PATENT SPECIFICATION 751,440

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COMPLETE SPECIFICATION

Improved Muscle Relaxant Composition

We, CARTER PRODUCTS, INC., a corporation organised under the laws of the State of Maryland, United States of America, of 53, Park Place, New York, State of New York, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement :—

The present invention relates to a muscle relaxant medicament having interneuronal blocking action.

The object of the present invention is to provide a muscle relaxant medicament having qualities not possessed by the presently used sedative and relaxant medications. The active ingredient of our muscle relaxing medicament is 2-methyl-2-n-propyl-1,3-propanediol dicarbamate.

2-methyl-2-n-propyl-1,3-propanediol dicarbamate is a white crystalline solid soluble in most organic solvents, but soluble only to a slight degree in water. It forms a stable solution in water, and upon boiling with acid or alkali hydrolyzes to give 2-methyl-2-n-propyl-1,3-propanediol, ammonia and carbon dioxide. It is prepared by the reaction of 2-methyl-2-n-propyl-1,3-propanediol with phosgene to form the dichlorocarbonate derivative. This reaction is advantageously promoted by the addition to the reacting compounds of any suitable acid combining compound, such as sodium hydroxide, "Antipyrine" (Registered Trade Mark) or dialkylaniline. This step in the method is followed by ammoniation of the dichlorocarbonate, using anhydrous ammonia and aqueous ammonium hydroxide as suitable sources of ammonia for this purpose. The following example, in which all parts and percentages are by weight, serves to illustrate the method of preparation.

EXAMPLE I

A solution containing 52·8 parts of 2-methyl-2-n-propyl-1,3-propanediol and 128 parts of acetone is added with stirring to 112 parts of liquid phosgene at such a rate that the temperature of the reaction is maintained at −5° to 0° C. The reaction is stirred one hour at about 0° C. then cooled to −15° C. 32 parts of a cooled 30% solution of sodium hydroxide is added with stirring to the reaction mixture at such a rate that the temperature is maintained at −15° to −5° C. The mixture is stirred for an additional ½-hour at about 0° C. then cooled to −20° C. 180 parts of cooled ammonium hydroxide solution (28·6% NH_3) are added while cooling and with stirring at such a rate that the temperature rises slowly to 20° C. and stirring is continued for an additional ½-hour. The mixture is poured with agitation into 1,700 parts of ice water. The solid which separates is removed by filtration and dried. Recrystallization from water gives 55 parts (63% of theoretical yield) of 2-methyl-2-n-propyl-1,3-propanediol dicarbamate, m.p. 104-105° C., approximately 0·2% soluble in water at ordinary room temperature. Analysis of this compound gave : N, 12·5%. Calculated for $C_9H_{18}N_2O_4$: N, 12·8%.

Clinical investigations on both humans and animals have shown 2-methyl-2-n-propyl-1,3-propanediol dicarbamate to be a valuable medication in the reduction of tenseness, restlessness, easy fatiguability, tremulousness, palpitations, and reduction in the degree of hyperhidrosis.

In one clinical study, 58 individuals suffering from Anxiety Reactions, either acute or chronic, and who had failed to respond to barbiturate and mephenesin therapy, were given 2-methyl-2-n-propyl-1,3-propanediol dicarbamate during a twelve month period. The results of this study are recorded in the following Table I.

TABLE I

Disease	Total in Group	Recovered	Very Favourable	Some Favourable Effect	No Change
Anxiety Reactions	58	19	9	16	14
(a) Acute ..	25	10	3	8	4
(b) Chronic ..	33	9	6	8	10

The above results in Table I were evaluated and interpreted according to the following criteria :—

RECOVERED : Those cases where symptoms subsided completely, subjectively and objectively, and where the individual returned to work and became socially productive.

VERY FAVOURABLE : Those cases where the symptoms subsided considerably, subjectively and objectively, and where the individual returned to work, became socially productive, and either tolerated the minor symptoms or were undisturbed by them.

SOME FAVOURABLE EFFECT : Those cases where some favourable effects were felt with medication, subjectively, but the patient was still looking for something further in the way of improvement. (However, patient became socially productive in spite of the symptoms.)

NO CHANGE : Those cases who reported no effects upon their symptoms from the medication.

It is seen from Table I that in the group of 58 individuals, 19 were classified in the Recovered group, 9 in the Very Favourable group, and 16 were listed in the Favourable group, thus making a total of 44 or 76% of the patients who obtained good results from 2-methyl-2-n-propyl-1,3-propanediol dicarbamate, as opposed to 14 in whom no change was reported. Thus, the muscle relaxant of the present invention gave an improvement in 76% of the cases wherein previously the commonly used medications of barbiturates and mephenesin therapy were ineffective.

