ESSENTIAL MEDICINES LIST FOR CHILDREN

COMPOUND: RACECADOTRIL

Summary

Researcher Alan Lopez, PhD, and colleagues combed through thousands of data sources from all over the globe on 136 diseases and injuries in 2001.
Lopez works in Brisbane, Australia at the University of Queensland's School of Population Health. He and his colleagues published the results in *The Lancet.* Among their findings:
Slightly more than 56 million people died in 2001.
Those deaths included 10.6 million children, almost all of whom (99%) lived in low- and middle-income countries.
More than half of the children died from 5 preventable or treatable conditions:

- Respiratory infections
- Measles
- **Diarrhea**
- Malaria
- HIV/AIDS

The mortality rate for children under the age of 5 caused by acute diarrhea is estimated by WHO at 1.8 Million deaths annually.

To limit and to offset the losses of water and electrolytes are key measures in the treatment of acute diarrhea for children, in particular for the most exposed population: children under the age of 3 years.
Accordingly, this confirms WHO recommendation to use Oral Rehydratation Salts (ORS) for these cases and no other specific drug.
However when this recommendation was written the new class of antisecretory agents could not be considered since it was written before the discovery of the first entry in this class: Racecadotril.

Nevertheless, Racecadotril is extremely well positioned in the guidelines of WHO: it is the only medicine which has a proven efficacy in reducing water and electrolyte losses measured by the only criteria recognized by WHO: the stool output.

This efficacy has been proven in two randomized double blind clinical trials: placebo + ORS vs. Racecadotril + ORS which have been published in the two following scientific magazines:

- **Gastroenterology** 2001; 120 :799-805 for following study: *Cézard JP, et al., efficacy and tolerability of Racecadotril in acute diarrhoea in children.*
- **New England Journal of Medicine** 2000; 343:463-7 for following study: *Salazar-Lindo E, et al., Racecadotril in the treatment of acute watery diarrhoea in children.*

Therefore the action of Racecadotril is supplementary to the rehydration and improves the compliance of the use of ORS.
It reduces also the need for future care with less intravenous rehydration and less secondary consultation (*Cojocaru, et al., Effect of Racecadotril in acute diarrhea in infants and children Arch Pediatr (Paris) 2002;8:774-9 (trial not sponsored by Bioprojet)*)
Racecadotril does not cause any complications such as the ones caused by other anti-diarrheal medications, as it does not slow the forward propulsion of intestinal contents and has no effect on the nervous system and no respiratory distress. Its excellent safety profile has been highlighted (i) during clinical trials whith side effects in line in frequency and in type with the ones of the placebo group (ii) in pharmacovigilance with an extremely low frequency of adverse events reported in infants and young children treated with 10mg Racecadotril (weight below 13 kg, then below 2 of age) : 1.68 AE's per million, i.e. one adverse event for 600,000 treatments (data from Periodic Safety Update Report 2006).
Racecadotril complies with WHO guidelines as highlighted various international groups which update WHO recommendations, in particular following groups :

- the French speaking group of Hepatology, Gastroenterology and Pediatric Nutrition : "***Racecadotril is the only drug which proved a significant reduction in stool output***" *(Cezard JP, et al., Treatment with medicines of infectious acute diarrhea in infants and children; Arch Pediatr (Paris) 2002;9 :620-8)*
- the Canadian Paediatric Society: "***Racecadotril, an antisecretory agent, is safe and efficient and can be routinely used in acute watery diarrhea in addition to ORS.***" *(Canadian Paediatric Society. Treatment of diarrheal disease; Position statement; Paediatr Child health 2003;8:455-8 and 463-66).*

Introduction

Dehydration is the dominant risk to cope with in the management of acute diarrhea in young children, and the treatment of this risk has been dramatically improved since the use of ORS's (WHO, Geneva, 1990: *A manual for the treatment of diarrhea – for use by physicians and other senior health workers –WHO document WHO/CDD/SER/80.2 Rev. 2, 1990*). The reduction of the stool output is the corner stone of the symptomatic treatment of acute diarrhea with children either to prevent or to correct the dehydration.
The therapeutic management as recommended by WHO has not changed from 1995 to 2003 and is built on prevention and treatment of dehydration, with no place for any anti-diarrheal medication as stated in following recommendation: " *these agents though commonly used, have no practical benefit and are never indicated for the treatment of acute diarrhea in children. Some of them are dangerous" (i) WHO, Geneva, 1995: Division of Diarrheal and Acute Respiratory Disease Control: The treatment of Diarrhea, A manual for physicians and other senior health workers WHO/CDR/95.3 10/95. (ii) WHO, Geneva, 2003: The Treatment of Diarrhea –A manual for physicians and other health workers: WHO/CAH/03.7)*

