RACECADOTRIL IN THE TREATMENT OFACUTE WATERY DIARRHEA AMONG CHILDREN: A PIONEER STUDY IN DEVELOPING COUNTRY

THESIS
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Contents

Abstract

The study was done among 100 cases admitted in GE Unit, Children's hospitals, Cairo University. It was done on fifty cases receiving racecadotril (Group A) and another fifty cases as a control group (Group B).

It was revealed that the mean weight of stool in the 2nd day was 155.76 g with standard deviation of 37.174 in group A, while in group B it was 226.40g with a standard deviation of 29.881. The mean weight of stool in the 3rd day was 91.10 g with standard deviation of 21.863 in group A, while in group B it was 229.38g with a standard deviation of 33.340.

It also revealed that the mean weight of patient in the 2nd day was 9.682kg with standard deviation of 3.050 in group A, while in group B it was 10.694kg with a standard deviation of 1.524.

The study shows that racecadotril reduces significantly the volume and weight of stool, and protects the patient from weight loss due to dehydration. This study revealed that racecatodril showed improvement and correction of mild acidosis.

Key words:

Racecadotril – Acute watery diarrhea – Weight of stool – Intestinal motility

List of Abbreviations

• **CHO**	**Carbohydrates**
• **SI**	**Small Intestine**
• **UWL**	**Unstirred Water Layer**
• **AA**	**Amino Acids**
• **TG**	**Triglycerides**
• **FFA**	**Free Fatty Acids**
• **SER**	**Smooth Endoplasmic Reticulum**
• **RER**	**Rough Endoplasmic Reticulum**
• **Ach**	**Acetyl Choline**
• **VIP**	**Vaso-active Intestinal Peptide**
• **CCK**	**Cholecystokinin**
• **NA**	**Noreadrenaline**
• **GRP**	**Gastrin Releasing Peptide**
• **PNS**	**Parasympathetic Nervous System**
• **SNS**	**Sympathetic Nervous System**
• **GIP**	**Gastrin Inhibitory Peptide**
• **ETEC**	**Enterotoxigenic *E.coli***
• **EPEC**	**Enteropathogenic *E.coli***
• **EHEC**	**Enterohemorrhagic *E.coli***
• **EIEC**	**Enteroinvasive *E.coli***
• **EAggEC**	**Enteroaggregative *E.coli***
• **CT**	**Cholera Toxin**
• **IBS**	**Irritable Bowel Syndrom**
• **WHO**	**World HealthOrganization**
• **UNICEF**	**United Nations Children's Fund**
• **ORS**	**Oral Rehydration Solution**
• **ORT**	**Oral Rehydration Therapy**
• **LPS**	**Lipopolysaccharides**

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Introduction

Diarrheal disease is a leading cause of illness and death in children worldwide ***(O'ryan et al., 2005)***.

Diarrhea, an unpleasant inconvenience for people in the industrialized world, is a deadly affliction in developing countries, where it kills as many as 2 million people each year. Many of the deaths are caused by dehydration resulting from loss of water and electrolytes due to intestinal malabsorption or increased secretion. Replacement of these losses by oral rehydration solution is the mainstay of therapy for children with watery diarrhea ***(De Petrisl & Luchetti, 2001).***

Gastrointestinal infections have their major impact in the developing world: diarrhoeal diseases are responsible, directly or indirectly, for approximately three million deaths each year among children under five years of age—that is, 1 every 10 seconds. There are an estimated 1.8 billion episodes of childhood diarrhoea per year and virtually all of these acute diarrhoeal episodes are related to infectious agents. In some parts of Africa preschool children may suffer up to seven attacks of acute diarrhoea annually, although the average worldwide is approximately three episodes per year ***(Guerrant et al., 2003).***

During the past 10 years there have been some major improvements in our knowledge base regarding the treatment of infectious diarrhoea.

Racecadotril (acetorphan) is an enkephalinase inhibitor that decreases intestinal hypersecretion but not motility in animals and humans ***(Szajewska et al., 2007).***

It has proved effective and safe in children and adults with acute watery diarrhea when taken orally. It exerts its antidiarrheal effects by preventing the breakdown of endogenous enkephalins in the gastrointestinal tract ***(Hamza et al., 1999).***

In recent years, advances in diagnostic techniques have led to the identification of new causative agents and have improved our understanding of the etiologic role of previously recognized pathogens. Guidelines for the management of diarrhea have been refined, and new strategies for prevention and control have been identified ***(Guerrant et al., 2003).***

Aim of work:

The aim of the current study is to assess the effect of racecadotril as an adjuvant to rehydration therapy in infant and children in treatment of acute watery diarrhea.

Physiology of digestion and absorption in gastrointestinal tract:

Proteins, fats and complex carbohydrates (CHO) are broken down, digested, principally in the small intestine. The products of this digestion, plus the vitamins and minerals cross the mucosa and enter the portal blood or lymph, absorption orderly process, involving a large number of digestive enzymes, originating in the saliva, stomach, small intestine (SI) and exocrine pancreas. The action of these enzymes is aided by the action of HCl in the stomach and by bile in the SI the mucosa of the SI has a brush border made of numerous microvilli. This is covered by a layer of neutral and amino-sugars, the glycocalyx the membranes of the mucosal cells contain glycoprotein enzymes which hydrolyze CHO and peptides ***(Aldelman and Solhaug, 2000).***

The glycocalyx is made, in part, of the CHO portions of these glycoproteins which extend into the intestinal lumen next to the brush border and the glycocalyx is a 100-400 m unstirred water layer (UWL). The mucous coat overlying the mucosa is also a significant barrier to diffusion.

