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Research Article

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Effects of Oleic and Ricinoleic Acids on Net Jejunal Water and Electrolyte Movement

PERFUSION STUDIES IN MAN

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ABSTRACT To examine the effects of oleic acid and ricinoleic acid on jejunal absorption, steady-state jejunal perfusions were performed in healthy volunteers. Taurocholate, used to solubilize the fatty acids, did not influence absorption. Both fatty acids (concentration, 10 mM) reversed electrolyte and water net movement; that is, they induced fluid secretion; this effect was rapidly reversible. Ricinoleic acid (the active principle of castor oil) was the more potent, producing fluid secretion when perfused at concentrations at which oleic acid was without effect. However, ricinoleic acid was absorbed more slowly than was oleic acid, and hence was associated with higher intraluminal concentrations. Addition of lecithin and monoolein did not diminish the secretory effect of ricinoleic acid; addition of a secretory bile acid (taurodeoxycholate) did not enhance the effect. The response of the jejunal mucosa to a known cathartic provides observations pertinent to the pathophysiology of steatorrheal diseases in man. Dietary fatty acid also has secretory properties with respect to the human intestine; bacterial hydration, to hydroxy fatty acids, is not required to induce fluid secretion.

INTRODUCTION

Hydroxy fatty acids were identified in human feces by James, Webb, and Kellock (1), who proposed that these compounds might act as cathartics in patients with steatorrhea. These fatty acids, formed in the intestine

by bacterial hydration of unsaturated dietary fatty acids (2), are chemically similar to a known cathartic, ricinoleic acid. This hypothesis of the action of hydroxy fatty acids is supported by the results of other investigations: the study of animals with an experimental "blind loop syndrome" (3), perfusion of the intestine with fatty acid solutions (4), and analysis of steatorrheal stools in man (5). Specifically, hydroxy fatty acids provoke water secretion in the rat colon (4) and impair net fluid movement in the human colon (6). In the canine ileum, however, water absorption has been blocked not only by 10-hydroxystearic acid and ricinoleic acid (the active principle of castor oil) but also by oleic acid (7). In fact, the dietary fatty acid, its bacterial hydration derivative, and a potent cathartic modified ileal fluid absorption to comparable degrees. These findings suggested that dietary fatty acids, when poorly absorbed in steatorrheal states, might also impair water transport; they would thereby contribute to the diarrhea that occurs in these diseases.

In the present studies we describe the influence of oleic and ricinoleic acids on jejunal water movement in healthy volunteers, under conditions of a steady-state perfusion system. Both fatty acids were potent secretagogues. Earlier perfusion studies in man (8) had shown that conjugated chenodeoxycholic acid also caused fluid secretion in the jejunum, but this effect was blocked by lecithin. In the present experiments, ricinoleic acid was used as a test compound to examine the ability of conjugated chenodeoxycholic acid and lecithin to modify the secretory effects of fatty acids. Monoolein was added because it is normally present in the micellar phase of postprandial jejunal contents. Secretory phenomena were unaltered by the addition of bile acids, lecithin, or monoolein. Quantitative differences between the secretory effects of ricinoleic and oleic acids were small and were

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due mainly to different rates of disappearance from the lumen (absorption) of the fatty acids; the results provide insight into the different clinical effects that follow their ingestion.

METHODS

Preparation of perfusates. Conjugated bile acids were synthesized as described previously (9). Of the unconjugated precursors, cholic acid was obtained from Matheson, Coleman and Bell, Div. of Matheson Co., Inc., East Rutherford, N. J., and chenodeoxycholic acid from Weddel Pharmaceuticals, London, England. Purity of conjugates was greater than 95%, as determined by thin-layer and gas chromatography. Ricinoleic acid (12-hydroxy- Δ -9,10, octadecenoic acid) was prepared by saponification of castor oil with subsequent serial solvent extraction in petrol ether/methanol; [9,10- 3 H]ricinoleic acid was kindly supplied by Dr. L. J. Morris, Unilever Research, Sharnbrook, Bedford, England. The purity of both these compounds was greater than 95%, as determined by gas chromatography. Monoolein was synthesized according to the method of Martin (10), [14 C]oleic acid (New England Nuclear, Boston, Mass.) being used as the labeled precursor. The final product contained, on thin-layer chromatography, 85% 2-monoolein, 9% 1-monoolein, and 6% oleic acid; its specific activity was 2 μ Ci/mM. Oleic acid (Δ -9,10-octadecenoic acid; Nu Chek Prep., Elysian, Minn.; purity >99%), lecithin (Schwartz/Mann Div., Becton, Dickinson & Co., Orangeburg, N. Y.), [14 C]polyethylene glycol ([14 C]PEG)¹ and [3 H]oleic acid (both from New England Nuclear) were obtained from commercial sources.

