26372

PHILIPPINE PATENT [19]

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[54] Title: NOVEL MEDICINAL USE OF 5-(2-CHLOROETHYL)-4-METHYLTHIAZOLE, OR A SALT OR SOLVATE THEREOF

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Use of chlormethiazole in the prevention and/or treatment of neurodegeneration.

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26372

26372

SPECIFICATION

TO THE HON. DIRECTOR:

BE IT KNOWN THAT WE, ROBIN B. BOAR, ALAN J. CROSS and RICHARD A. GREEN, all citizens of Great Britain and residents of 25 Meadow Way, Hertfordshire SG6 3JB; 54 Birchwood Road, West Byfleet, Surrey KT14 6DW; and 22 Laurel Drive Southmoor, Abingdon, Oxon OX13 5DC, Great Britain, respectively; have invented a new and useful --

"NOVEL MEDICINAL USE"

of which the following is the specification:

26372

26372

NOVEL MEDICINAL USE

ABSTRACT

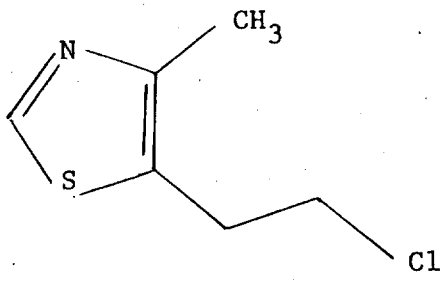
Use of chlormethiazole in the prevention and/or treatment of neurodegeneration.

NOVEL MEDICINAL USE

SUMMARY OF THE INVENTION

This invention relates to a new medical use for a heterocyclic compound and pharmaceutical compositions containing it. In particular, it relates to the use of 5-(2-chloroethyl)-4-methylthiazole and the pharmaceutically acceptable salts and solvates thereof, in the prevention and/or treatment of neurodegeneration in pathological conditions such as stroke, cerebral ischaemia, hypoxia, epilepsy and neurodegenerative diseases such as Alzheimer's disease, multi-infarct dementia and Huntington's disease. This thiazole compound with which the present invention is concerned has the following structural formula:

26372



and is known alternatively as chlormethiazole, chlomethiazole or chlorethiazole.

BACKGROUND OF THE INVENTION

Preparations containing chlormethiazole, particularly in the form of its acid addition salts, especially, as disclosed in GB 847,520, the acid addition salt with ethanedisulphonic acid, are known to possess valuable therapeutic properties. The general pharmacology and therapeutic applications of chlormethiazole have been extensively reviewed in a recent publication (Acta Psychiatr. Scand., Suppl. 329, 73, 1986). Thus, for example, chlormethiazole possesses sedative and hypnotic properties and is used clinically as a hypnotic in the elderly, particularly in the management of psychogeriatric patients. Chlormethiazole also possesses anti-convulsant properties and is used clinically for the treatment of different types of convulsive states, such as, for example, status epilepticus and pre-eclampsia. Chlormethiazole is also used

clinically for the treatment of ethanol (alcohol) withdrawal states including delirium tremens.

The present invention can be distinguished from the above prior art in that it is concerned with a new medical use which is unexpected and which can be clearly distinguished from the applications in the above described disorders. Usefulness in any or all of the above clinical disorders would not suggest or in any way make obvious the use of the compounds which are the subject of the present invention in the prevention and/or treatment of neurodegeneration.

There are a few contradictory reports on the effects of chlormethiazole on cerebral circulation and metabolism. I, Pichlayr and co-workers (Anaesthesist, 1973, 22, 496-500) found that i.v. infusion of chlormethiazole into dogs caused an initial increase in cerebral blood flow, followed by a decrease in both cerebral blood flow and

oxygen consumption rate, a finding which they interpreted as indicating that chlormethiazole possibly offers a degree of protection to cerebral functions. Others (J. Pogady, M. Ruscak and J. Orlicky, Activ. Nerv. Sup. (Prague), 1972, 14, 87) have presented results which are interpreted as possibly indicating a deleterious effect of chlormethiazole in situations associated with impaired brain circulation. Significantly, in the most recent study (Acta Anaesth. Scand., 1979, 23, 259-266) Carlsson and Rehncrona were unable to demonstrate either a protective or a detrimental effect of chlormethiazole when it was administered during reversible, incomplete ischaemia in the rat. None of the above studies considered an action of chlormethiazole on neurodegeneration following pathological insult.

The present invention provides a method for the prevention and/or treatment of neurodegeneration in the above mentioned pathological conditions.

