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NARCOTIC MEDICAMENTS

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1 Claim. (Cl. 167—67)

1

This invention relates to new pharmaceutical products and has particular relation to new and improved narcotics consisting of mixtures of several active ingredients.

It is known that in the application to patients of various compounds having a narcotic effect, such as morphine, codeine, their salts and rerivatives, and other products having morphine-like physiological effects, certain unwelcome phenomena, for example nausea, vomiting and reduction of biliary and pancreatic secretions often occur. It also was observed that when certain other drugs were administered simultaneously with the narcotics, for instance drugs having parasympathetic depressant properties, some side effects made themselves less felt. However, none of these drugs reduce the incidence of side-actions greatly and many of them do not relax spasms induced by most of the opium-derivatives.

It has now been found that improved narcotic preparations are obtained if narcotic compounds, such as opium derivatives and other compounds with morphine-like action, are used in mixture with those synthetic antispasmodic drugs which exert powerful musculotropic and neurotropic effects and give relief of unstriated muscle spasms in gastrointestinal, biliary and genito-urinary tract disorders. The addition of one or more of these anti-spasmodic drugs to narcotics produces beneficial results, consisting in diminished untoward effects and in making the nature of these effects milder, when they occur. Unexpectedly it was found that when narcotics are administered in combination with the anti-spasmodics according to my invention, the analgesic action usually will start faster than when the narcotic is given by itself. Furthermore, the analgesic action frequently is more potent and often lasts longer than when no such anti-spasodic is given. It has also been found that the toxicity of the preparations embodying the present invention is lower than the toxicity of the individual ingredients so that larger doses can be administered safely.

In order to fully disclose my invention, I will now describe a number of examples illustrating some preferred embodiments of the invention.

Example 1.—10 parts of morphine sulphate by weight are mixed with 1.5 parts of homatropine methylbromide by weight. This mixture interferes less with the propulsive movement of the small bowel than morphine alone and increases the muscular tone less. It can, therefore, be used with benefit before and after operations and causes the patient less distress than morphine administered by itself. It does not produce some of the unpleasant side-effects of morphine combined with atropine and gives the patient faster relief. Dose: 2.5–10 mgm.

2

Example 2.—Four parts of dihydrocodeinone terephtalate by weight are mixed with ten parts of diphenylacetyldiethylaminoethanol hydrochloride by weight. This mixture can be given on an empty stomach without nauseating the patient, in contrast to dihydrocodeinone by itself which should be administered immediately following meals. It can, therefore, be used in cases where patients do not eat well or where patients already are subjected to emetic influences as for instance in whooping cough. Relief from cough is longer than from dihydrocodeinone alone. Dose: 7–21 mgm.

Example 3.—50 parts of ethyl 1-methyl-4-phenylpiperidine-4-carboxylate hydrochloride by weight are mixed with 100 parts of beta-diethylamino-ethyl fluorene-9-carboxylate hydrochloride by weight. This mixture can be given in larger doses than the analgesic alone, but will cause less gastrointestinal irritability, less gastric hypermotility, less flushing and less sweating. Dose: 100–250 mgm.

Example 4.—Two parts of dihydromorphinone hydrochloride by weight are mixed with fifty parts of the phosphate of the d,l-tropic acid ester of 3-diethylamino-2,2-dimethyl-1-propanol by weight. This mixture tends to relax the intestinal musculature so that it will still further reduce the constipating effects of dihydromorphinone, which are less than those of morphine. As dihydromorphinone is widely used in cancer and other chronic diseases where patients often are bedridden and already tend to constipate and where the analgesic drug has to be administered over prolonged periods of time, it is important to obtain the weakest constipational effects possible. Dose: 40–100 mgm.

Example 5.—Five parts of dihydrohydroxycodeinone hydrochloride by weight are mixed with fifty parts of methylamino-iso-octene mucate by weight and one part of homatropine methylbromide by weight. The peristaltic waves in the colon, which may disappear upon administration of dihydrohydroxycodeinone hydrochloride are less influenced by this mixture and the tone of the musculature of the large bowel is seldom increased to the point of spasm. Feces are therefore less desiccated and the tone of the anal sphincter less augmented. Dose: 25–75 mgm.

