United States Patent

Semonský et al.

[15] 3,681,497

[45] Aug. 1, 1972

[54] **THERAPEUTIC METHODS OF EMPLOYING HYDROGEN MALEATE SALT OF N-(D-6-METHYL-8-ISOERGOLENYL)-N',N'-DIETHYL-CARBAMIDE**

[72] Inventors: **Miroslav Semonský; Viktor Zikán,** both of Prague, Czechoslovakia

[73] Assignee: **Spofa Spojene Podniky Pro Zdravotnick-ou Vyrobu,** Prague, Czechoslovakia

[22] Filed: **May 25, 1967**

[21] Appl. No.: **641,160**

[30] **Foreign Application Priority Data**

June 7, 1966 Czechoslovakia 3860/66

[52] **U.S. Cl.** **424/261**

[51] **Int. Cl.** **A61k 27/00**

[58] **Field of Search** 424/261; 260/285.5

[56] **References Cited**

UNITED STATES PATENTS

3,218,324	11/1965	Hofmann et al.	424/261
3,228,944	1/1966	Bernardi et al.	260/285.5
3,238,211	3/1966	Camerino et al.	260/285.5

FOREIGN PATENTS OR APPLICATIONS

100,832 9/1961 Czechoslovakia

OTHER PUBLICATIONS

Rysanek et al.; Chem Abst. Vol 63 (1965) page 6221h

Votava et al.; Chem Abst. Vol. 59 (1963), page 9221d

Votava et al.; Chem. Abst. Vol. 62 (1965) page 15307h etc.

Cerny et al.; Chem. Abst. Vol. 59 (1963) page 7581d etc.

Spofa; Chem. Abst. Vol. 57 (1962) page 15005f

Grollman; Pharmacology and Therapeutics, 1965, Publisher Lea & Febiger, pages 244– 247

Primary Examiner—Sam Rosen

Attorney—Michael S. Striker

[57] **ABSTRACT**

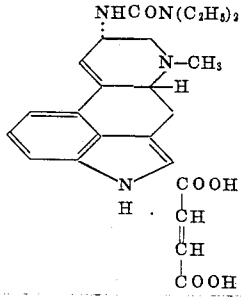
Method of using N-(D-6-methyl-8-isoergolenyl)-N', N'-diethylcarbamide hydrogen maleate in the therapeutic treatment of migraine headache, urticaria, hypertension and allergic conditions, in the last case along or in the form of an enhanced effect when administered together with an anti-histamine.

6 Claims, No Drawings

THERAPEUTIC METHODS OF EMPLOYING HYDROGEN MALEATE SALT OF N-(D-6-METHYL-8-ISOERGOLENYL)-N',N'-DIETHYL-CARBAMIDE

This invention relates to therapeutic compositions containing N-(D-6-methyl-8-isoergolenyl)-N',N'-diethylcarbamide or a physiologically acceptable salt thereof and more particularly to methods for using the same.

N-(D-6-methyl-8-isoergolenyl)-N',N'- diethylcarbamide hydrogen maleate (Lysenyl, $C_{20}H_{26}N_4O.C_4H_4O_4$) is a known material (see Czechoslovakian Patent 100832 dated Sept. 15, 1961. It has a molecular weight of 338.4 + 110.-3; and a specific rotation (active base) of $[\alpha]_D^{20°} = +313 \pm 3°/C = 0.60$ pyridine.



Clinical tests carried out with Lysenyl establish that the same constitutes a specific serotonin antogonist and can be employed as a medicament in those conditions and diseases, caused or aggravated by serotonin.

It has also been established by appropriate pharmacological tests that the administration of Lysenyl as compared with analogous preparations produces little or no undesirable side effects i.e., the compound in the free base form or salt form is substantially non-toxic.

The following table represents the data obtained in taxicity studies with Lysenyl.

TOXICITY OF LYSENYL

Acute Toxicity:			
LD_{50}	i.v.	s.c.	oral
mice	14.4 mg/kg	82 mg/kg	90 mg/kg
rats	1.5 mg/kg	3 mg/kg	12.5 mg/kg

It has been established that the clinical therapeutic oral dose of Lysenyl for humans amounts to 0.00125 mg/kg daily and is therefore about a 1/70,000 (one seventy-thousandth part) of the oral LD_{50} in mice, or about 1/10,000 (one ten-thousandth part) of the corresponding dose in rats.

Chronic Toxicity

The chronic toxicity was investigated in rats which received daily doses of 0.005 mg/kg or 0.025 mg/kg s.c. for three months and in a second series of tests, the same doses for 6 months. Data obtained at the conclusion of these tests, when compared with the data from the control animals, did not reveal any alterations which could be regarded as signs of undesirable or toxic effects of Lysenyl. The data included blood counts, biochemical determinations, histological studies, growth studies, etc.

