Specification

The invention relates to the use of 3-β-methoxy-ethyl 5-isopropyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-pyridine [sic] for the preparation of medicaments having cerebral activity.

It has already been disclosed that 1,4-dihydropyridine derivatives can be used as coronary agents and blood pressure agents (compare DT-OS 2,117,517). The abovementioned compound has already been described in British Patent Specification 1,358,951 of the applicant as a compound having coronary activity. It has also been disclosed that certain basic 1,4-dihydropyridine esters have a cerebral action (compare DT-OS 2,302,855 and DT-OS 2,407,115).

It has now been found that the compound 3-β-methoxy-ethyl 5-isopropyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-pyridine [sic] has a very advantageous action on disturbances of cerebral blood flow.

Surprisingly, the compound to be used according to the invention shows in very low doses a cerebral-specific action which permits its use for the treatment of cerebral insufficiencies, in particular of disturbances of cerebral blood flow of various origins. The compound is superior, both in the strength of action and in the mode of action and specificity, to the known substances having cerebral activity.

It is particularly suitable for treatment of age-related and sclerosis-related cerebral vascular disorders and of cerebral hypoxidoses, post-traumatic brain damage, general vascular and metabolic cerebral insufficiencies, disturbances of balance and other vestibular disorders, and

vascular disturbances of vision.

No such strong and organ-specific cerebral action has hitherto been disclosed in the series of cerebral therapeutics known from the state of the art, so that the use of the compound according to the invention as a cerebral therapeutic represents an enrichment of pharmacy.

The compound 3-β-methoxyethyl 5-isopropyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-pyridine [sic] (short name: Bay e 9736 or nimodipine) is obtained in a manner known per se by, for example, reacting β-methoxyethyl 3-nitrobenzylideneacetoacetate with isopropyl β-aminocrotonate in an inert organic solvent at elevated temperature. The compound has a melting point of 125°C.

Other possible preparation processes are described in DT-OS 2,117,571 and DT-OS 2,117,573.

The advantageous organ-specific action of the compound according to the invention is coupled with very good tolerability and a long-lasting duration of action. Comparison with the compound which is stressed in DT-OS 2,407,115 as being particularly active, 3-β-(N-benzyl-N-methylamino)-ethyl 5-methyl 2,6-dimethyl-4-(3-nitrophenyl-1,4-dihydropyridine-3,5-dicarboxylate [sic],
shows that the compound according to the invention not only causes a distinctly greater increase in cerebral blood flow but also has a more advantageous profile of action besides the greater duration of action.

The surprising advantageous properties are to be demonstrated by the following investigations.

In dogs, cats, rats, rabbits and rhesus and and squirrel monkeys, the compound according to the invention increases the cerebral blood flow after enteral and parenteral administration in a wide dose range. The cerebral vasodilating action is in the foreground of the spectrum of

actions of the substance: it takes place after a low dosage and very specifically in the cerebral vessels. The compound according to the invention differs in this surprising predilection for a cerebrovascular action distinctly from all the commercially available products of this category as well as from other dihydropyridine derivatives for which a certain cerebral dilating action in animal experiments has also been alleged (compare DT-OS 2,407,115; YC-93).

It is possible using the compound according to the invention to carry out successful and effective prophylaxis and therapy of the sequelae of an ischaemic cerebral insult. Thus, for example, in cats a post-ischaemic reduction in cerebral blood flow is completely prevented, the post-ischaemic EEG changes are distinctly improved, and the mortality after an experimental cerebral isult [sic] is drastically reduced.

There is as yet no competition to the compound according to the invention having this cerebral antiischaemic action. It has not been possible to achieve an action of this type with any of the existing drugs of this category.

In rats and mice, the experimentally induced disturbances of learning and memory of vascular and non-vascular origin (cerebral ischaemia, hypoxia, convulsions, sleep deprivation etc.) are, surprisingly, distinctly improved or completely normalized by treatment with the compound according to the invention. In the extent of this action, the compound is far superior to the commercially available products.

The surprising advantageous effect of the compound according to the invention is to be demonstrated, by way of example, by the data in the table which follows.

