Combined Corticosteroid and Antibiotic Therapy in Bovine Respiratory Disease (BRD) of Young Cattle: Clinical Results

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Over the past few years, the use of anti-inflammatory corticosteroids in Bovine Respiratory Disease (BRD) of young cattle has been the subject of several updates (2), discussions and debates (5), stemming solely from the observations by Christie *et. al.* in which it appeared that the combination of oxytetracycline and dexamethasone produced less effective clinical results and led to more relapses than oxytetracycline alone. Therefore, we considered it important to check these statements under production conditions in France.

Materials and Methods

Animals and production conditions.

One hundred and ninety-three bull calves at pasture were observed during a general trial. Forty-eight of these animals were selected (18 in 1984 and 30 in 1985), since they had received comparable formulas. They were male Salers cattle, aged 8 to 10 months, with a mean weight of 280 kg, and had been shipped during the autumn from pastures in central France to Normandy for fattening. Upon arrival, they were identified, weighed, placed in homogeneous groups in half-open housing, vaccinated (against anaerobic bacteria) and treated (wormed, vitamin AD_3E).

Test products.

Injectable solutions of oxytetracycline (5%) + chloramphenicol (10%) in dimethyl sulfoxide (DMSO) with or without corticosteroids.

TABLE 1. Composition of test products (g/100 ml).

Formulation	F1	F2	F3
Oxytetracycline (0)	5	5	5
Chloramphenicol (C)	10	10	10
DMSO q.s. 100	+	+	+
Prednisolone acetate (PA)	0.5	0	
Methyl prednisolone (MP)		0	0.4

F1 = Chlortetrasone (proprietary name - R.M.)
F2 = Cortcycline (proprietary name - R.M.)
F3 = Experimental formulation

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Therapeutic protocols.

Upon diagnosis of BRD, the animals were treated for five consecutive days, following a double blind protocol. The test products were administered by deep intramuscular injection, not exceeding 25 ml at each injection site, at the rate of 10 ml/100 kg body weight.

TABLE 2. Distribution of therapeutic protocols.

Number of animals Total = 48	Formulation used each day (F) Day 1	Day 2	Day 3	Day 4	Day 5	Code
28	F1	F1	F1	F1	F1	11111
6	F1	F1	F2	F2	F2	11222
8	F3	F3	F2	F2	F2	33222
6	F2	F2	F2	F2	F2	22222

Clinical monitoring.

The animals affected with BRD were monitored clinically each day, and the data were processed individually using the Standard Clinical Examination during the 15 consecutive days following beginning of treatment. Six symptoms were scored: 3 respiratory symptoms (polypnea, nasal discharge, cough) and 3 general symptoms (fever, appetite, general behavior). An overall evaluation of the disease was made with a Mean General Score (MGS), using a previously published procedure (3).

Paraclinical monitoring: bacteriology and serology.

On the first day of treatment and five to ten days later, samples of tracheobronchial mucus were taken from 39 animals by transtracheal aspiration (TTA) (8). A bacteriological analysis of these samples was conducted (7). Serum samples were taken from 78 animals on the first day of treatment and 15 to 21 days later for detection of Infectious Bovine Rhinotracheitis (IBR) antibodies by ELISA (ELIFFA IBR Kit, Rhône Mérieux).

Results

Characterization of disease on first day of treatment.

The etiology of the disorders analyzed agrees well with that of BRD encountered in France. The major pathogen was *Pasteurella (hemolytica or multocida),* and IBR viruses were of minor importance.

TABLE 3. Summary of bacteriological examinations of TTA products (tracheobronchial mucus) on first day of treatment.

	1984		1985	
	Positive	Negative	Positive	Negative
Total	14/23=61%	9/23=39%	10/16=62%	6/16=38%
Pasteurella multocida	1/14=7%		7/10=70%	
Pasteurella hemolytica	10/14=71%		2/10=20%	
Moraxella sp.	2/14=14%			
Actinobacillus sp.	1/14=7%			
Neisseria sp.			1/10=10%	

TABLE 4. Results of paired IBR serum analyses.