Processes involved in the absorption of substances include:

a. diffusion

b. facilitated diffusion

c. solvent drag

d. active transport

e. secondary active transport

f. endocytosis

Carbohydrates CHO

Digestion

The principal dietary CHO is composed of:

a. polysaccharides

b. monosaccharides

c. disaccharides

- Starches, polymers of glucose and their derivatives are the only polysaccharides of importance to humans.
- In glycogen, glucose molecules are joined by 1-4~ linkages, with some chain branching by 1-6α linkages.
- Amylopectin, which ~ 80-90% of dietary starch, is similar but has less branches.
- Amylose possesses only 1-4~ linkages and is a straight chain.
- The disaccharides lactose & sucrose are also ingested, along with the monosaccharides glucose & fructose.

Starch is first degraded by ptyalin, the α-amylase of saliva. However, the optimal pH for this is 6.7 and activity is terminated by gastric acidity. Once in the SI, pancreatic α-amylase is added. Both of these attack the 1-4α linkages but spare,

a. the 1-6α linkages.

b. the 1-4α linkages next to branch points.

c. the terminal 1-4α linkages.

Thus, the end products of this digestion are,

a. the disaccharide maltose.

b. the trisaccharide maltotriose.

c. larger polymers of glucose with 1-4α linkages.

d. branched polymers, ~ 8 units, the α-limit dextrins.

These are further digested by the oligosaccharidases located at the outer portion of the membrane of the microvilli,

a. maltase

b. lactase

c. sucrase

d. α-limit dextrinase

In many mammals and some races of humans, intestinal lactase activity is high at birth, declines to low levels in childhood and remains low. Subsequently, low levels being associated with intolerance of milk as lactose remain in the GIT and act as an osmotic agent prior to being broken down by bacteria in the colon. However, most Caucasians retain their lactase activity but most adult blacks are intolerant ***(Manganaro et al., 2001).***

Absorption

Hexoses and pentoses are rapidly absorbed across the intestinal mucosa. These then enter the capillaries which drain to the portal vein. Glucose and Na+ share the same symport, thus a high [Na] at the mucosal surface facilitates glucose absorption due to the action of the basal Na-K-pump ***(Manganaro et al., 2001).***

Secondary active transport

The same mechanism also transports galactose. Fructose utilizes a different carrier, and its absorption is independent of luminal Na+ ***(Manganaro et al., 2001).***

Facilitated diffusion

Insulin has minimal effect on the intestinal transport of sugars, as is the case for reabsorption in the proximal nephron.

Both are essentially normal in diabetes but are depressed by the drug phlorhizin. The maximal rate of glucose absorption is **~ 120 g/h *(Manganaro et al., 2001).***

Proteins & Nucleic Acids

Protein Digestion

It begins in the stomach, where pepsins cleave some of the peptide linkages. These are secreted in an inactive form, as ***pepsinogens***, and are activated by the low luminal PH.

There are a large number of these; however, they can be divided into two distinct immunohistochemical groups:

a. pepsinogen I - found only is HCl secreting region
b. pepsinogen II - also found in the pyloric region

Maximal acid secretion correlates with pepsinogen I levels, and patients with high circulating levels have a 5 times higher incidence of ulceration pepsins hydrolyse bonds between an aromatic aminoacids (AA), such as tyrosine or phenylalanine, and a second AA.

Thus, the products of this digestion are diverse peptides. The optimum PH ~ 1.6-3.2, therefore, action is terminated on exit from the stomach. The PH in the duodenal cap ~ 2.0-4.0, but the rest of the duodenum is ~ 6.5 ***(Aldelman and Solhaug, 2000).***

In the SI, these smaller peptides are further fragmented by proteolytic enzymes of the pancreas, which may be divided into:

a. endopeptidases - trypsin, chymotrypsin & elastase.

b. exopeptidases – carboxydipeptidases and the aminopeptidases of the brush border.

Some di and tripeptides are absorbed and finally broken down by intracellular peptidases ***(Aldelman and Solhaug, 2000).***

Thus, the final digestion of peptides occurs in three locations:

a. the lumen

b. the brush border

c. within the cell

Absorption

The l-AA's are absorbed more rapidly then their d-AA isomers and following a meal there is a sharp transient rise in the nitrogen content of portal blood. The d-isomers are absorbed soley by passive diffusion whereas, most of the ***l-isomers*** are actively transported from the lumen.

There are 4 seperate systems:

a. neutral AA's

b. basic AA's

c. proline, hydroxyproline and glycine

d. dicarboxylic AA's - glutamic and aspartic acids

There is a separate system for the di & tri-peptides. Transport is linked to Na+ and is facilitated by an increase in luminal [Na], as for glucose from the cells, diffusion of AA's into the portal blood is passive ***(Jenkins and Taylor, 2004).***