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3,314,852

METHOD OF PRODUCING ATARAXIC, ANTICONVULSANT ACTIVITY AND SKELETAL MUSCLE RELAXATION

Daniel M. Green and Russell F. Krueger, University City, Mo., assignors to Bristol-Myers Company, a corporation of Delaware

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15 Claims. (Cl. 167—65)

This application is a continuation-in-part of application Serial No. 188,950, filed Apr. 20, 1962 and now abandoned.

This invention relates to methods for inducing skeletal muscle relaxation, ataraxia and/or relief of convulsions in animals. It has utility in treating conditions for which any one or any combination of these effects is sought to be obtained.

It is known in the prior art that the relaxation of involuntary spasms of skeletal muscles can be affected by the administration of certain well-known classes of drugs, among which are certain polyol derivatives. Typical examples of muscle relaxants of this type include mephenesin, glyceryl guaiacolate, mephenesin carbamate, meprobamate, etc. These products, however, leave much to be desired in their effectiveness.

It has now been found that, as a general proposition, the effect of the skeletal muscle relaxants and particularly, those which are administrable orally, may be potentiated by the simultaneous administration of antihistamines. In addition, it has been found that ataractic and anticonvulstant properties of the combination of the skeletal muscle relaxant and the antihistamine are greater than the sum of these activities induced by the individual drugs. These are unobvious and unexpected, particularly in view of the fact that antihistamines in large doses are known convulsants, and their use with muscle relaxants would seem to be contraindicated.

It is accordingly an object of the present invention to provide an effective method for inducing skeletal muscle relaxation and for potentiating the properties of skeletal muscle relaxants.

It is a further object of the present invention to provide an effective method for inducing ataraxia and for potentiating the ability of antihistamines or skeletal muscle relaxants to induce ataraxia.

Still another object of this invention is to provide a method for relieving convulsions and for potentiating the ability of antihistamines or skeletal muscle relaxants to relieve convulsions.

It is also an object of the present invention to provide a method for inducing any combination of effects set forth in the above objects.

Other and more detailed objects will be apparent from the following description and claims.

Compositions containing certain muscle relaxants and antihistamines have been suggested for use in the prior art as therapeutic agents. Thus, for example, preparations including glyceryl guaiacolate and phenyltoloxamine dihydrogen citrate have been suggested for use in obtaining relief from coughs, and nasal and bronchial congestion. These conditions, however, are unrelated to those which are treated in accordance with the present invention. The involuntary spasms of skeletal muscles, tension or anxiety manifestations and the convulsive symptoms, which the present invention seeks to relieve, are not present in those bronchial and nasal conditions mentioned in the prior art.

Prior art products of the same general character as those described in the paragraph above have also been characterized as being spasmolytic. This activity, however, is clearly associated with smooth muscle, for example, the bronchial tubes or uterus, and not voluntary skeletal muscle with which the present invention is concerned.

The prior art further teaches that narcotics or hypnotics are potentiated by antihistamines, i.e., the sleeping time is prolonged. This also is far removed from the effects produced by the present invention and the conditions under which it is used.

As used herein, the term "skeletal muscle relaxant" is defined as an orally active skeletal muscle relaxant, active centrally in the central nervous system on the internuncial neurons of the spinal cord and subcortical centers, which selectively depresses polysynaptic reflex arcs without affecting monosynaptic reflexes, autonomic activity, peripheral nerves or myoneural junctions or eliciting sleep spindles on the electroencephalogram as do the barbiturates. Central nervous system alertness and wakefulness are maintained by a sensory feedback from the muscles.

The term "ataraxic" is used herein to designate a drug capable of inducing perfect peace or calmness of mind. It is used particularly to designate a drug suitable for producing an effect of detached serenity without depressing mental facilities or clouding consciousness.

"Anticonvulsant" is used to describe a drug which is effective in preventing an involuntary violent contraction or series of contractions of the voluntary muscles.

The muscle relaxant or relaxants that may be utilized in accordance with the present invention may vary considerably. The preferred materials are related to each other more by their mode of action than by their chemical structure in that they are preferably effective when taken by mouth and act substantially only on the central nervous system. However, they will generally be selected from the following groups of compounds:

(a) Ethers or esters (particularly, esters of carbamic acids) of mono- or polyhydroxy aliphatic alcohols or of aryl substituted mono- or polyhydroxy aliphatic alcohols,

(b) Heterocyclic compounds and particularly, benzoxazole derivatives, and

(c) Aryl substituted polyhydroxy aliphatic alcohols.

The ether and ester linkages of the group of compounds included in (a) above may appear individually or together in the same compound. Thus, the compounds may be ethers, ether-esters, or esters. Furthermore, they may contain one or more of the ether or ester linkages. Moreover, the aryl substituted compounds may likewise contain one or more aromatic radicals, which may be bonded directly to the aliphatic chain of the alcohol or indirectly through intermediate linkages.

Typical examples are given in Table I below of the muscle relaxants falling within the categories defined above in items (a), (b) and (c). In addition, there is given for each compound the usual recommended oral human therapeutic dosage.