Perfusion technique. The subjects were healthy volunteers (postmenopausal women or men older than 21 yr) who gave written informed consent. The perfusion technique was the same as that previously described and validated, in which a four-lumen tube with an occluding balloon proximal to the perfusion site was used (11). After the subjects had fasted overnight, the tube was positioned fluoroscopically until the balloon reached the level of the ligament of Treitz. The balloon was inflated with air until it produced mild epigastric discomfort; this signaled occlusion of the intestinal lumen, usually after inflation of 35 ml. Inflation of the balloon was then adjusted so that the discomfort just subsided. Occlusion could be verified by the absence of bile staining in the effluents during the perfusion.

Perfusates (at 37°C) were delivered at a constant rate of 10 ml/min and were sampled 25 cm distally by siphonage. The proximal aspiration lumen was suctioned intermittently to remove duodenal contents. An additional gastric tube was inserted for aspiration of gastric secretions.

Test solutions were perfused for 90 min. The first 30 min were used for equilibration; thereafter, each study period comprised six consecutive 10-min samples. Steady-state conditions were confirmed by analysis for PEG and all results refer to observations during the steady state.

Analytical methods. Sodium and potassium values were determined by flame photometry. Chloride concentration was measured by electrometric titration with a silver nitrate solution, PEG was determined chemically, by a modification of Hyden's method or by determination of [14 C]-

PEG (12). For isotope determinations, 1 ml of perfusate or effluent was mixed with 15 ml of a scintillation "cocktail" composed of toluene and emulsifier (Ready Solv #VI, Beckman Instruments, Inc., Fullerton, Calif.) and counted by liquid scintillation spectrometry. Quench correction was made by external standardization.

Fatty acids were measured on aliquots of perfusates or samples. These were acidified with 1 N HCl and extracted in toluene-ethanol mixture (2:1) that contained heptadecanoic acid as an internal standard (13). Methyl esters were prepared with diazomethane and were quantified by gas chromatography (Barber-Colman series, 5,000 GLC: 4.3% OV-17 [phenylmethylsilicone] on Gas-Chrom Q 100-120 mesh packing [column temperature, 210°C], Barber-Colman Company, Rockford, Ill.).

Calculations and statistical analysis. Absorption of water and electrolytes over the 25-cm test segment was calculated relative to a change in the concentration of PEG; it was expressed in milliliters per min as mean (\pm SEM) of the six 10-min collection periods. Differences in the net movement of water were evaluated statistically by paired and unpaired *t* tests. Electrolyte movements were not compared by this technique since electrolyte and water movements were so closely related. Linear regressions were calculated by the method of least squares.

Experimental design

Each experimental day included perfusions with four solutions. Four groups of studies were performed.

Group 1. Effect of *C₁₈* fatty acids (10 mM). In six subjects, the secretory effect of 10 mM ricinoleic acid or oleic acid was tested and the reversibility of secretion induced by fatty acid was examined. Further, the lack of secretory potential of taurocholate, used for solubilization of fatty acids, was demonstrated.

Perfusing solutions were (a) the control electrolyte solution (C), containing Na, 125 meq/liter; K, 10 meq/liter; Cl, 95 meq/liter; HCO₃, 40 meq/liter; glucose, 11.2 mM; PEG, 5 g/liter with [14 C]PEG, 5 μ Ci/liter; the pH was 8.0 and the osmolality, 280 mosmol/liter; (b) the taurocholate solution (TC), containing in addition 5 mM sodium taurocholate; and (c) the fatty acid solutions (FA), containing 10 mM ricinoleic or oleic acids with taurocholate (5 mM).

