European **Rev**iew for **Med**ical and **Pharmacol**ogical **Sci**ences 1998; 3-4: 131-136

Comparison of two non-absorbable antibiotics for treatment of bacterial enteritis in children

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Abstract. – **Thirty-one children with bacterial diarrhoea were administered an oral suspension of rifaximin (14 children, mean age: 4.3 yrs; dosage: 5 ml, equal to 100 mg, x 4/day for 3 days on average) or of neomycin+bacitracin (17 children, mean age: 3.6 yrs; dosage: 5 ml x 4/day for 4 days on average). Etiologic agents were: minor Salmonella spp in 9 and 7 cases respectively; enteropathogenic E. coli in 5 and 10 cases. Rifaximin yielded bacteriological cure in 12/14 children; the reference drug in 13/17. With both antibiotics, stool number/day fell, after one day, from 6 on average, to normality (2-3 stools); within two days stool consistency and characteristics shifted to normal.**

Symptomatology was quickly eliminated in all of the cured children. Both treatments showed excellent systemic tolerability; rifaximin was completely tolerated also locally, while two cases of stomach ache were reported with the reference drug.

Key-Words:

Bacterial diarrhoea, Paediatrics, Antibiotic treatment, Intestinal antibiotic, Rifaximin.

Introduction

The problem of identifying a proper antimicrobial treatment for paediatric diarrhoea has received increasing attention during years, although it is acknowledged that drug administration may in several cases be not necessary, since this condition is self-limiting. A successful outcome can be in most cases obtained through correction of fluid loss and electrolyte imbalance by oral or parenteral rehydration[1]. Bacteria, viruses and protozoan parasites are commonly involved as causative agents of diarrhoeal episodes. Only when infection and the consequent clinical picture are really severe, anyway, an adequate pharmacological treatment is felt as necessary, mainly in order to prevent the spread of infection by decreasing faecal shedding of organisms[2]. This is true also in the case of the so-called "homeing diarrhoea"[3], that affects children of emigrants in the return journey from their country of origin: the positive outcome of the acute bacterial enteritis that usually develops is nearly always obtained with an antibacterial treatment.

An effective therapy is not yet available for diarrhoea due to enteric viruses. Very good and quick results can be obtained, on the other hand, in severe amebiasis, giardiasis, and when bacterial strains are involved (mainly Salmonella and Shigella spp, Campylobacter jejunii, Yersinia enterocolitica, E. coli).

Choosing the right antibacterial drug is very important, since the administered molecule may (if absorbed into the general circulation) produce toxic phenomena or select resistant strains, so invalidating both the present and any future antidiarrhoeal treatment with the same active substance. In paediatric patients with bacterial diarrhoea (but this rationale is correct for adults as well)[4,5], treatment should be by means of a wide-spectrum bactericidal agent capable of reaching high concentrations within the intestine – where the intact molecule should exert its activity –, and at the same time characterised by negligible intestinal absorption as well as by very low potential of inducing resistant strains. An answer to this demand seemed to be provided, in the past, by aminoglycoside antibiotics[6], as well as by other molecules, such as fluoroquinolones[7] or polypeptide antibiotics[8]. All these substances show, nonetheless, a cer-

tain rate of absorption after oral administration and therefore could induce systemic toxicity[6-8]. A non-absorbable antibiotic really devoid of this risk, since pharmacokinetic studies clearly demonstrated the lack of intestinal absorption[9,10], is rifaximin* (INN), a rifamycin derivative exclusively indicated for the oral treatment of infections located in the gastrointestinal tract[11,12]. Rifaximin has – like the other rifamycin antibiotics – a wide spectrum of bactericidal activity, that includes Gram-positive and Gram-negative, aerobic and anaerobic strains[12-14]. Another requirement for the ideal antibiotic treatment of bacterial diarrhoea is met by rifaximin: a very low rate – furthermore, reversible after treatment suspension – of resistant strains induction[15,16], attributable again to the lack of intestinal absorption and to the absence of other therapeutic uses besides the treatment of infections involving the alimentary tract[9]. Rifaximin in fact is exclusively indicated for the treatment of bacterial diarrhoea in children and adults[17-21], of hepatic encephalopathy[22-28], of bacterial overgrowth and diverticular disease of the colon[29-34], and for the prophylaxis of septic complications after large bowel surgery[35-37]. It is also worth mentioning the constant report of good local and systemic tolerability of rifaximin, for which a picture of complete safety – particularly important in paediatric treatment – emerged during the years of drug use.

