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PHARMACOLOGY OF LAXATIVES

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INTRODUCTION

Effective laxative action results in an increase in fecal water excretion, and increased fecal water excretion is usually secondary to altered intestinal fluid and electrolyte movement. Both an understanding of the process(es) by which laxatives work and a classification of laxatives therefore should be based on the mechanism(s) by which cathartics either increase fecal water excretion or alter intestinal fluid and electrolyte movement. Since most laxatives were initially introduced into clinical practice on an empirical basis, the traditional classification of laxatives found in textbooks of pharmacology and therapeutics employ arbitrary categories that do not reflect the pathophysiological principles of altered intestinal fluid and electrolyte transport (1–3).

Diarrhea, as well as laxative action, is characterized by increased fecal water excretion. Recent studies of intestinal fluid and electrolyte movement in patients with various diarrheal illnesses have revealed alteration of water and sodium movement (4–6). Dihydroxy bile acids and ricinoleic acid are classical laxatives and have also been implicated in the pathophysiology of diarrhea of ileal resection and the diarrhea of steatorrhea respectively (7, 8). Further, laxative abuse has been identified as responsible for an occasional case of previously undiagnosed watery diarrhea (9, 10). Although clinicians are now beginning to consider diarrhea in terms of increased fecal water excretion, altered intestinal electrolyte movement, and intestinal electrolyte secretion, much less attention has been given to similar considerations in regard to the pharmacology of laxatives (11). This review summarizes recent observations of the effect of laxatives on intestinal function, which indicate that most laxatives alter intestinal electrolyte transport, and provides a basis for the development of a classification of laxatives based on the effect of these drugs on intestinal electrolyte transport.

ALTERATION OF ELECTROLYTE MOVEMENT

Since an increase in fecal water excretion is common to both laxatives and diarrhea, I first review certain aspects of intestinal fluid and electrolyte movement that are derived from studies of patients with diarrhea in order to provide a basis for a discussion of the effect of laxatives on intestinal water and electrolyte transport.

When segmental perfusions of the intestine are performed in normal subjects, net absorption of fluid
are performed in patients with diarrhea of various etiologies, either a decrease in fluid and electrolyte movement or fluid and electrolyte accumulation is observed in the involved segment of intestine (4–6, 12–15). Therefore, the phenomenological observation is either a decrease in fluid absorption or luminal fluid accumulation (which often is referred to as secretion[1]). Demonstration of either of these two phenomena (i.e. diminished absorption or fluid accumulation) does not provide any information regarding the mechanism(s) responsible for these events. For example, a decrease in net absorption may be secondary either to a decrease in the active absorptive process or to an increase in the active secretory process. Conversely, more than one mechanism may be responsible for the phenomena of net fluid accumulation; that is, active electrolyte secretion is not the only mechanism that can result in net fluid accumulation. Increased osmolarity of luminal contents can result in net fluid
that occur in patients with lactose intolerance (16). Inhibition of an active absorptive process alone should not result in net fluid accumulation unless a coexisting secretory process is also present. Whether stimulation of an active secretory process results in either a decrease in net absorption or net fluid accumulation depends on the magnitude of the secretory process.

Active Ion Secretion

Several substances stimulate active ion secretion which may result in either fluid accumulation or decreased net fluid absorption. These secretory stimulants (secretogogues) can be grouped as either (*a*) bacterial enterotoxins, (*b*) enteric and nonenteric hormones, or (*c*) certain luminal products. The best-known and most thoroughly studied secretogogue is cholera enterotoxin (17–20). It is currently accepted that cholera enterotoxin stimulates adenylate cyclase and the resulting increased mucosal cyclic AMP then stimulates, by processes that are totally unknown at present, an active secretory process. In addition to cholera enterotoxin, there are at least six other bacterial enterotoxins that stimulate net fluid accumulation (21, 22), but not all bacterial enterotoxins activate secretion by means of the

[1]I prefer to employ the term fluid and electrolyte *accumulation* rather than *secretion* to describe the addition of water to a solution perfusing a segment of intestine. I restrict the term *secretion* to describe the active transport process that is stimulated, for example, by cholera enterotoxin. Significant confusion has resulted from the use of *secretion* to describe both the phenomena of fluid accumulation and the active transport process.