Example 6.—30 parts of codeine phosphate by weight are mixed with 60 parts of bis-gamma-phenylpropylethylamine citrate by weight. Restlessness and excitement are seldom seen from this mixture even when given in large doses. Miosis, nausea and constipation are less prominent than from the same quantity of codeine administered without antispasmodic. Dose 50–100 mgm.

The preparations according to my invention may be used in the form of tablets, capsules, solutions, and suppositories and they may be administered by injection, per os or into the rectum.

In preparing the tablets, solutions and the like, accompanying ingredients, such as binders, diluents, lubricating agents, stabilizers and the like may be used. For example, tablets of the composition according to Example 1 may be prepared from the following ingredients:

Morphine sulphate_____grams__	250
Homatropine methylbromide____do____	37½
Milk sugar_____	5–2–72.5
Dextrine white_____	0–5–0
Starch _____	1–6–220
Talc _____	0–6–109
Zinc stearate_____	0–2–220

Water, Sufficient quantity.

From the above ingredients 25,000 tablets each containing ten mgm. morphine sulphate and one and one half mgm. homatropine methylbromide may be obtained by tabletting, each tablet to weigh 2.25 grains. The mixtures described in the other examples may be converted into tablets in a substantially similar manner.

In order to prepare an injectable solution of the product according to Example 2, one hundred and forty grams of the mixture are dissolved in ten thousand ccm. of an isotonic solution and one thousand multiple dose rubber stoppered ten cc. vials are filled.

My invention is not restricted to the specific ingredients and proportions and other details described in the above examples, and other narcotics and other synthetic antispasmodics, combining musculotropic with neurotropic effects, may be used to form mixtures embodying my invention. The narcotics and antispasmodics may be used in forms other than those described above, for example in the form of their salts with other suitable organic or inorganic acids, in the form of the free base or in the form of derivatives showing the desired narcotic and antispasmodic effect, respectively, and two or more narcotics and/or two or more antispasmodics in any form to each mixture.

As further examples of synthetic antispasmodics adapted to be used in carrying out my invention, the following may be mentioned: beta - diethylaminoethyl phenylpropylacetate, beta - diethylaminoethyl phenylcyclohexylacetate hydrochloride, beta - diethylaminoethyl phenylbenzylacetate.

The term "synthetic antispasmodic" is used in the present specification and claims to denote any antispasmodic compounds which combine musculotropic with neurotropic effect, do not occur in nature and are prepared by partial or complete synthesis of their molecules. Any of said synthetic antispasmodics may be used to produce the beneficial effects described in the introductory part of this specification on narcotics, when used in mixture with them.

Furthermore, it should be understood that the term "narcotic compound' is used in the present specification and claims to denote natural or synthetic compounds having narcotic effects, such as opium derivatives, for example morphine, codeine, dihydrocodeinone, 1-methyl-4-phenylpiperidine-4-carboxylate, 6-dimethylamino-4,4-diphenyl-3-heptanone, dihydromorphinone, dihydro-hydroxycodeinone, and salts and narcotic derivatives of these compounds, and other compounds or products having similar physiological effects.

While my invention has been described in connection with certain preferred embodiments of the same, it is not limited to the specific details disclosed and may be carried out wih various additions, substitutions and modifications, without departing from the spirit of the invention as defined in the appended claim.

The term "unit dose" is used to denote a single dose of the composition claimed, administered to an adult for therapeutic purposes.

What I claim is:

A new narcotic composition, in which the active ingredients consist of a major amount of narcotic compounds and a minor amount of an antispasmodic, and in which the narcotic ingredients consist, per unit dose, of at least one compound selected from the group consisting of at least 11.7 mg. codeine, at least 1.56 mg. dihydrocodeinone, at least 1.35 mg. dihydromorphinone and at least 1.97 mg. dihydrohydroxycodeinone compounds, and their salts, and the antispasmodic is homatropine methylbromide.

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