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CLINICAL EFFICACY OF DANOFLOXACIN 18% IN THE TREATMENT OF NATURALLY OCCURRING INFECTIOUS DISEASES IN CATTLE

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ABSTRACT

A study was conducted in Brazil to evaluate the efficacy of danofloxacin 18% (Advocin 180™ - Pfizer Inc.), in the treatment of infectious diseases in cattle including respiratory disease, enteritis, metritis or omphalitis. The clinical cases were scored as: 0 – normal; 1 – mild; 2 – moderate; 3 – severe. Animals with scores of 0 or 3 were not included in the study. On Day 0, animals with scores 1 and 2 received a SC injection of danofloxacin 18% (6 mg / kg). On Day 2, the animals were clinically scored as above and the cured animals (score 0) were removed from the study. Non-responder animals (same score or higher than Day 0 score) received a second injection of danofloxacin 18%. On Day 4, the animals were re-examined and the study finished. Before treatment on Day 0, fecal samples and nasal, vaginal and navel swabs, as appropriate to the disease, were collected for bacterial isolation and bacterial sensitivity testing using "Sensidisc" containing 5 mcg of danofloxacin. A total of 1,019 cattle were treated from which, 966 (94.8%) responded to the treatment, and 857 (84.1%) were cured: 52.4% with a single dose and 31.7% with two doses. The cure rates in each clinical category were: Respiratory disease = 79.8%; enteritis = 92.6%; metritis = 76.5% and omphalitis = 88.0%. A total of 805 bacterial isolates were obtained, of which 70.4% were sensitive, 20.0% partially sensitive and, 9.6% were resistant to danofloxacin. Danofloxacin 18% was safe and very effective in the treatment of naturally occurring infectious diseases in cattle.

KEY WORDS: Danofloxacin 18%, Advocin 180™, cattle, infectious diseases, treatment, efficacy.

RESUMO

EFICÁCIA CLÍNICA DE DANOFLOXACIN 18% NO TRATAMENTO DE DOENÇAS INFECCIOSAS NATURAIS EM BOVINOS. Um estudo foi realizado no Brasil para avaliar a eficácia de danofloxacin 18% (Advocin 180® - Pfizer Inc.), no tratamento de doença respiratória, enterite, metrite e onfalite em bovinos. Os casos clínicos foram classificados conforme a severidade em escores: 0 – normal; 1 – leve; 2 – moderado; 3 – severo. Os animais com escore 0 ou 3 não foram incluídos no estudo. No dia 0, os animais com escores 1 ou 2 receberam uma injeção SC de danofloxacin 18% (6 mg / kg). No dia 2, os animais foram reexaminados e aqueles curados (escore 0), foram removidos do estudo. Os animais que não responderam ao tratamento (escore ≥ dia 0) receberam uma segunda injeção de danofloxacin 18%. No dia 4, os animais foram reexaminados e o estudo terminado. Antes do tratamento no dia 0, foram coletadas amostras de fezes ou de secreções nasais, vaginais ou umbilicais para isolamento bacteriano e testes de sensibilidade bacteriana usando-se "Sensidisc" contendo 5 mcg de danofloxacin. Foram tratados 1.019 bovinos, dos quais, 966 (94,8%) responderam ao tratamento e 857 (84,1%) chegaram a cura: 52,4% com dose única e 31,7% com duas doses. As taxas de cura por doença foram: doença respiratória = 79,8%; enterite = 92,6%; metrite = 76,5% e onfalite = 88,0%. Um total de 805 bactérias foram isoladas, das quais 70,4% eram sensíveis, 20,0% parcialmente sensíveis e 9,6% eram resistentes ao danofloxacin. Danofloxacin 18% foi seguro e altamente efetivo no tratamento de doenças infecciosas de ocorrência natural em bovinos.

PALAVRAS-CHAVE: Danofloxacin 18%, Advocin 180®, bovino, doença infecciosa, tratamento, eficácia.