TABLE I

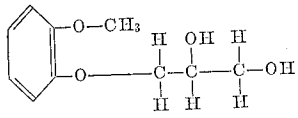
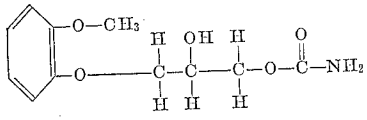
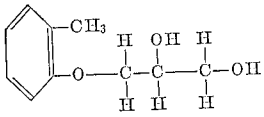
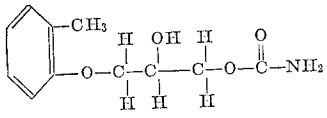
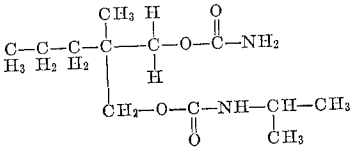
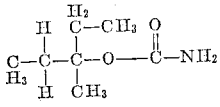
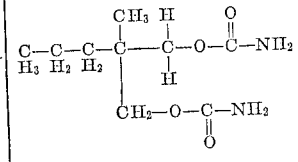
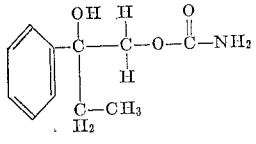
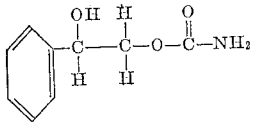
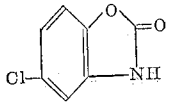
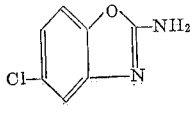
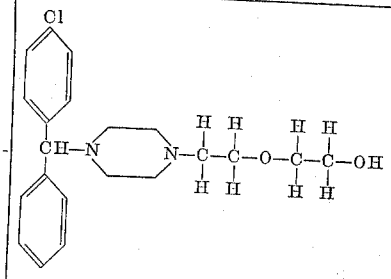
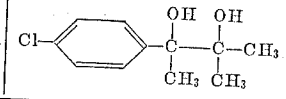
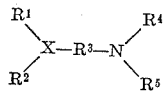
Skeletal Muscle Relaxant	Chemical Structure	Recommended Oral Human Therapeutic Dosage, mg.
Category (a):		
Glyceryl Guaiacolate		400-3,000
Methocarbamol		1,000-1,500
Mephenesin		1,000-3,000
Mephenesin Carbamate		1,000-3,000
Carisoprodol		250-350
Emylcamate		300-500
Meprobamate		200-800
Hydroxyphenamate		400
Styramate		200-400
Category (b):		
Chlorzoxazone		125-750
Zoxazolamine		250-750

TABLE I—Continued

Skeletal Muscle Relaxant	Chemical Structure	Recommended Oral Human Therapeutic Dosage, mg.
Hydroxyzine		25
Category (c): Phenaglycodol		200-300

Any of a variety of antihistamines may also be used in accordance with the present invention. Aside from the fact that the antihistamine selected should be orally active, there appears to be no other limitation on the antihistamine that may be employed. Compounds which are useful for the present purposes are described in Burger, A., Medicinal Chemistry, 2nd ed., Interscience Publishers, Inc., N.Y., p. 532, 1960 as of "the general formula where R^1 and R^2 are aromatic

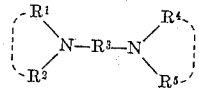


(or heterocyclic aromatic) systems, one of which may or may not be separated from X by a methylene group; X is O, N, or CH; R^3 is an ethylene group or a 2-carbon fragment of a nitrogen-heterocyclic system." . . . "R^4 and R^5 are methyl groups, but a small planar cyclic group such as the pyrrolidino group may be employed" . . . "for NR^4R^5."

Typical Examples are given in Table II below of antihistamines that can be incorporated in the compositions made use of in the present invention. In addition, there is given for each compound the usual recommended oral human therapeutic dosage.

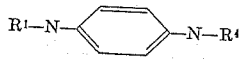
These compounds fall into several generic groups which may be described as follows:

(1)



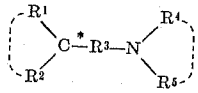
wherein R^1, R^2, R^4 and R^5 are selected from the group consisting of hydrogen, alkyl, aryl, aralkyl and heterocyclic radicals, or R^1 and R^2 together, or R^4 and R^5 together form a ring structure, and R^3 is a divalent radical such as ethylene.

(2)



wherein R^1 and R^4 have the same value ascribed to them above.

(3)



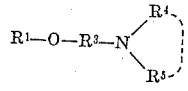
wherein R^1 and R^4 have the significance ascribed to them it above, in addition to which an unsaturated bond may be located between R^3 and the asterisked carbon atom.

(4)



wherein R^1 and R^4 have the significance ascribed to them above.

(5)



Wherein R^1, R^3, R^4 and R^5 have the same significance ascribed to them above.

