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PROCESS OF AND COMPOSITIONS FOR COMBATING EPILEPTIC SEIZURES WITH ATROLACTAMIDE

Roger W. Stoughton, St. Louis, Mo., assignor to Mallinckrodt Chemical Works, St. Louis, Mo., a corporation of Missouri

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This invention relates to therapeutic compositions and processes, and more particularly to compositions and processes for controlling epileptic seizures.

Briefly, this invention is directed to a composition for controlling epileptic seizures, comprising atrolactamide and a pharmaceutical carrier. The present invention also is directed to a process for controlling epileptic seizures which comprises administering to a human being a daily dosage of not more than approximately 16 grams of atrolactamide.

Among the several objects of this invention may be noted the provision of new and effective compositions and processes for controlling epileptic seizures; the provision of compositions which are particularly effective against grand mal, psychomotor, Jacksonian and petit mal variant epileptic seizures, either when occurring alone or when associated with any other form of epilepsy; the provision of compositions of the class described which produce few side reactions; and the provision of such compositions which do not accentuate one type of seizure where it occurs together with other types. Other objects and features will be in part apparent and in part pointed out hereinafter.

The invention accordingly comprises the products and methods hereinafter described, the scope of the invention being indicated in the following claims.

There are in this country between 800,000 and 1,500,000 epileptics, according to figures obtained from the American League Against Epilepsy. Dr. Frederic A. Gibbs stated "there are over a million persons with epilepsy in the United States, for epilepsy is as common as diabetes" (The Journal of the Michigan State Medical Society, vol. 50, pp. 145–148, 167; February 1951).

Epilepsy is defined as a paroxysmal cerebral dysrhythmia (Gibbs, F., Gibbs, E., and Lennox, 1937); it is based on a disturbance of nerve cell metabolism which results in a disorder of the energy economy of cerebral neurones, and is evidenced by a failure of temporal and spatial regulation of energy release within the brain.

Those clinical seizures which are not generalized convulsions are classified as minor seizures. They are regarded as partial epilepsies in which the spatial and temporal regulation of energy release is sufficiently disorganized to produce clinical symptoms, but not so completely disorganized that the local signs and evidences of limited disorganization are lost. Such seizures are submaximal; they include petit mal, petit mal variant, psychomotor, focal, Jacksonian, myoclonic, thalamic and hypothalamic seizures.

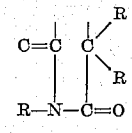
Generalized convulsions (grand mal epilepsy) are regarded as manifestations of maximal (or near maximal) cerebral dysrhythmias and as evidence that a seizure discharge has spread so far and become so intense that the local signs and special features of its origin are lost. This is the most dramatic of all epileptic seizures and, in fact, is the one which is commonly regarded as "an epileptic seizure." It is associated with an excessive release

of energy per unit time from the cerebral neurones. Clinically the patient becomes rigid for a matter of seconds or up to a minute. This is followed by generalized jerking movements which last a variable length of time and terminate in a stupor. During an attack a patient may bite his tongue or be incontinent of urine or feces. Some victims have many attacks a day while others may have only one or two attacks per year. About 8% of persons suffering from grand mal are subject to status epilepticus, a sometimes fatal condition in which one attack immediately follows another.

While diet and dehydration have been suggested as practical ways of raising a patient's resistance to epileptic seizures, experience has shown that both of these methods are usually ineffective.