Thus the new use of chlormethiazole that is the subject of the present invention could not in any way be expected from the above prior art.

Other compounds have been reported to be useful in the prevention and/or treatment of neurodegeneration (see, for example, EP 230 370 and EP 273 309), but there is no drug that is presently accepted as a standard for this use. None of the other compounds thus described would suggest the use of the compound of the present invention for the prevention and/or treatment of neurodegeneration.

DETAILED DESCRIPTION OF THE INVENTION

Different aspects of the present invention are:

the use of 5-(2-chloroethyl)-4-methylthiazole, or a pharmaceutically acceptable

salt or solvate thereof, in the manufacture of a medicament for the prevention and/or treatment of neurodegeneration, especially in connection with conditions such as stroke, cerebral ischaemia, hypoxia, epilepsy and in neurodegenerative diseases such as Alzheimer's disease, multi-infarct dementia and Huntington's disease;

a method for the prevention and/or treatment of neurodegeneration, especially in connection with conditions such as stroke, cerebral ischaemia, hypoxia, epilepsy and in neurodegenerative diseases such as Alzheimer's disease, multi-infarct dementia and Huntington's disease, comprising administering a sufficient amount of 5-(2-chloroethyl)-4-methylthiazole or a pharmaceutically acceptable salt or solvate thereof;

a pharmaceutical formulation for use in the prevention and/or treatment of neurodegeneration, especially in connection with conditions such as stroke, cerebral ischaemia, hypoxia, epilepsy and in neurodegenerative diseases such as Alzheimer's disease, multi-infarct dementia and Huntington's disease, comprising 5-(2-chloroethyl)-4-methylthiazole as active ingredient.

The clinically most important of the new fields of use are considered to be the prevention and/or treatment of neurodegeneration in connection with stroke, cerebral ischaemia, multi-infarct dementia and hypoxia.

The effectiveness of 5-(2-chloroethyl)-4-methylthiazole for use according to the present invention in the prevention and/or treatment of neurodegeneration may be demonstrated by the

ability to decrease damage to the CA1/CA2 hippocampal pyramidal neurones in gerbils following ischaemia induced by a period of occlusion of the carotid arteries followed by reperfusion. The detailed mechanisms that underlie ischaemia-induced degeneration of hippocampal neurones have yet to be clarified, but the above mentioned gerbil test system has been widely used as a predictive model of neuroprotective activity (see, for example, B.J. Alps, C. Calder, W.K. Hass and A.D. Wilson, Brit. J. Pharmacol., 1988, 93, 877-883; R. Gill, A.C. Foster and G.N. Woodruff, J. Neuroscience, 1987, 7, 3343-3349).

It is a particular feature that the compound of the present invention is effective in preventing and/or treating neurodegeneration not only when administered prior to the ischaemic insult, but also when administered solely after the ischaemic insult, even several hours after the ischaemic insult. It is to be expected that the

efficacy when administered post-ischaemia is of particular relevance to the likely clinical utility.

The administration in the novel method of treatment of this invention may conveniently be oral, rectal, or parenteral at a dosage level of, for example, about 1 to 3000 mg/kg, preferably about 10 to 1000 mg/kg and especially about 25 to 250 mg/kg and may be administered on a regimen of 1 to 4 times per day. The dose will depend on the route of administration, a particularly preferred route being by intravenous infusion of an aqueous solution containing chlormethiazole ethanedisulphonate, for example an aqueous solution containing chlormethiazole ethanedisulphonate 8 mg/ml. It will be appreciated that the severity of the disease, the age of the patient and other factors normally considered by the attending physician will influence the individual regimen and dosage most appropriate for a particular patient.

The pharmaceutical formulations comprising the compound of this invention may conveniently be tablets, pills, capsules, powders or granules for oral administration; sterile parenteral solutions or suspensions for parenteral administration; or as suppositories for rectal administration.

Neuroprotection Studies

Ischaemia was induced in gerbils by occlusion of the carotid arteries following the accepted general procedure as described in, for example, EP 230 370 and R. Gill, A.C. Foster and G.N. Woodruff, J. Neuroscience, 1987, 7, 3343-3349.

Typical procedures and results are exemplified as follows:

a) Administration of the Test Compound Prior to Induction of Ischaemia.

26372

Ischaemia was induced in gerbils by 10 minute occlusion of both carotid arteries. Restoration of blood flow after occlusion was checked visually and the animals were allowed to survive for 4 days. The extent of neuronal degeneration in the hippocampus was then assessed. The test compounds were administered (i.p.) as a single dose 30 minutes prior to occlusion. Typical results are shown in Table 1. As is seen in Table 1, chlormethiazole was effective in reducing the damage to the CA1/CA2 hippocampal neurones.