In four experiments the perfusion sequence was C, TC, FA, TC; in two experiments oleic acid was used, and in two others, ricinoleic acid. In two additional experiments the sequence was TC, FA, TC, FA, one each with oleic and ricinoleic acid. These experiments established the reversibility of fatty acid-induced secretion and the lack of secretory effect of taurocholate. In all subsequent experiments we were able to randomize the perfusion sequence.

Group 2. Secretory effects of different concentrations of oleic and ricinoleic acids. Each fatty acid was tested at three concentrations, 0.5, 2.0, and 5 mM, in four volunteers, each of whom was studied on two occasions. A 4 \times 4 latin square design (8) was used to eliminate the effect of perfusion sequence.

Control (C) solutions each contained Na, 120 meq/liter; K, 10 meq/liter; Cl, 100 meq/liter; HCO₃, 30 meq/liter; glucose, 11.2 mM; xylose, 11.2 mM; taurocholate, 5 mM; and PEG, 5 g/liter with [14 C]PEG, 5 μ Ci/liter; pH 7.5 and osmolality, 280 mosmol/liter. Fatty acid test solutions contained in addition ricinoleic or oleic acids at the stated concentrations.

Group 3. Influence of added lecithin and monoolein on

¹ Abbreviations used in this paper: C, control; FA, fatty acid solution; PEG, polyethylene glycol; TC, taurocholate solution.

secretion induced by ricinoleic acid. Each of four subjects was perfused in random sequence (8) with (a) a control solution; (b) the control solution with ricinoleic acid, 5 mM; (c) the control solution with ricinoleic acid, 5 mM and 2-monoolein, 2.5 mM; and (d) the control solution with 5 mM ricinoleic acid, 2.5 mM 2-monoolein, and 2.5 mM lecithin.

The control solution consisted of Na, 120 meq/liter; K, 10 meq/liter; Cl, 100 meq/liter; HCO_3 , 30 meq/liter; glucose, 11.2 mM; xylose, 11.2 mM; PEG, 5 g/liter; pH 7.5 and osmolality, 280 mosmol/liter. Taurocholate was used at a higher concentration (10 mM), to facilitate solubilization of lecithin, monoolein, and fatty acid in the four solutions. Appropriate test solutions contained [^{14}C]monoolein, 5 μCi /liter, or [^3H]ricinoleic acid, 25 μCi /liter, or both.

Group 4. Effects of ricinoleic acid and taurochenodeoxycholic acid. Each of four subjects received the following four perfusions in random sequence: (a) an electrolyte solution containing 5 mM taurocholate; (b) the electrolyte solution containing 5 mM taurocholate and 2.5 mM ricinoleic acid; (c) the electrolyte solution containing 5 mM taurochenodeoxycholate; and (d) the electrolyte solution containing 5 mM taurochenodeoxycholate and 2.5 mM ricinoleic acid.

The electrolyte solution contained Na, 115 meq/liter; K, 10 meq/liter; Cl, 100 meq/liter; HCO_3 , 25 meq/liter; PEG, 5 g/liter with [^{14}C]PEG 5 μCi /liter; it also contained xylose, 11.2 mM; L-leucine, 10 mM; L-lysine, 10 mM; pH 7.5 and osmolality, 280 mosmol/liter.

RESULTS

Reversibility of fatty acid-induced secretion and effect of taurocholate (Table I). Water absorption was not decreased significantly by taurocholate ($0.1 > P > 0.05$). Oleic and ricinoleic acids induced pronounced fluid secretion when perfused at a concentration of 10 mM. Secretion was reversible, since fluid absorption in the two periods which bracketed perfusion with fatty acids was not different (Table I). No differences were observed between the secretory effects of oleic and ricinoleic acids (at 10 mM).