Various drugs have been employed for controlling epilepsy heretofore. Bromides were the first compounds employed, but these are very ineffective and, furthermore, continued medication results in boils and other skin lesions, somnolence, and mental sluggishness as well as toxic psychosis. Among other anticonvulsant drugs which have been employed may be mentioned: 5-ethyl-5-phenylbarbituric acid (phenobarbital); 5,5-diphenylhydantoin ("Dilantin"); 5-ethyl-3-methyl-5-phenylhydantoin ("Mesantoin"); 3,5,5-trimethyloxazolidine-2,4-dione ("Tridione"); 3,5-dimethyl-5-ethyloxazolidine-2,4-dione ("Paradione"); 5-phenyl-5-thienylhydantoin ("Thiantoin"); phenylacetyl urea ("Phenurone") and 5-ethyl-3-methyl-5-phenylbarbituric acid ("Prominal"). While many of these drugs are often effective in controlling epileptic seizures, their use is subject to the following limitations and objections: Most are effective against only one form of epilepsy, and, moreover, while controlling this form of seizure, they may aggravate another form present in the patient and cause it to be more frequent and more severe. For example, patients suffering from both petit and grand mal epilepsy very often become worse with respect to petit mal when treated for control of grand mal with one or more of the above agents. Many of these compounds are relatively ineffective unless they are employed in combination with other anticonvulsant drugs. The most serious disadvantage of the antiepileptic drugs employed heretofore is that their use gives rise to severe side reactions which are very disagreeable and which in many instances force discontinuation of the medication.

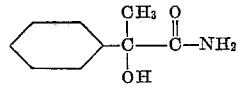
It has been generally believed that compounds to be of maximum effectiveness in controlling epilepsy must contain the following group as part of their structure:



where R represents lower alkyl radicals, phenyl radicals or hydrogen (Toman, J. E. P. and Goodman, L. S.; Physiological Reviews, 28, 446 (1948)). The hydantoins, oxazolidinediones, barbiturates and ureides mentioned previously contain this grouping as part of their structure.

In accordance with the present invention, it has been found that therapeutic compositions containing atrolactamide (the amide of alpha-methyl-mandelic acid) possess valuable and unobvious properties in controlling epileptic seizures of the grand mal, psychomotor, Jacksonian or petit mal variant types without accentuating any one type of epilepsy when, as often happens, it occurs with others. Moreover, it has been found that these novel compositions produce few side reactions.

Atrolactamide has the following structural formula:



Thus, it is readily apparent that atrolactamide does not possess the essential features of chemical structure common to the useful anticonvulsants known heretofore, and therefore it represents a significant departure from the previously well-trod paths of research in this field, even through atrolactamide is a known compound (Staudinger and Ruzicka; Annalen 380, 291 (1911)). However, insofar as is known, the physiological properties of this compound have never before been investigated or utilized, nor has a therapeutic composition including the compound ever been made or suggested.

Atrolactamide occurs as a colorless, odorless, crystalline substance, which has a melting point of 100°–101° C. A freshly prepared aqueous solution (5%) has a pH of about 6.7. Atrolactamide is soluble in water to the extent of about 6% at 25° C. Under ordinary conditions of handling and storage, it is a stable compound. An aqueous solution can be sterilized without decomposition by subjecting it to 15 lbs. steam pressure for fifteen minutes.

According to the present invention, therapeutically useful compositions are provided in dosage form comprising atrolactamide and a pharmaceutical carrier which may be either liquid or solid material. For example, these compositions include tablets of atrolactamide and a carrier (such as fillers, binders and lubricants) or hard gelatin capsules filled with atrolactamide, or other dosage forms particularly useful for oral ingestion. Examples of solid pharmaceutical carriers include starch, gelatin, lactose, talc, stearic acid, magnesium stearate or the like. Any of the conventional tableting materials used in pharmaceutical practice may be employed as carriers herein where such materials are compatible with atrolactamide. These atrolactamide compositions may also be in the form of sterile parenteral solutions, preferable 6% or more by weight of atrolactamide, dissolved in a sterile parenteral solvent such at water, water and glycerin, water and propylene glycol, or water and paraldehyde. In still other embodiments, these novel atrolactamide compositions may be prepared in the form of oral solutions or suspensions. Further, since atrolactamide is compatible with other well-known drugs useful in treating epileptic patients, it can be associated with them in the dosage forms mentioned above.

