruch 3, wobei sich die Vorbeugung auf die Attenuierung von Albuminurie bezieht.

5. Verwendung nach irgendeinem der Ansprüche 1 bis 4, wobei der COMT-Inhibitor Nitecapone ist.

6. Verwendung nach Anspruch 1, wobei sich die Vorbeugung auf Neuropathie bezieht.

7. Verwendung nach Anspruch 6, wobei der COMT-Inhibitor Nitecapone ist.
Revendications

1. Utilisation d'inhibiteurs de la COMT ou de leurs sels ou esters acceptables du point de vue pharmaceutique pour la fabrication d'un médicament utile pour la prévention des dysfonctionnements vasculaires diabétiques.

2. Utilisation suivant la revendication 1, dans laquelle ladite prévention concerne une micro-angiopathie.

3. Utilisation suivant la revendication 2, dans laquelle ladite prévention concerne une néphropathie et/ou une rétinopathie.

4. Utilisation suivant la revendication 3, dans laquelle ladite prévention concerne l'atténuation d'une albuminurie.

5. Utilisation suivant l'une quelconque des revendications 1 à 4, dans laquelle l'inhibiteur de la COMT est la nitécapone.

6. Utilisation suivant la revendication 1, dans laquelle ladite prévention concerne une neuropathie.

7. Utilisation suivant la revendication 6, dans laquelle l'inhibiteur de la COMT est la nitécapone.