TABLE II

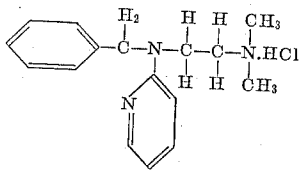
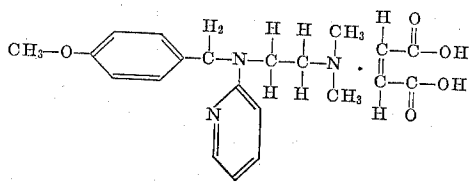
Antihistaminic generic name	Chemical Structure	Recommended Oral Human Therapeutic Dosage, mg.
Tripelennamine HCl		25-100
Pyrilamine Maleate		25-50

TABLE II—Continued

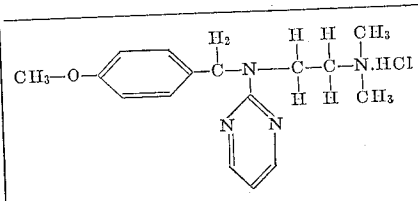
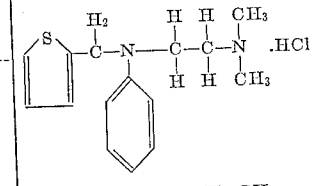
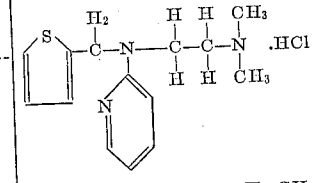
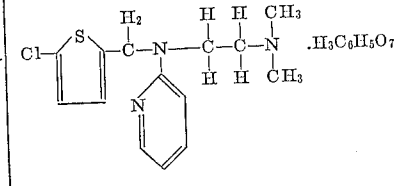
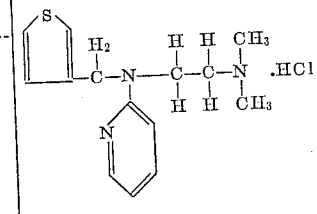
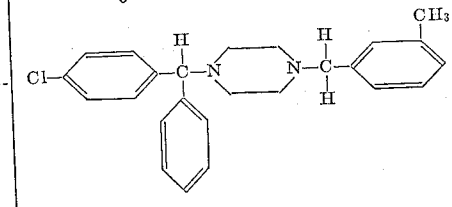
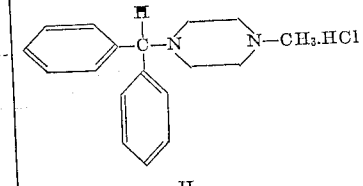
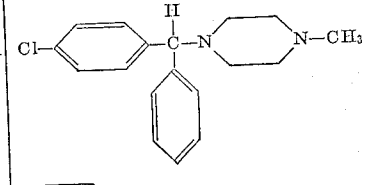
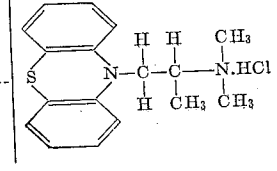
Antihistaminic generic name	Chemical Structure	Recommended Oral Human Therapeutic Dosage, mg.
Thonzylamine HCl		50–100
Metaphenilene HCl		12–50
Methapyrilene HCl		50–100
Chlorothen Citrate		25
Thenyldiamine HCl		15–30
Meclizine Hydrochloride		12–50
Cyclizine Hydrochloride		50
Chlorcyclizine		50
Promethazine Hydrochloride		12.5–75