	Total sera	Positive		Uncertain		Negative	
		Day 1	Day 15-21	Day 1	Day 15-21	Day 1	Day 15-21
1984	50	0	2	0	4	50	44
1985	28	5	4	0	0	23	24

Comparison of formulas and protocols: Clinical course.

Figure 1 shows the evolution of the MGS for each treatment protocol by presenting the results in terms of disease severity. MGS: 1.0 to 1.1 = normal, 1.2-1.9 = moderately severe disease, 2 = severe disease.

Table 5. Comparison of areas under the curve of MGS evolution, using covariance analysis, from day 1 to day 3 or from day 1 to day 5 of treatment. The readjusted MGS on the first day of treatment is 2.03, and the mean slopes for day 1 to day 3 is 1.41 and for day 1 to day 5 is 2.03. The significance level (***= p 0.01) is highly significant. There were significant differences between treatments with different letter codes.

During the ten days following the end of a treatment, two categories of relapse-recurrence could be distinguished. They were: benign conditions requiring no further treatment and severe conditions where the clinician considered a new treatment necessary. Their distribution and time to onset are given in Table 6.

FIGURE 1. Evolution of MGS of disease for different treatment protocols.

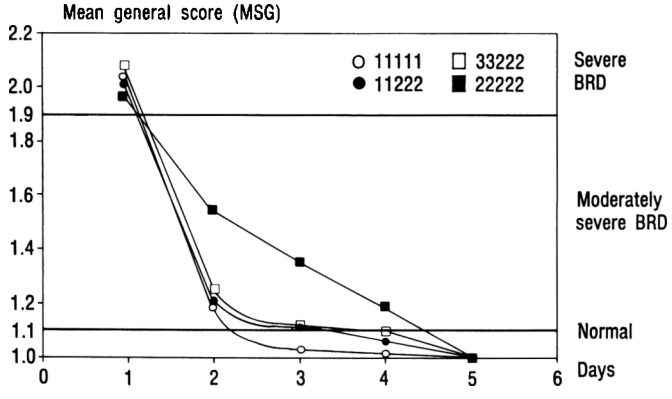

TABLE 5. Comparison of areas under the curves of MGS evolution from days 1 to 3 and days 1 to 5.

Protocol codes	11111	11222	33222	22222
1. Days 1 to 3 of treatment				
Area under curve	0.71	0.79	0.77	1.30
Index	(100)	(111)	(108)	(183)
Significance ***	A	A	A	B
2. Days 1 to 5 of treatment				
Area under curve	0.72	0.91	0.90	1.69
Index	(100)	(126)	(125)	(234)
Significance ***	A	AB	AB	B

TABLE 6. Distribution of relapse-recurrence and day (D) of onset.

Protocol codes	11111	11222	33222	22222
Benign relapse-recurrence (5/48)	0/28	1/6 (D9)	2/8 (D5-D8)	2/6 (D5)
Severe relapse-recurrence (1/48)	0/28	0/6	1/8 (D10)	0/6

Discussion

Figure 1 and Table 5 reveal no disadvantages in the treatment protocols containing a corticosteroid in comparison with antibiotic treatment alone. On the contrary, on day 3, there was a highly significant difference (p 0.01) in favor of the treatments containing corticosteroids, although it was impossible to distinguish between PA and MP. After five days of treatment, all the animals were cured irrespective of the protocol used. But, in terms of areas under the curve of MGS evolution, the protocol without corticosteroids was less effective than that with corticosteroids during the 5-day period.

Table 6 shows no risk of relapse-recurrence following the combined use of corticosteroids and antibiotics, even when a distinction is made between benign and severe forms. The only case that required renewal of treatment on the tenth day involved an animal in protocol 33222 in which the tracheobronchial mucus had been cleared of *Pasteurella* after the first treatment. Thus, in this case, it would be more appropriate to talk of a recurrence rather than a relapse, since a reinfection is implied.