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INTRODUCTION

The efficacy of danofloxacin formulated as a 2.5% injectable solution and administered subcutaneously at a dose rate of 1.25 mg / kg by daily injections for 3 or 5 consecutive days in the treatment of bacterial pneumonia or enteritis is well documented. This fluoroquinolone antibacterial has a broad spectrum of activity against many Gram negative, and Gram positive bacteria and mycoplasmas, of importance in Veterinary Medicine, as demonstrated by *in vitro* studies conducted some 10 years ago (McGuirk et al., 1989; Cooper et al., 1993). The efficacy of danofloxacin 2.5% in the treatment of respiratory disease or enteritis was confirmed by several authors under different field management conditions in confined, semi-confined or extensive grazing cattle (Muniz et al., 1990; Giles et al., 1991a; 1991b; Lang, 1993). A new formulation of danofloxacin at a concentration of 18% (Advocin 180™ – Pfizer Inc., NY, USA), was developed to allow the delivery of a high dose with bactericidal concentration-dependent activity (McKellar et al., 2000). Danofloxacin 18% was demonstrated to be effective in the treatment of bacterial pneumonia caused by *Pasteurella multocida*, *Mannheimia* (*Pasteurella) hemolytica* and *Haemophilus somnus* (Rowan et al., 2000), or bacterial enteritis (Sunderland et al., 2000) given as a single injection at a dose rate of 6 mg / kg of body weight, or two doses 48 hours apart, as needed. This formulation has the advantage of being safe and effective with a single dose or at maximum two doses, as handling animals many times for treatment is not practical. The concept of the high dosage in a single injection is that, after injection, the drug is available in high concentrations sufficient to kill all the sensitive bacteria during a relatively short period of time (McKellar et al., 2000). This reduces the selection pressure for resistance. In fact, the pharmacokinetic profile of danofloxacin 18% given as a single SC injection showed a peak concentration (C_{max}) in the plasma and lung or enteric tissues by 1 to 2 hours with a half life time of 4.21 hours in the plasma of ruminating cattle (Sarasola et al., 2000). After about 10 years of field use, the sensitivity profile of the various bacterial species tested remained essentially the same as previously shown by the *in vitro* minimum inhibitory concentration (MIC)assays for danofloxacin (Rowan et al., 2000; Sunderland et al., 2000; Lopes et al., 1999). The present study was designed to confirm the efficacy of danofloxacin 18% in the treatment of naturally acquired bacterial infections in cattle including respiratory disease, enteritis, metritis and omphalitis under field conditions in various regions of Brazil, and to assess the sensitivity of the bacterial isolates to danofloxacin.

MATERIAL AND METHODS

The field part of the study was conducted by 100 Veterinary Practitioners in various regions of Brazil, which treated about 10 cattle each using the same study design.

Animals, clinical cases and criteria for inclusion in the study.

A total of 1,019 beef and dairy cattle of various breeds, including both sexes and ages varying from 3 days to 120 months, participated in the study. The cattle were monitored daily for clinical signs of respiratory disease, enteritis, metritis and omphalitis.

The criteria for inclusion in the study were clinical scores of 1 and 2 (mild to moderate disease) according to the following scoring system: **a) Respiratory disease:** score 0 – Normal (Normal respiratory rate and character, and normal appetite / rumen full, bright, alert and responsive); 1 – Mild (Slightly increased respiratory rate and / or slightly abnormal character, reduced responsiveness, decreased appetite); 2 – Moderate (Moderately increased respiratory rate and / or abnormal character, depressed, may be reluctant to stand); 3 – Severe (Severely increased respiratory rate and markedly abnormal character, depressed, may exhibit open-mouth breathing, unable to stand without assistance). **b) Enteritis:** 0 – Normal (Normal calf feces, normal skin turgor, skin returns to normal position immediately after lifting (tenting), normal appetite, bright, alert, responsive); 1 – Mild (Loose or sloppy feces which retain their form, tenting of skin for about 5 seconds, decreased appetite, reduced responsiveness); 2 – Moderate (Loose to watery feces which do not retain their form, moderate persistence of skin tenting lasting 5 to 8 seconds), depressed, may be reluctant to stand); 3 – Severe (Profuse watery feces, marked persistence of skin tenting >8 seconds, unable to stand without assistance) c) **Metritis**: 0 – Normal (Normal post-partum uterine involution and vaginal secretion including lochia, symmetric horn development and normal ovarian activity); 1 – Mild (Uterus may be normally involuted to mildly distended with fluid abnormal vaginal discharge, odorless and minimal purulent secretions, symmetric horn development and normal ovarian activity); 2 – Moderate (Uterus may be mildly to moderately distended with fluid and / or gas, abnormal vaginal discharge characterized by odorless mucopurulent secretions, horns may be symmetric and ovarian activity may be affected as determined by palpation); 3 – Severe (Uterus markedly distended with fluid and / or gas,