Extensive clinical testing has proved these novel atrolactamide compositions to be highly effective for controlling grand mal, psychomotor, petit mal variant and Jacksonian epileptic seizures, either alone or in association with any other form of epileptic seizure. Atrolactamide has also been found to have a high activity rating when tested in vivo by accepted anti-convulsant screening methods employing mice as subjects. Moreover, it was found to be effective in counteracting the action of a wide variety of convulsant agents whereas previously known anticonvulsants have been more or less specific in their action.

As used herein, the word "controlling" should not be construed as implying a cure for epilepsy or the elimination of epileptic tendencies; but the term is used solely to denote substantial reduction in the occurrence and severity of seizures for as long as the medication is continued but not after medication is stopped. Since it is the occurrence of seizures, not the tendency towards them, which is harmful to the physical, mental, social and economic welfare of the patient, the substantialy benefits afforded by the present invention will be readily apparent.

To maintain optimum levels of atrolactamide in the blood stream the daily dosage is preferably divided into four approximately equal doses which can conveniently be taken before each meal and before retiring for the night. The optimum daily dosage for a particular patient

is arrived at in the following manner: The initial dosage is usually about 3 g. for children and 4 g. for adults. The dosage is then increased weekly by increments of 2 g. until the seizures are controlled, or until a further increase in the dosage produces no further decrease in the frequency or severity of the seizures, or until the maximal dosage is reached. While greater dosages have apparently been well tolerated for brief periods, a maximum daily dosage of about 12 g. is usually preferred. If side reactions occur, the dosage is reduced or the drug is discontinued until the symptoms disappear. Treatment can then usually be resumed, at a lower dosage if necessary. If the patient is receiving other medication, this is continued at least until maximal control has been established. These other drugs can then usually be withdrawn more or less rapidly depending upon their nature and the condition of the patient. Where more than one form of epilepsy is present, it is sometimes advantageous to continue with at least part of the prior medication.

Animals have been found to tolerate atrolactamide in quantities much greater than those required for control of convulsions. The LD_{50} (a standard statistical value which corresponds to the single dose which is lethal to 50% of the test animals) is 1859 mg. per kg. orally and 1417 mg. per kg. intraperitioneally in white mice. The oral LD_0 (a standard statistical value which roughly corresponds to the maximum, sublethal single dose for 100% of the test animals, and which together with the LD_{50} is a significant measure of the safety of the drug) is 1500 mg. per kg. of body weight in mice. Atrolactamide when given intravenously to a dog at a dosage of 100 mg. per kg. produced definite leg relaxation within forty minutes, while a dosage of 500 mg. per kg. produced marked depression and ataxia within twenty minutes. The effects lasted for twenty-four hours, but the dog recovered completely. In chronic toxicity studies, autopsies on mice, sacrificed after receiving approximately 1000 mg. per kg. per day each for eighteen days, revealed no gross tissue pathology.

The following examples illustrate the invention:

Example 1

Atrolactamide (500 mg.), gelatin (5 mg.) and magnesium stearate (5 mg.) were combined and tableted in a standard tableting machine to form pharmaceutical tablets.

Example 2

Tablets were also prepared containing 2.5 mg. starch in addition to the components shown in Example 1. These tablets, while retaining good mechanical strength, possessed the advantage of disintegrating more rapidly in water.

Example 3

A capsule was prepared by filling a No. 0 hard gelatin capsule weighing 50 mg. with 500 mg. of powdered atrolactamide.

Example 4

A sterile parenteral composition was prepared by dissolving atrolactamide (3 g.) in a solution consisting of pyrogen-free water (27 ml.) and paraldehyde (3 ml.), and subjecting the solution to 15 lb. steam pressure for 15 minutes.

Example 5

A sterile parenteral composition was prepared by dissolving atrolactamide (3 g.) in a solution consisting of pyrogen-free water (27 ml.) and propylene glycol (3 ml.), and subjecting the solution to 15 lb. steam pressure for 15 minutes.