cyclic AMP system (23). Of the several hormones associated with net fluid accumulation, vasoactive intestinal polypeptide (VIP) has gained significant attention in recent years and probably produces fluid accumulation in a manner similar to cholera enterotoxin (24, 25). Other hormones that stimulate fluid accumulation include gastric inhibitory polypeptide, cholecystokinin, secretin, thyrocalcitonin, prostaglandin E_1, and glucagon (26–31). Many of these hormones have been implicated as the causative agents in the watery diarrhea syndrome (pancreatic cholera) (32–34). Perfusion of the lumen of intestine with several substances such as bile acids, fatty acids, and hydroxy fatty acids will also provoke net fluid accumulation (35–41). These agents have been implicated in the pathophysiology of certain diarrheal illnesses and have also been employed as laxatives. Other luminal compounds besides bile acids and fatty acids which may induce fluid accumulation include caffeine, which inhibits cyclic nucleotide phosphodiesterase activity resulting in increased mucosal cyclic AMP levels, and several laxatives (42).

Role of Motility

The exact role of motility in the production of alterations of fluid and electrolyte movement is ill defined and requires further study. Many drugs alter intestinal motor function both in vitro and in vivo and affect intestinal transit (43–45), and changes in motility accompany various diarrheal illnesses. There is, however, no direct evidence that changes in motility, motor function, or transit alter intestinal electrolyte absorption. Although an increase in transit may diminish absorption, an increase in intestinal transit (i.e. a decrease in transit time) alone should never result in fluid and electrolyte accumulation. It is possible that increased luminal flow which occurs secondary to alteration of intestinal electrolyte movement may be responsible for the observed changes in motility. Therefore, additional studies are required to determine whether motility affects fluid absorption, especially if changes of fluid and electrolyte movement and transit are observed simultaneously. This information is extremely important to an understanding of laxative action since the general assumption has been that laxatives are effective by their action on intestinal motility.

In contrast, an opposite effect on motility (i.e. a decrease in intestinal transit) may alter absorption. Pharmacological agents (e.g. codeine), which decrease transit or increase transit time, may decrease fecal water excretion but probably do so by increasing the time that the absorbing surface is exposed to luminal contents. There is no experimental evidence to date that indicates that drugs like codeine directly affect absorptive or secretory transport processes.

Mucosal Permeability

Several different mechanisms may result in net fluid and electrolyte accumulation and therefore increase fecal water excretion. Active electrolyte secretion, a hyperosmolar load, and a decrease in the absorptive process as already mentioned may result in net fluid accumulation. Additional mechanisms have also been implicated as possible causative factors in the production of net fluid accumulation and include

increased hydrostatic pressure and increased mucosal permeability. Although increased hydrostatic pressure is not responsible for cholera enterotoxin–induced fluid accumulation (46), Lifson and associates have provided convincing evidence that increased hydrostatic pressure in the in vitro canine jejunum results in net serosal to mucosal sodium movement (47, 48). Whether this phenomenon occurs in vivo is not known. Increased mucosal permeability has also been suggested to cause net fluid accumulation; however, an alteration of permeability should result in equal increases in solute and fluid movement in *both* lumen to plasma and plasma to lumen directions without any change in net movement. Although an increase in permeability is present during both bile acid and fatty acid–induced fluid accumulation, altered mucosal permeability is not required for fluid accumulation per se since in cholera enterotoxin–induced fluid accumulation, an increase in tissue resistance is found (20), and no change in mucosal permeability is noted in the fluid accumulation that is secondary to an hyperosmolar load (49). Therefore, the importance of increased mucosal permeability in the genesis of intestinal fluid accumulation is uncertain. It would be intriguing to speculate that increased hydrostatic pressure becomes a driving force for net fluid accumulation only in the presence of increased mucosal permeability—a circumstance that may explain the diminished net absorption observed following volume expansion in experimental animals (50, 51).

Mucosal Damage

The role of intestinal mucosal damage or morphological abnormalities on the production of fluid accumulation is also difficult to assess. The decrease in net absorption or net fluid accumulation that is associated with intestinal morphological changes may directly reflect a decrease in an absorptive process or stimulation of a secretory process secondary to mucosal injury. Alternatively, certain substances may be responsible for both the morphological abnormalities and stimulation of secretory process or inhibition of the absorptive process. If an increase in mucosal permeability is also present, this may only reflect the mucosal damage. The pathophysiological role of histologic changes in the intestinal mucosa in the production of altered fluid movement is therefore unclear.

When fluid accumulation or diminished absorption is present simultaneously with alteration of several different processes of intestinal function, it may be difficult to define which particular factor or factors are primarily responsible for the alteration of fluid and electrolyte movement. As is discussed subsequently, this is presently the primary problem in the determination of the mechanism(s) responsible for the fluid accumulation produced by several laxatives.