The administration of daily oral doses of 0.01 mg/kg to pregnant rats for the entire duration of the pregnancy did not cause any significant increase of the incidence of fetus resorption. The delivered offspring were alive and free from developmental abnormalities.

Tests carried out with humans established that single oral doses of up to 0.2 mg of Lysenyl, or serial intravenous injections not exceeding 0.12 mg of Lysenyl per dose did not initiate any psychological changes indicative of a hallucinogenic activity.

It has now been found that Lysenyl has a remarkable therapeutic effect upon certain conditions, notably migraine headache, allergy, and dumping syndrome.

The following clinical studies were carried out in order to evaluate the effectiveness of Lysenyl.

a. Migraine

A comprehensive evaluation of results obtained in several different clinics with the therapeutic administration of Lysenyl in cases of vascular headache of the migraineous type was carried out. The evaluation establishes that in a sample comprising 144 patients the following results are obtained:

1. in 73 (50.7 percent) of the patients, either a complete disappearance of migraineous attacks, or a very substantial amelioration (a very marked decrease of the intensity and frequency of the attacks);
2. in 47 (32.6 percent) patients, an amelioration;
3. in 24 (16.7 percent) patients, no apparent effect.

A beneficial effect was therefore observed in approximately 83 percent of patients.

The preparation was administered orally in a very low dosage, on the average 25 mcg was administered twice daily, at the most 25 mcg was given three times daily. This dosage is only 1/40th of that usually given for methysergide, making Lysenyl a more effective preparation with respect to the dosage necessary to produce the desired action when compared to the most widely heretofore used preparation. Lysenyl, similarly to methysergide, is suited for long-term therapy but not for the suppression of an attack already developed.

b. Allergic Conditions

In accordance with the recently established concepts of the participation of serotonin in the pathogenesis of allergic conditions, Lysenyl was also evaluated in various allergic diseases (urticaria and Quincke's edema, eczema, bronchial asthma, vasomotor rhinitis, etc.), and mostly in such cases which were resistant against the usual antiallergic therapy (antihistamines, desensitization). The dosage used amounted to 25 mcg twice to three times daily. The obtained results were very good, in some cases even surprising, specifically when Lysenyl was administered together i.e., in combination with known antihistamines and thus the combined therapeutic activities of the respective components, i.e., the antihistamine and the antiserotonin effect, could be brought about at the same time. The best results were achieved in the urticaria and Quincke's edema while the effect in vasomotoric rhinitis was relatively weaker.

The antiallergic effectiveness of Lysenyl was further established by the preventive oral administration of 25mcg of the drug three-fourths to 1 hour before intracutaneous testing of inhalation allergens. In comparison with the control group, a partial inhibition of the local reaction was observed. The average diameter of the local reaction areola was diminished by 7.8 mm (Lysenyl 11.0 mm, control 18.8 mm).

c. The Dumping Syndrome

The symptoms of the post-resection syndrome, especially the increased rate of intestinal passage, can be considered as consequences of an increased production and release of serotonin in the small intestine. In accordance with this concept, Lysenyl was administered in preliminary trials to 9 patients, following surgery for resection of the stomach, and who suffered from a pronounced post-resection syndrome. These outpatients received low doses during the first week which were gradually increased thereafter to doses of 75 – 200 mcg daily. The therapeutic effect manifested itself as early as after 24 hours in 6 patients of the 9 by a suppression of the diarrhea, and in the course of the first week of the therapy, the condition of two further patients improved. The patients noted that at the same time as the frequency of stools diminished, the disappearance of the feeling of abdominal tension, an increase of the appetite, and an improvement of both physical and psychical condition.

Tolerability. In a long-term clinical study aimed at the pharmacological investigation of Lysenyl, the preparation was administered to 56 hypertensive patients for 3 – 14 months. The initial dosage, 12.5 mcg daily, was gradually increased to an average dosage of 25 mcg three times daily. In all patients, the following analyses were carried out before the treatment, once a month during treatment, and three months after termination of treatment; examination of the urine and urine sediment, creatinine clearance, non-protein nitrogen, blood count, sedimentation of erythrocytes, and electro-cardiogram.

In 26 patients treated for more than 6 months, at the intervals set forth above, the following additional analyses were carried out: serum bilirubin, thymol turbidity reaction, SGPT (serum glutamate-pyruvate transaminase) phosphatase, and glycemia on an empty stomach.

In 8 patients treated for more than 8 months, the renal blood flow (clearance of para aminohippuric acid) and the glomerular filtration rate (clearance of inulin) were determined before and after the treatment in addition to all of the above recited analyses.

All values established throughout the testing were compared with those values found before the treatment and were found to have remained without pathological changes. In the majority of those patients who had had proteinuria before the treatment, the latter disappeared completely in the course of the therapy.