Example 6

The anticonvulsant efficacy of atrolactamide was tested by the supramaximal electroshock method. White mice, Harlan strain, weighing from 17–21 g. were employed as the subjects of the test. None of the animals had been

used previously for any experiments. All animals had free access to food and water for at least three days. One hour prior to dosing, the animals were taken off food and water and weighed. Each test group contained the same number of animals of approximately equal weight, as did each control group. In every experiment, an aqueous solution of approximately 1% atrolactamide, with the pH adjusted to neutrality, was employed. All dosage was on a weight basis and dosing was done orally, unless otherwise noted. The minimal ataxic dose, i. e., that dose which just produced signs of drug action, was chosen as the test dose to the used in the experiments. For atrolactamide this was found to be 0.4 g. per kg. of body weight.

The apparatus, described by Lanphier, "The Evaluation of Antiepileptic Drugs by Laboratory Methods," Thesis (M. S.), University of Illinois, 1949, which utilizes a sine wave stimulator delivering a 0.3 second stimulus through eye electrodes, was used. This instrument will supply stimuli of varying currents. The response of a normal mouse to a supramaximal stimulus is a seizure pattern that begins with a brief clonus followed by tonic flexion of all limbs, and then by a longer tonic extension of the limbs and terminates with a few clonic jerks. About 5% of the mice are anoxic at the end of the tonic phase and die unless given artificial respiration Surviving mice show a typical post-seizure depression. Effective compounds abolish these responses in the reverse order. In general, there is a clinical-laboratory correlation between chemicals effective against this supramaximal electroshock in animals and those useful in the treatment of grand mal epilepsy in humans.

It was determined that 7.5 ma. is the threshold current for the mice, and that if 0.25 g. per kg. of body weight of atrolactamide is administered it will raise the threshold current to 15 ma.

It was also determined that the test dose of 0.4 g. of atrolactamide per kg. of body weight gave complete protection at a 90 ma. current stimulus and that not one mortality occurred among the six mice in the test group.

Example 7

The anticonvulsant efficacy of atrolactamide was tested by the "Metrazol" method utilizing test subjects, dosages, etc., as described in the first paragraph of Example 6.

In accordance with the timed intravenous infusion method of Orloff, Williams and Pfeiffer, Proc. Soc. Exper. Biol. and Med., 70, 254–257, 1949, a 0.5% solution of "Metrazol" was injected in the mouse's tail vein at the rate of 0.05 ml. every 10 seconds. The apparatus employed consisted of a cone-shaped mouse holder made of "Plexiglas." The reaction of the mouse to the timed "Metrazol" infusion follows a definite pattern. The seizure pattern begins with a sharp single twitch followed by intermittent clonic movements which lead to a persistent clonic convulsion. This persistent convulsion often begins by the mouse pulling its head down under his body. That initiates a tonic flexor component and the seizure generally terminates in a fatal tonic extensor component. In general, the drugs which are clinically useful in petit mal are also active in elevating the thresholds of the "Metrazol" tests.

In the group of ten untreated control mice, an average of 0.140±.021 ml. of an 0.5% "Metrazol" solution was required to produce the first twitch, while an average of 0.405±.069 ml. of the solution was required to produce a persistent clonus. All the untreated animals suffered immediate deaths. At the test dose of 0.4 mg. atrolactamide per kg. the thresholds of the "Metrazol" test for the treated group of ten animals was found to be elevated. In the case of the first twitch, a ratio of 1.21 was observed while in the case of the persistent clonus a ratio of 1.25 was observed. No cases of tonic extension (maximal seizure) were observed in the group of treated animals. Among the ten treated mice, there were no immediate deaths, eight delayed deaths and two mice survived over 24 hours.

The ratios give above were calculated by comparing the number of milliliters of the "Metrazol" test solution required to produce a seizure in the treated animals to the number of milliliters required to produce seizures in a similar group of untreated animals that same day.

Example 8

The anticonvulsant efficacy of atrolactamide was tested by the strychnine method utilizing test subjects, dosages, etc., as described in the first paragraph of Example 6.