TRADITIONAL CLASSIFICATION OF LAXATIVES

The present classification of laxatives neither reflects these pathophysiologic considerations concerning alteration of intestinal fluid and electrolyte transport nor possesses any other logical basis to explain laxative action. Various textbooks on pharmacology offer a variety of differing and overlapping classifications (1–3). The Food and Drug Administration's over-the-counter drug panel on laxatives, an-

tidiarrheal, antiemetic, and emetic products (52) adapted a classification of laxatives similar to most other classifications and suggested five categories: (*a*) stimulant or irritant, (*b*) stool softeners, (*c*) saline, (*d*) bulk, and (*e*) lubricant. It is evident that this classification does not relate to mechanisms responsible for either increasing fecal water excretion or altering intestinal fluid movement (11).

Stimulants

The largest member of laxatives belong to the stimulant or irritant category, and most recent studies of laxatives have evaluated the effect of these agents on intestinal function. The terms *stimulant* and *irritant* are not mechanisms of altered intestinal fluid and electrolyte movement, but rather are used to suggest that these agents possess laxative properties by virtue of their "stimulation" of peristalsis by "irritation" of colonic mucosa. However, recent studies of four of the most common laxatives in this category provide compelling evidence that these laxatives alter fluid and electrolyte absorption in both man and experimental animals and that net fluid accumulation is often observed. These four laxatives are ricinoleic acid which is the active ingredient of castor oil, dihydroxy bile acids, bisacodyl, and oxyphenisatin. These laxatives are surface-active compounds and appear to possess a similar pattern of action with multiple effects on intestinal function. These agents can convert net fluid and electrolyte absorption to net fluid accumulation; in addition they alter mucosal permeability, induce certain changes in intestinal motor activity, on occasion produce mucosal damage, and in the case of dihydroxy bile acids stimulate active anion secretion.

BILE ACIDS Investigations of the effect of bile acids on intestinal electrolyte transport are more extensive than those of fatty acids and hydroxy fatty acids. Bile acids have well-known laxative properties and are often included in multiple-ingredient preparations. Further, diarrhea is a significant side effect of chenodeoxycholic acid therapy when given to dissolve cholesterol gallstones (53), and bile acid alteration of colonic electrolyte transport has been implicated as the causative factor in cholerrheic enteropathy which is the diarrhea that occurs in patients with ileal dysfunction (7).

Several different bile acids alter fluid transport although dihydroxy bile acids such as deoxycholic acid are more effective than trihydroxy bile acids, and unconjugated bile acids may be more effective than conjugated bile acids (35–37, 54–56). Perfusion of the human colon and ileum with deoxycholic acid results in net fluid and electrolyte accumulation. Similar changes have been noted in the jejunum of human volunteers. Several, although not all studies, have indicated that significant histological damage is present in colonic mucosa following perfusion with unconjugated dihydroxy bile acids (54, 57). Bile acids also produce marked alteration of colonic mucosal permeability. Evidence of these changes of mucosal permeability include (*a*) a decrease in electrical potential difference (PD), (*b*) an increase in the passage of inulin from plasma to lumen, (*c*) an increase in the movement of EDTA from serosa to mucosa, (*d*) an increase in urea and oxalate absorption, and (*e*) an increase in oxalate clearance by the colon (58–60).

Evidence has been obtained recently that dihydroxy bile acids stimulate active anion secretion (61). These studies suggest that bile acids stimulate secretion in a manner analogous to the secretion produced by cholera enterotoxin because the colon possesses a cyclic AMP–mediated secretory system and because in in vitro studies bile acids decrease net sodium absorption, produce net chloride secretion, and increase mucosal cyclic AMP levels (61, 62). Additional studies have confirmed that dihydroxy bile acids stimulate adenylate cyclase activity in the colon (63), and bile acids also increase mucosal cyclic AMP in the small intestine (64). In contrast to the studies with cholera enterotoxin, which increases tissue resistance, bile acids increase mucosal permeability in addition to stimulating active anion secretion.

Therefore, bile acids produce fluid and electrolyte accumulation, and stimulation of active anion secretion may be the primary driving force responsible for the net fluid accumulation. The importance of increased mucosal permeability, mucosal damage, and changes in motor activity in the genesis of fluid accumulation must be considered (65). As already suggested, motility changes cannot result in net fluid accumulation. Increased permeability should result in an increase in both lumen to plasma and plasma to lumen movement without a resulting change in net movement unless there is also an increase in hydrostatic pressure. Morphological damage is not a constant observation. Therefore, although these changes in permeability, morphology, and motility may contribute to the production of net fluid accumulation, active anion secretion, which is probably mediated by cyclic AMP, is likely to be the primary determinant of these changes in fluid and electrolyte movement.