TABLE II—Continued

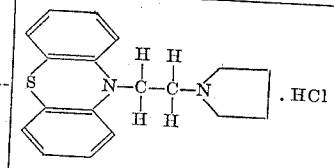
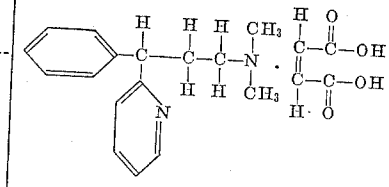
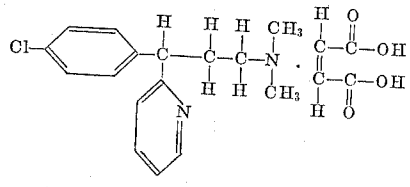
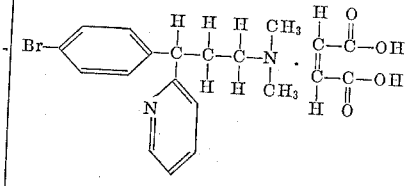
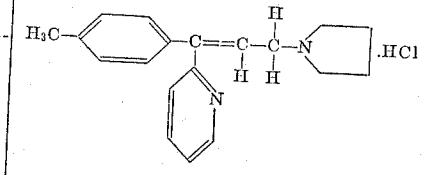
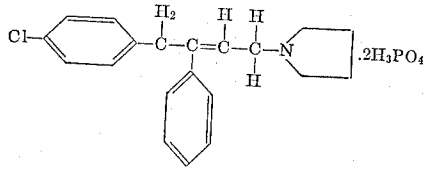
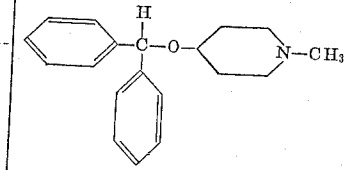
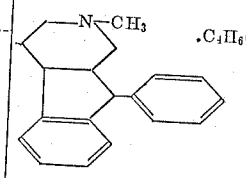
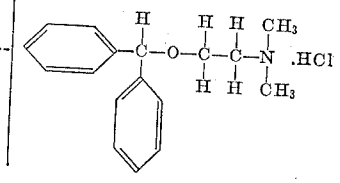
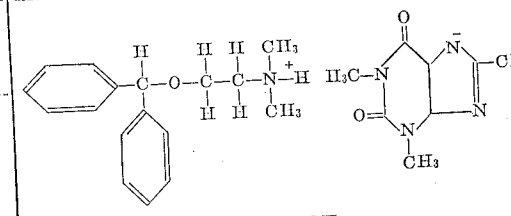
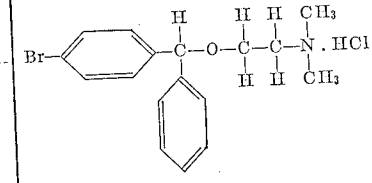
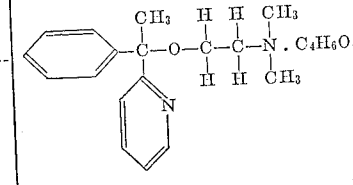
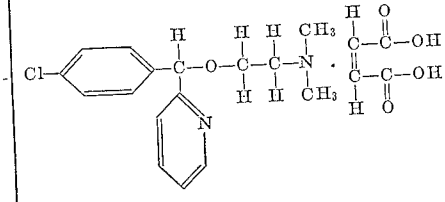
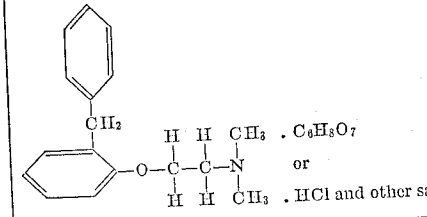
Antihistaminic generic name	Chemical Structure	Recommended Oral Human Therapeutic Dosage, mg.
Pyrathiazine Hydrochloride		25–50
Pheniramine Maleate		25–50
Chlorpheniramine Maleate		2–4
Brompheniramine Maleate [d-isomer]		4 [2 mg.]
Triprolidine Hydrochloride		2.5
Pyrrobutamine Phosphate		15
Diphenylpyraline Hydrochloride		2–4
Phenindamine Tartrate		10–50
Diphenhydramine		25–50

TABLE II—Continued

Antihistaminic generic name	Chemical Structure	Recommended Oral Human Therapeutic Dosage, mg.
Dimenhydrinate		50–100
Bromodiphenhydramine		25–50
Doxylamine Succinate		12–25
Carbinoxamine Maleate		2–4
Phenyltoloxamine Dihydrogen Citrate, or Hydrochloride.		25–50

In the present invention any antihistamine described above or combinations thereof may be used in conjunction with any skeletal muscle relaxant or combinations thereof, also defined above. In addition, where desired, other pharmacologically active materials may also be introduced. Among these may be mentioned analgesics, diuretics, hypotensives, etc. Typical examples of these materials include aspirin, salicylamide, phenacetin, acetaminophen, theophylline, 7-B-hydroxypropyl theophylline, theobromine, chlorothiazide, hydroflumethiazide, mannitol, ethyl alcohol, ammonium chloride.

The enhanced pharmacological activity of the compositions employed in this invention is evident over a fairly wide range of proportions of the two principal ingredients. The relative proportions of the ingredients utilized will be dependent on the particular skeletal muscle relaxant utilized and the specific antihistaminic that is selected. These are related to the recommended oral human therapeutic dosages of these materials as follows:

1. Skeletal muscle relaxants: from one-half the minimum dosage given in the range of recommended oral human dosage through the dosage range given (Table I).
2. Antihistaminics: from one-half the minimum dosage given in the range of recommended oral human dosage through twice the dosage range given (Table II).

However, in general, the range of ratios of parts of skeletal muscle relaxant to antihistamine may vary from 4 to 500 parts of skeletal muscle relaxant to one part of antihistamine by weight, and preferably, from 4 to 32 parts of muscle relaxant per part of antihistamine. Most desirably, about 4 to 8 parts by weight of the former per part of the latter is used.

The unit dosage that is suitable for human use may also vary considerably depending on the degree of effect desired, the age of the patient, the muscle relaxant employed or the antihistamine utilized. In general, the oral human dosage will vary from about 13.5 mg. of the combined principal active components to about 3200 mg. in which the skeletal muscle relaxant and the antihistamine will be included in the ratios outlined above.

The active ingredients of the composition can be administered in unit dosage form without diluents or with the conventional pharmaceutical carriers. Each unit dosage form of the composition containing conventional carriers can have from about 5% to about 95% and preferably, from about 10% to 80% of the combination of muscle relaxant and antihistamine by weight of the entire unit dosage with the remainder comprising conventional pharmaceutical carriers. By the term "pharmaceutical carrier" we intend to include materials which are conventionally used with unit dosages and include fillers, diluents,

binders, lubricants, or disintegrating agents. The compositions can be administered either prior to or after the onset of the discomfort, e.g. nervous excitement or skeletal muscle tension.

