United States Patent Office 3,158,538 Patented Nov. 24, 1964

3,158,538

ANTIDIARRHEAL COMPOSITIONS AND METHOD OF USING

Slaughter W. Lee, Short Hills, N.J., assignor to White Laboratories, Inc., Kenilworth, N.J., a corporation of New Jersey

No Drawing. Filed Feb. 23, 1961, Ser. No. 90,972
8 Claims. (Cl. 167—55)

This invention relates to new compositions of matter useful as antidiarrheal agents and to processes for the treatment of diarrhea utilizing such compositions.

Diarrhea may be of the acute or chronic type. Although acute diarrhea may be caused by enteric infections (dysentery, et cetera) it is likely that most acute diarrhea is due to abuse of cathartics, ingestion of irritant food, or to minor upsets such as nervous indigestion, acute febrile illnesses or simple fatigue. Because of the difficulty of clinically distinguishing one type from another, the etiology is most frequently unknown and, consequently, symptomatic treatment of the condition is usually undertaken without diagnosis. Chronic diarrheas result from ulcerative colitis, regional inflammation of the bowel, neoplasm, etc. In such cases symptomatic treatment is also usually necessary since the cause is often not known or is difficult or impossible to eliminate.

The most widely used pharmaceutical preparations for the treatment of diarrheal states are based on combinations of kaolin (or other clays intended for the removal by absorption of bacteria, toxins and other irritants), pectin (allegedly a "detoxifier") and, not infrequently, one or more intestinal antibiotics. Although several products based on combinations of the above agents enjoy wide use for the treatment of diarrhea, their use is not accompanied by any great conviction on the part of the physician that the medication is adequate—even for the palliation of symptoms. The following excerpt from the authoritative text (V. A. Drill, "Pharmacology in Medicine," McGraw-Hill, New York, 1958) provides an indication of the medical profession's appraisal of available antidiarrheal products:

"A number of substances have been suggested for the control of diarrhea, but the majority of them are relatively ineffective. Charcoal, kaolin, bismuth and chalk which remove gas or toxic substances by absorption have been used extensively but really are no particular value."

Opium derivatives, having a marked inhibiting effect on peristaltic activity of the bowel, are often prescribed for control of diarrhea. However, in view of their addictive properties, opiates should be administered only for a short period of time and their usefulness in chronic diarrheal states is, thus, decidedly limited. Pertinent is the following quotation from an authoritative medical text (Walter Modell, "Drugs of Choice 1958–1959," C. V. Mosby Co., St. Louis, Mo., 1958):

"The threat of addiction is so great that one should hesitate to use the opium derivatives in the chronic diarrheal states except for the limited indications listed above, and then as short a period of time as possible."

That diarrheal states are widely prevalent is well known. Similarly, the discomfort—and indeed danger—often associated with this condition is also common knowledge. The superimposition of these facts on the inadequacy of existing antidiarrheal agents emphasizes the tremendous need for a rapid, safe, easily administered, effective agent for the symptomatic management of this disease.

From the symptomatic point of view diarrhea is an unpleasant physiological condition characterized by a too rapid evacuation of the contents of the large intestine. This condition is further characterized by the fact that the evacuated contents of the bowels are abnormally

fluid and often watery. It has been discovered that certain swellable resins of the type described in U.S. Patents 2,798,053, 2,810,716, and 2,923,692, act to relieve this latter condition by absorbing large amounts of the liquid present within the bowels. But such an approach does not act directly to alleviate the hypomotility of the intestinal tract actually causing the too rapid evacuation.

The present invention resides in the concept of a novel composition of matter containing a resin possessing selective intestinal-swellability in conjunction with an anticholinergic agent having a relatively selective inhibiting effect on intestinal hypermotility and the process for treating diarrhea which comprises the oral administration of dosage quantities of such a synergistic combination.

By treating both aspects of diarrhea simultaneously with the same medicament, the condition is more efficiently and rapidly relieved than by the use of either ingredient alone or when the same ingredients are independently administered. While it is not our intention to limit the scope of this invention to any particular theoretical mode of operation, it is our belief that the anticholinergic agent slows down peristalsis sufficiently for the full absorptive capacity of the resin to be expended within the intestinal tract. Thus the resin is more efficiently utilized and smaller doses can be administered and still be effective. In addition, when the anticholinergic agent is administered in combination with the resin, it is more slowly and evenly released directly in the intestinal tract. This sustained local release avoids undesirable peak effects and minimizes the side effects attributed to more massive doses of the anticholinergic agent.