Dose-response of secretion induced by oleic and ricino-

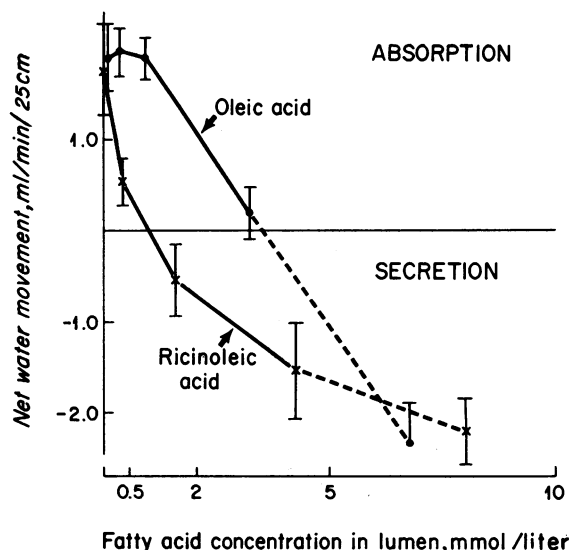


FIGURE 1 Change in net water movement in 25 cm of human jejunum induced by perfusion with oleic acid and ricinoleic acid. Ordinate is net water movement (milliliter per minute) at perfusion rate of 10 ml/min; abscissa is mean segment concentration of fatty acid (logarithmic mean input and recovery concentrations). Four studies in the same four healthy volunteers featured perfusion with 0, 0.5, 2.0, and 5.0 mmol/liter fatty acid; in an additional four subjects 10.0 mmol/liter fatty acid was used.

leic acids (Fig. 1). The changes in water absorption were dose-dependent and, at lesser concentrations, there were differences between the potencies of the two fatty acids. Oleic acid inhibited net water movement only when infused at a concentration of 5 mM ($P < 0.01$); it had no effect at lesser concentrations. Ricinoleic acid inhibited net water movement significantly ($P < 0.01$) at a concentration of 0.5 mM in the infusate. At 2 and 5 mM, ricinoleic acid induced net secretion. Thus, ricino-

TABLE I
Effect of Taurocholate (5 mM) (TC) and Fatty Acids (10 mM) (FA) on Jejunal Water Absorption (ml/min/25 cm \pm SEM)

Subject no.	Control solution (C); electrolytes only	C with TC	C with TC and FA	C with TC	C, TC, and FA
1	2.77 \pm 0.36	1.69 \pm 0.43	-1.13* \pm 0.10§	2.42 \pm 0.14	—
2	2.27 \pm 0.13	1.44 \pm 0.04	-3.90 \pm 0.11§	0.95 \pm 0.18	—
3	0.64 \pm 0.12	0.79 \pm 0.20	-1.44 \pm 0.22†	0.83 \pm 0.14	—
4	1.95 \pm 0.15	1.05 \pm 0.04	-2.74 \pm 0.17†	0.88 \pm 0.21	—
5	—	0.74 \pm 0.11	-2.89 \pm 0.25†	-0.06 \pm 0.38	-1.69 \pm 0.09§
6	—	1.37 \pm 0.05	-2.52 \pm 0.10§	1.45 \pm 0.04	-1.68 \pm 0.26†

* — = fluid secretion; perfusion sequence was from left to right in each subject.

† Tests with ricinoleic acid.

§ Tests with oleic acid.

leic acid was significant more potent than oleic acid at 0.5, 2, and 5 mM concentrations ($P < 0.01$).

Effects of 2-monoolein and lecithin (Table II). Fluid absorption was observed when the control solution, containing 10 mM taurocholate, was perfused. Ricinoleic acid, 5 mM, induced water secretion. The secretory effect of ricinoleic acid was not altered by the addition of monoolein, 2.5 mM, or monoolein and lecithin, 2.5 mM, to the perfusate ($P < 0.1$).

Comparison of ricinoleic acid and taurochenodeoxycholic acid. Ricinoleic acid, 2.5 mM, induced fluid secretion, to the same degree as in experiments of group 2 (-0.48 ± 0.76 ml/min/25 cm). Taurochenodeoxycholic acid (5 mM) inhibited water absorption ($P < 0.05$). When perfused together, the effects of the two combined on water absorption (-0.27 ± 0.54 ml/min/25 cm) did not differ from those observed during perfusion with either of the compounds alone ($P > 0.05$).

Relationship between water and electrolyte movements. Electrolyte movement was determined on 12 of 14 experimental days (48 perfusions) in groups 1 and 2 and in all experiments of group 3. Sodium, potassium, and chloride moved in parallel (absorption or secretion) with water in all studies (the correlation coefficients were 0.91–0.99). The regression coefficients between electrolyte and water movements were close to 1.0 (0.83–1.18) when absorption and secretion were expressed as percentages relative to amounts infused. Regression lines for each electrolyte and for the different sets of experimental conditions did not differ.