The pharmaceutical compositions of this invention can be administered to animals, by the conventional methods, the conventional types of unit dosages or with the conventional pharmaceutical carriers to produce their pharmacological effect. Oral administration by the use of solid dosage forms such as tablets, pills or capsules or in liquid form such as suspensions, or emulsions can be employed. Oral administration by tablets is preferred. When formed into tablets, the conventional binding and disintegrating agents used in therapeutic unit dosages can be employed. Illustrative of binding agents there can be mentioned: glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate and talc. Illustrative of disintegrating agents there can be mentioned: corn starch, keratin, and potato starch.

The antihistamine is preferably used in the form of its acid addition salts. These can be produced by the conventional techniques of neutralizing the amine portion of a compound with either an organic or inorganic acid. Illustrative of the acids there can be mentioned: hydrochloric, sulfuric, citric, acetic, malic, maleic, and phosphoric acids (e.g., for phenyltoloxamine, the preferred salt is dihydrogen citrate).

The invention is illustrated by the following examples of suitable pharmaceutical compositions in unit dosage form, although it is not intended that the compositions or dosages be limited by any of the proportions, amounts, types of carriers, or dosage units set forth therein.

EXAMPLE 1

A suitable formulation of tablets to be employed as muscle relaxant can have the following composition per tablet:

	Weight in milligrams
(1) Glyceryl guaiacolate	200.0
(2) Aspirin	300.0
(3) Phenyltoloxamine dihydrogen citrate	12.5
(4) Corn starch	51.0
(5) Talc	6.0
(6) Gelatin	2.0

EXAMPLE 2

A suitable dosage, particularly for muscle relaxation, can contain the following ingredients in a water-soluble capsule:

	Weight in milligrams
(1) Glyceryl guaiacolate	200.0
(2) Phenyltoloxamine dihydrogen citrate	12.5
(3) Salicylamide	300.0

EXAMPLE 3

Another suitable dosage can contain the following ingredients in a tablet with binding and disintegrating agents:

	Weight in milligrams
(1) Glyceryl guaiacolate	100.0
(2) Phenyltoloxamine dihydrogen citrate	17.5
(3) 7-beta hydroxypropyl theophylline	62.5
(4) Ephedrine sulfate	10.0

EXAMPLE 4

Another suitable dosage can contain 200 mg. of glyceryl guaiacolate and 40 mg. of phenyltoloxamine dihydrogen citrate.

EXAMPLE 5

Another suitable capsule dosage form can contain 400 mg. of glyceryl guaiacolate with any one of the following antihistamines:

	Weight in milligrams
(1) Chloropheniramine maleate	8
(2) Phenindamine tartrate	50
(3) Pyrilamine maleate	50
(4) Tripelennamine HCl	25

EXAMPLE 6

Another suitable dosage can be 50 mg. phenyltoloxamine dihydrogen citrate with any one of the following muscle relaxants:

	Weight in milligrams
(1) Carisoprodol	200
(2) Meprobamate	200
(3) Mephenesin	500
(4) Methocarbamol	500

EXAMPLE 7

Another suitable dosage in a tablet can have the following ingredients:

	Weight in milligrams
(1) Glyceryl guaiacolate	200
(2) Phenyltoloxamine dihydrogen citrate	25
(3) Acetaminophen	300

The employment of experimentally induced audiogenic seizures in certain susceptible animals and electroshock seizures in laboratory animals to test the protective effect of anticonvulsants, ataraxic drugs and muscle relaxants has been widely reported.

Among previous reports so using audiogenic seizures are the following: Bielec, S., Arch. Int. Pharmacodyn, 119: 352, 1959; Busnel, R., Path. et Biol., 6: 749, 1958; Fink, G. B. and Swinyard, E. A., J. Pharmacol. Exper. Therap., 127: 318, 1959; Mercier, J., C. R. Soc. Biol., Paris, 144: 117, 1950; Plotnikoff, N. P., Arch. Int., 116: 130, 1958; Plotnikoff, N. P., Psychopharmacol., 1: 429, 1960; Plotnikoff, N. P., and Green, D. M., J. Pharmacol. Exper. Therap., 119: 294, 1957; and Wilson, C. W. M., Brit. J. Pharmacol., 14: 415, 1959.

The animals used in these tests are sensitive to auditory stimuli to which they are subjected. They react to the stimulus by running, jumping, circling or going into convulsions or catalepsy. The degree to which this response is reduced by the administration of a drug is taken as a measure of the protective effect of this drug. This correlates generally with the amelioratory effect that the drug has on similar conditions in humans.

To test the protective effect that a combination of skeletal muscle relaxant and antihistamine would have on audiogenic seizures in mice and to compare the same with the sum of the effects of the two drugs when administered separately, the following experiments were carried out:

Male albino mice weighing 14 to 30 gm. (audiogenic strain, Research Animals Incorporated, Pittsburgh, Pa.) were used. They were maintained on a standard diet at a room temperature between 23 and 26 degrees C. (74 and 79 degrees F.) and allowed food and water ad libitum except during test time. Twenty-five mice were used for each dose studied.

On the first day of study the mice were given 0.15% hydroxyethylcellulose (HEC) in distilled water, 0.5 ml./20 gm. mouse, intragastrically, and the drugs were given on the following day in 0.15% HEC in distilled water, 0.5 ml./20 gm. mouse, intragastrically. Thus, each mouse served as its own control.