The swellable resins useful for the present invention are, in general, irregular granules of very high molecular weight carboxylic type ion-exchange resins loosely cross-linked by means of about 0.2–2.0 percent by weight of a polyunsaturated copolymerizable cross-linking agent but which have only a negligible amount of uncross-linked chains present. The major component of such swellable resins is an alpha-beta, mono-olefinically-unsaturated, lower-aliphatic carboxylic acid capable of both homopolymerization and copolymerization such as acrylic acid, salts of acrylic acid, methacrylic acid, salts of methacrylic acid, fumaric acid, maleic acid, maleic anhydride, itaconic acid, and others of the type described in U.S. Patent 2,798,053, with acrylic acid being preferred.

Representative poly-unsaturated copolymerizable cross-linking agents are shown in U.S. Patents 2,798,053 and 2,810,716. The only essential requirement of the cross-linking agent is that it have two or more double bonds capable of copolymerizable cross-linkage with the monomeric materials previously defined. Preferred cross-linking agents are divinylbenzene and 3,4-dihydroxy-1,5-hexadiene.

As stated above, the swellable resins useful in the practice of the present invention contain from about 0.2 to about 2 percent of cross-linking agent. When more than about 2 percent of the cross-linking agent is employed, the resins do not swell appreciably and their absorptive capacity becomes limited. When less than about 0.2 percent of the cross-linking agent is employed, the linear chains remain unconnected and there is insufficient cross-linking to maintain the resin lattice required for full absorption. About 0.4 to 0.8 percent cross-linking constitutes the preferred range.

It is apparent that the resins must contain an accurately defined, closely-controlled amount of cross-linking agent. The general approach of U.S. Patent 2,810,716 can be used to obtain resins having only the desired amount of cross-linking present. While the method of that patent is especially directed to reacting the mono-

meric material with 0.01–0.2 percent of cross-linking agent, it is also suitable for the slightly higher amounts of cross-linking agent needed to make the resins used here. As shown in the patent, copolymerization is carried out by contacting the monomeric material and the cross-linking agent in the presence of an aqueous solution of a soluble non-redox divalent inorganic ion employed in a concentration above about one-half molar (e.g. saturated magnesium sulfate brine) at temperatures above room temperature and up to reflux. A suitable polymerization initiator e.g., benzoyl peroxide or azobis-isobutyronitrile is employed in an amount between 0.01 percent and 1.0 percent by weight of the monomer present.

The unusual utilities of these resins is due, at least in part, to their selective intestinal-swellability. The swelling characteristics of these resins are dependent upon the pH of the media in which they are placed with the amount of swelling increasing as the pH rises. Thus, in the low pH regions of the stomach the preferred resins absorb only about 15–35 milliliters of the gastric juice per gram of resin, and as the resin proceeds through the gastro-intestinal tract, the pH of the body fluids rises and swelling increases until in the neutral or basic intestinal juices, the resins absorb about 100 milliliters of intestinal juice per gram of resin. As can be seen, comparatively little bulk is provided in the stomach, with maximum bulk being provided in the colon just prior to elimination.

Any anticholinergic agent that acts selectively to inhibit intestinal hypermotility may be combined with one of the previously described swellable resins to form the synergistic antidiarrheal composition comprising the present invention. The term "anticholinergic" is applied to any member of a large group of drugs that act to inhibit motor and secretory activity in organs such as the gastrointestinal tract which are supplied with excitatory cholinergic nerve fibers. This group of drugs includes the natural belladonna alkaloids, one of which (atropine) is used generally as a standard of reference for the potency of all anticholinergics, and a large number of synthetic compounds more or less closely related in chemical structure. All are substituted amines, the principal belladonna alkaloids being tertiary amines and most of the synthetic anticholinergics having a quaternary structure. Anticholinergic drugs, in general, have a varying usefulness in the treatment of diarrhea, depending on the selectivity with which they act to inhibit intestinal hypermotility. However, effective antidiarrheal doses of these drugs cause, to a greater or less degree, undesirable side effects such as dryness of the mouth and nose, flushing and dryness of the skin, mydriasis, tachycardia and urinary retention. These unwanted effects are a consequence of the actions of the drugs on body structures other than the intestinal tract. A preferred anticholinergic is thihexinol methylbromide. Chemically, this synthetic compound is alpha-di-thienyl-(4-dimethylamino-cyclohexyl)-carbinol-methbromide. Pharmacologic studies in animals and humans have shown that orally administered thihexinol methylbromide acts with an unusual degree of specificity to inhibit gastrointestinal motility.