Blood pressure decreased during the monotherapy with Lysenyl especially in patients in the initial stages of hypertension marked by a moderately high diastolic pressure. During treatment a number of subjective complaints either disappeared or were substantially alleviated, especially headache and cephalemia. A comprehensive evaluation of reports from all of the clinical studies carried out reveals that side effects were observed in about 10 percent of cases. The most frequent side effects were nausea, a feeling of lassitude, nasal stiffiness, and dryness in the mouth; less frequent side effects were vomiting or a slight vertigo. Diarrhea was encountered only sporadically (in patients with migraine and allergy). Headache was seen only infrequently (in those patients with the dumping syndrome). All these side effects were transient and disappeared as soon as the dosage had been decreased. Only in quite exceptional cases did the therapy have to be discontinued. The majority of the observed side effects developed in such cases where the therapy had been started with a full dosage (25 mcg three times daily), and their frequency fell to a minimum when the optimum dosage scheme was used, i.e., when the dosage was gradually increased.

In comparison to the frequency of undesirable side effects seen with the use of methysergide, the side effects of Lysenyl are significantly less in number and severity.

The following Examples illustrate pharmaceutical preparations for use in the practice of this invention, but the same are not to be construed as a limitation thereof.

EXAMPLE I

Tablets of the formula:

	milligram
Lysenyl	0.025
Lactose	97.875
Corn starch	11.00
Magnesium stearate	1.1
Total weight	110.000

Tablets were prepared according to the usual procedure for the preparation of tablets for pharmaceutical use.

EXAMPLE II

The dosage used in combination of Lysenyl with antihistamines; Lysenyl 25 mcg + Bromadryl (= mebrophenhydramine hydrochloride) 25 mg twice to three times daily, or Lysenyl 25 mcg + Medrin (= mebrophenhydrinate) 25 mg twice to three times daily.

The results of the clinical tests permit the following conclusions:

1. Lysenyl is, with respect to the size of the clinically effective dosage, the most active of the known serotonin antagonists.
2. It is the drug of choice for the long-term therapy of vascular headache of the migraine type.
3. In allergic conditions, it substantially enhances, by its antiserotonin activity, the therapeutical usefulness of antihistamines.
4. In the dumping syndrome it exerts a reliable blocking effect upon the untoward action of serotonin on the intestinal motility.
5. Side effects observed during the therapy with Lysenyl are, in comparison with analogous preparations, both of less intensity and of lesser frequency and they are practically negligible if an appropriate dosage scheme is used.

We claim:

1. A method of relieving vascular headaches of a patient suffering from migraine which comprises administering to such patient N-(D-6-methyl-8-isoergolenyl)-N',N'-diethyl-carbamide hydrogen maleate in a dose of 25 mcg two to three times daily, said N-(D-6-methyl-8-isoergolenyl)-N',N'-diethylcarbamide hydrogen maleate acting as a specific serotonin antagonist to excessive production of serotonin.

2. A method of treating a patient for suppressing or mitigating the development of allergic reactions to an allergic stimulus which comprises orally administering to such patient N-(D-6-methyl-8-isoergolenyl)- N', N'-

diethyl-carbamide hydrogen maleate in a dose of 25 mcg two to three times daily, said N-(D-6-methyl-8-isoergolenyl)--N',N'-diethyl-carbamide hydrogen maleate acting as a specific sertonin antagonist to excessive production of serotonin.

3. A method of treating a patient for suppressing or mitigating the development of urticaria or Quincke's edema in response to an allergic stimulus which comprises orally administering to such patient N--(D-6-methyl-8-isoergolenyl)-N',N'-diethyl-carbamide hydrogen maleate in a dose of 35 mcg two to three times daily, said N-(D-6-methyl-8-isoergolenyl)-N',N'-diethyl-carbamide hydrogen maleate acting as a specific serotonin antagonist to excessive production of sertonin.

4. Method according to claim 3 wherein said N-(D-6-methyl-8-isoergolenyl)-N',N'-diethyl-carbamide hydrogen maleate is administered together with 25 mg of another antihistamine, each of said agents being administered two to three times daily, said N-(D-6-methyl-8-isoergolenyl)-N',N'-diethyl-carbamide hydrogen maleate acting as a specific serotonin antagonist to excessive production of serotonin.

5. Method according to claim 4 wherein said antihistamine is a member selected from the group consisting of mebrophenhydramine and mebrophenhydrinate.

6. A method of treating hypertension which comprises orally administering to a hypertensive patient N-(D-6-methyl-8-isoergolenyl)-N',N'-diethyl-carbamide hydrogen maleate in a dosage of about 25 mcg twice daily, said N-(D-6-methyl-8-isoergolenyl)-N',N'-diethyl-carbamide hydrogen maleate acting as a specific serotonin antagonist to excessive production of serotonin.

* * * * *