Fifteen minutes after administration of either the HEC or the test drug, the mice were placed in the audio chamber and subjected to an auditory stimulus for sixty seconds. The responses consisted of one or more of the following: running, jumping, circling, convulsing, and catalepsy. Each of these responses was given a score of one point. The differences between the total scores on the control day and on the treated day were used as the measure of protection afforded by the drug. The percent protection that the drug afforded was calculated as follows:

$$\frac{\text{Drug response}}{\text{Control response}} \times 100 = N; \quad 100 - N = \text{percent protection}$$

The PD_{50} (fifty percent protective dose) was estimated according to the method of Litchfield and Wilcoxon (J. Pharmacol. Exp. Therap., 96:99, 1949).

Table III below summarizes the results of these tests using a combination of glyceryl guaiacolate and phenyltoloxamine dihydrogen citrate in various ratios. In each category of ratio studied, it can be seen that the actual protection afforded by the combination of the drugs was far greater than the arithmetic sum of the effects of the individual drugs. This clearly illustrates the potentiating effect which is characteristic of the present invention.

TABLE III.—CONTRIBUTION OF GLYCERYL GUAIACOLATE AND PHENYLTOLOXAMINE DIHYDROGEN CITRATE IN RATIOS OF 4 TO 1, 8 TO 1, 16 TO 1 AND 32 TO 1, TO THE THEORETICAL AND THE ACTUAL PROTECTION OF MICE FROM AUDIOGENIC SEIZURES, AT THE PD_{50} DOSAGE

Active Ingredients	4 to 1 Ratio		8 to 1 Ratio		16 to 1 Ratio		32 to 1 Ratio	
	Mouse Dose (mg./kg.)	Percent Protection	Mouse Dose (mg./kg.)	Percent Protection	Mouse Dose (mg./kg.)	Percent Protection	Mouse Dose (mg./kg.)	Percent Protection
Glyceryl guaiacolate	280.0	[1] 22.2	330	29.5	375	35.8	435	43.5
Phenyltoloxamine dihydrogen citrate	70.0	[2] 4.4	41.25	0.2	23.4	0.0	13.6	0.0
Theoretical additive amount of protection		26.6		29.7		35.8		43.5
Actual amount of protection from combination		50.0		50.0		50.0		50.0

[1] Determined from dose-response curves. [2] Estimated from tabular data only.

Table IV below summarizes the results of a series of tests similar to those summarized in Table III. In this case, however, glyceryl guaiacolate is used in conjunction with a series of different antihistamines. The results obtained are similar. In each case the actual protection is far in excess of the expected protection calculated on the basis of the individual effects.

TABLE IV.—THEORETICAL SUM OF PROTECTION AFFORDED BY COMBINATIONS OF GLYCERYL GUAIACOLATE AND THE ANTIHISTAMINIC CHLORCYCLIZINE HYDROCHLORIDE, CHLORPHENIRAMINE MALEATE, PHENINDAMINE TARTRATE, TRIPELENNAMINE HYDROCHLORIDE AND PYRILAMINE MALEATE, IN VARIOUS RATIOS, AS COMPARED WITH THE ACTUAL PROTECTION OF MICE FROM AUDIOGENIC SEIZURES

Active Ingredients	4 to 1 ratio		8 to 1 ratio		8 to 1 ratio		16 to 1 ratio		8 to 1 ratio	
	Mouse Dose, mg./kg.	Percent Protection	Mouse Dose, mg./kg.	Percent Protection	Mouse Dose, mg./kg.	Percent Protection	Mouse Dose, mg./kg.	Percent Protection	Mouse Dose, mg./kg.	Percent Protection
Glyceryl guiacolate	400	[1] 24.7								
Chlorcyclizine hydrochloride	100	2.8								
Glyceryl guaiacolate			400	24.7						
Chlorpheniramine maleate			50	4.2						
Glyceryl guaiacolate					400	24.7				
Phenindamine tartrate					50	0				
Glyceryl guaiacolate							400	24.7		
Tripelennamine hydrochloride							25	0		
Glyceryl guaiacolate									400	24.7
Pyrilamine maleate									50	[2] (+4.9)
Theoretical sum of protection		27.5		28.9		24.7		24.7		19.8
Actual amount of protection from combination		53.2		80.6		62.2		42.9		56.7

[1] Determined from the dose response curves. [2] Increase in audiogenic seizure.

Table V summarizes the result of a series of tests similar to those summarized in Tables III and IV. In this case, however, the same antihistamine, i.e. phenyltoloxamine, is used with a series of different skeletal muscle relaxants. The results are similar to those shown in Tables III and IV.

