A Comparative Study of Racecadotril and Single Dose Octreotide as an Anti-Secretory Agent in Acute Infective Diarrhoea

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Abstract
Objective: To assess the efficacy of single dose of octreotide and compare it with another antisecretory agent racecadotril in the management of acute infective diarrhea.

Methods: A randomized control study was done in the Department of Medicine and Infectious Disease Hospital (Department of Preventive and Social Medicine) of SMS Medical College and Hospital. 150 patients with moderate to severe acute diarrheal illness needing hospitalization were randomly allotted into 3 categories of 50 patients each. The control group received only fluids and antibiotics, the racecadotril group received fluid, antibiotics and oral racecadotril at dose of 1.5 mg/kg three times a day and the octreotide group received octreotide (100 microgram stat) along with fluid and antibiotics. The following end points of the study were compared, namely- frequency, quantity and consistency of stools and fluid requirement per day.

Results: The mean (±SE) frequency of stools was significantly less (p<0.001) from day 2 onwards in the octreotide group compared to the control and racecadotril group. Diarrhea stopped in half of the patients in the octreotide group by day 3. The consistency of stools changed significantly in the octreotide group (p<0.001). No significant difference was seen between the racecadotril and control group (p>0.05) in terms of the frequency and consistency of stools. The mean (±SE) quantity of stools was significantly decreased in the octreotide group (p<0.001) on day 2 compared to the other two groups. The mean (±SE) quantity of fluid required was almost the same in all 3 groups on day 1 (p>0.05) but it was significantly less in the octreotide group on day 2 (p<0.001). No significant difference was seen with respect to the fluid requirement between the control and racecadotril group (p>0.05).

Conclusion: Patients who received single dose of octreotide fared better than those patients in control and racecadotril group in terms of frequency, quantity and consistency of stools passed. The fluid requirement was also less in octreotide group. However more trials need to be done to substantiate this finding before octreotide becomes a standard of therapy in acute infective diarrhea.

Introduction
Acute infectious diarrhea continues to cause high morbidity and mortality worldwide. 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.

In recent years, the standard of therapy of acute diarrhea involves antibiotics, fluid and anti-diarrheal agents. There are a variety of anti-diarrheal agents already available in the market – e.g. racecadotril, loperamide, diphenoxylate etc. However all these agents have many drawbacks.

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). Racecadotril, an enkephalinase inhibitor, potentiates the action of enkephalins which are endogenous opioids whose proabsorptive, antisecretory activity occurs mainly through delta receptor activation. Racecadotril scores over standard opioid antidiarrheal agents in that it does not produce enteropooling and rebound constipation. However its antisecretory activity is weak.

Octreotide is a somatostatin analogue which has documented antisecretory activity in neuroendocrine tumors of GIT like VIPoma, gastrinoma and carcinoid syndrome. There are 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.

In view of the antisecretory role of octreotide in neuroendocrine tumors and cholera, we wanted to assess its role in acute infective diarrhea of diverse etiologies and simultaneously compare it with the enkephalinase inhibitor, racecadotril which is already available in the market as an anti diarrheal agent.

Materials and Methods
A randomized control study was conducted in Department of Medicine of SMS Medical College and Hospital 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 fluid, 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 fluid 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.

**Measurement of Variables**

1. Frequency of stools- Number of stools passed by the patients in 24 hours was counted by attendant and duty doctor.
2. Quantity of stool per day- Patients’ attendants were asked to bring calibrated jar and instructed to collect stool in jar. Quantity of each stool was noted by the duty doctor.
3. Consistency of stool- noted by the duty doctor
4. Fluid requirement per day- fluid requirement in litres was calculated by adding total amount of IV fluid plus oral intake of liquids.

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%.

**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 1). 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 racecadotril 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 racecadotril 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 2). On day 2, consistency changed in 92% cases, 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 racecadotril 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 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 litres) required in octreotide group was 5.43±1.17 litres, as compared to 5.45±0.72 litres in control and 5.44±0.80 in racecadotril group respectively (Table 4). The respective values on day 2 were 3.62±0.58 litres for octreotide group; while it was 4.45±0.59 litres for control group and 4.36±0.69 litres for racecadotril group respectively. Thus mean (±SE) quantity of fluid required was least in octreotide group (p<0.001).

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Discussion

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

A potent inhibitor of enkephalinase, racecadotril offers a novel and promising approach to the control of secretory diarrhea. Eduardo et al. 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 its antisecretory activity is weak.

Loperamide and diphenoxylate are orally active antidiarrheal agent available in the market. They act by intestinal μ opiate receptors, leading to increased intestinal transit time. Side effects include constipation and bacterial overgrowth and hence can be harmful.

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 Moid I Khan et al. 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.

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

Conclusion

The present study compared octreotide and racecadotril in patients with acute onset diarrhea and found that those who received single dose of octreotide fared better than those patients in control and racecadotril group, in terms of frequency, volume and consistency of stools passed. The fluid requirement was also decreased in octreotide group.

Hence, octreotide as an antisecretory agent is very effective in management of acute infective diarrhea in adults. However more trials need to be done before it becomes a standard of therapy. Because no similar study was done before, it is not possible to compare with previous results.

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References

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