EXPERIMENTAL ARGUMENTS FOR RATIONAL USE OF SPIRAMYCIN (EMBONATE) AGAINST RESPIRATORY INFECTIONS IN CALVES

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INTRODUCTION

Respiratory diseases represent the main cause of morbidity and mortality in veal calf production. Viruses (PI_3, RSV,...), bacteria *(Pasteurella spp., Haemophilus somnus, ...)* and mycoplasma *(M. bovis)* are the main causative agents of such infections. Therapeutic treatment remains based upon the administration of antibiotics in order to limit bacterial and mycoplasmal surinfections.

The purpose of the studies described hereafter was to demonstrate the marked affinity of spiramycin for tissues and, consequently, the efficacy of this macrolid antibiotic in the treatment of respiratory diseases in calves.

MATERIAL AND METHODS

Pharmacokinetics study. Thirteen female Holstein calves originating from different farms were gathered in the same unit at the age of 7-14 days. One week after their arrival, 12 out of the 13 animals were fed on a spiramycin-supplemented milk replacer (25 mg/kg bw/day - i.e.: $8x10^4$ IU/kg bw/day) while the remaining calf was fed on a control milk replacer. The control calf was slaughtered at Day 0 (first day of treatment). Then, spiramycin-treated animals were slaughtered at D1, D3, D7 and D14 (3 animals/day) 8 hours after the last meal. Each animal was blood sampled 0, 1, 2, 4, 6 and 8 hours after its last meal. Immediately after sacrifices, samplings were performed from liver, kidneys, lungs, lymph nodes, muscles and fat. Spiramycin in tissues and blood was assayed microbiologically, using gel diffusion technique with *Sarcina lutea* as test micro-organism.

Clinical study. One hundred and fifty-one Holstein veal calves were allocated to 3 rooms containing 56 males (Room A), 47 females (Room B) and 48 males (Room C). At the onset of Infectious Enzootic Bronchopneumonia (IEBP) which occurred about 3 weeks after allocation of the animals, the population of each room was divided into 2 halves : animals receiving a control milk replacer and animals receiving a spiramycin-supplemented milk replacer (25 mg/kg bw/day - i.e.: $8x10^4$ IU/kg bw/day) for 7 days. A clinical follow-up was performed over a 3-week period after the beginning of spiramycin distribution (Day 0). The follow-up consisted of a daily clinical examination of dyspnea, nasal discharge, coughing, prostration, anorexia and rectal temperature. On the basis of this clinical examination, each ill animal recorded received an antimicrobial treatment for 3 days, irrespective of its group (control or spiramycin-treated group). For each ill animal the onset of the first disease and, possibly, that of the first and the second relapses were recorded daily and quoted from 1 to 22. A cumulative chart was drawn representing, for each experimental group ("control" and "spiramycin"), the percentage of ill animals as a function of time.

RESULTS

Pharmacokinetics study. Plasma concentrations of spiramycin remained very low. They varied within a narrow range of values and rarely exceeded 0.10 µg/ml. A plasma peak concentration was observed 4-6 hours after the last meal. In contrast, high levels of the antibiotic were recorded in tissues from the first few days of treatment and maximum concentrations were obtained as of Day 7 (Fig. 1). For the tissues studied, the maximum values were 20.3 µg/g in liver, 15.8 µg/g in kidneys, 13.9 µg/g in lungs, 7.2 µg/g in lymph nodes, 2.1 µg/g in fat and near the detection limit in muscles.

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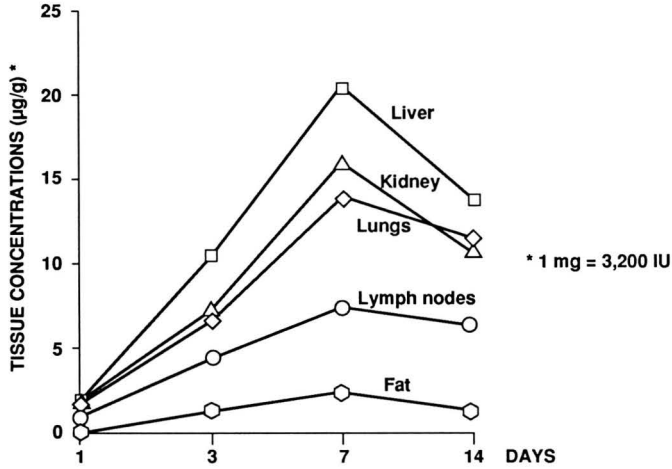
Figure 1 - **Spiramycin tissue concentration in calves fed on spiramycin-supplemented milk replacer** (25 mg/kg bw/day).