The resin-anticholinergic combination, as usually administered consists of hard, sand-like, gritty granules of resin approximately 12 to 14 mesh. These granules are prepared by standard pharmaceutical techniques. For example, the resin and the anticholinergic agent may be granulated together or the resin granulated alone and the anticholinergic agent applied in the form of a coating. Granulation is best accomplished by blending the resin with a granulating or bonding agent such as sugar syrup. A small amount of alcohol may be added to improve the surface qualities of the tablet to be prepared. After drying, the material is encapsulated or compressed to tablet form and allowed to age before coating. When the anticholinergic agent is added as a coating, it is applied to the compressed resin as an alcoholic-sugar syrup solution prior to color coating. The exact method of formulation employed is not critical save that the anticholinergic agent and the resin be in intimate contact with each other in the finished capsule or tablet. The beneficial synergistic interaction between the resin and the anticholinergic agent has been demonstrated by the results obtained in the clinical administration of such combinations.

The antidiarrheal compositions of the invention are administered orally and progress through the digestive tract. It is believed that the anticholinergic agent is further absorbed onto the resin as the resin swells in contact with intestinal fluids. The simultaneous slow desorption of the anticholinergic agent results in its gradual or sustained release within the intestinal tract. The usual dosage of resin is from 1 to 4 grams daily with 2 grams representing the average dose. The amount of anticholinergic agent to be employed depends on its nature and known therapeutic dosage. Below is a list of suitable anticholinergic agents together with their daily dose ranges.

Anticholinergic agent:	Dosage in milligrams
Atropine sulfate	0.8–3.2
Belladonna extract	30–120
Diphenmethanil methylsulfate	160–400
Homatropine methylbromide	4–16
Thihexinol methylbromide	30–120

The use of tablets, containing 0.5 gram of the swellable resin made from acrylic acid copolymerized with divinylbenzene and 15 milligrams of thihexinol methylbromide, has been extensively evaluated in cases of acute and chronic diarrheas. In a cumulative total of more than 600 cases, consisting mainly of relatively severe, chronic or recurrent diarrhea due to functional or organic bowel disease, the diarrheal state was responsive to treatment with this composition in approximately 85 percent of the patients. Anticholinergic side effects, usually mild in degree, were only seldom encountered. An equally satisfactory antidiarrheal response, without appreciable anticholinergic side effects, has been observed in patients with acute and chronic diarrheas treated with a tableted combination of swellable acrylic resin copolymerized with 3,4-dihydroxy-1,5-hexadiene and thihexinol methylbromide.

A preferred embodiment of the present invention includes the addition of a small amount of non-cross-linking, non-toxic polymer lubricant to the resin composition, e.g., glyceryl distearate or Italian talcum. These may be added during the manufacture of the resin or when the resin is compressed into tablets. The use of such polymer lubricants in small amounts (up to about 5 percent by weight of the resin) tends to accelerate swelling rate and increase amount of swelling.

The following examples will aid in illustrating some of the compositions of the present invention but are not to be construed as limiting its scope.

Using swellable polyacrylic resins copolymerized with 0.2 to 2.0 percent of cross-linking agent manufactured according to the general methods of U.S. Patents 2,798,053, 2,810,716, and 2,923,692, granular materials were prepared as follows:

(1)

Resin	grams	750
Purified water	milliliters	20

Procedure: Using a planetary mixer at slow speed, slowly add water to the resin and mix until a uniform granulation is obtained.

(2)

Resin	grams	500
Sugar syrup	do	12.5

Procedure: Same as for No. 1.

(3)

Resin	grams	250
Polyethylene glycol	do	4.0
Ethanol	milliliters	15.0

Procedure: Using a planetary mixer at slow speed, add polyethylene glycol the alcoholic solution to the resin and mix until a uniform granulation is obtained.

