A NOVEL APPROACH IN THE TREATMENT OF ACUTE INFECTIVE DIARRHEA

INTRODUCTION

Diarrheal disease is the second leading cause of infectious disease morbidity and mortality worldwide, resulting in an estimated 2.2 million deaths in 2004. Although diarrheal disease affects persons of all age groups and in all geographic locations, the greatest burden of severe illness and death falls on infants and young children in developing countries. During 2000-2003, diarrhea ranked second behind pneumonia among the leading causes of death in children younger than 5 years of age, responsible for 18% of all deaths in this age group. Diarrheal disease also produces substantial morbidity, with 4 billion acute episodes estimated to occur annually. A survey among the general US population reported a rate of 1.4 episodes of diarrhea per year, translating to 200 to 375 million episodes annually.

The standard therapy of acute diarrhea involves antibiotics, fluids and anti-diarrheal agents. Fluid and electrolyte replacement are of central importance to all forms of acute diarrhea. Although oral rehydration therapy has reduced the mortality associated with acute diarrhea, the diarrheal attack remains unchanged and stool volume often increases during rehydration process. Judicious use of antibiotics is appropriate in selected instances of acute diarrhea.

In moderate to severe non-bloody diarrhea, antimotility/antisecretory agents can be useful adjuncts to control symptoms. There are a variety of anti-diarrheal agents currently available in the market – e.g. racecadotril, loperamide, diphenoxylate etc. However, all these agents have many drawbacks. The side-effects of opioids (loperamide, Diphenoxylate, atropine) include anorexia, nausea, vomiting, distension of abdomen, pancreatitis, paralytic ileus, toxic megacolon and CNS symptoms. Racecadotril, an enkephalinase inhibitor, potentiates the action of enkephalins which are endogenous Opioids whose pro-absorptive, antisecretory activity occurs mainly through delta receptor activation. Racecadotril scores over standard opioid antidiarrheal agents in that it does not produce entero-pooling and rebound constipation. However, its antisecretory activity is weak.

Therefore the limitations of current therapy are as follows:

1. Fluid replacement- No significant reduction of diarrheal rate and stool volume often increases during rehydration.
2. Antidiarrheals- limited efficacy, GIT/CNS side-effects, rebound constipation.
3. Antibiotics- resistance and unwanted side-effects.

In last 20 years there has been search for agents that will directly inhibit the secretory mechanisms and thus reduce the diarrheal volume and episodes. A number of potential targets for antisecretory agents have emerged which include loci within the enterocyte (chloride channel, calcium calmodulin) and recently enteric nerves and endogenous mediators (5-HT, substance P, VIP).

PATHOPHYSIOLOGY OF INTESTINAL SECRETIONS

The understanding of the mechanisms of secretion of intestinal fluid in health and disease is vital in knowing the novel approach in the treatment of acute diarrhea (Tables 1 and Figures 1, 2). Intestinal fluid secretion results from the active secretion of chloride and bicarbonate ions. Active chloride ion
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4. has a high therapeutic index
5. has minimal CNS effects
6. has low abuse potential

At present, none of the currently available agents in the market fulfill the above criteria in total. However, Octreotide, a somatostatin analogue, has potential role as potent and efficacious anti-secretory agent.

**MECHANISM OF ACTION OF OCTREOTIDE:**

Octreotide has documented antisecretory activity in neuroendocrine tumors of GIT like VIPoma, gastrinoma and carcinoid syndrome by inhibiting release of VIP and 5-HT.11,12 There are also reports that somatostatin and its analogues can inhibit intestinal secretions in VIPoma patients in absence of reduction of plasma VIP indicating that antisecretory activity may be operating through a direct effect either on enterocyte nervous system or enterocyte itself.12

In view of the antisecretory role of Octreotide in neuroendocrine tumors and cholera,13 we undertook this study to assess its role in acute infectious diarrhea of diverse etiologies and simultaneously compared it with the enkephalinase inhibitor, racecadotril which is currently available in the market as an anti-diarrheal agent.

**MATERIALS AND METHODS**

A randomized control study was conducted in Department of Medicine and Infectious Disease Hospital of SMS Medical College to assess the efficacy of Octreotide compared to another antisecretory agent Racecadotril.

150 patients (≥ 15 years of age) with moderate to severe acute diarrheal illness of less than 5 days duration were randomly allotted into 3 treatment categories of 50 patients each with help of chit box method.

The control group received only fluids and antibiotics, the racecadotril group received fluids, antibiotics and oral racecadotril at dose of 1.5 mg/kg three times a day. The Octreotide group received Octreotide (100 microgram stat at the time of hospitalization) along with fluids and antibiotics. Fluid was given according to the severity of dehydration.
Intravenous Ciprofloxacin and Metronidazole were given to all the patients.

