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GASTRIC ANTI-SECRETORY COMPOSITIONS

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This invention relates to new compositions of matter and to methods of using the same. More particularly, this invention relates to therapeutic compositions containing the compound 2-dimethylamino-3,5,6-trimethylpyrazine or a nontoxic acid addition salt thereof, which compositions are useful as gastric anti-secretory agents.

Although the exact etiology of ulceration of the gastrointestinal tract still remains relatively obscure, some factors, mainly biochemical, have been clearly established; namely, that hypersecretion and hyperacidity nearly always form part of the clinical picture which accompanies stomach and duodenal ulcers.

Many method of treatment have, therefore, been advanced to counteract these factors. These methods generally fall into two classes; namely, surgical treatment such as removal of the ulcer and medical treatment such as dietary restrictions of certain food intake or drug therapy. For obvious reasons, drug therapy is the usual treatment of choice.

Drugs useful for this therapy are, for example, the antacids which neutralize gastric acidity in vivo and the anticholinergics which nullify the effects of acetylcholine and are, therefore, depressants of the parasympathetic nervous system. The rationale of the use of the anti-cholinergic drugs is based on the theory that parasympathetic overactivity results in hypersecretion and hyperacidity. Chemically these agents are represented by the belladonna alkaloids such as atropine, tertiary amines, such as dicycloamine hydrochloride, quaternary amines such as methantheline bromine and methscopolamine bromide. Since these drugs depress the overall parasympathetic nervous system, although the primary site of action desired is the gastro-intestinal tract, side effects such as blurring of the vision, tachycardia, constipation, salivary disturbances and the like have seriously limited their therapeutic applications.

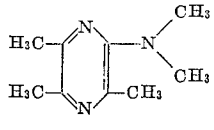
As it can be readily appreciated, treatment of gastric ulcers requires prolonged therapy. Under these circumstances, any undesirable side effects can be quite a serious clinical problem. From the foregoing, it is quite evident that the need for therapeutic compositions, effective in inhibiting gastric hypersecretion and hyperacidity without producing undesirable side effects still awaits realization.

It is, therefore, a primary object of this invention to provide a novel therapeutic composition which has effective anti-secretory activity with a low incidence of side effects.

A further object of this invention is to provide therapeutic compositions containing anti-secretory agents which can relieve gastric hyperacidity and hypersecretion.

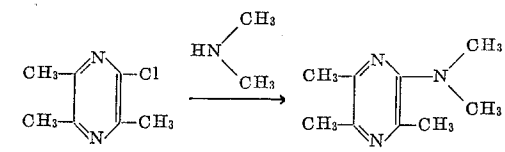
Other objects and advantages of this invention will become more apparent from the following detailed description.

In experimentation in this field, we have found quite surprisingly that therapeutic compositions containing an effective amount of 2-dimethylamino-3,5,6-trimethylpyrazine of the formula:



or of its acid addition salts, are remarkably effective in inhibiting gastric secretion. This discovery is quite surprising since the above compound is quite unrelated chemically to any of the known anti-secretory drugs. Thus, for example, in laboratory animals such as rats, the administration of the foregoing compound at a dosage level of 4 mg. per kilo of body weight has been found to suppress the volume of gastric secretion to such extent that it is reduced to the levels of about 50% of that of untreated rats. On the other hand, the compound has not been observed to produce the side effects commonly associated with anti-cholinergic medication.

The compound 2-dimethylamino-3,5,6-trimethylpyrazine is prepared, for example, by treating 2-chloro-3,5,6-trimethylpyrazine with an excess of dimethylamine. This reaction may be represented by the following equation:



The above reaction may be carried out, for example, in a sealed tube employing a reaction temperature of about 175 to 185° C. for about 3 days. The desired reaction product is obtained as a yellow oily base. Since hydrochloride salt is usually the desired form to be incorporated into dosage forms, the base is converted into the hydrochloride by adding an ethereal solution of hydrogen chloride. The salt is then recovered by filtration techniques. Although the hydrochloride salt is preferred, other salts such as the sulfate, phosphate, citrate, nitrate, acetate, hydrobromide, and the like may also be prepared by adding the corresponding acid to the free base and recovering the salt so formed by filtration.

The compound 2-dimethylamino-3,5,6-trimethylpyrazine either as the free base or in the form of its nontoxic salts may be formulated with a conventional pharmaceutical carrier and used to form tablets, capsules, elixirs, solutions or suspension for injection, suppositories and the like. Each dosage unit will normally contain about 2 to about 100 mg. of the active ingredient with a range of 5 to 25 mg. being generally preferred. The total daily dosage, for example, in the treatment of hyperacidity is normally in the range of 5 to 200 mg.

The following examples are included in order further to illustrate this invention.