In the above referred to study complete blood counts and urinalyses, from the 58 clinical subjects, taken prior to and two months after continuous use of 2-methyl-2-n-propyl-1,3-propanediol dicarbamate failed to reveal any evidence of toxicity. A study of the aforementioned blood counts and urinalyses showed no evidence of anaemia, leukopenia, glycosuria, acetoneuria, albuminuria or other alterations of the microscopic picture of the blood and urine. Thus, 2-methyl-2-n-propyl-1,3-propanediol dicarbamate, within limits of dosage, may be safely used without serious side effects or toxic manifestations. Experiments have shown 2-methyl-2-n-propyl-1,3-propanediol dicarbamate to be approximately five times less toxic than most barbiturates, the most widely used sedative medication.

Moreover, in this investigation there were no complaints of dizziness, vertigo, nausea, vomiting, diarrhea or dermatological manifestations, nor have there been any indications, based on the study, that 2-methyl-2-n-propyl-1,3-propanediol dicarbamate is habit forming.

It is believed that 2-methyl-2-n-propyl-1,3-propanediol dicarbamate is effective as a muscle relaxant because of its interneuronal blocking action. Pharmacological studies have shown that paralysis is produced by a depressant effected on the central nervous system. The nerves and nerve endings remain unaffected by its use. The structures most sensitive to the effect of it in the central nervous system are the interneurons. The action of this compound is similar to that of mephenesin in numerous respects, but differs from it in possessing a very much longer duration of action, and in being somewhat more effective on oral administration. Mephenesin is a widely used drug of value in the treatment of muscle spasm, anxiety and many disorders of the nervous system. The very short duration of action of mephenesin is its greatest drawback. The duration of the action of mephenesin was compared with 2-methyl-2-n-propyl-1,3-propanediol dicarbamate in the series of tests on mice recorded in Table II.

TABLE II

Dose Mgm. per Kgm.	Mephenesin % Paralyzed	Mephenesin Duration of Paralysis in Minutes	2-methyl-2-n-propyl-1,3-propanediol dicarbamate % Paralyzed	2-methyl-2-n-propyl-1,3-propanediol dicarbamate Duration of Paralysis in Minutes
1,400 ..	100	113·0 ± 14·5	100	420
940 ..	100	57·4 ± 10·4	100	317·2 ± 42·0
620 ..	80	19·2 ± 2·0	100	182·1 ± 24·8
420 ..	50	11·0 ± 2·0	100	90·0 ± 16·9
280 ..	10	4·5	20	82·2

It will be noted that at the various dose levels at which the comparison was carried out the action of this compound of the invention was five to ten times as long as that of mephenesin.

2-methyl-2-n-propyl-1,3-propanediol dicarbamate is preferably administered orally in the form of pills, tablets or capsules, formed by well-known procedures. A typical composition comprises the active ingredient, 2-methyl-2-n-propyl-1,3-propanediol dicarbamate, intermixed in a dry pulverulent state with gelatin, starch, magnesium stearate and algenic acid, pressed into a tablet. The active ingredient may also be dissolved in a suitable solution, such as propylene glycol or alcohol for injection. An effective dose of the active ingredient generally is in the range of 0·04 grams to 2·0 grams.

It is believed, therefore, that the use of 2-methyl-2-n-propyl-1,3-propanediol dicarbamate as a muscle relaxant is a decided contribution to the art. It is most effective in anxiety and tension states through a

lessening of tension, reduced irritability and restlessness, more restful sleep and generalized muscle relaxation.

What we claim is :—

A muscle relaxant composition containing as the active ingredient 2-methyl-2-n-propyl-1,3-propanediol dicarbamate with a carrier or diluent therefor.

STEVENS, LANGNER, PARRY & ROLLINSON,
Chartered Patent Agents,
Agents for the Applicants.

PATENTS ACT, 1949

SPECIFICATION NO. 751,440

In accordance with the Decision of the Superintending Examiner, acting for the Comptroller-General, dated the twentyeighth day of February, 1957, this Specification has been amended under Section 29 in the following manner:-

Page 2, lines 121-124, *delete* "The active ..... injection".

Page 3, *delete* lines 5-8. *Insert*

"1. A muscle relaxant solid composition in the form of a tablet, pill or capsule for relief of anxiety and tension states in human beings without serious side effects or toxic manifestations adapted for oral administration, containing as an active ingredient 2-methyl-2-n-propyl-1, 3-propane diol dicarbamate with a solid carrier or diluent, said active ingredient being in an amount from 0.04 grams to 2.0 grams.

2. A tablet substantially as described."

THE PATENT OFFICE,
11th April, 1957

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