Clinical study. The diagnosis of IEBP was confirmed by isolation of *M. bovis, P. multocida* and *H. somnus* from samples obtained on Day 0 by transtracheal aspirations on 18 ill calves (6 animals/room). Serological tests carried out on the same ill animals by means of samplings performed on Day 0 and Day 22 evidenced a non-ambiguous positive RSV serotesting (indirect immunofluorescence test).

The 18 animals which were ill before the beginning of spiramycin supplementation remained in the experimental groups. As mentioned in Table 1, only 2 relapses were recorded in spiramycin-treated animals versus 10 relapses in controls during the 3 week-observation period.

Table 1 - **Influence of spiramycin supplementation on relapse rates** (calves ill on Day 0 and relapsing between Day 3 and Day 22)

		Nb of relapses / Nb of animals	
		Control	Spiramycin
Room A	1st relapse	2/3	1/3
	2nd relapse	2/3	0/3
Room B	1st relapse	1/4	1/2
	2nd relapse	0/4	0/2
Room C	1st relapse	3/3	0/3
	2nd relapse	2/3	0/3
Occurrence of relapses		**10/10**	**2/8**

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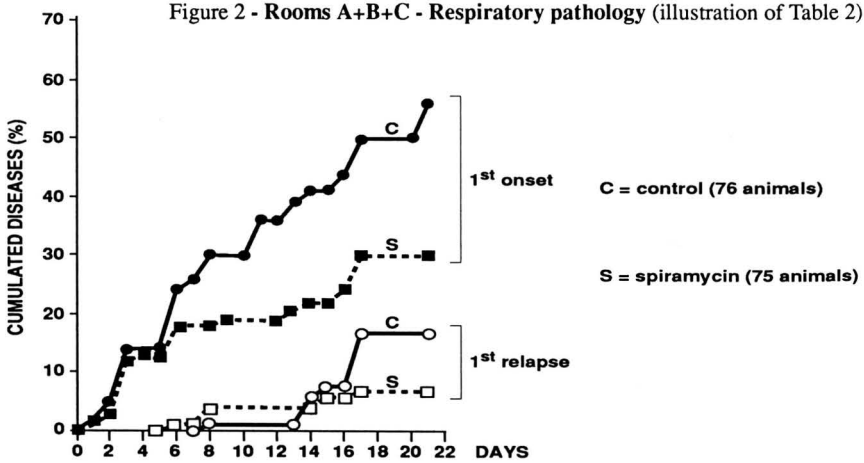
Clinical status of the remaining animals (66 "control" and 67 "spiramycin") is summarized in Table 2 and Figure 2 : 56.1% of control animals experienced at least one respiratory disease versus 29.8% in spiramycin-treated group ($p < 0.02$). The relapse rate in control group was 16.7% versus 7.5% in the spiramycin-treated group.

Table 2 - **Influence of spiramycin supplementation on respiratory pathology** (calves experiencing at least one disease between Day 1 and Day 22)

		Nb of onsets / Nb of animals	
		Control	Spiramycin
Room A	1st onset	12/25(48.0%)	6/25(24.0%)
	1st relapse	1/25	1/25
	2nd relapse	1/25	1/25
Room B	1st onset	9/20(45.0%)	6/21(28.6%)
	1st relapse	3/20	3/21
	2nd relapse	0/20	0/21
Room C	1st onset	16/21(76.2%)	8/21(38.1%)**(a)
	1st relapse	7/21(16.7%)	1/21(4.8%)*
	2nd relapse	0/21	0/21
Rooms A+B+C	1st onset	37/66(56.1%)	20/67(29.8%)***
	1st relapse	11/66(16.7%)	5/67(7.5%)
	2nd relapse	1/66	1/67
Occurrence of diseases in the 3 rooms (total)		**49/66**	**26/67**

(a) BOYD's Chi^2 test $p < 0.05$ * $p < 0.02$ ** $0.001 < p < 0.01$ ***

Figure 2 - **Rooms A+B+C - Respiratory pathology** (illustration of Table 2)



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The total number of individual curative treatments due to respiratory diseases can be calculated from Table 1 and Table 2 as follows :

	Nb of treatments / Nb of animals	
	Control	Spiramycin
• Treatments applied to calves ill on Day 0 and relapsing between Day 3 and Day 22	10/10	2/8
• Treatments applied to calves experiencing at least one disease between Day 1 and Day 22	49/66	26/67
Total number of treatments	**59/76**	**28/75**

Adjusted to 2 groups of 100 animals each, the total number of treatments would be :

$$\frac{59 \times 100}{76} = \mathbf{78}$$ treatments for the **control group**

$$\frac{28 \times 100}{756} = \mathbf{37}$$ treatments for the **"spiramycin" group**