Table 1

Test compound	Dose	Number of Animals	% Damage to CA1/CA2 Hippocampal Neurones
None	--	10	94.9 ± 2.0
Chlormethiazole ethanedisulphonate	100mg/kg	7	< 5
Chlormethiazole ethanedisulphonate	50mg/kg	8	37.6 ± 13.4
Prior Art Compounds			
MK 801[a]	3mg/kg	6	< 5
Ifenprodil[b]	4mg/kg	7	62 ± 8.0

References to Prior Art Compounds

a: See, for example, EP 230 370

b: See, for example, E.T. MacKenzie, B. Gotti, J-P. Nowicki & A.R. Young (1984) in 'Neurotransmitters and the Cerebral Circulation'. Raven Press, New York, pp219-243.

b) Administration of the Test Compound Following Induction of Ischaemia.

The general procedure described in (a) above was followed except that the test compound was administered (i.p.) as a single dose at the stated time following the end of the occlusion. No administration was made prior to the occlusion. Typical results are shown in Table 2. As is seen in Table 2, chlormethiazole was effective in reducing the damage to the CA1/CA2 hippocampal neurones when administered after the ischaemic insult.

Table 2

Test compound	Dose	Time of Dosing after Induction of Ischaemia	Number of Animals	% Damage to CA1/CA2 Hippocampal Neurones
None	--	--	9	80.4 ± 7.9
Chlormethiazole ethanedisulphonate	100mg/kg	30 minutes	8	12.8 ± 10.4
Chlormethiazole ethanedisulphonate	50mg/kg	30 minutes	8	69.4 ± 6.9
Chlormethiazole ethanedisulphonate	100mg/kg	1 hour	9	14.3 ± 8.7
Chlormethiazole ethanedisulphonate	100mg/kg	2 hours	8	7.25 ± 4.8
Chlormethiazole ethanedisulphonate	100mg/kg	6 hours	10	45.6 ± 14

26372

What we claim is:

1. A method for the prevention or treatment of neurodegeneration, by administering to a patient in need of such prevention or treatment a sufficient amount of 5-(2-chloroethyl)-4-methylthiazole, or a pharmaceutically acceptable salt or solvate thereof.

2. A method for the prevention or treatment of neurodegeneration in connection with stroke, by administering to a patient in need of such prevention or treatment a sufficient amount of 5-(2-chloroethyl)-4-methylthiazole, or a pharmaceutically acceptable salt or solvate thereof.

3. A method for the prevention or treatment of neurodegeneration in connection with cerebral ischaemia, by administering to a patient in need of such prevention or treatment a sufficient

amount of 5-(2-chloroethyl)-4-methylthiazole, or a pharmaceutically acceptable salt or solvate thereof.

4. A method for the prevention or treatment of neurodegeneration in connection with hypoxia, by administering to a patient in need of such prevention or treatment a sufficient amount of 5-(2-chloroethyl)-4-methylthiazole, or a pharmaceutically acceptable salt or solvate thereof.

5. A method for the prevention or treatment of neurodegeneration in connection with multi-infarct dementia, by administering to a patient in need of such prevention or treatment a sufficient amount of 5-(2-chloroethyl)-4-methylthiazole, or a pharmaceutically acceptable salt or solvate thereof.

6. A pharmaceutical formulation for use in the prevention or treatment of neurodegeneration

comprising 5-(2-chloroethyl)-4-methylthiazole as active ingredient in admixture with a suitable carrier.

7. A pharmaceutical formulation for use in the prevention or treatment of neurodegeneration in connection with stroke comprising 5-(2-chloroethyl)-4-methylthiazole as active ingredient in admixture with a suitable carrier.

8. A pharmaceutical formulation for use in the prevention or treatment of neurodegeneration in connection with cerebral ischaemia comprising 5-(2-chloroethyl)-4-methylthiazole as active ingredient in admixture with a suitable carrier.

9. A pharmaceutical formulation for use in the prevention or treatment of neurodegeneration in connection with hypoxia comprising 5-(2-chloroethyl)-4-methylthiazole as active ingredient in admixture with a suitable carrier.

26372

10. A pharmaceutical formulation for use in the prevention or treatment of neurodegeneration in connection with multi-infarct dementia comprising 5-(2-chloroethyl)-4-methylthiazole as active ingredient in admixture with a suitable carrier.

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