(4)

Resin	grams	250
Ethanol	milliliters	10.0
Purified water	do	1.0

Procedure: Using a mixture of the alcohol and water, proceed as in No. 3.

(5)

Resin	grams	750
Colloidal gum	do	1.5
Ethanol	milliliters	30
Purified water	do	4.5

Procedure: Dissolve the colloidal gum in water, add the alcohol and granulate by same general procedure as in No. 3.

(6)

Resin	grams	750
Polyvinylpyrrolidone	do	4.5
Ethanol	milliliters	30
Purified water	do	3

Procedure: Dissolve the polyvinylprrolidone in the alcohol, add the water and granulate by same general procedure as in No 3.

(7)

Resin	grams	500
Gelatin, USP	do	5
Purified water		Q.s.

Procedure: Blend the gelatin with the resin, add the water and granulate by same general procedure as No. 3.

(8)

Resin	grams	500
Acacia powder, USP	do	5
Purified water		Q.s.

Procedure: Blend the powdered acacia with the resin, add the water and granulate by same general procedure as in No. 3.

(9)

Resin	grams	500
Acacia powder, USP	do	8.32
Sucrose powdered	do	14.2
Purified water		Q.s.

Procedure: Blend the powdered acacia with the sugar, add to resin and blend. Add water and granulate by same general procedure as in No. 3.

(10)

Resin	grams	500
Powdered sugar	do	75
Purified water		Q.s.

Procedure: Blend the powdered sugar with the resin, add the water and granulate by same general procedure as in No. 3.

Formulations 7, 8, 9, and 10 can also be granulated by dissolving the binding agent in the water and adding to the swellable resin.

The anticholinergic containing tablet was obtained (*a*) by incorporating the anticholinergic agent into the granulation step or (*b*) by coating onto the compressed granules. Sufficient anticholinergic agent was added to give the desired ultimate concentration in the half gram resin tablet.

The use of these tablets was investigated in the nonspecific treatment of diarrhea. In a typical series, clinical material consisted of 65 private patients with relatively severe diarrheal disorders. With the exception of two

patients whose diarrhea was due to acute gastroenteritis, all had histories of protracted diarrhea extending over periods of months to years. As would be expected, the irritable bowel syndromes accounted for almost half of the total cases of chronic diarrhea. The remaining cases were of organic origin, including mostly chronic ulcerative colitis and surgically short-circulated gastrointestinal states.

The test tablets contained 0.5 gram of a loosely cross-linked polyacrylic resin and 15 milligrams of thihexinol methylbromide prepared as described. Initially, most pateints received a dosage of one tablet three or four times daily. When symptomatic control was achieved, it was usually possible to maintain the antidiarrheal effect with a reduced dosage of one or two tablets daily. The duration of treatment in this group of patients ranged from two weeks to twelve months. Clinically satisfactory control of diarrhea was noted in all but 3 of the patients with chronic diarrheal disorders. In the two patients with acute gastroenteritis, the drug was completely ineffectual.

The attainment of diarrheal control in all but 5 of the total group of 65 cases is noteworthy particularly since the drug was used with continued symptomatic relief in most patients for prolonged periods. Undoubtedly, one of the factors contributing to its usefulness for long-term therapy was the infrequent appearance of untoward reactions during the course of the study. Side effects were limited to complaints of difficulty in urination in 3 patients, and of severe abdominal distension in another.

Certain observations made during the course of the study merit further comment. The polyacrylic-thihexinol combination often alleviated diarrhea after other drugs, including opiates, had been ineffectual. Since one generally relies on the opiates for anti-diarrheal therapy only as a last resort, the availability of an effective but less hazardous drug to control previously refractory diarrhea is worthy of emphasis. Noteworthy, too, is the observation that a maintenance dosage of only one or two tablets a day often proved adequate after the chronic diarrheal state had been brought under control with initially higher dosage of the drug.

With respect to the X-ray studies of gastrointestinal transit in patients treated with the resin-anticholinergic combination, the demonstrated inhibition of jejunal motility without a marked delay of gastric emptying is remarkable. Such selective depression of enteral motor activity has not been produced by other antiperistaltic drugs. This selectivity of action may well explain the beneficial effects of the combination in the nonspecific treatment of intestinal hypermotility disorders of both organic and functional origins.