markedly abnormal vaginal secretions characterized by fetid odors and presence of blood and / or abundant mucopurulent fluids, static ovarian activity, may or may not be associated with severe systemic infection); **d) Omphalitis**: 0 – Normal (Complete absence of swelling, normal tissue); 1 – Mild (Mild swelling of the umbilicus, no signs of discomfort or pain, no draining of the swollen area); 2 – Moderate (Moderate swelling of the umbilicus, swollen tissue is easily palpable but restricted to the umbilicus, may be slightly painful and warm upon palpation, drainage, if present, may be very mild and serosanguineous or purulent); 3 – Severe (Severe swelling in the umbilical zone, swollen tissue is easily palpable, moderate to markedly painful and warm upon palpation, may be draining purulent material and may be associated with swelling beyond the umbilical region, likely to be associated with internal omphalophlebitis).

Animals with clinical disease scores of 0 or 3 (normal or severe, respectively), were not included in the study. Animals showing evidence of placental retention, systemic complications of acute or chronic infections, concurrent diseases as well as pneumo-enteric complex and animals that had been treated with antimicrobials during the previous 10-day period, were not enrolled in the study.

Treatment and clinical assessment.

Animals fulfilling the inclusion criteria were treated on Day 0 with a SC injection of danofloxacin 18% at a dose rate of 6 mg / kg (1 mL / 30 kg) of body weight. Clinical assessment was conducted on Day 0 and again on Days 2 and 4. On those days, rectal temperature was taken as an ancillary measure of the clinical status. On Day 2 examination, a second injection was given to animals showing a clinical score equal to or greater than the Day 0 score (non-responder). If the animal returned to normal (score 0) on Days 2 or 4, it was considered cured and removed from the study. The study terminated on Day 4. Animals still showing signs of infectious disease (not cured) at study termination were treated with an alternative product.

Clinical outcome.

Clinical assessments following treatment were performed on Days 2 and 4 and the animals were classified as: **Cure** if on Days 2 or 4, following one or two treatments, the clinical disease score was 0. **Responder** if, on Days 2 or 4, the clinical disease score was reduced (but not 0) when compared to the initial Day 0 score. **Non-responder** if, on Days 2 or 4, the clinical disease score was the same or increased when compared to the initial Day 0 score. **Relapser** if the animal was identified as a responder on Day 2 examination and, on Day 4 had the same or higher score than the Day 0**.**

After completion of treatment relapsing and non-responding animals received conventional treatment on Day 4. The milk of danofloxacin 18% treated cows was banned for human consumption during the treatment and for 41 hours after the last injection.

Bacteriology

Samples (fecal samples and nasal, vaginal and navel swabs, as appropriate to the disease) for bacteriological assay were collected on Day 0 from each animal before treatment and shipped to the Diagnostic Laboratory (Faculty of Veterinary Medicine and Zootechny – USP) within 3-4 days in an isothermic box with ice. Swab samples were preserved in Stuart transportation medium. For bacterial isolations, the samples were cultured in blood agar and McConkey agar and then incubated at 37 ºC for approximately 24 to 48 hours. For the isolation of fungi, the samples were cultured in Sabouraud dextrose agar (Difco Co., USA) supplemented with chloramphenicol (Farmitalia Carlo Erba, Brazil) and then incubated at room temperature for at least 7 days. The bacterial identification was accomplished by means of Gram stain technique, colony morphology, and hemolysis profile as well as reaction to biochemical testing. Confirmatory species identification was conducted according to KRIEG & HOLT (1994), LENNETTE et al. (1985), MURRAY et al. (1999) and API Bacteriology System (Merieux, France). Bacterial isolates were submitted to sensitivity testing using the danofloxacin sensidisc containing 5 mcg of danofloxacin. The criteria adopted for sensitivity classification was: Sensitive = diameter of inhibition halo ≥ 21mm; Partially sensitive = diameter >15 to <21 mm; and Resistant = equal to or lesser than ≤ 15mm.

RESULTS AND DISCUSSION

From a total of 1,019 cattle with clinical signs of respiratory disease, enteritis, metritis, or omphalitis that participated in the study, 94.8% (966 / 1,019) were cured by or responded to treatment with one or two doses of danofloxacin 18% administered at a dose rate of 6 mg / kg of body weight (Table 1). Two hundred and thirteen (213) cattle had respiratory disease, 365 had enteritis, 341 cows had metritis and 100 calves had omphalitis. The cure / responder rates for each disease category were: respiratory disease = 93.9%; enteritis = 97.5%; metritis = 91.8% and omphalitis = 97.0%. On

Day 2 after one treatment, 41.8%, 60.3%, 40.2% and 37.0% of cattle with respiratory disease, enteritis, metritis and omphalitis, respectively, were cured (score 0) totaling 483 (47.4%) cattle. Additionally, 38.0%, 32.3%, 36.4% and 51.0% of cattle with respiratory disease, enteritis, metritis and omphalitis, respectively, were cured on Day 4. One hundred and nine (109) cattle responded to treatment, however, their clinical scores did not decrease to 0 by Day 4. Fifty two (52) cattle were non-responders and one animal was classified as a relapser.

