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Preventive Veterinary Medicine 25 (1996) 357–361

PREVENTIVE VETERINARY MEDICINE

Prophylaxis using paromomycin of natural cryptosporidial infection in neonatal kids

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Accepted 24 May 1995

Abstract

The chemoprophylactic effects of paromomycin sulfate against natural cryptosporidiosis in young kids were investigated. Two studies were carried out using two groups of 18 and 12 animals in two pens. In each pen, kids were allocated to treated or control groups. The treatment consisted of oral paromomycin given at 100 mg kg^{-1} body weight day^{-1} for 11 consecutive days from 2 days of age. All kids were weighed at 2, 6 and 10 days of age. Infection was monitored by collecting fecal samples and staining fecal smears every 3–4 days from days 4 or 5 to days 15 or 19. The results clearly showed the efficacy of paromomycin in reducing cryptosporidial oocyst output. Moreover, paromomycin prevented clinical signs and mortality.

Keywords: Goat; *Cryptosporidium parvum*; Chemoprophylaxis; Paromomycin

1. Introduction

Cryptosporidiosis due to *Cryptosporidium parvum* is an important disease of neonatal kids. Animals are mainly affected until their second or third week of life and clinical signs include acute diarrhea with dehydration between 5 and 15 days or progressive emaciation between 5 and 8 days (Angus, 1990). Morbidity may approach 100% and mortality ranges from 1 to 44% (Yvoré et al., 1984; Thamsborg et al., 1990). Besides *C. parvum*, several agents have been incriminated in neonatal-kid diarrhea including *Escherichia coli* K99, rotavirus, coronavirus and adenovirus (Gouet, 1984). Until now, more than 140 drugs have been tested for anticryptosporidial activity in man and animals and only five of them were effective in controlling the infection without causing important side effects: alborixin,

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SSDI 0167-5877(95)00511-0

azithromycin, halofuginone, maduramycin and paromomycin (Fayer, 1993). The most promising results were obtained with paromomycin in curing symptoms of cryptosporidiosis in AIDS patients (Fichtenbaum et al., 1993) and in preventing development of *C. parvum* in experimentally infected mice and calves (Fayer, 1993).

The objective of the present study was to test paromomycin for prophylaxis in naturally infected kids on a French dairy goat farm. This farm was chosen as mortality of kids reached 80% in a group of 60 animals between 8 and 15 days of age in November 1993. Examination of stained feces smears from ill kids revealed numerous *Cryptosporidium* oocysts.

2. Materials and methods

The goat farm, located in Deux-Sèvres (western France), comprised an Alpine herd of 100 milking does raised indoors using a zero-grazing system. The kids were immediately separated from their dams at birth and received two feedings during the first 12 h of life, each consisting of 150 ml of pooled goat colostrum. This was followed by milk replacer feed containing 50% skimmed milk powder distributed from a multiteat outlet container.

In February 1994, two groups of male kids were selected. In each group, the animals were reared in the same pen on deep litter straw bedding. The first group consisted of 18 kids; of these, nine had been born on 9 February and had been treated with paromomycin; the other nine, born 2 days later were untreated controls. The second group ($n=12$), born the same day 1 week later, was divided into treated ($n=7$) and control ($n=5$) kids using a random numbers generator. The treatment was conducted by the farmer with paromomycin sulfate (HUMAGEL enfants, Parke-Davis, France) at a total daily dose rate of 100 mg kg^{-1} body weight (BW) for 11 consecutive days beginning at 2 days of age (Fayer and Ellis, 1993). The powdered drug was dispensed into water and given orally with a syringe in two daily dosages. Feces samples were individually taken with rectal curettes every 3 or 4 days from days 4–5 to days 15–19. Demonstration of oocysts was made by staining fecal smears with Ziehl fuchsin and observing at $\times 100$ magnification under a phase-contrast microscope according to Heine (1982). Oocyst numbers were scored semi-quantitatively on a scale from 0 to 5: 0, no oocyst; 1, less than one oocyst per field; 2, 1–10 oocysts; 3, 11–20 oocysts; 4, 21–30 oocysts; 5, more than 30 oocysts. The presence or absence of diarrhea was recorded blind by the farmer's wife on a daily basis. Kids were weighed at the age of 2, 6 and 10 days with a stand-on scale ($+50$ g). Comparisons of the weights and mean daily weight gains between groups were made by one-tailed Mann–Whitney test at the 0.05 level of confidence on each set of kids.