The timed intravenous infusion method of Orloff, Williams and Pfeiffer, supra, was used. The technique employed is similar to that of the "Metrazol" test of Example 7 except that 0.01% aqueous solution of strychnine is employed. The end point is the tonic extension of the hind legs of the mouse. The strychnine convulsions are always fatal in control animals. Some correlation has been found between strychnine antagonism in mice and activity against psychomotor epilepsy in humans and therefore thhe strychnine test serves as an additional measure of anticonvulsant activity.

An average of 0.200±.026 ml. of 0.01% strychnine solution were required to produce a maximal seizure in the eight control animals, and all the control animals suffered immediate deaths. A ratio of 1.25 was observed for the group of six treated animals and no immediate deaths occurred among this group. Three of the treated animals suffered delayed deaths and three survived more than 24 hours.

The ratio given above was calculated by comparing the numbers of milliliters of the strychnine test solution required to produce a seizure in the treated animals to the number of milliliters required to produce seizures in a similar group of untreated animals that same day.

Example 9

The anticonvulsant efficacy of atrolactoamide was tested by the ammonium ion method utilizing test subjects, dosages, etc., as described in the first paragraph of Example 6.

The timed intravenous technique of Orloff, Williams and Pfeiffer, supra, was employed, but utilizing a 5% ammonium acetate solution. This substance has been demonstrated to produce convulsions with remarkable consistency. A 5% solution of ammonium acetate having a pH of 7.1 was used. The response of the mouse to this infusion is very similar to the "Metrazol" infusion. In both, the tonic extension of the hind legs is taken as the end point. It has been observed that the compounds effective in modifying the ammonium-induced seizures in mice, are also effective against grand mal seizures in man.

In the group of six control animals, an average of 0.366±.141 ml. of a 5% ammonium acetate solution were required to produce this tonic extension (maximal seizure), and all the animals suffered immediate deaths. Ratios of 1.38 and 1.49 were observed for two groups of six treated animals, all of whom suffered immediate deaths.

The ratios given above were calculated by comparing the number of milliliters of the ammonium acetate test solution required to produce a seizure in the treated animals to the number of milliliters required to produce seizures in a similar group of untreated animals that same day.

Example 10

A group of 202 patients afflicted with various forms of epilepsy were treated. In approximately 95% of these cases, the seizures could not be satisfactorily controlled using other known anticonvulsant agents. The treatments were over periods of up to two years. The patients, most of whom were already receiving medication for

epilepsy, were started with a daily dose of 4 g. of atrolactamide, the atrolactamide treatment supplementing other epilepsy drug therapy. The daily dosage was gradually increased to an average of 8 g. per day, supplementary medication being discontinued in many instances. The results are summarized in the following table:

TABLE 1

Diagnosis	Total No. of Cases	Seizures 50% Controlled	Seizures [1] 75% Controlled	Seizures 100% Controlled	Unimproved	Improved,[4] percent
Grand Mal	31	7	13	8	3	90.3
Petit Mal	10	0	2	1	7	30.0
Psychomotor	44	13	19	6	6	86.4
Grand Mal and Petit Mal	24	7	8	1	[2] 8	66.6
Grand Mal and Psychomotor	77	[2] 20	35	6	[3] 16	79.2
Jacksonian	5	0	3	1	1	80.0
Jacksonian-Gr. Mal-Psychomotor	4	3	1	0	0	100.0
Jacksonian and Psychomotor	3	0	3	0	0	100.0
Jacksonian and Grand Mal	1	1	0	0	0	100.0
Petit Mal and Psychomotor	2	2	0	0	0	100.0
Grand Mal-Petit Mal-Psychomotor	1	0	1	0	0	100.0
Totals	202	53	85	23	41	80.0

[1] Included in this group are many who have gone 3–4 months seizure free and subsequently have had a few seizures—perhaps due to failure to take medication.
[2] One patient admitted not taking atrolactamide regularly.
[3] Two patients admitted not taking atrolactamide regularly.
[4] Percentage of patients in whom seizures were at least 50% controlled.

