

SPECIFICATION

Compositions containing 1,3-dimethyl-5-aminoadamantane

- 5 Disorders of the central nervous system, including Parkinson's disease, depressions, spasticity, hyperkinesia and rigidity, are usually treated nowadays with L-dopa, aminoadamantanes or anticholinergics, agents having different modes of action and widely different structures. Depending on the form and intensity of the disease involved, rigor, tremor and bradyphrenia are the target of the treatment. In many cases, however, single doses of 200 to 300 milligrams of the active agent are necessary to achieve a satisfactory effect on
- 10 rigidity, but such dosages are already regarded as undesirably pathological. Such drugs act on akinesia and rigidity, but a wide range of effects, including also desirable reduction of tremor and treatment of bradyphrenia, can in most cases only be effected through the employment of greatly increased dosages.
- Among the substances previously proposed for influencing the central nervous system, and as especially useful in the treatment of hyperkinesia and rigidity, and particularly in the treatment of Parkinson's disease,
- 15 is 1,3-dimethyl-5-aminoadamantane and its pharmaceutically acceptable salts which act upon rigor, tremor and akinesia. Animal experiments have revealed the anticonvulsant and locomotor activity of this compound at doses of 5 to 20 mg/kg body weight.
- Many recent publications have dealt with the range of activity of 1,3-dimethyl-5-aminoadamantane and its pharmaceutically acceptable salts, e.g. Drugs of the Future Vol. I, No. 9 (1976), 427 ff; Arzneimittel-Forschung
- 20 "Drug Research" 27 (II), No. 7 (1977), 1477 ff; European Journal of Pharmacology 26 (1974), 9-14, North-Holland Publishing Company; Arzneimittel-Forschung "Drug Research" 23, No. 12 (1973), 1737-1739; and U. S. Patent Specification No. 4,122,193 which discloses compositions of 1,3-dimethyl-5-aminoadamantane and its pharmaceutically acceptable salts and a method of treating hyperkinesia therewith.
- 25 German Offenlegungsschrift No. 2,518,677 discloses dopaminergic stimulating compositions comprising certain alkaloids together with phosphodiesterase inhibitors. Caffeine and theophyllamine are reported to be phosphodiesterase inhibitors, but the structure and activity of the alkaloids are very different from 1,3-dimethyl-5-aminoadamantane.
- U. S. Patent Specification No. 3,961,060 discloses the combination of a phosphodiesterase inhibitor such
- 30 as caffeine with dopa, m-tyrosine, apomorphine or a compound designated ET495, for the alleged purpose of potentiating dopaminergic effect. Dopa, the only compound for which evidence of potentiation (by caffeine) is given, and the other compounds disclosed in that specification where dopaminergic activity is allegedly potentiated, have structures very different from 1,3-dimethyl-5-aminoadamantane.
- According to the present invention, a pharmaceutical composition comprises 1,3-dimethyl-5-
- 35 aminoadamantane, or a pharmaceutically acceptable salt thereof, and a methylxanthine, the amount by weight of the methylxanthine being not more than 15 times the amount of weight of the 1,3-dimethyl-5-aminoadamantane or salt thereof.
- The compositions of the invention include two compounds which can act synergically on disorders of the central nervous system. In particular, administration of the compounds of the invention can reduce rigidity,
- 40 at a lower dosage level than has been previously possible on the administration of 1,3-dimethyl-5-aminoadamantane alone. Since the compositions of the invention can allow the administration of lower dosage levels than has been previously been required for the individual compounds, side effects can be reduced.
- The compositions of the invention generally comprise a pharmaceutically acceptable carrier in addition to
- 45 the active ingredients. Preferably, the compositions are provided in unit dosage form, e.g. for oral or parenteral administration.
- Unit dosages of the novel compositions preferably comprise no more than 10, and often no more than 5, mg of the 1,3-dimethyl-5-aminoadamantane or salt thereof. There are usually at least 0.25, 0.5 or one, and often no more than 3 or 1.5, parts by weight of the methylxanthine per part by weight of the
- 50 1,3-dimethyl-5-aminoadamantane or salt thereof. The preferred methylxanthines are caffeine and theophylline.
- For administration by the oral or parenteral, e.g. intraperitoneal, route, the novel compositions may suitably be formulated as tablets, capsules, solutions or injectable solutions. Suitable carrier substances, if desired, may be administered together with the active ingredients and the common organic and inorganic
- 55 adjuvants which do not react with the active ingredients, for example, water, ethanol, polyethylene glycol, gelatine, lactose, starch, magnesium stearate, talc and cellulose may be employed for this purpose. If necessary, the formulations may be stabilised and/or sterilised by admixture with one or more preservatives, wetting agents, buffers, colourants, essences or flavours. Preparations providing sustained release of the active ingredients may also be provided in known manner. In all of these compositions, the 1,3-dimethyl-5-
- 60 aminoadamantane compound is either present as the free base or as a pharmaceutically acceptable salt thereof.
- Suitable salts of 1,3-dimethyl-5-aminoadamantane which can be employed in the invention are well known and include the usual amine and acid addition salts, either of an organic or inorganic nature, such as the hydrochloride, hydrobromide, sulphate, citrate or tartrate, as disclosed in U.S. Patent Specification No.
- 65 4,122,193 and elsewhere. These salts are made from the free basic compound in known manner.

