

New Diarex in Diarrhoea

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Acute diarrhoeas often resulting from an infection of the intestinal tract. The infectious agents, viruses, bacteria, or parasites, entering the intestinal tract act directly on the luminal side of the enterocytes. The loss of water and electrolytes produces dehydration, the severity of which depends upon the frequency of diarrhoea and the amount of water and electrolyte loss.

PHYSIOLOGICAL MECHANISMS

The circulation of water in the intestine

The disturbances of the entero-systemic cycle of water explain the signs and symptoms of diarrhoea^{1,2}. The enterocytes covering the intestinal wall can present with 2 types of disturbances.

- i. Infectious agents stimulate secretion to such an extent that it exceeds the re-absorptive capacity for water and electrolytes,
- ii. The re-absorption capacity is diminished and becomes unable to cope with the amounts secreted.

The first mechanism is that of the secretory diarrhoeas, caused e.g. by the toxins of *Vibrio cholerae* or *Escherichia coli*³. The second one implies destruction of the enterocytes and their increased regeneration, as seen in rotavirus infections^{4,5}.

The role of the enterocytes

Diarrhoea can be considered as a disturbance of the enterocyte transport systems. There is an increased Cl⁻ secretion and a decreased absorption of NaCl. These two mechanisms have an additive effect, causing an accumulation of water and electrolytes in the intestinal lumen. The glucose-driven sodium absorption is usually conserved⁶. It decreases, however, in rotavirus or cryptosporidium infections⁷⁻⁹ and may increase in cholera. At the level of the colon, it should be possible to stimulate sodium absorption by the short chain fatty acids produced by the fermentation of carbohydrates¹⁰⁻¹⁴.

The secretory immunoglobulins barrier

An infection of the intestine quickly gives rise to the recognition of microbial antigens by the mucosa-associated lymphoid tissue present in the Peyer's patches of the small intestine. Activated specific lymphocytes and memory cells spread all over the intestinal mucosa. The resulting mature plasmocytes produce immunoglobulin A (IgA) that binds to a specific receptor, the secretory piece,

derived by proteolytic cleavage from the basal membrane of the enterocytes. The tetravalent dimeric secretory IgA enters the gut and binds specifically to the infecting micro-organisms in the intestinal lumen and the mucous covering the enterocytes. This leads to a very efficient "immunological exclusion" preventing the contact between microbial antigens and enterocytes. Daily, more than 3 gram of IgA reach the mucosal secretions¹⁵, blocking the massive entry of pathogens in the body. There is experimental proof *in vivo* that IgA alone can protect the gut from bacterial colonisation and the ensuing diarrhoea. For example, the induced secretion of a monoclonal IgA directed against a glycosylated epitope of the surface lipopolysaccharide of *V. cholerae* protects infected mice from diarrhoea and death¹⁶. These studies underscore the powerful protective effect on the intestinal mucosa of specific IgA, if present in sufficient amounts. This has been convincingly demonstrated in rotavirus infection¹⁷⁻¹⁹.

Infectious agents act directly on the epithelium

Despite the protective systems of the mucosa, infectious agents can directly lock on to the enterocytes. This results in changes of the concentrations of intracellular messengers that, in turn, acting on phosphorylation mechanisms, modify the concentration or the activity of the transport systems of the cellular membrane^{20,21}. The B-subunit of cholera toxin binds to the GM¹ gangliosides of the luminal membranes of the enterocytes. It allows the A-subunit to enter the cell and stimulate adenylate cyclase, an enzyme of the basolateral cell membrane. This causes a rise of cyclic AMP and an increased phosphorylation by protein kinase of the transport proteins located in the luminal membrane. The transport proteins include CFTR protein and NHE₃ protein. The former activates the selective Cl⁻ secretion channel, and the latter inhibits active coupled NaCl absorption from the mucosal to the serosal side of the gut. Beside *V. cholerae*, all other infectious agents that act directly on the enterocytes use similar mechanisms, though the membrane receptors are not necessarily GM¹ gangliosides and the intracellular messengers include cyclic GMP, cytosolic Ca⁺⁺ or IP₃, all of which modulate the expression of the cellular transport systems^{3,22-30}.

