New Approaches to Antidiarrheal Therapy

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Recent studies of the pathophysiology of diarrhea have resulted in both increased understanding of how existing antidiarrheal drugs work and a rational approach to the development of new antidiarrheal therapies. No longer can one assume that all antidiarrheal medicines are effective solely by virtue of their effects on intestinal smooth muscle with prolongation of intestinal transit time.

The concept has emerged that diarrhea most often represents an increase in stool water excretion and that most diarrheal disorders are associated with changes in intestinal fluid and electrolyte movement (1). Thus, it is not surprising that antidiarrheal therapy can also be considered in relation to intestinal fluid and electrolyte movement. By definition, successful antidiarrheal therapy will result in a decrease in stool fluid output, which may result either from (a) an increase in intestinal fluid and electrolyte absorption or (b) an inhibition of intestinal fluid and electrolyte secretion (Fig. 1).

What are the mechanisms by which an antidiarrheal agent increases fluid and electrolyte absorption? Antidiarrheal agents may affect fluid and electrolyte absorption either directly or indirectly. This classification is used to distinguish between direct stimulation of the absorptive process and one in which the absorptive process is not directly affected by the antidiarrheal drug. In the latter circumstance, it is generally recognized that some antidiarrheal agents affect intestinal motor function, resulting in retention of luminal contents with a decrease in the distal flow of fluid (2). As a consequence, there will be an increase in the time in which luminal contents are in contact with intestinal mucosa. This increase in contact time combined with a normal rate of fluid and electrolyte absorption by mucosal epithelial cells results in an increase in absorption. Thus, the overall absorptive process becomes more efficient.

In contrast to this indirect stimulation of fluid and electrolyte absorption, studies in recent years provide considerable evidence that some antidiarrheal drugs act by directly stimulating the absorptive process (3-5). The first demonstration of this phenomenon was the observation that glucose increases fluid and electrolyte absorption (6,7). Although there has been modest controversy regarding the actual mechanism by which glucose augments water and sodium absorption, there is no doubt that the observed increase in fluid absorption is directly linked to glucose absorption. The demonstration that in clinical and...
FIG. 1. Antidiarrheal drugs are effective by altering intestinal fluid and electrolyte movement. Conversion of net fluid secretion to net fluid absorption can occur either by inhibition of secretion or stimulation of absorption, which may represent either a direct or indirect event. See text for full explanation.

Experimental cholera both absorptive function and intestinal morphology were normal (8) prompted the initial use of so-called oral therapy in the treatment of mild cholera (9). In “oral therapy” an oral glucose-electrolyte solution is administered, and despite the persistence of cholera enterotoxin-mediated active ion secretion, net fluid secretion is diminished as a result of glucose-stimulated water absorption. As a consequence, stool fluid excretion diminishes, and intravenous fluid replacement requirements decrease. The long-standing use of Coca-Cola® syrup by pediatricians in the treatment of infantile diarrhea probably also represents use of the principles of “oral therapy.”

Several other drugs that are effective as antidiarrheal agents or have been used in experimental secretory states directly augment fluid and electrolyte absorption (3–5,10–14). Table 1 identifies several other potential or established antidiarrheal drugs that increase active sodium absorption. Recent studies provide evidence that opiates and opioid peptides directly increase sodium and chloride transport (3,4). Figure 2 illustrates that [d-Ala]met-enkephalin increases active sodium and chloride absorption across rabbit ileal mucosa in vitro. Although codeine and morphine produce similar effects on active ion transport (4,14), studies from Fordtran’s laboratory conclude that the primary effect of codeine in man is to delay jejunal transit (2).

Epinephrine and dopamine also increase active sodium and chloride absorption (15,16). Recent studies indicate that this increase in ion transport is mediated
by their interaction with $\alpha_2$-adrenergic agonist receptors. Clonidine and lidamidine (a newly developed experimental antidiarrheal agent) have been effective in the treatment of a few patients with the watery diarrheal syndrome and also stimulate active sodium and chloride absorption by an $\alpha_2$-adrenergic agonist mechanism (11,17). Since recent experiments indicate that $\alpha_2$ adrenergic agonists most likely increase active sodium and chloride absorption by acting as calcium channel blockers (16), and A23187, a calcium ionophore, serotonin, and muscarinic cholinergic agonists inhibit active sodium chloride absorption by a calcium-dependent, non-cyclic-AMP process (18–20), it is probable that both absorptive and secretory processes are modulated by the cytosolic calcium concentration of the intestinal epithelial cell. Thus, pharmaceutical manipulation of cellular calcium represents an interesting approach to the development of new antidiarrheal medications.

It is of interest that glucocorticoids increase water and sodium absorption by virtue of increasing $\text{Na}^+–\text{K}^+$ ATPase activity (13). It is an interesting speculation that prednisone is effective in the treatment of inflammatory bowel disease

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secondary to its stimulation of sodium transport rather than (or in addition to) its antiinflammatory properties.

