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THERAPEUTICALLY ACTIVE COMPOSITIONS CONTAINING AMPHETAMINES

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This invention relates to new and improved compositions consisting of amphetamine compounds and has particular relation to a new and useful therapeutic agent containing the aforementioned compounds. More specifically, the present invention relates to amphetamine compounds such as dl-amphetamine sulfate, dl-amphetamine hydrochloride, dextroamphetamine sulfate, and methamphetamine hydrochloride, combined with critical amounts of an amphoteric antacid such as aluminum hydroxide, magnesium trisilicate, or dihydroxy aluminum aminoacetate. The compositions of my invention are appetite satients effective for the treatment of obesity.

The amphetamines are used not infrequently in the treatment of mental depression, narcolepsy, lethargy and several other conditions. Their most common use, however, is as appetite depressants in the treatment of overweight and obesity.

It is well known that amphetamine compounds such as amphetamine sulfate and hydrochloride, dextroamphetamine sulfate, methamphetamine hydrochloride, etc., act as stimulants for the central nervous system and are capable of exerting valuable effects in the treatment of obesity. However, said compounds have also certain undesirable gastrointestinal effects, such as heartburn, nausea, vomiting, and diarrhea. These symptoms are not infrequently observed in patients receiving amphetamine compounds.

It is the main object of the present invention to provide an amphetamine composition, the beneficial effects of which are greater and the undesirable side effects of which are less than known amphetamine compositions.

It is another object of the present invention to improve the action of amphetamine compounds by buffering or combining them with critical amounts of amphoteric antacids such as aluminum hydroxide, magnesium trisilicate, and dihydroxy aluminum aminoacetate.

Another object of the present invention is to provide a therapeutic agent, the anorexigenic or appetite-depressant effects of which are higher than those of the amphetamines alone.

Still another object of this invention is to reduce the undesirable side effects such as epigastric distress and heartburn which are occasionally encountered with the amphetamines alone.

Other objects and advantages of the invention will be apparent from the appended claims and the following specification which describes by way of example some embodiments of the invention.

I have now discovered that the appetite depressing action of amphetamines may be synergized and the undesirable side effects of amphetamine compounds reduced by combining or buffering them with critical amounts of certain amphoteric antacids. More specifically, the novel appetite satient composition of the present invention includes, in addition to the amphetamine compound or mixture of amphetamine compounds, at least 8 milli-equivalents of a mixture of aluminum hydroxide, magnesium trisilicate, and dihydroxyaluminum aminoacetate.

The amphetamine compound which I have found effective in my compositions is dextroamphetamine (dextro-1-phenyl-2-amino propane). It is known that this compound is more effective when mixed with the dl-amphetamine. I prefer to use in a single dosage unit approximately 3 mgm. of an amphetamine compound such as dextroamphetamine sulfate together with 3 mgm. of dl-amphetamine sulfate. To this I add at least 8 milliequivalents of a mixture of aluminum hydroxide and magnesium trisilicate. To minimize the occasional undesirable stimulation of the nervous system caused by administering amphetamine compounds, I may add to my composition a sedative such as amytal (5-ethyl-5-isoamyl barbituric acid), barbital (5,5'-diethyl barbituric acid), or phenobarbital (5-ethyl-5'-phenyl barbituric acid) in variable doses.

Because of their amphoteric character, there is no critical limitation on the maximum amount of antacid that is present in my compositions. As magnesium trisilicate is a laxative and large amounts of aluminum hydroxide would cause constipation, it is desirable to combine these two antacids. Satisfactory compositions prepared according to this invention contain about two or three parts by weight of magnesium trisilicate to one part by weight of aluminum hydroxide. Dihydroxy aluminum aminoacetate may be substituted in whole or in part for the aluminum hydroxide.

My compositions may more conveniently be used in the form of tablets of lozenges (pleasant tasting). The tablets may be prepared by mixing the active ingredients (amphetamine compounds, barbiturates, magnesium trisilicate, and aluminum hydroxide) with excipients (sugar, talc, corn starch and binders) and flavoring oils (oil of peppermint, oil of fennel and methyl salicylate). The tablet may be prepared by processes well known in the pharmaceutical line, such as by "slugging" or by a wet granulation process. Lozenges containing similar dosage of active ingredients may also be prepared by known methods. It is an advantage of the lozenges that they may be chewed and swallowed without the aid of water. As the amphetamines are most effective when taken about one-half to one hour before meals when water is not always readily available for administration, the lozenges are a most convenient dosage form.

EXAMPLE I

Ingredient:	Per tablet, mgm.
A. Dextroamphetamine sulfate	3.0
dl-Amphetamine sulfate	3.0
Phenobarbital	15.0
Aluminum hydroxide	350.0
Magnesium trisilicate	800.0
B. Starch	4.25
Magnesium stearate	4.25
Acacia	4.00

Granulate part A with 10% gelatin solution and dry at 50° C. Regranulate and mix with B. Compress into tablets weighing 1183.5 mgm.

