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VASOCONSTRICTOR COMPOSITION

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7 Claims. (Cl. 167—65)

1

This invention relates to preparations of ephedrine and related compounds, and more particularly to improved compositions for oral administration of such drugs.

Ephedrine is, as is well-known, the principal alkaloid of the pharmacologically active species of ephedra, or mahuang, particularly *Ephedra equisetina* Bunge, *E. sinica* Stapf, *E. nebrodensis, E. intermedia, "E. vulgaris"* (so-called), and others. In these species the usual content of ephedrine varies between about ½% and 1¼% by weight, and occasionally as high as 1.9%. Ephedrine may also be obtained synthetically. Related compounds may also be synthesized, and will be further referred to hereinbelow.

Pharmacologically, ephedrine acts in a similar manner to epinephrine, stimulating the sympathetic nervous system. It is a vasoconstrictor, and is particularly useful in the symptomatic treatment, of allergic manifestations such as asthma, urticaria, angioneurotic edema, and the like, and has the great advantage over epinephrine of being effective when given orally.

The crude drug ephedra is seldom given to obtain the therapeutic action of ephedrine (except possibly by Chinese herb doctors) because of undesirable side reactions caused by other constituents of the crude drug. Ephedrine itself, whether obtained naturally or synthetically, is likewise not without disadvantageous secondary reactions, commonly causing anxiety, palpitation, restlessness, sleeplessness, and the like, particularly in the allergic individual, who is often predisposed to such symptoms. It is therefore common to compound ephedrine with sedatives such as the barbiturates in order to overcome the undesired reactions. The use of such sedatives, while accomplishing the immediate purpose, is in turn undesirable, particularly when barbiturates are used, as these may be habit-forming, and may cause such degenerative conditions as agranulocytosis with long-continued use.

One of the objects of this invention is to provide a means of administering ephedrine and related compounds while avoiding the undesirable subsidiary reactions therefrom.

Another object of the invention is to provide a means of administering ephedra while avoiding the undesirable subsidiary reactions therefrom.

Another object of the invention is to provide a means of prolonging the action of oral vasoconstrictor medication while at the same time reducing the intensity of the initial effects of treatment.

2

Another object is to provide a novel and useful medication for allergic disorders.

I have discovered that a remarkable synergism between ephedrine and ephedra when taken together in certain ratios. As stated above, neither ephedrine nor ephedra is wholly satisfactory when used alone, but when so combined that the ratio of total ephedrine to ephedra is between about 1:20 and 1:2, and more desirably between about 1:10 and 1:3, the hereinbefore cited undesirable side reactions of ephedrine are greatly reduced. At the ratios given not enough ephedra is taken in to cause in turn the reactions incident upon it, and indeed the ephedrine itself appears to modify these. It will be appreciated that ratios of this magnitude do not occur in natural mahuang, ephedrine contents of respectively 1% and 2% giving ephedrine:ephedra ratios of 1:99 and 1:49.

The pharmacology of ephedra as to all of its minor constituents has not been sufficiently elucidated that an explanation of the phenomena of this invention can be given; but it seems not unlikely that hitherto unappreciated constituents of ephedra have the property of modifying the pharmacological action of ephedrine so that the purpose of this invention can be realized, but that the ephedrine:ephedra ratio in naturally occuring ephedra has such values that the effect is defeated when enough ephedra is taken to provide a therapeutic quantity of ephedrine. However, it should be understood that I do not wish to be limited to any particular theory of action.

It is in some cases desirable, but not necessary for the purposes of this invention in its broadest aspects, to include other ingredients in a preparation for allergic relief embodying the principles of the invention. Thus, diuretics and cardiac stimulants such as caffeine, theobromine, theophylline, and aminophylline are sometimes useful as adjuncts, as are antispasmodics such as belladonna, stramonium, and hyoscyamus and their alkaloids, and also alkali metal and alkaline-earth halides such as calcium, sodium, and potassium iodides, and potassium and calcium chlorides. Sedatives such as bromides, chloral hydrate, and barbiturates can of course be added, but their use is made large unnecessary by the synergistic action of the ephedra with the ephedrine.

To prolong the effect of the medication, and at the same time to lessen the impact of the drugs on the system, it is desirable to add a suitable quantity of a substance exhibiting base exchange, such as clays of moderate or high base exchange

capacity like fuller's earth, illite, bentonite, and similar clays; or zeolites such as analcite, matrolite, heulandite, stilbite, common "greensand" zeolites, and even synthetically made zealites of of the alumino-silicate type; or even such of those of the recently introduced organic cation exchangers of, for example, the sulfonated coal or the synthetic resin type, as are non-toxic. These will naturally be finely divided and may be present in such quantity (as may be readily calculated from the base exchange capacity for large cations of the exchange substance and the stoichiometric equivalence of the ephedrine or other alkaloid or organic base present) as to bind all or only a portion of the organic base, viz., ephedrine. The base exchange reaction may be carried out during manufacture, as for example by mixing the two reacting substances with water, drying, and comminuting; or they may be simply mixed dry, allowing reaction to take place when they are moistened by the gastric juices.

I prefer to bind up only a portion of the organic base, viz., ephedrine, in this manner, so that the remainder is available for absorption as soon as it reaches the stomach, while the exchanged portion is withheld from availability until the alkaline regions of the intestines are reached, whereupon the base tends to be liberated from the cation exchanger as a consequence of the higher pH. Where another base besides the vasoconstrictor is present, such as for example caffeine or theophylline, a portion or all of this other base may likewise be bound by base exchange. Where the reaction is not effected during manufacture, it may be desirable to separate the various organic bases in separate capsules or pills or portions thereof, each with its proper amount of cation exchanger, so that the reaction of the stronger base with the cation exchanger to the exclusion of the weaker is avoided.