Dosages containing up to 5 or 10 mg of 1,3-dimethyl-5-aminoadamantane (or equivalent amount of a suitable salt) may be administered two to four times daily for the ameliorative or maintenance treatment of the condition of the subject. The exact amount and frequency of administration will depend upon the usual parameters including the nature of the condition and the weight of the patient.

5 The following Examples illustrate compositions of the invention. 5

Example 1: injectible solutions

0.1 g of 1,3-dimethyl-5-aminoadamantane and 1.0 g of theophylline are dissolved in double distilled water with the addition of 0.6 g of sodium chloride, to a total volume of 100 ml. Subsequently, the solution is 10 filtered through degerminating layers, filled into two ml. ampoules and subjected to thermal sterilisation for twenty minutes at 120°C. 10

Example 2: solution

1 g of 1,3-dimethyl-5-aminoadamantane and 6 g of theophylline are dissolved in an ethanol-water mixture 15 (10 g ethanol 83 g water). The solution is filtered until it remains clear. The solution contains 5 mg of 1,3-dimethyl-5-aminoadamantane and 30 mg of theophylline per 20 0.5 ml drops. 15

Example 3: tablets

Tablets containing 10 mg of 1,3-dimethyl-5-aminoadamantane and 100 mg of caffeine per 300 mg tablet 20 are prepared from: 20

1,3-dimethyl-5-aminoadamantane	100 g	
Caffeine	1000 g	
Lactose	1530 g	
25 Polyvinylpyrrolidone	40 g	25
Polyvinylpyrrolidone solution		
10% w/v in isopropanol)	100 g	
Potato starch	250 g	
Talc	49 g	
30 Magnesium stearate	21 g	30

The 1,3-dimethyl-5-aminoadamantane, caffeine, lactose and PVP are mixed and subjected to wet granulation with the PVP solution. After drying, potato starch, talc and magnesium stearate are admixed with the granulate, and tablets of 300 mg compressed.

35 *Example 4: coated tablets* 35

For the manufacture of coated tablets, tablet cores of 100 or 300 mg are compressed from the composition given, and as described, in Example 3. These tablet cores are then coated, according to the sugar-coating procedure, with a coating suspension, coloured with coloured syrup, and polished. The coating comprises, 40 per 100 mg tablet: 40

Polyethylene glycol	0.2 mg	
Magnesia usta	1.3 mg	
Colourant	0.2 mg	
45 Sugar	65.0 mg	45
Talc	39.0 mg	
Calcium carbonate	13.0 mg	
Gum arabic	6.5 mg	
Corn starch	3.7 mg	
50 Shellac	1.1 mg	50

The effectiveness of compositions of the invention will now be illustrated with reference to the accompanying drawing which shows five curves (A to E), the abscissa representing the amount of methylxanthine in combination with a fixed amount of 1,3-dimethyl-5-aminoadamantane, and the ordinate 55 representing the mean degree of rigidity of male Wistar rats receiving food *ad libitum*. Catalepsy was induced by administration of Spiroperidol according to the well-known method of Delini-Stula and Mergurgo, and was examined every 30 minutes during a period of 150 minutes. According to the standard procedure, before injecting 1,3-dimethyl-5-aminoadamantane, a peripheral decarboxylase inhibitor (RO-4-4602) was also administered to the animals for ten days by the peroral route (TH=theophylline; 60 CF=caffeine). 60

Curve A represents the effect on rigidity of 5 mg 1,3-dimethyl-5-aminoadamantane/kg in admixture with varying amounts of caffeine. The maximum potentiating effect of caffeine is at 50 mg/kg.