The cure rates for each clinical disease (Table 2) were: respiratory disease = 79.8%, enteritis = 92.6%, metritis = 76.5% and omphalitis = 88.0%. The overall cure rate was 84.1% of which, 52.4% cured with only one dose and 31.7% cured with two doses of danofloxacin 18%. On Day 4, there were many responder animals that did not reduce to score 0, although the scores were reduced compared to Day 0 scores. The rapid and high cure rates obtained in this study are due to the pharmacokinetic with rapid absorption and distribution of the drug that rapidly exceed the MIC_{90} level for the various pathogens in the lung and enteric tissues (Friis, 1989; 1993; Sarasola et al., 2000), associated with the bactericidal concentration-dependent activity of danofloxacin 18% (McKellar et al., 2000). The cure rates obtained following one or two doses of danofloxacin 18% in this study for respiratory disease and enteritis are in close agreement with the results of other authors that reported successful responses of 76.3% in the treatment of respiratory disease (Rowan et al., 2000) and 93.9% in the treatment of enteritis due to Escherichia coli (Sunderland et al., 2000). The percentage of cattle reported as successfully treated with a single dose of danofloxacin 18% was 45% for respiratory disease (Rowan et al., 2000) and for enteritis was 66.1% (Sunderland et al., 2000), while in the present study, 43.2% (92/213) and 65.5% (239/365) of cattle with respiratory disease and enteritis respectively, were cured with a single injection. Additionally, 44.8% (153/341) of cows with metritis and 50.0% (50/100) of calves with omphalitis were cured with a single injection of danofloxacin 18% at a dose rate of 6 mg/kg.

Table 1 - Clinical outcome in cattle with respiratory disease, enteritis, metritis, or omphalitis following one (Day 0) or two (Days 0 and 2) treatments with danofloxacin 18% (6 mg/kg of body weight).

Clinical disease	n	Clinical outcome	Days of study				Total	
			2		4			
			n	%	n**	%	n	%
Respiratory disease	213	Cure	89*	41.8	81	38.0	170	79.8
		Responder	10	4.7	30	14.1	30	14.1
		Non-responder	114	53.5	13	6.1	13	6.1
		Relapser	0	0.0	0	0.0	0	0.0
Enteritis	365	Cure	220*	60.3	118	32.3	338	92.6
		Responder	20	5.5	18	4.9	18	4.9
		Non-responder	125	34.2	8	2.2	8	2.2
		Relapser	0	0.0	1	0.3	1	0.3
Metritis	341	Cure	137*	40.2	124	36.4	261	76.5
		Responder	30	8.8	52	15.2	52	15.2
		Non-responder	174	51.0	28	8.2	28	8.2
		Relapser	0	0.0	0	0.0	0	0.0
Omphalitis	100	Cure	37*	37.0	51	51.0	88	88.0
		Responder	15	15.0	9	9.0	9	19.0
		Non-responder	48	48.0	3	3.0	3	3.0
		Relapser	0	0.0	0	0.0	0	0.0
Overall	1,019	Cure	483*	47.4	374	36.7	857	84.1
		Responder	75	7.4	109	10.7	109	10.7
		Non-responder	461	45.2	52	5.1	52	5.1
		Relapser	0	0.0	1	0.1	1	0.1

*Removed from the study after receiving a clinical score of 0.

**This number includes animals which received 2 doses and animals which were responders on Day 2 and hence did not receive a second dose.

Table 2 - Number and percentage of cattle with respiratory disease, enteritis, metritis, or omphalitis cured (score 0) following treatment with one or two doses of danofloxacin 18% (6 mg/kg of body weight).

Clinical diseases	Total number of cattle	Number of cattle cured					
		One dose		Two doses		Total	
		n*	%	n	%	n	%
Respiratory disease	213	92	43.2	78	36.6	170	79.8
Enteritis	365	239	65.5	99	27.1	338	92.6
Metritis	341	153	44.8	108	31.7	261	76.5
Omphalitis	100	50	50.0	38	38.0	88	88.0
Total	1,019	534*	52.4	323	31.7	857	84.1

*The total number of cattle cured after one dose includes animals (483) cured by Day 2 plus animals (51) which were responders on Day 2 (did not receive second treatment) and were cured by Day 4.