Table: Effect of substances on the flow in the cerebral and extracerebral vessels in dogs

| Substance | Dose mg/kg i.v. | Number of animals | Increase in cerebral blood flow ($^{133}$xenon clearance) | Increase in flow ext. carotid art. (el.-magn. flowmeter) | femoral art. |
|---|---|---|---|---|---|
| BAY e 9736 | 0.01 | 22 | 30% | 26% | 0.5% |
| YC 93 | 0.01 | 3 | 16% | 40% | 10.0% |
| Bencyclan (Fludilat®) | 10.0 | 5 | 34% | - | 152% |
| Cinnarizine (Stutgeron®) | 10.0 | 4 | 43% | - | 65% |

The compound can be converted in a known manner into the customary formulations such as tablets, capsules, coated tablets, pills, suppositories, granules, aerosols, syrups, liquid, solid and cream-like emulsions and suspensions and solutions, by use of inert, non-toxic pharmaceutically suitable vehicles or solvents. The therapeutically active compound should be present in each of the these in a concentration of about 0.1 to 90% by weight of the total mixture, that is to say in amounts which suffice to reach the indicated dosage range.

The exceptionally good absorption of the compound according to the invention through the mucosa of the gastrointestinal tract makes it possible to use many pharmaceutical formulations: the substance can be used as a medicament in the form of coated tablets, capsules, bitable capsules, tablets, drops, syrup or suppositories and even ointments.

The formulations are prepared, for example, by extending the active compound with solvents and/or vehicles, where

appropriate using emulsifiers and/or dispersing agents, it being possible to use, for example where water is employed as diluent, organic solvents and auxiliary solvents where appropriate.

Examples of auxiliaries which may be mentioned are: water, non-toxic organic solvents such as paraffins (for example petroleum fractions), vegetable oils (for example peanut-sesame oil), alcohols (for example ethyl alcohol and glycerol), glycols (for example propylene glycol and polyethylene glycol); solid vehicles such as, for example, natural rock powders (for example highly disperse silica, and silicates), sugars (for example raw sugar [sic], lactose and glucose); emulsifiers such as non-ionic and antionic [sic] emulsifiers (for example polyoxyethylene fatty acid esters, polyoxyethylene fatty alcohol ethers, alkyl sulphonates and aryl sulphonates), dispersing agents (for example lignin, sulfite waste liquors, methylcellulose, starch and polyvinylpyrrolidone) and lubricants (for example magnesium stearate, talc, stearic acid and sodium lauryl sulphate).

Administration is effected in a customary manner, preferably enterally or parenterally, in particular orally.

In the case of enteral use, it is of course possible for tablets to contain not only the said vehicles but also additives such as sodium citrate, calcium carbonate and dicalcium phosphate together with various additional substances such as starch, preferably potato starch, gelatine and the like. It is also possible for lubricants such as magnesium stearate, sodium lauryl sulphate and talc to be used for making tablets. In the case of aqueous suspensions and/or elixirs which are intended for oral uses, it is possible to add to the active compound not only the abovementioned auxiliaries but also various flavourings or colorants.

In the case of parenteral use, it is possible to employ

solutions of the active compound using suitable liquid vehicles.

On intravenous administration, it has in general proved advantageous to administer amounts of about 0.0001 to 0.5 mg/kg, preferably about 0.001 to 0.1 mg/kg, of body weight per day to achieve effective results, and on enteral administration the dosage is about 0.001 to 1 mg/kg, preferably 0.01 to 0.5 mg/kg, of body weight per day.

Nevertheless, it may be necessary where appropriate to deviate from the said amounts, and in particular to do so as a function of the body weight or the nature of the route of administration, as well as by reason of the species and its individual behaviour towards the medicament or interval at which the administration takes place. Thus, in some cases it may suffice to make do with less than the abovementioned minimum amount, whereas in other cases the said upper limit must be exceeded. In the case of administration of large amounts, it may be advisable to divide these into several single doses over the day. The same dosage range is intended for administration in human medicine. In this connection, the above statements similarly apply.

Examples of pharmaceutical formulations:

1. Soft gelatine capsules with 5 mg of active compound per capsule: for about 10,000 capsules a solution of the following composition is prepared:

| | |
|---|---|
| Bay e 9736 active compound | 58.8 g |
| Glycerol | 240.0 g |
| Polyethylene glycol 400 | 3833.2 g |
| Water | 400.0 g |
| | 4532.0 g |

The solution is dispensed in a manner known per se into oblong soft gelatine capsules of size 6 minims. The capsules are suitable for chewing or swallowing.

