Editorial

Racecadotril–Is There Enough Evidence to Recommend it for Treatment of Acute Diarrhea?

Racecadotril is being proposed as a new "wonder" drug for the treatment of acute diarrhea in children. It is a synthetic enkephalinase inhibitor and its anti diarrheal effects are attributed to its anti secretory properties mediated by inactivating endogenous opioid peptides, enkephalins, secreted by myenteric and submucus plexus in the digestive tract. Enkephalins act as neurotransmitters and are rapidly broken down by the enkephalinase, present throughout the gastro intestinal tract (1). Racecadotril, therefore potentiates the physiological anti-secretory properties of the enkephalins. Studies in animal models have shown that the effects of racecadotril are antagonized by the opioid receptor antagonists nalaxone, therefore further confirming involvement of endogenous opioid peptides(2).

The anti-secretory mechanisms are independent of effects on intestinal motility, differentiating this compound from μ-opiate receptor agonists like loperamide and diphenoxylate. Experimental studies in rodents and human volunteers demonstrated no delay on gastrointestinal transit or increase in experimental bacterial proliferation in small bowel of germ free piglets with racecadotril as compared to loperamide(2,3). Thiorphan, the active metabolite of racecadotril, activates the antisecretory mechanisms via the d receptors and by reduction of intracellular cAMP. These effects have been well documented in animal studies and have been detailed in another article in this edition of the journal(4).

Prompted by the potential benefits in experimental trials in animals and human volunteers, this drug has since been evaluated in a few randomized controlled trials in children and adults with diarrhea with varying results. A significant reduction in total and initial 48 hours stool output, ORS intake and duration of diarrhea was reported with use of racecadotril with 135 Peruvian boys aged 3-35 months. It was found to be equally effective in rotavirus positive or negative patients(5). Another trial by Cezzard, *et al*. found similar results when racecadotril was given as an adjunct to ORT but included a total of 172 boys and girls, aged less than 4 years. The results of this study are questionable because collection of stool uncontaminated with urine is difficult to obtain in girls therefore compromising the most important primary outcome measure. Further, there is inconsistency in the number of patients who became trial deviates. Among the patients who were withdrawn from the study a larger number were from the racecadotril group(6).

Some beneficial effects were seen in adults with milder diarrhea and in whom the causative agents were not known(7) however the antisecretory activity of racecadotril seen in animal and human models with cholera toxin induced diarrhea have not been replicated in adults with severe cholera(8).

In a few clinical trials where racecadotril has been compared with loperamide it was found to be equally effective without the anti-propulsive effects of loperamide(9,10). However, there are no studies to evaluate adverse, possibly rebound, effects after the drug has been discontinued.

We are aware that after the two above-

mentioned studies in children, both funded by the drug company, the same company conducted a multi centre study to further evaluate the efficacy of racecadotril. We are unable to locate a publication discussing the results of this multi center trial. It raises the issue that the scientific evidence shown to physicians is not the total evidence obtained through clinical trials and may represent selective presentation of trials. While we recognize the hesitation of journals to publish negative trials it is nevertheless an issue of concern. The problem of unpublished negative trials has been highlighted in the literature before. Therefore recommending use of this drug today without considering all the evidence is not advisable.

The revised IAP recommendations for treatment of acute diarrhea are use of reduced osmolarity ORS for treating and maintaining dehydration, and 2RDA of zinc for at least 14 days(11). Antimicrobials should be used only for patients with gross blood in stool, culture positive shigella, cholera and associated systemic infection. Presently, use of anti-secretory drugs, like racecadotril should await more evidence from well designed randomized controlled studies done in our settings.

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