3. Results

In the first group, all nine untreated kids showed persistent diarrhea from day 6 to day 13. Cryptosporidial oocyst output peaked at days 7 and 10, all animals having an oocyst score above 2 at some point (Table 1). Five kids died between day 10 and day 13. At day 17, three of the four remaining kids maintained a low oocyst excretion. In contrast, medicated kids showed only a transient diarrhea at days 4 and 5; four animals had a low oocyst output

Table 1
Comparison of cryptosporidial oocyst shedding in treated (paromomycin from day 2 to day 13 of age) and untreated kids; trial 1

Age (days)	Treated group kid number									Untreated group kid number								
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
3										0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0									
7										3	5	4	5	3	3	2	5	5
9	0	1	1	0	1	0	0	0	1									
10										2	†	†	2	3	5	5	2	4
12	0	1	1	0	1	0	0	0	0									
13										2			†	2	3	2	†	†
15	0	0	1	0	0	0	0	0	0									
17										0				1	1	1		
19	0	0	0	0	0	0	0	0	0									

†, mortality.
0, no oocysts; 5, over 30 oocysts per field.

(score 1) from day 9 to day 15 and the five other kids had an oocyst count of zero until day 19. By day 19, all treated animals were negative for cryptosporidial oocyst output and no mortality was recorded. Between day 2 and day 10 the mean daily body weight gain of control kids was impaired compared with medicated kids (30 g vs. 80 g) but the difference was not statistically significant.

In the second group, neither control nor medicated kids showed persistent diarrhea. The patterns of oocyst excretion and mortality in the control kids of the second trial were similar to those in the first group, with an output peak on day 7 and two mortalities on day 11 (Table 2). Only three out of seven medicated kids had oocyst excretion (score 1) and one died at the end of the survey (day 15). The growth of control kids was inferior to that of medicated kids throughout the study (mean daily body weight gain days 2–10, 100 g vs. 180 g), but the difference was not significant.

The eight kids that died during the two trials were necropsied. Except for the medicated kid from the second trial, all animals showed a distension of small and large intestines by

Table 2
Comparison of cryptosporidial oocyst shedding score in treated (paromomycin from day 2 to day 13 of age) and untreated kids; trial 2

Age (days)	Treated group kid number							Untreated group kid number				
	1	2	3	4	5	6	7	8	9	10	11	12
4	0	0	0	0	0	0	0	0	5	0	0	0
7	0	0	0	1	0	0	0	2	2	5	5	2
11	0	0	1	1	0	0	0	3	†	2	†	0
15	1	0	1	†	0	0	0	2		0		1

†, mortality.
0, no oocysts; 5, over 30 oocysts per field.

yellow pasty content. No other lesions were encountered. *Escherichia coli* strains were isolated from the small intestine but not from the liver and were not further identified.

4. Discussion

The experiments have shown that administration of paromomycin from day 2 to day 13 after birth can strongly reduce but not completely prevent the cryptosporidial oocyst output of naturally exposed kids. Moreover, in the first group of animals where control kids were severely affected, paromomycin prevented diarrhea and mortality. At the end of the studies, on days 15–19, oocyst excretions of medicated animals did not differ from those of the controls.

Our results are in agreement with those of Fayer and Ellis (1993) obtained in calves experimentally infected once with *C. parvum* oocysts and treated with paromomycin at 100 mg kg^{-1} BW for 11 consecutive days. At lower dosages (25 or 50 mg kg^{-1} BW), calves began shedding oocysts 7 days after the start of treatment but the severity of the diarrhea was less than in control animals (Fayer and Ellis, 1993).

Paromomycin is an orally administered aminoglycoside antibiotic that is produced from *Streptomyces*. The paucity of adverse effects in man (Clezy et al., 1991) and the very high LD_{50} in mice (15 000 mg kg^{-1} orally) may be attributable to the lack of systemic absorption. Our results seemed to indicate, at least in the few treated animals of this study, that paromomycin is well tolerated. In addition, the poor absorption may lead to a very limited distribution of paromomycin residues in kid organs and thus to a very short meat withdrawal time. This aspect is of concern in France where dairy-goat farmers produce commercial kids which are slaughtered at a very early age (28 days). One of the most limiting factor in using paromomycin, besides the work constraint, could be the cost as this drug is not available for veterinary use in France. The administration of human medicine packaged paromomycin to a kid for 11 days is very expensive (35 French Francs) and represents 15–40% of the kid gross margin. However, in the case of replacement female kids, this high cost is of less concern.

Halofuginone lactate reduces clinical signs and oocyst output in ruminants (Naciri and Yvoré, 1989; Villacorta et al., 1991). Recent studies conducted in calves at 60–120 μg kg^{-1} for 7 days in experimental conditions (Naciri et al., 1993) should be duplicated in kids in field conditions and compared with the paromomycin prophylaxis schedule in order to define the most effective and convenient way to control cryptosporidiosis in goats.

Although cryptosporidial infection is probably present in adult goats at a very low level as was demonstrated in adult cattle and sheep (Lorenzo Lorenzo et al., 1993; Xiao et al., 1994), the chemical control of cryptosporidial oocyst output in neonates should result in a reduction of environmental contamination and thus the potential transmission of infection to humans (Smith, 1993).

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