EXAMPLE II

Ingredient:	Per tablet, mgm.
A. Dextroamphetamine sulfate	3.5
Methamphetamine hydrochloride	1.5
Amytal	20.0
Aluminum hydroxide	110.0
Magnesium trisilicate	350.0
B. Starch	4.25
Magnesium stearate	4.25

Granulate part A with 10% gelatin solution. Dry at

50° C. Regranulate and mix with B. Compress into tablets weighing 493.5 mgm.

EXAMPLE III

Ingredient:	Per tablet, mgm.
A. Dextroamphetamine sulfate	5.0
Amytal	15.0
Aluminum hydroxide	250.0
Magnesium trisilicate	500.0
B. Starch	4.25
Magnesium stearate	4.25

Granulate part A with 10% gelatin solution and dry at 50° C. Regranulate and mix with B. Compress into tablets weighing 778.5 mgm.

EXAMPLE IV

Ingredient:	Per tablet, mgm.
A. Dextroamphetamine sulfate	3.0
dl-Amphetamine sulfate	3.0
Amytal	30.0
Aluminum hydroxide	110.0
Magnesium trisilicate	600.0
Dixhydroxy aluminum aminoacetate	300.0
B. Sucrose	1000.0

Granulate part A with 10% gelatin solution and dry at 50° C. Regranulate and mix with B. Compress into lozenges weighing 2,046 mgm.

The proportions of the various ingredients of my composition may be varied widely. The amphetamine compound may vary from about 3 to about 6 mgm. per dosage unit. The barbiturate may be eliminated entirely or may be present in an amount up to approximately 30 mgm. The lower limit of the amphoteric antacid is critical as too small an amount is not effective. I have found that at least 4 milli-equivalents of aluminum hydroxide (104 mgm.) in combination with at least 4 milli-equivalents of magnesium trisilicate (350 mgm.) is required to synergize the appetite depressing action of amphetamines. An equivalent amount of dihydroxy aluminum aminoacetate may be substituted for the aluminum hydroxide. Since the amphoteric antacids employed are non-toxic, the upper limit of the amount of antacid present is not critical.

The practical effect of my amphetamine compositions may be appreciated from clinical results on 62 unselected overweight patients ranging in age from 17 to 72 years and in weight from 132 to 291 pounds. These patients were divided into three groups and treated for a period of eight weeks. The 26 patients in group I were treated with tablets prepared according to Example I. Dosage was three tablets daily about one-half to one hour before meals, yielding a total of 15 mgm. of amphetamines per day.

Group II also consisted of 26 patients similarly treated with the exception that the aluminum hydroxide and magnesium trisilicate were omitted. The amphetamines were in the same dosage as noted for group I.

The 10 patients in group III were a control group. These patients received antacids (aluminum hydroxide and magnesium trisilicate) alone.

The clinical results are tabulated in Table I.

Table I

Group	Number of patients	Treatment	Total lbs. lost, 8 wks.	Average lbs. lost per patient per week
I	26	Amphetamines and antacids	479	2.30
II	26	Amphetamines alone	261	1.25
III	10	Antacids alone	0	

It is apparent that there is a significant difference in the degree of weight loss induced by the three treatments. It may be noted that the antacids have no appetite-depressing action. Since, however, upon combination with amphetamines the anorexigenic effect of the latter was enhanced, it may be concluded that the antacids produced a synergistic effect with the amphetamines. Experimental findings in laboratory animals corroborate this observation.

In addition to the better results observed with the use of aluminum hydroxide and magnesium trisilicate, the patients in group I reported less hunger and fewer gastrointestinal side effects such as heartburn, nausea, vomiting and diarrhea.

What is claimed is:

1. An obesity control composition suitable for oral administration comprising in the following relative proportions, 3-4 mgm. of a dextroamphetamine compound, 1–2 mgm. of d-methamphetamine hydrochloride, 0–20 mgm. of 5-ethyl-5-isoamyl barbituric acid, 4 milli-equivalents of aluminum hydroxide, and 4 milli-equivalents of magnesium trisilicate.

2. An obesity control composition suitable for oral administration comprising in the following relative proportions, 3 mgm. of dextroamphetamine sulfate, 3 mgm. of dl-amphetamine hydrochloride, 20 mgm. of 5-ethyl-5-isoamyl barbituric acid, 350 mgm. of aluminum hydroxide, and 800 mgm. of magnesium trisilicate.

3. An obesity control composition suitable for oral administration comprising from about 3 to about 6 mgm. of a mixture of amphetamine compounds and at least 8 milli-equivalents of a mixture of aluminum hydroxide and magnesium trisilicate.

References Cited in the file of this patent

Wilson: The American Drug Index, 1956, Lippincott Co., Philadelphia, Pa., pp. 292 and 337.