

News on pharmacotherapy of acute diarrhea

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Summary

The aim of this presentation is to review the current literature, focusing on the therapeutic approach to acute diarrhea in pediatrics.

Acute diarrhea

Acute diarrhea is one of the most important life-threatening conditions for children. Every year 1 billion of pediatric cases are reported and 2 millions of children < 5 years old, particularly in developing countries, die. In countries with high-level health organizations a dramatic decrease of mortality was obtained, although acute diarrhea is still associated with high morbidity. For example in the United States diarrhea is responsible for 220,000 hospital admissions in children < 5 years old,

About 70% of acute diarrhea is caused by virus, particularly Rotavirus, 15% by bacteria. Major complication is represented by dehydration. Thus, prevention of dehydration and optimal rehydration are the major goals of management.

Nowadays, pharmacologic options of acute diarrhea are limited to probiotics and antibiotics. On the contrary intestinal motility inhibitors, such as loperamide, are contra-indicated.

In recent years the new antidiarrheal drug racecadotril has been developed, with strong antise-

tory activity, rapidly hydrolyzed in its active metabolite, tiorfan, which inhibits enkephalinase. The inhibition of this enzyme prevents the inactivation of endogenous enkephalins, released by submucosal and mesenteric neurons, and prolongs their physiological actions. The enkephalins are neurotransmitters of the gastrointestinal tract that mediate their effect with the activation of δ -opioid receptors and consequent selective increase of chloride absorption, inhibiting AMP cyclic. The result is a reduction of water and electrolyte secretion without gut motility alterations. Moreover racecadotril action is present only in conditions of hypersecretion and does not have effects on basal secretory activity. With an oral administration of 1.5 mg/Kg of racecadotril, the inhibition of plasmatic enkephalinase starts after 30 minutes, while peak (90%) is reached after 2 hours. The inhibition of plasmatic enkephalinase remains for about 8 hours and half-life is about 3 hours, but these are dose-dependent effects. 90% of tiorfan is bound to plasmatic proteins and only 1% of administered dose distributes into tissues. Then the drug is transformed as non active metabolites, which are eliminated mainly with urines.

Many studies are available in pediatrics. In a population of children 3 months to 3 years old affected by acute diarrhea without blood and without significant dehydration it was demonstrated a reduction in the number of episodes in the first 48 hours (6.8 vs 9.5; $p < 0.001$), duration of diarrhea (97.2 vs 137.7 h; $p < 0.001$) and less frequent medical consultation (18.4% vs 34.6%; $p < 0.05$)¹.

Similarly, in another study fecal output in the first 48 hours with racecadotril was 46% lower (92 g/kg vs 170 g/kg; $p < 0.001$) if compared with placebo². Total output was 53% lower than placebo. Mean duration of diarrhea in children treated with racecadotril, either with positive either with negative rotavirus tests, was 52-72 h. Furthermore the drug allowed a 1/3 reduction of rehydration solution (439 ml vs 658 ml in the first day e 414 ml vs 640 ml in the second day).

Similar results were reported by other authors. Moreover a urinary Na/K < 1 was observed in 1/5 in racecadotril treated, compared in 1/2 of control, suggesting a better hydration in the former group³.

Recommended dosages in published studies are 1.5 mg/Kg every 8 hours for 5 days for a maximum of 7 days. The drug is not utilized for bloody diarrhea or antibiotic-induced diarrhea.

Side effects frequency is similar to the placebo group (vomiting 5.2% and fever 2.2%). Headache, hypokalemia, paralytic ileus, skin rashes and bronchoconstriction have been reported only very rarely.

Finally, experimental studies have demonstrated that racecadotril does not promote bacterial growth in the gut and does not pass in the CNS after oral administration. Thus the drug is not associated with neurotoxic effects.

References

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