We decided to investigate, in children with severe episodes of bacterial diarrhoea, the antidiarrhoeal efficacy of rifaximin, in comparison with that of another widely used intestinal antibiotic, containing neomycin (aminoglycoside antibiotic) plus bacitracin (polypeptide antibiotic).

Materials and Methods

During a one-year period (May 1995-July 1996) 31 children followed as out-patients, who were suffering from severe episodes of bacterial enteritis, subsequently confirmed by a pre-treatment stool culture, were administered either rifaximin or the association neomycin+bacitracin, both given as oral suspension (one spoonful every 6 hours; one 5 ml spoonful of rifaximin contained 100 mg of the active drug). Children of both sexes were included, aged 2 to 5 years; they presented with severe symptoms of bacterial enteritis (fever, abdominal cramps a/o pain, nausea, tenesmus), furthermore had passed in the previous 24 hours more than 3 unformed stools containing mucus or blood. Were on the contrary not included patients with persistent vomiting, those who had been administered symptomatic antidiarrhoeal drugs in the previous 24 hours, who were simultaneously under antibiotic treatment for other concomitant diseases, or who were suffering from severe systemic diseases, including the tumoral ones and the HIV infection.

Consecutive patients judged eligible were alternatively attributed to treatment with rifaximin or with the control drug, the maximum allowed treatment length being in all cases of 5 days. Stools were defined as unformed if watery (i.e. could be poured) or soft (i.e. acquired the shape of the container), while were considered formed (that is, normal) when maintained their own shape. If a viral or parasitical aetiology emerged from the pre-treatment stool culture, the patient was withdrawn from the study.

In each day of treatment, the following parameters were monitored: number and form (formed=0; mixed, that is soft+watery, =1; soft=2; watery=3) of stools passed; presence and intensity (absent=0; moderate=1; intense=2) of mucus or blood in stools; type and intensity (absent=0, mild=1; moderate=2; severe=3) of symptoms. A second stool culture was performed three days after the treatment's end to monitor the antibacterial efficacy of the administered drugs; when a Salmonella strain was involved, stool culture was repeated 30 days after the treatment's end and this was to be considered as the end-of-treatment microbiological assessment. At the end of the study, an overall evaluation of efficacy was expressed by the physician for each patient, according to the following scale: *no cure* (persistence of the bacterial strain, of symptoms and of pathological characteristics of stools); *sufficient outcome* (elimination of the bacterial strain, stools still unformed but reduced in number, symptoms slightly re-

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duced in number a/o intensity); *good outcome* (no bacterial strain, normal stools but persistence of some symptoms; or: no bacterial strain, more than 3 stools per day, but formed, clear-cut reduction of symptoms); *complete cure* (no bacterial strain, normal number and form of stools, no symptoms).

Also the tolerability of both treatments was monitored in this study: before and after the administration period a blood and urine sample was collected to perform the routine laboratory tests of systemic tolerability (*Red Cell Count, White Cell* and differential *Count*, hemoglobin, hematocrit, total protein and electrophoretic fractions, azotemia, glycaemia, total bilirubin, aspartate aminotransferase, alanine aminotransferase, blood creatinine, alkaline phosphatase, and complete urinalysis). The gastroenteric tolerability of the two antibiotic suspensions was checked daily, as well as the manifestation of adverse events of any kind.

The results of this investigation were analysed statistically by means of the paired and unpaired Student t test for between groups and within group comparisons of parametric data. To analyse semi-quantitative or qualitative data, the Chi Square test and the Wilcoxon's rank sum and signed-rank tests were applied. The p value of 0.05 was taken as lower limit of statistical significance.

Results

We had originally enrolled 40 patients, 20 in each group, all suspected of a bacterial aetiology of their diarrhoea. Anyway, 9 of these patients turned out to carry a viral agent and were withdrawn from the study. Fourteen out of the remaining 31 cases received 400 mg/day of rifaximin, while 17 were treated with the association neomycin+bacitracin; the two groups were initially comparable as to age, sex, and characteristics of the infectious episode (Table I). Minor Salmonella spp and E. coli strains were detected in the start-of-treatment stool cultures. Treatment lasted on average for 3 days with rifaximin and for 4 with the association (p= ns); clinical results were similar, but slightly better microbiological outcomes was evidenced for rifaximin (Table II). Only two children were administered rifaximin for 5 days (they were found to maintain the pathogenic E. coli strain in stools after treatment), while treatment had the same length in 7 patients of the control

Table I. Baseline characteristics of the two treatment groups.

