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Enzootic Rabbit Enterocolitis (ERE) [2,3]. A powder for oral use to be mixed with drinking water (BACIVET-S®) has been developed and successfully tested in a number of clinical cases. The aim of this study was to determine the optimum therapeutic dose based on a pharmacokinetic/pharmacodynamic (PK/PD) approach before dose confirmation in clinical trials.

MATERIALS AND METHODS

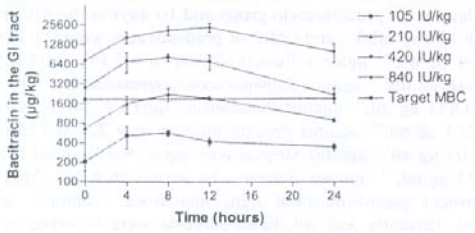
Minimum inhibitory concentrations for bacitracin were determined under anaerobic conditions and in accordance with CLSI guidelines against 85 clinical strains of *C.perfringens* isolated from rabbits with ERE in France and Belgium. Investigations concerning the bactericidal properties of bacitracin were also carried out *in vitro* using incremental antibiotic concentrations (MIC x0.5 to x8). Pharmacokinetic data included a description of free bacitracin concentrations in the gut lumen (caecum) of rabbits treated with increasing doses of bacitracin orally (BACIVET-S® 105, 210, 420 or 840 IU kg^{-1} day^{-1} for 7 days) via the drinking water. Bacitracin was extracted from the gastrointestinal tract with methanol/water/acetic acid (90/9/1); the supernatant was centrifuged then diluted with water and acidified before analysis by HPLC with MS/MS detection (positive mode) after ionisation using an Electro-Spray Interface (ESI). The studies were performed in accordance with OECD principles of Good Laboratory Practice.

RESULTS

All the strains were susceptible to bacitracin giving MIC of 0.5–2.0 µg mL^{-1} with only minor differences between the two study regions. The MIC_{90} was 0.93 µg mL^{-1}. A concentration approaching twice MIC was required to reach bactericidal levels (i.e. reduction by 10^3 of the initial inoculum size). This effect was not enhanced by increasing the concentration whereas the duration of the effect appeared to be prolonged at the highest concentration tested. This revealed a typical time-dependent bactericidal profile for each tested strain. The target MBC was thus twice 0.93, i.e. 1.86 µg mL^{-1}, i.e. bacitracin 1.860 µg kg^{-1} caecal content). Pharmacokinetic data obtained after 7 days are shown below. These results show that 105 IU kg^{-1} did not expose the caecum to inhibitory concentration and 210 IU kg^{-1} failed to maintain bactericidal levels for more than a few hours. The dose of 420 IU mg^{-1} maintained bactericidal concentrations (free bacitracin) for the entire 24-h period with 2102 µg kg^{-1} as the lowest mean concentration measured during the considered period, a value close to the target MBC of 1860 µg mL^{-1} estimated for bacitracin *in vitro*. Concentrations obtained at 840 IU kg^{-1} were far above these levels.

DISCUSSION

Bacitracin was shown to be a time-dependent (concentration-independent) bactericidal drug, i.e. (i) increasing the concentration does not increase the level of bacterial killing, (ii) short post-antibiotic effects, (iii) bacteriological cure depends primarily on time for which the free drug concentration at the site of infection exceeds the MBC (T>MBC), (iv) T>MBC should be maintained for at least half and possibly all the treatment duration. These results justify the daily dose of 420 IU kg day^{-1} in the treatment of *C. perfringens* infections such as those encountered in rabbit ERE. Confirmation of this dose and duration of treatment were further derived on a clinical basis, leading to an approved therapeutic regimen for BACIVET-S® of 420 IU kg^{-1} body weight per day for a minimum of 14 consecutive days.



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Antimicrobial susceptibility testing of *Mannheimia haemolytica* and *Pasteurella multocida* isolated from dairy calves with pneumonia

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INTRODUCTION

Mannheimia haemolytica and *Pasteurella multocida* are frequently isolated from the purulent bronchopneumonic lung associated with dairy calf pneumonia (DCP). Antimicrobial therapy is the most effective method for the prevention and treatment of DCP. Various antimicrobial agents are licensed and used to treat DCP, including aminopenicillins, cephalosporins, aminoglycosides, tetracyclines, macrolides, lincosamides alone or in combination with spectinomycin, potentiated- sulfonamides, fluoroquinolones, and florfenicol. However, previous studies have indicated that resistance to these compounds is frequently encountered. As the pattern of bacterial resistance is constantly changing, monitoring of antimicrobial susceptibility is important. It provides information on the pathogenic bacteria isolated from DCP, and assists in choosing the most appropriate antimicrobial therapy. The purpose of the study described here was to determine the antimicrobial susceptibility patterns of *Mannheimia haemolytica* and *Pasteurella multocida* recovered from dairy calves with pneumonia to antimicrobial agents commonly used to treat DCP.

MATERIALS AND METHODS

One hundred and thirty Holstein calves from 2 weeks up to 6-months old in dairy farms of Mashhad suburb with dairy calf pneumonia were enrolled in the study between September 1, 2002 and August 31, 2003. Samples for microbiological evaluation were obtained from the upper respiratory tracts of calves using nasopharyngeal swabs. Nasopharyngeal swabs were plated onto blood agar and MacConkey agar. Blood agar plates were incubated for 48 h at 37°C in 5% CO_2, and the

MacConkey plates were incubated for 48h at 37°C in air. Bacteria were identified by standard laboratory procedures. All isolates identified as *M. haemolytica* and *P. multocida* were subcultured onto Mueller-Hinton agar with antimicrobial sensitivity discs to determine sensitivity patterns to commonly used antimicrobials. These antimicrobials were: florfenicol (30 μg), chloramphenicol (30 μg), oxytetracycline (30 μg), amoxicillin (25 μg), gentamicin (10 μg), cephalothin (30 μg), lincomycin (2 μg), Enrofloxacin (5 μg), trimethoprim- sulphamethoxazol (25 μg) and penicillin (10 IU).