EXAMPLE 1

2-dimethylamino-3,5,6-trimethylpyrazine hydrochloride

A solution of 5.0 g. (0.032 mole) of 2-chloro-3,5,6-trimethylpyrazine in 20 ml. of liquid dimethylamine is heated in a sealed tube at 180° C. for three days. The reaction mixture is cooled and the excess dimethylamine vented. Anhydrous ether (50 ml.) is added to the residue and the by-product dimethylamine hydrochloride which forms is filtered off. The ethereal filtrate is washed with 50 ml. of 10% KOH and dried over anhydrous potassium carbonate. The desiccant is separated by filtration and the filtrate is treated with 25 ml. of 2.7 N ethereal hydrogen chloride to give 2-dimethylamino-3,5,6-trimethylpyrazine hydrochloride as a yellow salt which separates and is filtered, washed with ether and dried in a vacuum desiccator. The material obtained is recrystallized from a solution of 200 ml. ethyl acetate–5 ml. 2-propanol to give 4.3 g. (67%) of 2-dimethylamino-3,5,6-trimethylpyrazine hydrochloride as yellow crystals melting at 162–164° C.

The recrystallization may be accomplished also by forming a solution in a minimum of 2-propanol and adding ether to the solution until it becomes just turbid.

EXAMPLE 2

Twenty-five grams of 2-dimethylamino-3,5,6-trimethylpyrazine hydrochloride is thoroughly blended with 416 grams of lactose and 9 grams of magnesium stearate. Four hundred and fifty mg. of the resulting mixture is then filled into No. 1 hard gelatin capsules, each capsule containing 25 mg. active ingredient.

EXAMPLE 3

The effectiveness of 2-dimethylamino-3,5,6-trimethylpyrazine hydrochloride as gastric anti-secretory agent is determined in accordance with the following procedure.

One of the accepted methods for the determination of anti-secretory activity is that described by Shea, S. M., British J. Pharmacol. 11: 171 (1956), and Visscher, F. E., et al., J. Pharmacol. & Exper. Therap. 110: 187. The basis of this method is the determination of the volume of gastric juice secreted in pyloric ligated rats.

Young adult rats of either sex may be used; however, each group of 12 rats should each be of one sex only and it is preferable that a single study (comparison of a standard with an unknown) be made on one sex. Each group receives a different dose level of the drug, e.g., 1 mg./kg.; 5 mg./kg. and the control receives normal saline solution. The rats are fasted in cages with wide meshed wire bases to minimize coprophagy. The duration of the preoperative fast is 48 hours. During the first 36 hours of this period, the animals are free to drink tap water and Mead Johnson's 5% amigen and 5% dextrose electrolyte solution. The amigen-dextrose solution is removed from the cages the evening before the operation and the rat is allowed access to water only. This procedure allows the fasting rat to receive adequate nutrients and electrolytes and avoids the erratic results obtained when inadequate precautions are taken with regard to hydration and nutrition.

Under light ether anesthesia a four centimeter midline abdominal incision is made and a ligature is placed tightly around the pylorus being careful to avoid trauma to surrounding blood vessels. After closure of the abdominal layer with sutres, five milliliters of normal saline are placed in the peritoneal cavity. The skin wound is closed with Mechel clips and painted with collodion. The drug, or normal saline in the case of the controls, is injected intramuscularly, high in the back of the thigh, in a volume of 1.0 ml./kg. The entire operation takes about four minutes.

The rats are deprived of both water and food and confined in individual cages during the three hour collection period. The animals are then killed with ether, the abdomen opened, and the stomach removed. The entire stomach contents are caught in a graduated centrifuge tube and the fluid volume recorded after centrifugation. If the rats have been handled properly during the fast and collection period, the solid portion of the stomach contents will be negligible. The average volume in untreated rats will be from six to eight milliters. If the average volume of the control rats is less than four millilters, the experiment is considered unsatisfactory and is repeated.

The pH of the fluid portion of the centrifuged stomach juices is determined with the Beckman pH meter, and exactly two cc. (pipetted) of the stomach contents are titrated with 0.04 normal sodium hydroxide using one drop of two percent phenolphthalein in ethyl alcohol as an indicator.

While the values for free and total acid may be helpful in evaluating the results, the primary object of the test is to measure the fluid volume of the stomach contents. Logdose-response lines are drawn and an ED_{50} is determined for each drug. The ED_{50} is that dose of the drug which produces a 50% decrease in fluid volume as compared to the controls. The ED_{50} for 2-dimethylamino-3,5,6-trimethylpyrazine hydrochloride as determined by the above method has been found to be 4 mg./kg.

It is to be understood that the foregoing detailed description is given merely by way of illustration and that many variations may be made therein without departing from the spirit of our invention.

Having described our invention, what we desire to secure by Letters Patent is:

An anti-secretory composition in dosage unit form comprising an inert pharmaceutical carrier in combination with from about 5 to 200 mg. of a member of the group consisting of 2-dimethylamino-3,5,6-trimethylpyrazine and the non-toxic pharmaceutically acceptable acid addition salts thereof.

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