Absorption of fatty acids (Table III). Oleic acid was absorbed twice as fast as ricinoleic acid. Ricinoleic acid was absorbed more slowly from all perfusates and thereby achieved higher mean segment concentrations, despite the greater potential of this fatty acid to produce

TABLE II
Effect of Monoolein (2.5 mM) and Lecithin (2.5 mM)
on Water Secretion* Induced by Ricinoleic
Acid (RA) (5 mM)

Test circumstances	Water secretion ml/min/25 cm jejunum \pm SEM
Electrolyte solution + taurocholate¶	1.31 ± 0.15
Control + RA	-1.66 ± 0.53 ‡
Control + RA, monoolein	-1.53 ± 0.19 §
Control + RA, monoolein, lecithin	-1.37 ± 0.57

* — = fluid secretion; each value is mean from random sequence of studies in same four individuals.

‡ $P < 0.025$, control vs. test.

§ $P < 0.005$, control vs. test.

¶ 10 mM taurocholate solution used as "control" in these studies.

|| $P < 0.05$, control vs. test.

TABLE III
Infusion Concentration, Mean Segment Concentration* and
Absorption of Fatty Acids in Human Jejunum

Infusion concn	Oleic acid		Ricinoleic acid	
	Absorption	Mean concn	Absorption	Mean concn
	mM μ mol/min/25 cm	mM	μ mol/min/25 cm	mM
0.5	3.3 ± 0.3	0.31 ± 0.02	2.5 ± 0.7	0.38 ± 0.03
2.0‡	16.2 ± 1.4	0.92 ± 0.16	7.6 ± 2.1	1.55 ± 0.17
5.0§	28.2 ± 4.1	3.18 ± 0.30	10.2 ± 2.4	4.18 ± 0.22
10.0	41.9 ± 7.3	6.83 ± 0.43	21.6 ± 2.6	8.02 ± 0.08

Each value is mean (\pm SEM) from studies in random sequence in four subjects.

* Mean segment concentration, expressed as logarithmic mean of input and recovery concentrations.

‡ $P < 0.005$, absorption of oleic vs. ricinoleic acid.

§ $P < 0.025$, absorption of oleic vs. ricinoleic acid.

|| $P < 0.05$, absorption of oleic vs. ricinoleic acid.

fluid secretion. In the series of experiments featuring monoolein and lecithin in combination with ricinoleic acid, inclusion of these compounds did not influence the absorption of ricinoleic acid. Absorption rates (μ mol/min/25 cm) were as follows: 5 mM ricinoleic acid alone, 14.6 ± 1.2 ; with monoolein, 14.2 ± 5 ; with monoolein and lecithin, 13.3 ± 3.8 .

Absorption rates of monoolein, glucose, xylose, and amino acids were also measured. During perfusions in which fluid secretion was induced by fatty acids, absorption of all these compounds was reduced. Details of these observations will be presented separately.

DISCUSSION

Our perfusion system was designed to exclude bile from the test segment (11). The initial experiments established that taurocholate, which was necessary to solubilize the lipid constituents of our perfusates, had no influence on jejunal water absorption. Wingate, Phillips, and Hofmann (8) reported that glycocholic acid had no secretory effect in the human jejunum. The experimental design allowed the effect of perfusion sequence to be eliminated and thus the secretory effects we report can be attributed to the perfused fatty acids.

The results, in conjunction with reports of earlier experiments in which ileal and colonic segments were used (4, 6, 7), demonstrate that long-chain fatty acids influence fluid movement in all parts of the bowel. In contrast to our observations in the human colon and the canine ileum (6, 7), the secretory response of the jejunum to fatty acids was rapidly reversible. Although both oleic and ricinoleic acids had dose-dependent effects, each showed a different potency. Specifically, at low-infusate concentrations, oleic acid was ineffective but

ricinoleic acid induced secretion; both fatty acids, however, were equally effective when 10 mM concentrations were perfused. Differences in rates of absorption of the two fatty acids could explain in part the differences in their potencies, since the more slowly absorbed compound develops a higher intraluminal concentration. Even when "dose response curves" are corrected for mean segment concentrations, however, ricinoleic acid is more potent at low concentrations (Fig. 1). Thus, the presence of a hydroxyl group on the C_{18} molecule, though not essential, appears to potentiate the secretory effects of C_{18} fatty acids in the jejunum.