RESULTS

The most common micro- organisms isolated were *P. multocida* (80 (61.54%)), M. haemolytica (41 (31.54%)), *Bacillus* spp (15 (11.54%)), *Staphylococcus* spp (three (2.31%)), *Streptococcus* spp (4 (3.08%)), *Pseudomonas* spp (three (2.31%)), *Proteus* spp (three (2.31%)) and *E. coli* (five (3.84%)). Antimicrobial susceptibility testing was performed on all *Mannheimia haemolytica* and *Pasteurella multocida* employing the disk diffusion method (Kirby-Bauer). Each strain was tested with 10 antimicrobial agents. Of the *M. haemolytica* isolated, seven (17.07%), six (14.63%), four (9. 76%) and one (2.44%) were resistant to lincomycin, gentamicin, oxytetracycline and chloramphenicol, respectively. Resistance to penicillin, lincomycin, amoxicillin, gentamicin and oxytetracycline was observed in ten (12.50%), six (7.50%), six (7.50%), five (6.25%) and five (6.25%) of *P. multocida* isolates, respectively. All *M.a haemolytica* and *P. multocida* tested were found susceptible to florfenicol and cephalothin.

DISCUSSION

The results show the need for local veterinarians and producers to be more responsible in the use of antibiotics in the treatment of pneumonia in calves, and a growing danger of the dissemination of strains of *M. haemolytica* or *P. multocida* resistant to most antimicrobials could complicate, in the future, the treatment of calf pneumonia.

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Treatment of canine cystitis and prostatitis with pradofloxacin: clinical and microbiological results

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INTRODUCTION

The novel 8–cyanofluoroquinolone pradofloxacin is currently developed for the treatment of bacterial infections in dogs and cats. Pradofloxacin shows enhanced activity against Gram-positive and anaerobic bacteria while retaining broad-spectrum activity against Gram-negative bacteria [1,2]. Clinical efficacy, antibacterial efficacy and safety of pradofloxacin in the treatment of canine cystitis and prostatitis were assessed in a blinded, randomised multi-centre field study according to VICH GCP.

MATERIALS AND METHODS

One hundred and sixty-two dogs with clinical signs of urinary tract infections (UTI) were included in the study, eighty-five of which were treated with pradofloxacin (Veraflox™) and 77 with the control product amoxicillin/clavulanic acid (A/C). In the pradofloxacin group, sixty-five dogs presented with cystitis and 20 with prostatitis. Of the control animals, 58 had cystitis, 17 prostatitis and two upper UTI. Flavoured pradofloxacin tablets were administered at a dose of 3 mg kg^{-1} body weight once daily. The control group was treated with A/C tablets at a dose of 12.5 mg kg^{-1} body weight (10 mg amoxicillin, 2.5 mg clavulanic acid) twice daily. Treatment duration was 7–21 consecutive days in both groups. Clinical cure, bacteriological cure and the reduction of the total clinical score (TCS) were determined seven days after the end of treatment. Clinical and bacteriological cure were compared between the two treatment groups using the Chi-square test. The reduction of the TCS was analysed by two-way ANOVA for repeated measures. The statistical analyses were based on the total number of included UTI cases per group. MIC of pradofloxacin against bacteria isolated from urine samples were determined by agar dilution according to CLSI methodology. MIC_{50}, MIC_{90} and geometric mean MIC (GMIC) were calculated.

RESULTS

The clinical cure rate was 89.3% for pradofloxacin and 83.9% for A/C. A significant difference was not detected between the two groups for this parameter. The bacteriological cure rate was 85.3% in the pradofloxacin treated group and significantly higher ($P = 0.002$) compared to the bacteriological cure rate of 48% observed in the control group. The TCS was highly significantly reduced ($P < 0.0001$) in both treatment groups at the end of the study, by 96.8% in the pradofloxacin and by 93.4% in the A/C group. The difference in reduction of TCS between the treatments was not statistically significant. The clinical cure rate in cases of cystitis was 93.8% in the pradofloxacin and 91.4% in the A/C group. The bacteriological cure rate in such cases was 88.5% in dogs treated with pradofloxacin and 52.4% in the control group. For cases of prostatitis, the clinical and bacteriological cure rates were 80% and 75% in the pradofloxacin group, whereas in the A/C treated animals they were 76.5% and 50%. Mean time to cure was 9 days in the pradofloxacin group and 10 days in the A/C group. The MIC_{50}, MIC_{90} and GMIC of pradofloxacin were 0.03/0.06/0.04 μg mL^{-1} against *Escherichia coli* ($n = 139$), 0.03/0.125/0.046 μg mL^{-1} against *Staphylococcus intermedius* ($n = 28$), 0.5/1/0.631 μg mL^{-1} against *Pseudomonas* spp ($n = 24$), 0.25/0.25/0.213 μg mL^{-1} against *Proteus mirabilis* ($n = 22$), 0.125/0.25/0.101 μg ml^{-1} against *Streptococcus* spp ($n = 13$) and 0.25/0.5/0.33 μg mL^{-1} against *Enterococcus faecalis* ($n = 10$). Mild and transient gastro-intestinal signs (diarrhoea, vomiting, salivation), tiredness and polydipsia/polyuria were observed at low frequencies in both treatment groups.

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