Infectious agents also act on the enterocytes by way of the cells of the *lamina propria*

One of the most striking aspects of the pathophysiology of acute infectious diarrhoeas is that the infectious agents act not only directly on the enterocytes and their secretion and absorption of water and electrolytes. They also act on the complex structures of the *lamina propria* surrounding the intestinal epithelium. The *lamina propria* consists of a great variety of cells, including nervous and neuro-endocrine cells, lymphocytes, polymorphonuclear and eosinophilic leukocytes, macrophages, mastocytes and myofibroblasts. Once stimulated, all these cells interact and influence the function of the enterocytes.

Taking into account the multiple interactions between the infectious agents and the whole intestinal mucosa (enterocytes and cells of the *lamina propria*), one can divide the pathophysiological mechanisms of diarrhoeas in 4 broad categories²¹.

- i. The action of enterotoxins
- ii. The action of cytotoxins
- iii. The adherence of infectious agents on the enterocytes,
- iv. The invasion of, and effect on, the *lamina propria* through the epithelium.

Each of these mechanisms exerts their actions directly on the enterocytes and indirectly on the *lamina propria*.

The 3 other mechanisms also affect both the enterocytes (directly) and the *lamina propria* cells (indirectly). These produce many mediators acting on their own environment, on the enterocytes and, at a distance, on other parts of the organism. These mediators include neuro-mediators, such as serotonin and acetylcholine, vasoactive intestinal polypeptide (VIP), the arachidonic acid cascade, i.e. prostaglandins, thromboxanes and leukotrienes, and cytokines, such as TNF α and interferon- γ , free radicals, nitric oxide (NO), and many other mediators of inflammation.

Dynamic aspects

One of the remarkable features of the small intestinal epithelium is that the enterocytes covering this considerable surface – when the microvilli are included it has been estimated at not less than 340,000 square cm for a 1 year old child are renewed on average every 72 hours. This is a result of the cellular cycle of the stem cells, located at the bottom of the crypts, and, at least in part, driven by substances secreted by cells of the *lamina propria*. They include cytokines, such as TNF α and IL-6, growth factors, such as epidermal growth factor, (EGF) and hormones, such as norepinephrine and tri-iodothyronine. Immunological diseases, e.g. coeliac disease and host-versus-graft reaction, influence the structure and speed of renewal of the enterocytes. Similar changes occur in acute diarrhoeas. This has been observed in transmissible gastro-enteritis (TGE) of piglets that has many similarities with rotavirus infections in children^{7,9}. There is a partial destruction of the villi with an accelerated renewal of the enterocytes. The result is a decrease of the absorptive surface, and a reduction of the absorption of sodium-coupled glucose and amino acids, and NaCl. These anomalies takes place by stimulation of *lamina propria* cells. Also, in cryptosporidiosis, which is not considered an invasive infection, there are morphological and functional lesions, resembling an inflammatory infiltrate in the *lamina propria*⁸.

CAUSES

Normal intestinal variations

Food intolerance or sensitivity

Intestinal infections

Most of these are not serious, not treatable, and will resolve on their own with time:

- i. *Rotavirus* : One of the most common causes of diarrhoea, especially during late fall and winter months. It causes very foul smelling, watery, green or brown diarrhoea that can persist for weeks. Fever and vomiting are common at the onset of the illness.
- ii. *Other viruses* : There are a variety of these, none of which are serious.
- iii. *Bacteria* : These include *E. Coli*, *Salmonella*, and several others. Vomiting and fever may be present at the onset. Blood in the diarrhoea is a common finding with bacterial infections. Even these infections rarely require antibiotic treatment.
- iv. *Parasites* : There are a variety of these. They are usually caught from contaminated water (e.g. giardia) or during travel to foreign countries. The telltale sign of a parasite is very watery diarrhoea that lasts beyond two weeks.
- v. *Contagious* : These are all generally contagious as long as the diarrhoea continues.