Recent studies suggest that antidiarrheal drugs may also work by inhibiting intestinal secretory processes. In order to discuss inhibition of intestinal secretion, it is necessary first to review the present status of intestinal anion secretion. Figure 3 summarizes present theories of the intracellular mechanism(s) by which various hormones and bacterial enterotoxins stimulate active secretion either by cyclic AMP or by calcium-dependent, non-cyclic-AMP-mediated processes. The enterotoxin of *V. cholera*, the heat-labile (LT) enterotoxin of *E. coli*, and vasoactive intestinal peptide (VIP) all activate adenylate cyclase and increase mucosal cyclic AMP.

Other hormones, serotonin, and muscarinic cholinergic agonists stimulate active ion secretion by acting as calcium ionophores, and increased mucosal cyclic AMP may stimulate active anion secretion by increasing cytosolic calcium (19,20). By mechanisms that are not totally understood, calcium activates calmodulin, which presumably phosphorylates a protein kinase that in turn increases apical membrane chloride permeability (21). Although this sequence is very attractive, additional experiments are required to confirm and establish this model. Exactly how cyclic GMP, which is the intracellular mediator of the heat-stable enterotoxins of *E. coli* and *Y. enterocolitica* (22), affects ion transport is not known.

This model permits the speculation that antidiarrheal drugs may act on one or more of the processes associated with cyclic-AMP-mediated or calcium-dependent secretory processes. For example, inhibition of secretagogue-mediated

![Diagram](image-url)
increases in adenylate cyclase would prevent cholera enterotoxin stimulation of fluid secretion. Agents that bind calmodulin may interfere with the secretory process, and such drugs might be effective antidiarrheal drugs. For example, chlorpromazine has been found to be effective in experimental and clinical cholera (23). Chlorpromazine inhibits adenylate cyclase as well as inhibiting calmodulin (24). Thus, at least two mechanisms exist that may explain chlorpromazine's inhibition of intestinal secretion. Experimentally, trifluoperazine is a potent calmodulin inhibitor and has also been found to inhibit intestinal secretory processes (25). Morphine, as well as loperamide, a newly developed synthetic antidiarrheal agent, has been shown in recent studies to inhibit intestinal secretion (26). The exact mechanism by which opiates and related compounds interfere with this secretory process requires additional study.

Prostaglandins stimulate small and large intestinal fluid and electrolyte secretion (27,28). Several studies have suggested that the diarrhea of ulcerative colitis and some experimental secretory models (e.g., salmonellosis) is mediated by increased prostaglandin synthesis (29,30). Therefore, it should not be surprising that indomethacin, a prostaglandin synthesis inhibitor, has been employed as a possible antidiarrheal agent in both clinical and experimental conditions with varying degrees of success.

It would appear that some antidiarrheal agents may be effective by altering more than one mechanism. Somatostatin would be such an example. Recent studies with somatostatin demonstrate that somatostatin is extremely effective in controlling profuse diarrhea in carcinoid syndrome when administered intravenously (31). Somatostatin clearly affects intestinal smooth muscle and causes marked increases in transit time and fluid retention. In the rabbit ileum, somatostatin stimulates active sodium and chloride absorption, whereas in the rat colon, somatostatin inhibits VIP- and serotonin-mediated active secretory processes (10,32). Thus, somatostatin's ability to act as an antidiarrheal agent may result from three potential mechanisms: (a) inhibiting intestinal motility and, thus, only indirectly stimulating sodium absorption; (b) directly stimulating intestinal sodium absorption; and (c) directly inhibiting intestinal secretory processes.

The development of so-called gut-specific somatostatin analogs will be an important new development. Such analogs should be relatively devoid of their effects on carbohydrate metabolism and the central nervous system while retaining their ability to affect intestinal fluid and electrolyte function (33).

Since antidiarrheal agents may act by more than one mechanism, is it possible to distinguish between an antidiarrheal agent's ability to stimulate fluid and electrolyte absorption from its inhibition of secretion? The observation that an antidiarrheal agent reverses net fluid secretion to net fluid absorption does not provide clear-cut evidence that the drug acted either to stimulate intestinal absorption or to inhibit intestinal secretion, since such a reversal could be produced by drugs acting via either mechanism. In order to make this distinction, it is critical to determine the effect of the drug under basal conditions (i.e., in
the absence of secretory processes). A drug whose mechanism is to inhibit secretion will have no effect in control studies, whereas those that act by increasing sodium absorption will increase electrolyte transport during control periods. Although it is possible to distinguish between these two mechanisms, conclusions regarding a drug’s mechanism are often made with insufficient data to make such a distinction.

Studies in the past few years have provided new mechanisms to explain how long-established antidiarrheal drugs act. Similarly, these studies have led to the development of new antidiarrheal drugs that affect intestinal fluid and electrolyte transport. The next decade will undoubtedly result in the development of pharmacological agents based on recent observations that stimulation of fluid movement and inhibition of intestinal secretion represent a rational approach to the therapeutics of diarrhea.

REFERENCES


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