It will be noted that out of a total of 202 patients suffering from many forms of epilepsy 161 patients (80%) experienced 50% or better control of seizures.

Compositions of the present invention in the form of sterile parenteral solutions of atrolactamide, e. g., 5%–6% of atrolactamide in water are particularly effective in treating patients in status epilepticus. An illustrative intravenous dosage would be 40–50 ml. of a sterile parenteral solution containing 5%–6% of atrolactamide.

Patients having both grand mal and petit mal are regarded as being particularly difficult to treat, because in addition to petit mal activity in the electroencephalogram, most cases have petit mal variant activity. In the above cases where petit mal seizures were not effectively controlled, they were not aggravated as when most hitherto known anti-grand mal drugs were employed.

From the above, it will be seen that atrolactamide is highly effective in controlling epileptic seizures. Moreover, atrolactamide has not caused undesirable changes in behavior or personality. Side reactions were infrequent even though the daily dosage ranged up to 12 g., the usual daily dose being 4–8 g. per patient. Although in many instances seizures are controllable by other medications, patients are irritable, pugnacious or even violent, whereas when placed on atrolactamide therapy, these patients become cooperative, calm, and invariably express a feeling of well-being.

The instant compositions for combating epileptic seizures may be used in a variety of forms, and the percentage of active ingredients in these compositions may be varied. However, it is necessary that the active ingredient be present in such amount as will give a suitable dosage. While up to 16 grams per day have been administered, in general it is preferred that the daily dose for effective control of seizures in an adult patient, be between 3–12 grams per day. Based on the above-noted clinical studies the average daily dose is about 8 grams. It is preferred that dosage units containing at least approximately 0.5 gram of atrolactamide be used.

While, in general, it is preferred that the solid dosage forms such as tablets or capsules shall contain as much atrolactamide as is feasible without rendering these tablets or capsules unduly bulky, smaller tablets or capsules with a smaller amount of atrolactamide may be employed if desired. However, in that event a correspondingly larger number of tablets or capsules must be administered to provide the daily dosage specified above.

In view of the above, it will be seen that the several objects of the invention are achieved and other advantageous results attained.

As various changes could be made in the above methods and products without departing from the scope of the invention, it is intended that all matter contained in the above description shall be interpreted as illustrative and not in a limiting sense.

I claim:

1. A composition in dosage form for controlling epileptic seizures, comprising not less than approximately 5% by weight of atrolactamide and not less than approximately 2% by weight of a pharmaceutical carrier.

2. A composition in tablet form for controlling epileptic seizures, comprising not less than approximately 5% by weight of atrolactamide and not less than approximately 2% by weight of a pharmaceutical carrier.

3. A composition in tablet form for controlling epileptic seizures, comprising approximately 98% by weight of atrolactamide and approximately 2% by weight of a pharmaceutical carrier, said carrier comprising magnesium stearate and gelatin.

4. A composition in capsule form for controlling epileptic seizures, comprising not less than approximately 5% by weight of atrolactamide and not less than approximately 2% by weight of a pharmaceutical carrier.

5. A composition in capsule form for controlling epileptic seizures, comprising approximately 90% by weight of atrolactamide and approximately 10% by weight of gelatin.

6. A composition in sterile parenteral solution form for controlling epileptic seizures, comprising not less than approximately 5% by weight of atrolactamide and pyrogen-free water.

7. A composition in sterile parenteral solution form for controlling epileptic seizures, comprising not less than approximately 5% by weight of atrolactamide dissolved in a parenteral solvent comprising water and a substance selected from the group consisting of paraldehyde, glycerin, and propylene glycol.

8. A process for controlling epileptic seizures which comprises administering to a human being a daily dosage of not more than approximately 16 grams of atrolactamide.

9. A process for controlling epileptic seizures which comprises administering parenterally to a human being a dosage of approximately 2–5 grams of atrolactamide.

10. A process for controlling epileptic seizures which comprises administering to a human being a daily dosage of approximately 3–12 grams of atrolactamide.

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