The alteration of electrolyte and water movement induced by fatty acids is similar to that produced by conjugated dihydroxy bile acids (8) and to the secretion produced by cholera toxin. Electrolytes and water moved in parallel. We have emphasized volume changes, since these relate more directly to the symptomatic consequences of secretion induced by fatty acids; namely, increased water secretion and diarrhea. Moreover, the present experiments were not designed to specify the mechanisms of electrolyte and fluid secretion; changes in electrolyte movement could certainly be the primary mechanism, changes in water movement being a secondary event. We compared the effects of fatty acids and bile acids and sought evidence of interactions between these compounds. Lecithin, which abolished the secretory effect of glycodeoxycholic acid (8) when bile acid and lecithin were perfused in a ratio of 2:1, did not alter the secretory effect of ricinoleic acid. Monoolein, an obligatory component of the micelle formed during fat digestion, also did not block secretion induced by fatty acids. Thus, when the conditions of our perfusion system approximated postprandial conditions (fatty acids, bile acids, lecithin, and monoolein, in micellar dispersion), our model fatty acid still induced fluid secretion. Addition of taurochenodeoxycholic acid (5 mM), which is itself a secretory bile acid, neither augmented nor blocked the secretion induced by ricinoleic acid. These experiments, however, do not allow one to draw firm conclusions as to the mechanisms by which fatty acids and bile acids induce secretion. In particular, the physical chemistry of different solutions, especially in regard to monomeric concentrations of bile acids and fatty acids, is uncertain.

Absorption of fatty acids. Although ricinoleic acid absorption has been demonstrated in man with radioiodinated fatty acid (14), its rate of absorption has never been quantitated directly or compared with that of another fatty acid. In our system, ricinoleic acid was taken up from perfusates at approximately one-half the rate of oleic acid. Comparison of the chemical structures of the two fatty acids leads one to predict slower absorption of ricinoleic acid, since the presence of a

hydroxyl group should decrease its oil/water partition relative to oleic acid, and thereby decrease its transport rate across lipid membranes. Further, the intracellular transport of the fatty acids might differ; activation of ricinoleic acid by rat mucosal thiokinase is less efficient than that of oleic acid (15). Once absorbed, however, ricinoleic acid is metabolized along pathways standard for long-chain fatty acids (15) and can constitute a source of calories in some species (16, 17).

Physiologic significance. These experiments show that the difference between the response of the jejunal mucosa to oleic and ricinoleic acids is one of degree only. Thus, the effects of a known cathartic can be viewed as reflecting the pathophysiology of disordered fat absorption in man. Watson and Gordon (15) observed that when small doses of castor oil were ingested by fasting patients, absorption was nearly complete (i.e., fecal recovery was negligible) and no catharsis resulted. Larger doses yielded significant fecal recovery of fatty acid and resulted in diarrhea. In clinical circumstances, digestion and absorption of dietary fat may be comparable. Test-meal studies have demonstrated that fat absorption is normally complete in the upper small bowel, even by the time the meal reaches the proximal jejunum (18, 19). However, when lipolysis is normal but fat absorption is impaired, a longer segment of intestine is exposed to fatty acids; and in steatorrhea, the entire small and large bowel is exposed to excess fat. Even in the absence of steatorrhea, a greater length of small bowel will be necessary to maintain normal overall fat absorption if absorption per unit area is impaired by mucosal disease (20).

The significance of our findings to events in the proximal bowel is less clear. Glucose and amino acids, which stimulate absorption of electrolytes and water in the jejunum (21), are normally present in chyme, and test meals decrease in volume while traversing the upper small bowel (18, 22). Yet in health, most glucose, amino acids, and fatty acids are absorbed by the time a test meal reaches the jejunum (18, 19); in steatorrhea, excess intraluminal fat could have its major secretory effects more distally, in the ileum or colon. At these sites, hexoses and amino acids do not facilitate electrolyte and water absorption. Fatty acids are secretagogues in the ileum and colon (4, 6, 7) and lesser quantities than these provoking secretion could be clinically significant by impairing the capacity of the ileum and colon to reabsorb electrolytes and fluid.

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