A detailed history and clinical examination was done in all patients. Routine blood investigations and stool examination was carried out.

The following end points were compared in each group, namely-

1. Frequency of stools per day
2. Quantity of stool per day
3. Consistency of stool and
4. Fluid requirement per day

**STATISTICAL ANALYSIS**

Data were entered in excel sheet and analyzed with help of XL stat statistics. Quantitative data were summarized in form of mean ± S.D and average value of different treatment groups were compared using ANOVA test (analysis of variance) and post hoc test (Tukeys test) (with the help of SPSS version 17). Qualitative data were summarized in form of proportions and analyzed using chi square test. For all statistical analysis, level of confidence was kept 95%.

**OBSERVATIONS AND RESULTS:**

Patients in all the 3 groups were matched for age and sex. 80% of patients (120/150) were males. 76% of them (114/150) were of age group 15-44 years. 23 patients (15.33%) were above the age of 55 years.

The mean (±SE) frequency of stools was the same in all groups at the time of admission (Table 2). On day 2 the average frequency of stools passed in the octreotide group was 2.30±1.37. It was almost the same in the control and racadotril group at 6.82±2.77 and 6.70±2.77 respectively (p>0.05). Diarrhea stopped in 52% of patients (26/50) in octreotide group by day 3 and all the patients by day 4. Nearly 54% of patients (27/50) in control group and 52% (26/50) in racadotril group continued to have diarrhea by day 4.

The mean (±SE) quantity of stools passed (in ml) was same at the time of admission in all three groups (Table 3). On day 2, it was 362±196.67 ml in octreotide group, as compared to 757±322.84 ml in control group and 664.40±289.34 ml in racadotril group. Thus there was a 62% and 45% reduction in stool quantity in octreotide group compared from control and racadotril group respectively.

At the time of admission all subjects in Octreotide group (n=50, 100%) had watery stools (Table 4). On day 2, consistency changed in 92% cases receiving Octreotide; among these 27 (54%) had semisolid stools, 19 (38%) had passed loose stool and remaining 4 subjects (8%) had watery stools , which was significantly different when compared to control and racadotril group (p<0.001). By 3rd day, 26 out of 50 ceased to have diarrhea and among the remaining 24 subjects, 22 (91.67%) had passed semisolid stools, 2 (8.33%) had loose
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Key points:
- stools. The consistency of stools was almost the same in the control and racecadotril group (p > 0.05). On 2nd day, 43 subjects (86%) in racecadotril group and 41 subjects (82%) in control groups passed watery stools.
- On day 1, the average fluid (in liters) required in Octreotide group was 5.43±1.17 liters, as compared to 5.45±0.72 liters in control and 5.44±0.80 in racecadotril group respectively. The respective values on day 2 were 3.62±0.58 liters for Octreotide group; while it was 4.45±0.59 liters for control group and 4.36±0.69 liters for racecadotril group respectively. Thus mean (±SE) quantity of fluid required was least in Octreotide group (p < 0.001) (Table 5).

**DISCUSSION**

Diarrhea occurs as a result of increased intestinal secretion or decreased intestinal absorption or a combination of both.14, 15 It is now well established that enteric nervous system is involved in the promotion of intestinal secretory process.16

A potent inhibitor of enkephalinase, racecadotril offers a promising approach to the control of secretory diarrhea, based on its mechanism of action. Eduardo et al10 showed that treatment with racecadotril and oral rehydration therapy was more effective than oral rehydration alone in the treatment of acute watery diarrhea in children. However, Farthing MJ et al showed that antisecretory activity of racecadotril is weak.7-9 Our study demonstrated weak action of racecadotril on frequency, volume and consistency of stools which was comparable to control group.

Octreotide, the somatostatin analogue, has a role in short bowel syndrome and neuroendocrine tumours like VIPoma, gastrinoma and carcinoid. Octreotide has also been evaluated in a randomized study in patients with cholera by Khan et al.13 Patients were treated conventionally with fluid and antibiotics, but in addition were randomized to receive Octreotide or placebo. There was a reduction in stool volume, frequency and duration of diarrhea with Octreotide.13

The results of the present study show that Octreotide is effective in treatment of acute watery diarrhea. As compared to the control and racecadotril groups, the Octreotide group had clinically consistent and significant (p < 0.001) reduction in the frequency and volume of stools passed. The fluid requirement was also least in the Octreotide group. Also, consistency of stools improved significantly in the Octreotide group.

**CONCLUSION**

The results of this study provide strong evidence that Octreotide is an effective treatment for acute infective diarrhea in hospitalized adults independent of etiology of acute diarrhea. As compared with the control and Racecadotril groups, the Octreotide group had clinically consistent and significant results.

However, larger scale comparative clinical trials are required.
for any evidence-based definition of dosage and efficacy of Octreotide as a treatment modality to control diarrhea.

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REFERENCES