Ephedrine has been used as the example of the vasoconstrictor hereinabove; but it will be understood that there are other analogues and derivatives having an essentially similar action and likewise adapted for oral administration which can also be used in accordance with the principles of this invention. Examples of these are: racemic ephedrine (which of course contains half of the official stereoisomer), benzyl ephedrine, ethyl ephedrine, neo-synephrine (α-hydroxy-β-methylaminoethyl-3-hydroxybenzene), propadrine (α-hydroxy-β-aminopropylbenzene), amphetamine (1-phenyl-2-aminopropane), "benzedrex" (1-cyclohexyl-2-aminopropane), desoxyephedrine, privine (α-naphthyl-2-methyl imidazoline), and others, which for the most part may be structurally considered as derivatives of ethylamine, and more particularly as β aryl ethylamine derivatives. All of the foregoing compounds contain the group R—C—C—N— where R is a six membered carbon ring. Those skilled in the art recognize the six-membered carbon ring ethyl amine structure as contributing vasoconstrictive action, as described in "The Pharmacological Basis of Therapeutics" by Goodman and Gilman, page 427.

It will be understood that these vasoconstrictor amines can be employed as the free base, or in the salt form, for example, as the hydrochloride, sulfate, acetate, and so forth. Their action where used according to the invention is independent of whether they are in the free amine or salt form. Naturally, those which are volatile in the free state, such as 1-phenyl- and 1-cyclohexyl-2-aminopropane, are best used in the non-volatile salt form, to avoid loss by evaporation. Any other bases employed, such as xanthine diuretics, may of course also be in the free base or salt form.

In the examples and claims which follow, "ephedra" is the well-known crude drug ephedra, or mahuang, of species containing ephedrine in pharmacologically active quantities. The drug consists largely of the green stems of the plant.

Examples

1

	Grains
Ephedrine sulfate	3/8
Ephedra	2

The powdered ingredients are encapsulated.

2

	Grains
Ephedrine	3/8
Ephedra	1½
Aminophylline	1½

The powdered ingredients are formed into a pill.

3

	Grains
Ephedrine hydrochloride	3/8
Ephedra	4
Fuller's earth	3

The powdered ingredients are encapsulated. The amounts of fuller's earth is sufficient to adsorb about half of the ephedrine hydrochloride, assuming a base-exchange capacity of 30 milliequivalents per 100 grams.

4

	Grains
Propadrine hydrochloride	½
Ephedra	8
Atropine sulfate	1/200
Theobromine	3

The powdered ingredients are encapsulated.

5 (A)

	Grains
Ephedrine sulfate	3/8
Ephedra, powdered	4
Wyoming bentonite	1

5 (B)

Theophylline	2
Wyoming bentonite	5

Mixture A and Mixture B are packed into opposite ends of a gelatin capsule, which are then put together. Each alkaloid is provided with approximately half its equivalent weight in bentonite, and the manner of packing insures that each portion of bentonite will be saturated with its proper alkaloid.

6

	Grains
Amphetamine sulfate	⅛
Benzylephedrine hydrochloride	⅛
Neosynephrine hydrochloride	⅛
Ephedra	5
Sodium iodide	5

The powdered ingredients are encapsulated.

In the examples above, the quantities given are for a single dose.

What I claim is:

1. A composition for medicinal use comprising, ephedrine and vasoconstrictive ephedra in a weight-ratio of ephedrine:ephedra between the approximate limits of 1:20 and 1:2.

2. A composition for medicinal use comprising,

ephedrine and vasoconstrictive ephedra in a weight-ratio of ephedrine:ephedra between the approximate limits of 1:20 and 1:2, together with a comminuted solid cation-exchange material in quantity sufficient to adsorb by base-exchange a substantial proportion of the ephedrine.

3. A composition for medicinal use comprising; an orally effective vasoconstrictor containing the group R—C—C—N— where R is a six membered carbon ring and vasoconstrictive ephedra in a weight-ratio of vasoconstrictor:ephedra between the approximate limits of 1:20 and 1:2.

4. A composition for medicinal use comprising, an orally effective vasoconstrictor containing the group R—C—C—N— where R is a six membered carbon ring and vasoconstrictive ephedra in a weight-ratio of vasoconstrictor:ephedra between the approximate limits of 1:20 and 1:2, together with a comminuted solid cation-exchange material in quantity sufficient to adsorb by base-exchange a substantial proportion of the vasoconstrictor.

5. A composition for medicinal use comprising, an orally effective vasoconstrictor containing the group R—C—C—N— where R is a six membered carbon ring and vasoconstrictive ephedra; a xanthine diuretic chosen from the group consisting of caffeine, theobromine, theophylline, and their double salts with ethylene diamine, sodium acetate, and sodium salicylate; and a base-exchange material; in which the vasoconstrictor: ephedra ratio lies between the limits of 1:20 and 1:2, and in which the vasoconstrictor and ephedra are mixed with a partial stoichiometric equivalent of the base-exchange material, and in which the

xanthine diuretic is separately mixed with a partially stoichiometric equivalent of the base-exchange material, and in which the vasoconstrictor and xanthine diuretic portions are juxtaposed for simultaneous administration.

6. A composition according to claim 3 and wherein the ephedra is comminuted.

7. A composition according to claim 4 and wherein the comminuted solid cation-exchange material is selected from the group consisting of zeolites, fuller's earths, bentonites and illites.

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