Curve B is calculated for 10 mg 1,3-dimethyl-5-aminoadamantane/kg in admixture with varying amounts of theophylline. The potentiating effect is greater than the preceding test and provides a maximum of rigor 65 reduction at 25 mg theophylline/kg. 65

14

Curve C shows the effects of 5 mg 1,3-dimethyl-5-aminoadamantane/kg in admixture with theophylline; this shows a similar, but lesser, effect to that shown by Curve C.

Curves D and E represent the results of the same mixtures as those shown in Curves A and C, respectively, i.e. using caffeine and theophylline, respectively, in combination with 5 mg 1,3-dimethyl-5-

5 aminoadamantane/kg, except that catalepsy was induced by reserpine.

5

The results shown in the accompanying drawing show that the effect of 1,3-dimethyl-5-aminoadamantane can be potentiated by mixing it with a methylxanthine. All the results given are mean values of a number of tests.

10 CLAIMS

10

1. A pharmaceutical composition which comprises 1,3-dimethyl-5-aminoadamantane, or a pharmaceutically acceptable salt thereof, and a methylxanthine, in which the amount by weight of the methylxanthine is no more than 15 times the amount by weight of the 1,3-dimethyl-5-aminoadamantane or salt thereof.

15 2. A composition according to claim 1 in which the methylxanthine is caffeine or theophylline.

15

3. A composition according to claim 1 or claim 2 in unit dosage form.

4. A composition according to claim 3 which comprises up to 10 mg of 1,3-dimethyl-5-aminoadamantane, or an equivalent weight of a salt thereof, per unit dosage.

20 5. A composition according to claim 4 which comprises up to 5 mg of 1,3-dimethyl-5-aminoadamantane, or an equivalent weight of a salt thereof, per unit dosage.

20

6. A composition according to any preceding claim which additionally comprises a pharmaceutically acceptable carrier.

7. A composition according to claim 1 substantially as described in any of the Examples.



144

Curve C shows the effects of 5 mg 1,3-dimethyl-5-aminoadamantane/kg in admixture with theophylline; this shows a similar, but lesser, effect to that shown by Curve C.

Curves D and E represent the results of the same mixtures as those shown in Curves A and C, respectively, i.e. using caffeine and theophylline, respectively, in combination with 5 mg 1,3-dimethyl-5-

5 aminoadamantane/kg, except that catalepsy was induced by reserpine.

5

The results shown in the accompanying drawing show that the effect of 1,3-dimethyl-5-aminoadamantane can be potentiated by mixing it with a methylxanthine. All the results given are mean values of a number of tests.

10 CLAIMS

10

1. A pharmaceutical composition which comprises 1,3-dimethyl-5-aminoadamantane, or a pharmaceutically acceptable salt thereof, and a methylxanthine, in which the amount by weight of the methylxanthine is no more than 15 times the amount by weight of the 1,3-dimethyl-5-aminoadamantane or salt thereof.

15 2. A composition according to claim 1 in which the methylxanthine is caffeine or theophylline.

15

3. A composition according to claim 1 or claim 2 in unit dosage form.

4. A composition according to claim 3 which comprises up to 10 mg of 1,3-dimethyl-5-aminoadamantane, or an equivalent weight of a salt thereof, per unit dosage.

5. A composition according to claim 4 which comprises up to 5 mg of 1,3-dimethyl-5-aminoadamantane, or an equivalent weight of a salt thereof, per unit dosage.

20

6. A composition according to any preceding claim which additionally comprises a pharmaceutically acceptable carrier.

20

7. A composition according to claim 1 substantially as described in any of the Examples.