Mechanisms of diarrhoea:

There are at least 5 potential mechanisms which can produce diarrhoea:

- i. *Motility disorders* : Rapid transit with incomplete absorption
 - Irritable bowel syndrome
 - Carcinomas
- ii. *Osmotic disorders* : Osmotically active substances are not properly absorbed
 - Lactose intolerance in children
- iii. *Permeability defects* : Distorted mucosal architecture results in impaired permeability
 - Coeliac disease
 - Inflammatory bowel disease
- iv. *Active transport disorders* : Impaired membrane transporters
- v. *Secretory diarrhoeal disease* : Stimulation of intestinal secretory process without changes in histology

Cholera toxin : This is the best recognised of the secretory stimuli. Patients can lose 10-20 litres of fluid per day, which leads to rapid dehydration and death. Toxin attaches itself to specific receptors and enters the cell where it stimulates secretion. The specific mechanism is the production of cAMP, which opens specific apical membrane Cl⁻ channels. Opening of this channel effectively reverses the usual ionic fluxes with the result that ions and water are secreted into the intestinal lumen.

- Heat stable and heat labile *E. coli* toxins.

Management of diarrhoea

- If the diarrhoea is accompanied by fever and maybe vomiting, then it is probably an intestinal viral or bacterial infection.
- Rule out milk allergy / milk intolerance
- *Rule out food allergy* : Eliminate irritating foods.
- *Cow's milk-based formula* : If the diarrhoea is severe and has lasted more than 3 days, we suggest you switch to a soy formula for two weeks while the intestines have time to heal. Intestines that have been damaged by severe diarrhoea cannot digest cow's milk.

Clinical Abstract of the Study on New Diarex

Atisara (Diarrhoea) is one of the common problems of the patients attending the Ayurvedic outpatient department of any Ayurvedic hospital.

In Ayurveda, Diarrhoea has been classified in two broad groups depending upon mature stools and immature stools. They have been termed as Atisara and Ama-Atisara respectively. In Ama-Atisara there is a foul smell and is associated with painful flatulence, distressing constipation, abdominal pain, excess salivation and nausea. In case of Atisara excess liquidity, compactness, coldness and presence of mucous is reported by the patients.

Thirty patients of either sex in the age group of 16–70 years were selected from the outpatient department of Dravyaguna, Sir Sunder Lal Hospital, Banaras Hindu University, Varanasi.

The new antidiarrheal drug New Diarex was supplied by The Himalaya Drug Company, Bangalore. The patients were given New Diarex at dose of 2 tablets three times a day for 7 days and 2 tablets two times a day for subsequent 7 days to be taken after meals.

The patients were divided into 4 age groups i.e. 16-20 years, 31-45 years; 40-60 years; and 61-75 years. The maximum number of patients 13(43.3%) belonged to 16-30 years. Next to it 9(30%) belonged to 31-45 years. And 5(16.7%) belonged to 61-75 years and only 3(10%) belonged to 46-60 years of age group. Out of the 30 patients 18(60%) were male and 12(40%) females.

The majority of patients reported foul smell of stools and associated with painful flatulence and abdominal pain. Excess liquidity, nausea, anorexia, constipation and mucous was observed less frequently.

Twenty seven (90%) patients reported 3-6 loose motions per day and 3(10%) had 7-10 per day. Foul smell was reported by 25(83.4%) cases, painful defecation by 27(90%) cases; abdominal pain by 15(50%) cases; excess liquidity by 5(17%) cases; nausea by 12(40%) cases; anorexia by 9(30%) cases and mucous by 6(20%) cases.

Loose motions reduced in 90% of cases after seven days of treatment at a dose of 2 tablets three times a day. Foul smell was found absent in 80% of cases; painful defecation in 77.7% of cases; abdominal pain in 66.6% of cases; excess liquidity in 40% of cases; nausea in 75% of cases; anorexia in 66.6% of cases and mucous in 80% of cases.

Relief in loose motions was reported by almost all the cases except one case in which liquidity was persisting. Painful defecation, abdominal pain and nausea was also found significantly controlled by majority of the patients.

New Diarex is effective in Ama-Atisara group of patients than the Atisara patients. The symptoms like painful defecation, abdominal pain and nausea subsided in all the cases after fifteen days of treatment. The findings suggest that New Diarex is effective in Atisara as it contains *Holarrhena antidysenterica*, *Aegle marmelos*, *Punica granatum* and *Cyperus rotundus*. These ingredients also contain Tikta Rasa, which have been used in the treatment of Ama-Atisara in Ayurveda.

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