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PROCESS OF TREATING PEPTIC ULCER WITH A NON-ANTICHOLINERGIC AGENT

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ABSTRACT OF THE DISCLOSURE

Administration of 1-(2-dimethylaminoethyl)-1-phenylindene or 1-[2-(methylamino)ethyl]-1-phenylindene to mammals having peptic ulcer produces an antiulcer effect therein. The aforementioned compounds employed in the process have little demonstrable anticholinergic activity and produce their antiulcer effect by a mechanism which is non-antichlolinergic in character.

BACKGROUND OF THE INVENTION

The incidence of petic ulcer, which is a collective term for either gastric or duodenal ulcer, among the population of the United States is a major health problem. One accepted treatment of patients having a peptic ucler is the use of anticholinergic antispasmodic agents as adjuncts to dietary restrictions, rest, and use of antacids and sedatives. The antispasmodic agents which are generally employed are of the type exemplified by atropine, which is a well known anticholinergic agent. Although atropine has been used in the treatment of peptic ulcer, the administration of a therapeutic dose of atropine to a patient is generally unsatisfactory since the desired antiulcer effect is accompanied by a number of adverse side-effects. These side effects result from atropine's nonspecific anticholinergic activity which not only affects the target gastronintestinal tract, but broadly interferes with cholinergic function in the parasympathetic nervous system in general. Examples of unwanted side effects resulting from the anticholinergic effect of atropine are dryness of mouth, retention of urine, diminution or cessation of perspiration, reduction of other body secretions, blurred vision, and, in some patients with glaucoma, increased ocular pressure.

In the search for better drugs for the treatment of peptic ulcer, large numbers of anticholinergic agents have been synthesized in an attempt to find an antispasmodic agent which would be effective in the treatment of peptic ulcer, but which would not have the unwanted side-effects associated with atropine and other anticholinergic agents. However, this search has not been entirely satisfactory since a dose of an anticholinergic drug sufficient to produce an antiulcer effect generally results in a number of the aforementioned side effects (New Drugs, 1967 Ed., page 441).

SUMMARY OF THE INVENTION

We have discovered that 1-(2-dimethylaminoethyl)-1-phenylindene and 1-[2-(methylamino)ethyl]-1 - phenylindene or pharmaceutically acceptable acid addition salt thereof are effective antiulcer agents in mammals. This is a surprising discovery in view of the fact that these substances do not have any appreciable anticholinergic activity which heretofore has been a distinguishing characteristic of drugs having antiulcer action.

Antiulcer activity of 1-(2 - dimethylaminoethyl) - 1-phenylindene or 1-[2-methylamino)ethyl]-1-phenylindene and pharmaceutically acceptable acid addition salts thereof can be readily demonstrated in the laboratory in rats having peptic ulcers produced by restraint. In this test, groups of 7–10 rats weighing from 50 to 150 grams are starved

for 24 hrs. and then lightly anesthetized with ether. The test drug is administered subcutaneously and the rat placed on a wire screen. The wire screen is folded over the rat and stapled around the outer edges to restrict the movement of the rat. After the rat has regained consciousness, the screen is stapled more closely so as to restrict movement as completely as possible. After 4 hours the rats are killed and the stomachs removed and graded for incidence and severity of ulcers. The degree of incidence is graded on the basis of an all or none criterion, while severity is scored as 0 (no ulcers), 1 (minimal), 2 (average), and 4 (severe). A dose response curve is obtained according to accepted pharmacologic technique by administering various doses of the drug to groups of test animals. From the dose response curve one can determine the ED_{50} values which are the doses causing 50% reductions of the incidence and severity of ulcers. For 1-(2-dimethylaminoethyl)-1-phenylindene hydrochloride, ED_{50} values for the decrease in incidence and severity of ulcer formation in the restrained rat are, respectively, 6.2 milligrams per kilogram of body weight and 4.0 milligrams per kilogram of body weight.

The oral effectiveness of 1-(2-dimethylaminoethyl)-1-phenylindene hydrochloride as an antiulcer agent is demonstrated by a slight modification of the above test which comprises oral administration of 1-(2-dimethylaminoethyl)-1-phenylindene to the rat at the time of restraint which is also treated concomitantly with 2.0 mg./kg. of body weight of reserpine. The ED_{50} values for the decrease in incidence and severity of gastric ulceration are respectively 23.6 mg./kg. and 19.5 mg./kg. body weight.

The preparation of 1-(2-dimethylaminoethyl)-1-phenylindene, 1-[2-(methylamino)ethyl]-1-phenylindene, or a pharmaceutically acceptable acid addition salt thereof is disclosed in United States Pat. No. 3,360,435 which issued Dec. 26, 1967.

U.S. Pat. No. 3,360,435 also describes toxicity studies conducted in mice with 1 - (2 - dimethylaminoethyl)-1-phenylindene. Doses of 1 - (2 - dimethylaminoethyl)-1-phenylindene hydrochloride administered orally elicited detectable side effects in 50% of the test animals (TD_{50}) at 14 mg./kg. The LD_{50} values in mice by various routes of administration are: 84 mg./kg. (oral), and 52.5 mg./kg. (intraperitoneal). The oral LD_{50} in the rat is 385 mg./kg., and the intravenous LD_{50} in the dog is estimated to be about 30 mg./kg.