	Rifaximin Group	***Control Group***
No. of pts (M/F)	14 (5/9)	17 (7/10)
Age (yrs): mean ± SD range	3.4 ± 1.2 (3-5)	3.6 ± 1.0 (2-5)
Stool no./24 hrs: mean ± SD; (range)	5.5 ± 2.0; (4-8)	6.0 ± 1.0; (5-7)
Stool form:		
watery	10	11
soft	2	2
mixed	2	4
Stool containing:		
mucus	11	16
blood	7	5
Clinical symptoms:		
fever	14	15
abdominal cramps	13	10
abdominal pain	13	16
tenesmus	9	11
nausea	12	13

Table II. Results of the two antidiarrhoeal treatments.

	Rifaximin Group	***Control Group***
Drug posology mean (± SD) length; (range)	5 ml × 4 /day (400 mg/day) 3 ± 0.5 days (3-5)	5 ml × 4/day 4 ± 1.0 days (3-5)
Pre-treatment stool culture	Salmonella spp.: 9 cases Enteropath. E. coli: 5 cases	Salmonella spp.: 7 cases Enteropath. E. coli: 10 cases
Post-treatment stool culture	Enteropath. E. coli: 1 case	Salmonella spp.: 3 cases Enteropath. E. coli: 1 case
End-of-treatment symptoms	Nausea: 2 cases Abdominal pain: 1 case	Abdominal cramps: 1 case Tenesmus: 2 cases
End-of-treatment stool no. (mean ± SD) (range) *Stool form:* formed mixed with blood/mucus	 2 ± 1 (1-3) 12 - 1/1	 2 ± 2 (1-4) 9 4 2/1
Treatment outcome	Complete cure: 11 cases Sufficient outcome: 1 case No cure: 2 cases	Complete cure: 9 cases Good outcome: 2 cases Sufficient outcome: 2 cases No cure: 4 cases
Drug intolerance	None	Stomach ache: 2 cases

group (4 children not cured, plus 2 with sufficient outcome and 1 with a Salmonella strain in the end eliminated).

Both treatments quickly produced a clear-cut relief of symptoms, with statistically significant fall of fever and reduction in scores, with respect to baseline, already on treatment day 1 (for the various symptoms, $p<0.05$ to $p<0.01$ with the signed-rank Wilcoxon test), while the comparisons between groups (rank sum Wilcoxon test) were always not statistically significant.

The involved pathogens were eliminated in all but two cases treated with rifaximin and in 13/17 treated with neomycin+bacitracin. It is worth noting that the Salmonella strains detected in our survey (in 9 and 7 cases respectively) were no more detected, after rifaximin, in the stool culture performed one month after the end of treatment, while still persisted in stools of 3 patients treated with the reference drug. The frequency of enteropathogenic E. coli response to therapy was on the other hand greater with the antibiotic association (Table II).

The daily number of stools was significantly reduced already after one day of treatment both by rifaximin (from a mean of 5.5 to 2.5; $p<0.01$) and by the control drug (from 6.0 to 4.5; $p<0.05$), with rapid manifestation of a trend towards normalisation of characteristics and form. Formed stools were detected in the major part of patients on the second treatment day, with the exclusion of the 6 children with no microbiological cure, who passed still mixed (watery+soft) stools, in some instances with blood or mucus. Two cases treated with rifaximin and 4 treated with the control drug were not cured: to these, three further cases must be added (1 in the rifaximin and 2 in the control group) who evidenced only a sufficient outcome. The rate of positive responses was therefore 78.6% in rifaximin-treated patients and 64.7% in the children of the control group ($p=$ ns with the Chi Square test).

The local and systemic tolerability of rifaximin was extremely good: no intolerance phenomena were detected and also the final results of laboratory tests were superimposable with those registered at the start of treatment. The

association neomycin+bacitracin evidenced good systemic tolerability too, with no influence on the monitored laboratory parameters, while locally in two cases stomach ache was reported at the end of a five-day treatment period.

Discussion

A short treatment course (3 days on average) with rifaximin yielded, in our experience, highly satisfactory results in children suffering from severe episodes of bacterial diarrhoea. The antibiotic showed furthermore completely safe, so confirming the efficacy and tolerability data already reported in the literature.

Also the long-used and routinely applied treatment with neomycin and bacitracin was effective (after 4 days on average) and well tolerated at the systemic level, though locally some intolerance manifestations were reported. Even if in our study systemic tolerability was always good, when considering this parameter for the two drugs, the absorption rate of 2-3%, detected after the oral administration of the association neomycin+bacitracin, must be anyway taken into account, since this behaviour could produce systemic manifestations of intolerance.

Based on the world-wide accepted safety requirements of drug therapy, that are so important above all when dealing with paediatric patients, we deem that rifaximin may be put among the drugs of choice for a quick and safe treatment of acute bacterial diarrhoea in children.

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