In the context of BRD where the etiological components are represented essentially by bacteria *(P. haemolytica* and/or *P. multocida)* and where the IBR virus plays a minor role, which often seems to be the case in France, combined antibiotic and corticosteroid therapy accelerates recovery without therapeutic failures, relapses or recurrences. These observations moderate the conclusions drawn from the analytical study of the effects of corticosteroids on the immune system of cattle (2). With regard to the observations made by Christie *et. al.* (1), it should be pointed out that the

basic treatment was administered for only three days, the dexamethasone dosage could have been lower, no control measures had been applied and conventional observation criteria were not rigorous.

The dosages of prednisolone that we used (0.4 mg/kg body weight for MP and 0.5 mg/kg for PA) would be expected to exert an anti-inflammatory effect (5). MP may be considered a rapid-acting corticosteroid (flash corticosteroid) and PA a slow-acting one (delayed action). Yet, no clinical difference was found between treatments 11222 and 33222. In particular, despite observations made by Toutain *et. al.* (6) concerning the period of antehypophyseal inhibition in cattle (4 to 6 weeks), treatments 11111 and 11222 did not result in less recoveries and/or more relapses-recurrences than the others. If one really wished to take no pharmaco-immunological risks, our results would suggest choosing the therapeutic protocol 11222 or even better 33222.

Another element in contradiction with the possible immunodepressive effects of corticosteroids in clinical medicine is provided by the type of antibiotics used in this trial. Chloramphenicol and oxytetracycline are bacteriostatic, which, theoretically, should facilitate the expression of an immunodepression, especially since they also have a negative effect (4) on the immune system. Furthermore, one should not extrapolate to cattle affected with spontaneous respiratory disease the data concerning the pro-infectious role of anti-inflammatory corticosteroids obtained with corticosteroid-sensitive species (rats, mice, rabbits, dogs), using very different models where prior immunodepression after massive corticosteroid treatment (5) is involved. Even in cattle (2), the few experimental trials available concerning specific viral infections (IBR, BVD-Bovine Viral Diarrhea-Mucosal Disease) or parasitic infestations (coccidiosis) involve dosages and treatment periods—by corticosteroids—much greater than those required in clinical practice to produce anti-inflammatory effects (5).

Conclusions

Under the conditions of our observations, the deteriorating capacity of PA and MP in the treatment of BRD of young cattle, such as it has been stressed in recent years by a few authors, has not been demonstrated. Perhaps this difference results from a better clinical monitoring of the animals, longer antibiotic protection, corticosteroid dosage better adapted to needs and the systematic application of collective treatment when the threshold of 30% sick animals is reached. In view of the more rapid recovery of the animals treated with the antibiotic-corticosteroid combination, in comparison with those that received only antibiotics, we recommend the continued use of corticosteroids in the treatment of BRD.

Summary

In a trial involving young beef cattle being fattened, which were affected with Bovine Respiratory Disease, the Standard Clinical Examination and an adapted statistical analysis were used to examine the results of five days of treatment with three formulations of 5% oxytetracycline + 10% chloramphenicol + dimethylsulfoxide q.s. 100, with or without corticosteroids. The protocol of five daily injections comprised either five days with the corticosteroid formulation, or two days with corticosteroids and three days without, or five days without corticosteroids. Corticosteroid therapy combined with antibiotics, throughout the entire trial period produced a significant and favorable modification in the rate of clinical recovery, in comparison with the same formulation without corticosteroids, without increasing the number of relapses or recurrences of disease. The protocols of two days with corticosteroids and three days without produced intermediate results. In view of more rapid recovery, with no problems, we recommend that corticosteroids continue to be combined with antibiotics during all or part of the protocol for treatment of BRD.

References

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