It can be noted that the WHO analysis does not update the section related to anti-diarrheal medications: the products listed include following classes :

- *Adsorbents (e;g; kaolin, attapulgite, smectite, activated charcoal, cholestyramine).*
- *Antimotility drugs (e.g. loperamide hydrochloride, diphenoxylate with atropine, opiates and derivatives),*
- *Bismuth subsalycilate.*
- *Combinations of drugs.*

The class of intestinal antisecretory agents is not listed, simply because this new class was not available and widely spread when these guidelines were written by WHO.

The need to have a medicine which could prevent from intestinal hypersecretion without slowing down the bowel movement is an old need. Accordingly, the perfect profile of such an antidiarrheal medicine was defined some 20 years ago (*Edelman R, Prevention and treatment of infectious diarrhea. Am J Med 1985;78:99-106*) as a product which could rapidly inhibit the intestinal hypersecretion without causing constipation and without any central effect. This perfect profile was again confirmed in the 90's :

"*The perfect antidiarrheal drug should have a safe use thanks to a focused action purely on water and electrolytes movements, without any impact on the digestive motility*" (*Du Pont C, Benhamou PH. Treatment of acute diarrhea in children. In: Rambaud JC, Rampal P editors. Infectious acute diarrheas, Doin, Paris 1993: 157-169.*).

But this was only a wishful product until late 2000 when the first, and only one to date, product of this class has been launched in France with a paediatric presentation (in sachets). Furthermore it has been lauched outside France only since 2004 (except for Spain in 2002)
Racecadotril is now approved and launched in 7 European countries as well as in Latin America. In Asia the first registrations have just been obtained in the Philippines, Indonesia, Thailand and Vietnam and are still pending in most of the other asian countries. It is approved in Tunisia and Morocco, still pending in Algeria, Egypt and Lybia. The files for registrations should be submitted shortly in the rest of Africa.
The product has started to be more commonly available clearly **after the writing of WHO guidelines in 2003**. (*The Treatment of Diarrhea –A manual for physicians and other health workers: WHO/CAH/03.7)*.

The compliance of the benefit / risk ratio of the use of Racecadotril, taken together with an ORS in young children on one hand with the recommendations of the WHO on the other hand has been clearly highlighted by **Pr. Cezard** in the conclusion of his expert report *(Cezard JP. Tiorfan® - Paediatric form clinical documentation (Part IV); Expert report*) with following summary :

- **Efficacy**: "*For children between 6 months to 4 years of age, clinical studies have demonstrated a highly significant antidiarrheal effect on a measurable criteria: the stool output for the first 48 hours. It has a fast onset of action: the effect is very significantly proven during the first 24 hours. The other criteria for assessment such as:*
  - *dehydration index after 24 hours,*
  - *duration of treatment,*
  - *duration of diarrhea,*

  were significantly different from placebo".
- **Tolerability**: "*in children below 2 years, who have no access to any authorized antisecretory treatment, the frequency and nature of adverse reactions are in line with the ones with placebo. In particular no effect on central Nervous System has been noticed in children below 2 years who have a blood – brain barrier still immature and therefore permeable. This confirms the lack of neurotoxicity demonstrated during pre-clinical tests in the piglet, which also has*

a blood-brain barrier still immature after receiving a high dose of Racecadotril (60 times the therapeutic dose) ".