TABLE V.—THEORETICAL SUM OF PROTECTION AFFORDED BY COMBINATIONS OF THE MUSCLE RELAXANTS, CARISOPRODOL, MEPHENESIN, MEPROBAMATE AND METHOCARBAMOL, AND THE ANTIHISTAMINIC PHENYLTOLOXAMINE DIHYDROGEN CITRATE, AS COMPATED WITH THE ACTUAL PROTECTION OF MICE FROM AUDIOGENIC SEIZURES

Active Ingredients	4 to 1 Ratio		4 to 1 Ratio		4 to 1 Ratio		4 to 1 Ratio	
	Mouse Dose (mg./kg.)	Percent Protection	Mouse Dose (mg./kg.)	Percent Protection	Mouse Dose (mg./kg.)	Percent Protection	Mouse Dose (mg./kg.)	Percent Protection
Carisoprodol	100	11.1						
Phenyltoloxamine dihydrogen citrate	25	0						
Mephenesin			300	43.5				
Phenyltoloxamine dihydrogen citrate			75	6.7				
Meprobamate					200	48.0		
Phenyltoloxamine dihydrogen citrate					50	0.6		
Methocarbamol							300	8.8
Phenyltoloxamine dihydrogen citrate							75	6.7
Theoretical sum of protection		11.1		50.2		48.6		15.5
Actual amount of protection from combination		35.9		71.1		92.3		81.3

Protection against electroshock seizures in mice and rats has been employed by numerous investigators as a means of selecting and evaluating drugs useful for the treatment of certain disorders in man, including drugs with central nervous system depressant action, anticonvulsant, psychopharmacologic and muscle relaxant properties. Among some of the previous reports of such are those in mice (Chen, G., B. Bohner and E. R. Ensor: Proc. Soc. Exper. Biol. and Med., 87: 334, 1954; Chen, G. and B. Bohner: Proc. Soc. Exper. Biol. and Med., 106: 632, 1961; Fink, G. B. and E. A. Swinyard: J. Am. Pharm. Assoc., Sci. Ed., 49: 510, 1960; Gesler, R. M., C. E. Lints and E. A. Swinyard: Tox. and Appl. Pharmacol., 3: 107, 1961; Mitchell, C. L. and H. H. Keasling: J. Pharmacol. Exper. Therap., 128: 79, 1960; Weiss, B. and C. G. T. Ewing: Am. J. Pharm., 131: 307, 1959; Witkin, L. B., P. Spitaletta, F. Galdi and E. O'Keefe: Tox. and Appl. Pharmacol., 2: 264, 1960; Truitt, E. B. Jr. and J. M. Little: J. Pharmacol. Exper. Therap., 122: 239, 1958) in rats (Swinyard, E. A.: J. Am. Pharm. Assoc., Sci. Ed., 38: 201, 1949; Toman, J. E. P., E. A. Swinyard and L. S. Goodman: J. Neurophysiol., 9: 231, 1946) and in both mice and rats (Chen, G. and C. R. Ensor: Arch. Neurol. and Psychiat., 63: 56, 1950; Gray, W. D., C. E.

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To test the protective effect that the combination of skeletal muscle relaxant and antihistaminic would have on the supramaximal electroshock seizure in mice and to compare the same with the sum of effects of the two drugs when administered separately, the following experiments were carried out.

Male C.F.W. albino mice weighing 18 to 26 gm. were used. They were maintained on a standard diet at a room temperature between 23 and 26 degrees C. (74 and 79 degrees F.) and allowed food and water ad libitum until test time. They were then randomly selected and divided into groups of ten. Thirty mice were used for each dose studied.

The test measures the ability of a drug to prevent the hindleg tonic-extensor component of a maximal electroshock seizure evoked by a supramaximal current. A 60 cycle alternating current of 40 volts and 1.4 amperes was applied to the mouse ears by clips and was delivered up to a maximum of 10 seconds duration.

The mouse is subjected to the supramaximal current fifteen minutes after intragastric administration of either the drug with 0.15% hydroxyethylcellulose (HEC) in distilled water, 0.5 ml./20 gm. mouse, or of HEC alone, to control animals.

A decrease in the number of mice having the hindleg tonic-extensor component of the seizure, as compared with the control group, was used as a measure of protective activity. The PD_{50} (fifty percent protective dose) was estimated according to the method of Litchfield and Wilcoxon (J. Pharmacol. Exper. Therap., 96: 99, 1949).

The following data reports supramaximal electroshock seizure studies with glyceryl guaiacolate and phenyltoloxamine dihydrogen citrate, alone and in combination. These results demonstrate that the combination of a muscle relaxant and an antihistaminic, as exemplified by these drugs, affords the same unique synergistic protection against supramaximal electroshock seizures in mice, and over the same broad range of ratios, as was shown in audiogenic seizure studies.

TABLE VI.—CONTRIBUTION OF GLYCERYL GUAIACOLATE AND PHENYLTOLOXAMINE DIHYDROGEN CITRATE IN RATIOS OF 4 TO 1, 8 TO 1 AND 16 TO 1, TO THE THEORETICAL AND THE ACTUAL PROTECTION OF MICE FROM SUPRAMAXIMAL ELECTROSHOCK SEIZURES, AT THE PD_{50} [1] DOSE.

Active Ingredients	4 to 1 Ratio		8 to 1 Ratio		16 to 1 Ratio	
	Mouse Dose (mg./kg.)	Percent Protection	Mouse Dose (mg./kg.)	Percent Protection	Mouse Dose (mg./kg.)	Percent Protection
Glyceryl guaiacolate	397.0	[2] 1.4	474.0	10.5	500	16.2
Phenyltoloxamine dihydrogen citrate	99.25	[3] 0.0	59.25	0.0	31.25	0.0
Theoretical additive amount of protection		1.4		10.5		16.2
Actual amount of protection from combination (PD_{50}) [1]		50.0		50.0		50.0

[1] Fifty percent protective dose (PD_{50}) as determined from dose-response curves.