HYDROXY FATTY ACIDS Recent detailed studies have clearly indicated that ricinoleic acid influences intestinal fluid and electrolyte movement, alters colonic slow wave activity, increases mucosal permeability, and produces morphological changes that are observed on scanning electron microscopy (38–41, 67–73). Which of these changes are responsible for the increased fecal water excretion that occurs following castor oil ingestion is uncertain but several tentative conclusions can be made.

Study of the effect of ricinoleic acid and other hydroxy and nonhydroxy fatty acids on fluid and electrolyte movement has indicated that several fatty acids alter fluid absorption (38–41). In both the human and rodent colon, perfusion with ricinoleic acid diminishes net fluid absorption or produces net fluid and sodium accumulation. Further, hydroxy fatty acids are more effective than nonhydroxy fatty acids. Although hydroxy fatty acids are not absorbed as effectively as nonhydroxy fatty acids, and therefore their intraluminal concentrations may be higher than those of the nonhydroxy fatty acids, there is little correlation between absorption of fatty acids and their alterations of fluid movement. Perfusion of the dog ileum also results in similar effects on fluid absorption, and perfusion of the jejunum in human volunteers reveals that ricinoleic acid produces net fluid accumulation. In contrast, octanoic acid, a medium chain fatty acid which when employed therapeutically in medium-chain triglycerides often decreases diarrhea, does not alter fluid

and electrolyte movement (40, 58). These experiments provide conclusive evidence that ricinoleic acid can reverse net fluid absorption to net fluid accumulation and suggest that this production of fluid accumulation is related to the laxative properties of ricinoleic acid. However, these studies do not provide information concerning the mechanism by which ricinoleic acid induces fluid accumulation. In contrast to bile acids there is no conclusive evidence that ricinoleic acid stimulates an active secretory process. We have attempted to study the effect of ricinoleic acid on isolated intestinal epithelia utilizing the methods employed in previous studies with both bile acids and cholera enterotoxin, but the mucosal requirement for calcium has prevented the addition of ricinoleic acid to the mucosal solution (H. J. Binder, unpublished observations). Direct demonstration of the effect of ricinoleic acid on ion transport in vitro is still required although preliminary reports indicate that ricinoleic acid increases mucosal cyclic AMP in the colon (66; H. J. Binder, unpublished observations).

In other studies ricinoleic acid decreases both motility in vivo and muscular contractility in vitro (67–69). In addition, ricinoleic acid may uncouple the basal electrical rhythm (BER) of circular muscle of the isolated cat colon (70). The recent observation that similar changes of BER were present in the colon of cats with spontaneous diarrhea suggests that this change in slow wave activity may be a nonspecific effect secondary to increased fecal water excretion (71). Ricinoleic acid also increases colonic mucosal permeability as demonstrated by an increase in inulin clearance and a decrease in the electrical PD (38). Finally, Gaginella & Phillips have shown that focal abnormalities of surface epithelial cells are apparent in both ileal and colonic mucosa in the rabbit when examined by scanning electron microscopy following exposure of the mucosa to ricinoleic acid (72, 73). These histological changes may represent a toxic effect of ricinoleic acid on the surface epithelia, and the changes in mucosal permeability may then be secondary to these anatomical observations. Again it must be emphasized that the relationship of these changes in permeability, morphology, and motility to the production of net fluid accumulation is unknown. A unifying though unproven hypothesis is that fatty acids and hydroxy fatty acids, like bile acids, stimulate a cyclic AMP–mediated active secretory process which is the driving force for net fluid accumulation and increased fecal water excretion.

OTHER AGENTS Other compounds that are usually included in the irritant or stimulant category alter fluid and electrolyte movement and also affect more than one aspect of intestinal function. Bisacodyl has recently been studied in considerable detail (74–79). Perfusion of both the dog and the human colon with bisacodyl results in net fluid and electrolyte accumulation (74, 75). Further, perfusion of the small intestine of human volunteers and the rat also results in altered fluid and electrolyte movement (76). Focal changes in intestinal epithelial cells recently have been observed following exposure of colonic mucosa to bisacodyl (77). In addition, bisacodyl inhibits glucose absorption and intestinal Na-K-ATPase activity; changes in motor activity are also evident (78–80). It is not known as yet whether bisacodyl

alters mucosal permeability. Studies of the effect of bisacodyl on in vitro ion transport, adenylate cyclase, and mucosal cyclic AMP are awaited.