In summary, it can be said that the use of a combined enteral hydrosorbent and motility inhibitor was evaluated for the nonspecific treatment of diarrhea in 65 cases of mostly chronic diarrheal disorders. With initial dosage of 3 to 4 tablets a day, clinically satisfactory control of diarrhea was noted in all but 5 of the 65 cases. Maintenance of symptomatic control was often possible wtih a dosage of 1 to 2 tablets a day. Side effects were limited to the occurrence of dysuria in 3 cases and a complaint of abdominal distension in another case. X-ray studies, following symptomatic response to therapy, demonstrated a marked suppression of intestinal hypermotility that was characterized by definite inhibition of jejunal motor activity without any pronounced delay in gastric emptying. These observations support the conclusion that the combination constitutes a clinically safe and effective drug for the nonspecific control of relatively severe diarrheal states.

Various modifications, obvious to those skilled in the art, may be made in the present invention without departing from the spirit or scope thereof. Having described and illustrated my invention, I claim:

1. Antidiarrheal compositions comprising a swellable

resin, which resin is a cross-linked interpolymer of 98 to 99.8 percent by weight of a polymerizable alpha-beta, monoolefinically-unsaturated, lower-aliphatic carboxylic acid and 0.2 to 2.0 percent by weight of a polyunsaturated copolymerizable cross-linking agent, in admixture with an anticholinergic agent having a selective effect in inhibiting intestinal hypermotility.

2. Antidiarrheal compositions comprising a swellable resin, which resin is a cross-linked interpolymer of 98 to 99.8 percent by weight of acrylic acid and 0.2 to 2.0 percent by weight of a polyunsaturated copolymerizable cross-linking agent, in admixture with an anticholinergic agent having a selective effect in inhibiting intestinal hypermobility.

3. Antidiarrheal compositions comprising a swellable resin, which resin is a cross-linked interpolymer of 98 to 99.8 percent by weight of acrylic acid and 0.2 to 2.0 percent by weight of a polyunsaturated copolymerizable cross-linking agent, in admixture with thihexinol methylbromide.

4. Compositions according to claim 3 wherein the cross-linking agent is divinylbenzene.

5. Compositions according to claim 3 wherein the cross-linking agent is 3,4-dihydroxy-1,5-hexadiene.

6. The method of treating diarrhea which comprises the oral administration of dosage units of a composition comprising a swellable resin, which resin is a cross-linked interpolymer of 98 to 99.8 percent by weight of a polymerizable alpha-beta, monoolefinically-unsaturated, lower-aliphatic carboxylic acid and 0.2 to 2.0 percent by weight of a polyunsaturated copolymerizable cross-linking agent, in admixture with an anticholinergic agent having a selective effect in inhibiting intestinal hypermotility.

7. The method of treating diarrhea which comprises the daily oral administration of about 1 to 4 grams of a composition comprising a swellable resin, which resin is a cross-linked interpolymer of 98 to 99.8 percent by weight of acrylic acid and 0.2 to 2.0 percent by weight of a polyunsaturated copolymerizable cross-linking agent, in admixture wtih an anticholinergic agent having a selective effect in inhibiting intestinal hypermotility.

8. The method of treating diarrhea which comprises the daily oral administration of about 1 to 4 grams of a composition comprising a swellable resin, which resin is a cross-linked interpolymer of 98 to 99.8 percent by weight of acrylic acid and 0.2 to 2.0 percent by weight of a polyunsaturated copolymerizable cross-linking agent, in admixture with 30 to 120 milligrams of thihexinol methylbromide.

References Cited in the file of this patent

UNITED STATES PATENTS

2,798,053 Brown ---------- July 2, 1957

OTHER REFERENCES

Bull. Johns Hopkins Hosp., September 1949, pages 221–230 (pages 221, 224 and 225 relied upon) (167–65 M.U).

Calmon: Ion Exchangers in Organic and Biochemistry, 1957, Interscience Publishers, Inc., New York, N.Y., pages 478 and 479.

Modern Drug Encyclopedia, seventh edition, 1958, page 384, Drug Publications, Inc., New York, N.Y.