[2] Determined from dose-response curves.

[3] Estimated from tabular data only.

Although the invention has been described with reference to specific forms thereof, it will be understood that many changes and modifications may be made without departing from the spirit of this invention.

What is claimed is:

1. A method of (a) inducing relaxation of at least one of skeletal muscle in animals suffering from involuntary contractions of skeletal muscle; and (b) relieving convulsions in an animal suffering from the same; and (c) inducing ataraxia in an animal suffering from nervous tension; which comprises orally administering to said animal a therapeutically effective quantity of the combination of a skeletal muscle relaxant and an antihistamine or a pharmaceutically acceptable non-toxic acid addition salt thereof in the ratio of 4 to 32 parts of skeletal muscle relaxant per part of antihistamine; said muscle relaxant being selected from the group consisting

of glyceryl guaiacolate, methocarbamoyl, mephenesin, mephenesin carbamate, carisoprodol, emylcamate, meprobamate, hydroxyphenamate, styramate, chlorzoxazone, zoxazolamine, hydroxyzine and phenaglycodol; and said antihistamine being selected from the group consisting of tripelennamine HCl, pyrilamine maleate, thonzylamine HCl, metaphenilene HCl, methapyrilene HCl, chlorothen citrate, thenyldiamine HCl, meclizine hydrochloride, cyclizine hydrochloride, chlorcyclizine, promethazine hydrochloride, pyrathiazine hydrochloride, pheniramine maleate, chlorpheniramine maleate, brompheniramine maleate [d-isomer], triprolidone hydrochloride, pyrrobutamine phosphate, diphenylpyraline hydrochloride, phenindamine tartrate, diphenhydramine, dimenhydrinate, bromodiphenhydramine, doxylamine succinate, carbinoxamine maleate, phenyltoloxamine dihydrogen citrate and phenyltoloxamine dihydrogen hydrochloride.

2. A method according to claim 1 wherein the total dosages of from 13.5 to 3200 mg. of the combination of muscle relaxant and antihistamine is administered.

3. A method according to claim 2 wherein the muscle relaxant is glyceryl guaiacolate and the antihistamine is phenyltoloxamine dihydrogen citrate.

4. A method according to claim 2 wherein the muscle relaxant is glyceryl guaiacolate and the antihistamine is chlorcyclizine hydrochloride.

5. A method according to claim 2 wherein the muscle relaxant is glyceryl guaiacolate and the antihistamine is chlorpheniramine maleate.

6. A method according to claim 2 wherein the muscle relaxant is glyceryl guaiacolate and the antihistamine is phenindamine tartrate.

7. A method according to claim 2 wherein the muscle relaxant is glyceryl guaiacolate and the antihistamine is tripelennamine hydrochloride.

8. A method according to claim 2 wherein the muscle relaxant is glyceryl guaiacolate and the antihistamine is pyrilamine maleate.

9. A method according to claim 2 wherein the muscle relaxant is carisoprodol and the antihistamine is phenyltoloxamine dihydrogen citrate.

10. A method according to claim 2 wherein the muscle relaxant is mephenesin and the antihistamine is phenyltoloxamine dihydrogen citrate.

11. A method according to claim 2 wherein the muscle relaxant is meprobamate and the antihistamine is phenyltoloxamine dihydrogen citrate.

12. A method according to claim 2 wherein the muscle relaxant is methocarbamol and the antihistamine is phenyltoloxamine dihydrogen citrate.

13. A method of relieving convulsions in animals which comprises orally administering to said animals a composition containing glyceryl guaiacolate and a pharmaceutically acceptable non-toxic acid addition salt of phenyltoloxamine, the said composition containing from about 4 to about 20 parts of glyceryl guaiacolate per part of the phenyltoloxamine salt by weight.

14. A method according to claim 13 wherein the

phenyltoloxamine salt is phenyltoloxamine dihydrogen citrate.

15. A method according to claim 13 wherein said composition contains between about 212.5 to 3100 mg. of the combination of glyceryl guaiacolate and said addition salt of phenyltoloxamine.

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SAM ROSEN, *Primary Examiner.*

FRANK CACCIAPAGLIA, JR., JULIAN S. LEVITT, *Examiners.*

P. L. SABATINE, M. J. COHEN, *Assistant Examiner.*

UNITED STATES PATENT OFFICE

CERTIFICATE OF CORRECTION

Patent No. 3,314,852 April 18, 1967

Daniel M. Green et al.

It is certified that error appears in the above identified patent and that said Letters Patent are hereby corrected as shown below:

Column 17, line 64, cancel "of at least one"; same line 64, after "of", first occurrence, insert -- at least one of --.

Signed and sealed this 5th day of August 1969.

(SEAL)
Attest:

Edward M. Fletcher, Jr.
Attesting Officer

WILLIAM E. SCHUYLER, JR.
Commissioner of Patents