

## **Safety and efficacy of a novel anti-secretory anti-diarrheal agent Crofelemer (NP-303), in the treatment of adult acute infectious diarrhea and cholera, with or without the use of antibiotics**

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The effects of crofelemer were evaluated in patients with acute dehydrating watery diarrhea caused by various bacterial pathogens, such as enterotoxigenic strains of *Escherichia coli* (ETEC) and *Vibrio cholerae* infection. Crofelemer was evaluated in adult Indian patients with acute watery diarrhea of less than 24 hour duration with suspected bacterial infections, without the use of antibiotics. In this study, patients received oral doses of placebo or crofelemer at a dose of 250 mg every 6 hours for 2 days on the background of oral rehydration therapy only. The use of antibiotics was prohibited in this study. A total of 98 patients were randomized into this study (47 in placebo group and 51 in the crofelemer group). The key endpoint of this study was the resolution of watery diarrhea within 48 hours from the initiation of therapy. Other endpoints evaluated included stool weight and stool frequency. Crofelemer was well tolerated and there were no drug related adverse events. Twelve patients in the placebo group and four patients in the crofelemer group required antibiotic rescue therapy. Crofelemer at 250 mg every 6 hours was superior to placebo in improving the watery diarrhea and overall clinical success was achieved in about 75% of the crofelemer group compared to 37% in the placebo group. Stool cultures showed that 78% of the patients had *ETEC*, 15% had *Salmonella*, 2% had *Shigella* and about 5% had suspected viral pathogens.

In another study, a total of 100 adult patients, from Bangladesh, between the ages of 18 and 55, with acute, severely dehydrating watery diarrhea with confirmed cholera were treated with crofelemer on a background of an antibiotic (azithromycin) and oral rehydration therapy. After a four hour period of rapid rehydration therapy, patients were randomized 1:2:2 to placebo or 125 mg or 250 mg oral dose of crofelemer. Crofelemer or placebo doses were administered about one hour after the oral administration of azithromycin (1 gm dose). The primary objective was to evaluate the safety and effects of crofelemer on reducing the watery stool output normalized to body weight (mL/kg) in the first 24 hours on the background of azithromycin and rehydration therapy. Crofelemer was well tolerated and there were no drug related adverse events in this study. Both doses of crofelemer produced approximately 25-30% reduction in median watery stool volumes in the 0-6 and 0-12 hour period following initiation of therapy. Crofelemer showed a strong trend in the reduction of watery stool output in the 0-6 hour and 0-12 hour intervals ( $p=0.07$ ). Upon exclusion of three outlier patients, the crofelemer dose of 125 mg produced a statistically significant reduction in the normalized stool output ( $p=0.028$ ) and the dose of 250 mg crofelemer showed a strong trend for reduction of watery stool output ( $p=0.07$ ).

These results collectively show that crofelemer represents a first-of-a-kind treatment option as an antisecretory agent for the treatment of acute dehydrating watery diarrhea, with or without the use of antibiotics.

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