2. Tablets, lacquered tablets or coated tablets with 10 mg of active compound:

The following amounts relate to the preparation of 100,000 tablets or cores:

| | |
|---|---|
| Bay 3 9736 finely ground active compound | 1.00 kg |
| Lactose | 10.25 kg |
| Starch | 2.70 kg |
| Microcrystalline cellulose | 2.70 kg |

The above constituents are mixed in a planetary mixer and then mixed with a solution prepared from

| | |
|---|---|
| Polyvinylpyrrolidone (mol. weight for example 25,000) | 1.20 kg |
| Polysorbate 80 USP (Tween 80®) and | 0.06 kg |
| water | about 4.00 kg |

and granulated in a manner known per se by grating the moist mass and drying. The following is then added:

| | |
|---|---|
| Magnesium stearate | 0.09 kg |

The finished tablet mixture of 18 kg is compressed to form biconvex tablets weighing 180 mg. Diameter of the tablets 8 mm.

The tablets can be lacquered or coated in a manner known per se.

3. Drops with 4 mg of active compound per ml:

The following solution is prepared

For drops with 4 mg per ml

| | |
|---|---|
| Bay e 9736 active compound | 4.0 g |
| 96% strength ethanol | 450.0 g |
| Liquid flavouring | 6.0 g |
| Methylparaben | 1.0 g |
| Polyethylene glycol 400 | 50.0 g |
| 50% strength simple syrup | 400.0 g |
| Foodstuff colourant (yellow orange S) | 0.6 g |
| Water ad | 1000.0 ml |

The active compound, methylparaben and flavour are

dissolved at room temperature. Then polyethylene glycol 400 and the 50% strength simple syrup are slowly added, while stirring, the colorant is dissolved, and the mixture is made up to 1000 ml with water.

The solution is dispensed into brown bottles, it being possible to add, where appropriate, sweeteners in addition.

4. Syrup with 10 g of active compound per 10 ml:

| | |
|---|---|
| Bay e 9736 active compound | 1.0 g |
| Methylparaben | 1.0 g |
| 96% strength ethanol | 250.0 g |
| Liquid flavouring | 4.0 g |
| Polyethylene glycol 400 | 100.0 g |
| Glycerol | 250.0 g |
| 50% strength simple syrup | 300.0 g |
| Foodstuff colorant (yellow orange S) | 0.5 g |
| Water ad | 1000.0 ml |

Preparation is carried out in a manner analogous to Example 3.

Patent Claims

1. Use of 3-β-methoxy-ethyl 5-isopropyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-pyridine [sic] for the preparation of medicaments having cerebral activity.

2. Use of 3-β-methoxy-ethyl 5-isopropyl, 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-pyridine [sic] and micro-crystalline cellulose for the preparation of medicaments having cerebral activity.

3. Use of 3-β-methoxy-ethyl 5-isopropyl, 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-pyridine [sic] and micro-crystalline cellulose for the preparation of medicaments having cerebral activity in a solid formulation.

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As printed.

**Claims**

1. Use of 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-pyridine-3-β-methoxy-ethyl ester 5-isopropyl ester for the preparation of medicaments with cerebral action.

2. Use of 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-pyridine-3-β-methoxy-ethyl ester 5-isopropyl ester and microcrystalline cellulose for the preparation of medicaments with cerebral action.

3. Use of 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-pyridine-3-β-methoxy-ethyl ester 5-isopropyl ester and microcrystalline cellulose for the preparation of medicaments with cerebral action which are in the form of solid formulations.

**Revendications**

1. Utilisation de l'ester 3-β-méthoxyéthylique-5-isopropylique de la 1,4-dihydro-2,6-diméthyl-4-(3-nitrophényl)-pyridine pour la préparation de médicaments actifs sur le cerveau.

2. Utilisation de l'ester 3-β-méthoxyéthylique-5-isopropylique de la 1,4-dihydro-2,6-diméthyl-4-(3-nitrophényl)-pyridine et de cellulose microacristalline pour la préparation de médicaments actifs sur le cerveau.

3. Utilisation de l'ester 3-β-méthoxyéthylique-5-isopropylique de la 1,4-dihydro-2,6-diméthyl-4-(3-nitrophényl)-pyridine et de la cellulose microcristalline pour la préparation de médicaments actifs sur le cerveau à l'état de composition solide.

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