Both 1-(2-dimethylaminoethyl)-1-phenylindene and 1-[2 - (methylamino)ethyl]-1-phenylindene are relatively free of anticholinergic activity as shown in the in vivo "Shay rat test," which involves measurement of gastric secretion (Shay, Gastroenterology, 5, 43, 1946), and in the in vitro rabbit ileum acetylcholine test (Screening Methods in Pharmacology, R. A. Turner, Academic Press 1965, p. 224).

Tne fact that 1-(2-dimethylaminoethyl)-1-phenylindene and 1-[2-(methylamino)ethyl]-1-phenylindene effectively inhibit ulcer formation in rats and have very little demonstrable anticholinergic activity suggests that the mechanism whereby ulcer formation is prevented involves a central nervous system effect rather than an anticholinergic peripheral parasympatholytic effect. In any case, the use of these compounds in thetreatment of gastric ulcers in mammals avoids the usual untoward side effects, such as dry mouth and blurred vision, that accompany the use of anticholinergic antiulcer drugs.

For example, in clinical trials, oral administration of 1 - (2-dimethylaminoethyl)-1-phenylindene hydrochloride to man at a dose up to 150 mg. per patient produced no observable side effects which would resemble those associated with and produced by anticholinergic drugs.

In the process of the present invention for producing an antiulcer effect in mammals by the administration of

1-(2-dimethylaminoethyl)-1-phenylindene or 1-[2-(methylamino)-ethyl]-1-phenylindene and salts thereof, either oral or parenteral routes of administration can be used. Generally, the oral route is preferred as a matter of convenience. An antiulcer effect is produced by administering the abovementioned phenylindenes at dosages ranging from about 0.03 mg. to about 30 mg. per kilogram of body weight of the mammal being treated. The dose whereby an antiulcer effect is obtained is non-toxic. Side effects which are associated with anticholinergic activity such as reduction of gastric secretion, salivation, lacrimation, mydriasis, and so on are completely absent at dosages which produce the desired antiulcer effect.

In carrying out the process of the present invention for producing a non-cholinergic antiulcer effect in humans, we recommend a daily dose in the range of 2.5 mg. to 7.5 mg. per day and preferably a dosage ranging from about 0.03 to 0.1 milligram per kilogram of body weight. Formulations of the following type are satisfactory for administering the phenylindenes employed in the antiulcer process of the present application:

Solution for injection.—A sterile aqueous solution having a concentration of 2.5 mg./ml. of 1-(2-dimethylaminoethyl)-1-phenylindene hydrochloride is prepared by dissolving 25 g. of the substance in 9 l. of water for injection, U.S.P., adjusting the pH 5.5 with dilute aqueous sodium hydroxide, and dilution to 10 l. This solution is then filtered sparkling clear and filled into 2 ml. glass ampoules and sealed. The ampoules are then sterilized by heating.

Capsules.—A dry blend of 5.0 g. of 1 - (2-dimethylaminoethyl) - 1-phenylindene hydrochloride, 19.8 g. of lactose, and 0.2 g. of magnesium stearate is prepared. This mixture is then employed to fill No. 2 hard gelatin capsules, each with 25 mg. of the blend.

While several particular embodiments of this invention are shown above, it will be understood, of course, that the invention is not to be limited thereto, since many modifications may be made, and it is contemplated, therefore, by the appended claims, to cover any such modifications as fall within the spirit and scope of this invention.

What is claimed is:

1. The process for treating peptic ulcer which comprises administering to a mammal having a peptic ulcer an effective non-anticholinergic non-toxic oral or parenteral dose of from 0.03 to 30 mg./kg. body weight of a compound selected from the group consisting of 1-(2-dimethylaminoethyl) - 1 - phenylindene, 1 - [2-(methylamino)ethyl]-1-phenylindene, and the pharmaceutically acceptable acid addition salts of each.

2. The process of claim **1** wherein said compound is 1-(2-dimethylaminoethyl)-1-phenylindene.

3. The process of claim **1** wherein said compound is 1-2-dimethylaminoethyl)-1-phenylindene hydrochloride.

4. The process of claim **1** wherein said compound is 1-[2-(methylamino)ethyl]-1-phenylindene.

5. The process of claim **1** wherein said compound is 1-[2-(methylamino)ethyl]-1-phenylindene hydrochloride.

6. The process for treating peptic ulcer which comprises administering to a mammal having a peptic ulcer an effective nonanticholinergic non-toxic oral or parenteral dose of from 0.03 to 0.1 mg./kg. body weight of a compound selected from the group consisting of 1-(2-dimethylaminoethyl)-1-phenylindene, 1-[2-(methylamino) ethyl]-1-phenylindene and the pharmaceutically acceptable acid addition salts of each.

References Cited

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959,704	8/1962	Great Britain	424—336

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