Pr. Cezard concludes with following statement : "*Therefore the paediatric Racecadotril, a pure antisecretory agent, brings a therapeutical benefit. It represents an improvement in the medical service to the treatment of acute diarrhea for young children, in particular in reducing the faeces losses, (hence water losses) and in reducing accordingly the dehydration risks, always a crtitical risk, even in developed countries.* ***Furthermore, the Racecadotril meets the criteria set by WHO in 1990 to define the* efficacy of a drug that can be prescribed for acute diarrhea in children together with the rehydration salts: reduction of the duration of diarrhea and of the stool output with a proven lack of secondary effects.**"

Prescribing the Racecadotril together with the ORS is compliant with WHO guidelines as explained by Pr. Martinot (*Martinot A. Treatment of acute diarrhea in infants : practices still not in line with guidelines. Arch Pediatr (Paris) 2004;11: 895-97*) for the following two reasons:

- (i) it reduces the dehydration risk: "*the only medicines recommended by WHO and considered as "antidiarrheal medicines" are the ones reducing the stool output by at least 30% compared to placebo and therefore reducing the dehydration risks. This is the case with Racecadotril, an antisecretory drug without any impact on the motility and which cuts by half the stool output.* "
- (ii) One obstacle for a wider use of ORS is the following : ORS does not bring any **visible** effect in the diarrhea evolution. When the efficacy of Racecadotril can help to improve the observance of the use of ORS thanks to a "***prescription in association with* an antisecretory drug**" as proposed by Pr. Martinot (*Martinot A. Treatment of acute diarrhea in infants : practices still not in line with guidelines. Arch Pediatr (Paris) 2004;11: 895-97*).

Then Racecadotril prescription intensifies the use of ORS. This synergy has always been promoted by Bioprojet Pharma which also directly markets an ORS (**Fanolyte®**) in France and in Tunisia, compliant with WHO requirements.

Finally, what is the actual benefit of the association –ORS with Racecadotril-?

Pr. Martinot and his team have just issued an article on the therapeutic management of infants'gastroenteritis: in the section "how to assess the therapeutic strategies'usefulness?", following observation is made : "*it is important to assess to what extent this reduction in stool output thanks to the use of racecadotril practically helps in reducing the need for intraveneous rehydrations, the hospitalization rates or their respective durations, the secondary medical consultations*" (*Martinot A, Aurel M, Pruvost J, Hue V, Dubos F. Can the clinical epidemiology in emergency departments improve the therapeutic management in the infants' gostroenteritis cases? Arch Pediatr 2006;13: 553-*

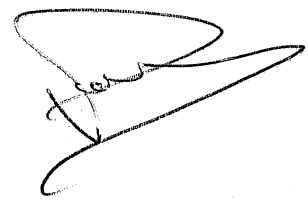
9). The Cojocaru *et al.* independent study brought relevant answers to this need (*Cojocaru B, Bocquet N, Timsit S, Wille C, Boursiquot C, Marcombes F, Garel D, Sannier N, Cheron G. Impact of Racecadotril in the need for care in the treatment of acute diarrhea in infants and children. Arch Pediatr (Paris) 20002;8:774-9*)

This supports the most recent recommendations issued by various international Groups and Societies such as the ones listed in the Summary :

- from the French speaking group of Hepatology, Gastroenterology and Paediatric Nutrition,
- and from the Canadian Paediatric Society,

but also from the following entities:

- the "Center of Disease Control (*Centers for Disease Control and Prevention. Managing acute diarrhea among children : oral rehydration maintenance and nutritional therapy. MMWR 2003;52 (N°: RR16)*),
- the Italian Society of Paediatric Hepatology and Gastroenterology (*Guarino A, Albano F. Guidelines for the approach to outpatient children with acute diarrhea. Acta Paediatr 2001;90:1087-95*),
- An international working group (India, Holland, United kingdom, USA, Thailand) who issued recommendations on the management of diarrhea in the adult segment which have been extended to the paediatric field "the Racecadotril is described as an efficient intestinal antisecretory agent for the treatment of acute diarrhea in adults and children" (*Mantsathit S, DuPont HL, Farthing M, Kostchaiwat C, Leelakusolvong S, Ramakrishna BS, Sabra A, Speelman P, Surangsrirat S. Guideline for the management of acute diarrhea in adults. J Gastroenterology Hepatol 2002;17:S54-S71*).



BIOPROJET PHARMA

By : Dr. Philippe BAUMER

Title: Medical Advisor

Date: April 23, 2007