Phenolphthalein is a classical American laxative. There is but one report available that has evaluated the effect of phenolphthalein on fluid and electrolyte movement. In the isolated rabbit ileum, 1 mM phenolphthalein converted net sodium absorption to net sodium secretion and at a rate similar to that produced by 10 mM ricinoleic acid (81). Although the laxative action of phenolphthalein has usually been ascribed to an effect on peristalsis, it is important to recognize that phenolphthalein and bisacodyl have very similar chemical structures. Since phenolphthalein inhibits Na-K-ATPase activity (79), this effect on fluid movement may be mediated in part by inhibition of sodium absorption. Oxyphenisatin was a popular laxative until its recent removal from distribution by the FDA because of its association with chronic active hepatitis. Oxyphenisatin also has a chemical structure similar to both phenolphthalein and bisacodyl and significantly alters intestinal fluid and electrolyte movement. In experimental animals oxyphenisatin has produced net fluid accumulation and in parallel studies, oxyphenisatin markedly increased mucosal permeability and inhibited glucose absorption (79, 82, 83). Once more it is tempting to ascribe the fluid accumulation produced by oxyphenisatin to active ion secretion, but further studies are required to substantiate this possibility.

Stool Softeners

Another major category of laxatives is the stool softeners. The principal drug in this group is dioctyl sodium sulfosuccinate (DSS). Of note is that DSS as well as bile acids and fatty acids are detergents. Although unequivocal evidence of the efficacy of DSS as a laxative in man is still lacking, we have recently reported that DSS produces net fluid and electrolyte accumulation in the rat cecum in addition to increasing mucosal permeability (84). In these studies DSS increased mucosal cyclic AMP and altered ion transport in a manner similar to bile acids. Cyclic AMP–mediated active anion secretion may then be the driving force for the observed net fluid accumulation produced by DSS. In other studies DSS also altered both fluid and electrolyte movement in the human and murine small intestine and the histological appearance of the surface cells of the colon (85). Therefore, DSS clearly alters fluid movement which may then be related to and responsible for its laxative effects. Clearly, the term *stool softener* could apply to all laxatives for if effective, all laxatives should result in "stool softening." I suspect that DSS was categorized as a stool softener since it is less potent in altering fluid and electrolyte movement than other laxatives.

Saline

Magnesium salts are described as saline or osmotic laxatives, and their laxative effect has been attributed to their poor absorbability with resulting hyperosmolarity. This proposed mechanism of laxative action is unproven. Isosmolarity is present at the ligament of Trietz following ingestion of hyperosmolar or hyposmolar meals, and magnesium salts are effective laxatives at relatively low concentrations. It has been

proposed as an intriguing, though totally unproven, speculation that the laxative action of magnesium may be mediated by cholecystokinin (CCK) (86). CCK is a secretagogue that alters fluid movement and stimulates intestinal motor activity and is released from duodenal mucosa by both magnesium and amino acids (27). Recent studies suggest that magnesium decreases both circular smooth muscle contractility of the ileum and decreases transit time (67, 87). Additional studies are required to assess the effects of magnesium on fluid absorption.

Bulk

Several different products are classified as bulk laxatives. The recent interest in dietary fiber has brought increased attention to these agents. There are no direct data to indicate that these products directly affect mucosal electrolyte transport. The general assumption has been that bulk laxatives work by virtue of their ability to adsorb fluid resulting in less fluid available for absorption. The recent demonstration that bran changes the composition of fecal bile acids suggests that other possible explanations may account for the laxative action of various bulk products (88).

CONCLUSION

Laxative action must be considered in terms of increases in fecal water excretion. Despite twenty-five years of emphasis on motility abnormalities it is uncertain (*a*) how various laxatives affect motility, (*b*) how changes in motor activity alter fluid and electrolyte movement, and (*c*) how changes in motor function result in fecal water excretion. Most of the laxatives studied to date alter intestinal fluid and electrolyte movement, and net fluid and electrolyte accumulation is often observed. Alteration of fluid and electrolyte movement, which often results in fluid accumulation, is central to effective laxative action. We propose that active ion secretion stimulated by laxative agents may be the driving force for the fluid accumulation produced by many of these drugs. Studies in the future should focus on the effect of various laxatives on ion transport with emphasis on their ability to stimulate active secretory processes or to inhibit active absorptive processes or both. Studies are also required to determine the possible contribution of other laxative-induced changes in intestinal function to alterations of electrolyte movement. Therefore, future classifications should be based on the pathophysiological mechanisms by which laxatives alter fluid and electrolyte movement.

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