Table 3 - Bacterial isolates from cattle with clinical signs of respiratory disease, enteritis, metritis, or omphalitis, and sensitivity to danofloxacin.

Bacterial species	Sensitivity to danofloxacin			
	Sensitive	Partially sensitive	Resistant	Total
Bacillus spp.	24	6	2	32
Citrobacter diversus	1	0	0	1
Citrobacter freundii	6	2	0	8
Citrobacter koseri	3	0	0	3
Enterobacter aerogenes	6	3	0	9
Enterobacter cloacae	3	0	0	3
Enterococcus faecalis	5	6	4	15
Enterococcus faecium	0	1	0	1
Enterococcus hirae	0	1	0	1
Escherichia coli	219	55	29	303
Klebsiella oxytoca	25	3	4	32
Klebsiella ozaenae	1	1	0	2
Klebsiella pneumoniae	57	13	7	77
Micrococcus luteus	3	1	0	4
Pasteurella multocida	1	1	0	2
Proteus mirabilis	49	8	4	61
Proteus vulgaris	9	3	0	12
Pseudomonas aeruginosa	2	4	0	6
Salmonella spp.	7	3	0	10
Staphylococcus aureus	3	4	1	8
Staphylococcus capitis	10	1	0	11
Staphylococcus chromogenes	2	1	0	3
Staphylococcus epidermidis	30	5	1	36
Staphylococcus intermedius	16	4	0	20
Staphylococcus saprophyticus	6	3	0	9
Staphylococcus warneri	26	2	0	28
Streptococcus agalactiae	27	19	17	63
Streptococcus dysgalactiae	24	11	8	43
Streptococcus uberis	2	0	0	2
Total	567 (70.4%)	161 (20.0%)	77 (9.6%)	805

Table 4 - Bacterial sensitivity to danofloxacin according to genera.

Bacterial species	Sensitivity to danofloxacin			Total
	Sensitive	Partially sensitive	Resistant	
Bacillus spp.	24 (75.0%)	6 (18.8%)	2 (6.2%)	32
Citrobacter spp.	10 (83.3%)	2 (16.7%)	0 (0.0%)	12
Enterobacter spp.	9 (75.0%)	3 (25.0%)	0 (0.0%)	12
Enterococcus spp.	5 (29.4%)	8 (47.1%)	4 (23.5%)	17
Escherichia coli	219 (72.3%)	55 (18.1%)	29 (9.6%)	303
Klebsiella spp.	83 (74.8%)	17 (15.3%)	11 (9.9%)	111
Micrococcus luteus	3 (75.0%)	1 (25.0%)	0 (0.0%)	4
Pasteurella multocida	1 (50.0%)	1 (50.0%)	0 (0.0%)	2
Proteus spp.	58 (79.5%)	11 (15.0%)	4 (5.5%)	73
Pseudomonas aeruginosa	2 (33.3%)	4 (66.7%)	0 (0.0%)	6
Salmonella spp.	7 (70.0%)	3 (30.0%)	0 (0.0%)	10
Staphylococcus spp.	93 (80.9%)	20 (17.4%)	2 (1.7%)	115
Streptococcus spp.	53 (49.1%)	30 (27.8%)	25 (23.1%)	108
Total	567 (70.4%)	161 (20.0%)	77 (9.6%)	805

A total of 805 bacterial isolates were obtained from the various clinical cases (Table 3). The overall number of sensitive bacterial isolates was 567 (70.4%), while 161 (20.0%) were partially sensitive and 77 (9.6%) were resistant to danofloxacin. *Enterococcus* spp. and *Streptococcus* spp. were the genera most resistant to danofloxacin with 23.5% and 23.1% of the respective isolated genera being resistant (Table 4).

The results reported herein demonstrate that a single subcutaneous injection of danofloxacin 18% administered at a dose rate of 6 mg/kg with an additional injection 48 hours later as needed, was highly effective in the treatment of naturally-occurring bovine infectious d iseases including respiratory disease, enteritis, metritis and omphalitis. Danofloxacin 18% represents an excellent alternative for the treatment of these infectious diseases in cattle with the advantages of rapid recovery following a single dose or at maximum two doses and safety in cattle as young as 3 days of age.

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