DISCUSSION - CONCLUSION

Since the beginning of its extensive use in practice, spiramycin has always been found to display a much greater clinical efficacy than might be expected from its *in vitro* activities (1). Several synergistic mechanisms may explain this phenomenon : the ability of spiramycin to concentrate in macrophages (2), its effect on adhesiveness and phagocytosis of micro-organisms at sub-inhibitory concentrations (3), its potent post-antibiotic effect on common pathogens (4), but also its original pharmacokinetic profile in calves. In spiramycin-treated calves, pharmacokinetic parameters evidence that spiramycin reaches concentrations in lungs that are active against *M. bovis* but also against *P. multocida* and *P. haemolytica*. In this respect, it must be noted that concentrations of spiramycin in calf lungs were previously erroneously considered too low to obtain MIC values against *Pasteurella*.

The previous data have been confirmed in the present controlled trial which was performed in a unit of 151 one-month old veal calves suffering from IEBP. During the 3 weeks following the initiation of treatment and in spite of significant seroconversion for RSV, the clinical status of spiramycin-treated animals was significantly superior to that of control animals.

With a marked affinity for lungs, spiramycin remains one of the major molecules for the prevention and the treatment of respiratory infections in calves.

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SUMMARY

In veal calves, plasma and tissue concentrations of spiramycin were measured during a 14-day oral treatment with 25 mg/kg bodyweight/day. Plasma concentrations of spiramycin remained very low and rarely exceeded 0.10 µg/ml. In contrast, high levels of the antibiotic were recorded in tissues from the first few days of treatment and maximum concentrations were obtained as of day 7. For the tissues studied, the maximum values were 20.3 µg/g in liver, 15.8 µg/g in kidneys, 13.9 µg/g in lungs, 7.2 µg/g in lymph nodes, 2.1 µg/g in fat and near the detection limit in muscles.

A controlled clinical trial was then performed in a unit of 151 one-month old calves suffering from infectious Enzootic Bronchopneumoniae. Each animal was fed either on a control milk replacer or on a spiramycin-supplemented milk replacer (25 mg/kg bodyweight/day) for 7 days. During the 3 weeks following initiation of treatment and in spite of positive RSV serotesting, the clinical status of spiramycin-treated animals was significantly superior to that of control animals kept in the same unit.

RESUME

Les concentrations plasmatiques et tissulaires de spiramycine sont mesurées chez des veaux de boucherie recevant pendant 14 jours l'antibiotique par voie orale à la posologie de 25 mg/kg vif/jour. Les concentrations plasmatiques en spiramycine restent très faibles et excèdent rarement 0.10 µg/ml. En revanche, de fortes teneurs tissulaires sont enregistrées dès les premiers jours du traitement et atteignent des valeurs maximales dès le 7e jour. Les valeurs maximales sont de 20.3 µg/g dans le foie, 15.8 µg/g dans les reins, 13.9 µg/g dans les poumons, 7.2 µg/g dans les ganglions lymphatiques, 2.1 µg/g dans le tissu adipeux et voisines de la limite de détection dans les muscles.

Une étude clinique contrôlée est ensuite réalisée sur un effectif de 151 veaux d'un mois atteints de broncho-pneumonie infectieuse enzootique. Chaque animal reçoit un lait témoin ou un lait supplémenté en spiramycine (25 mg/kg vif/jour) pendant 7 jours. Au cours des 3 semaines suivant le début du traitement et malgré le passage du virus RSV, l'état clinique des animaux traités est significativement supérieur à celui des témoins.

RESUMEN

Las concentraciones plasmaticas y tisulares de la espiramicina han sido medidas en terneros que recibieron el antibiotico oralmente (25 mg/kg vivo/ dia) durante 14 dias. Las concentraciones plasmaticas de la espiramicina siguen siendo muy bajas raramente superiores a 0.10 µg/ml. Al contrario, fuertes concentrationes tisulares fueron observadas desde los primeros dias con valores maximos desde el dia 7. Los valores maximos son de 20.3 µg/g en el higado, 15.8 µg/g en los rinones, 19.3 µg/g en los pulmones, 7.2 µg/g en los gauglios limphaticos, 21 µg/g en la grasa y cerca del limite de deteccion en los musculos.

Un estudio clinico controlado ha sido realizado en 151 terneros de 1 mes con bronconeumonia infecciosa enzootica. Cada animal recibia una leche control o una leche con suplemento de espiramicina (25 mg/kg vivo/dia) durante 7 dias. Durante las 3 semenas siguientes al initio del tratamiento y aunque todos los animales fueron detectados RSV positivos, el estado clinico de los animales tratados es significativamente superior al de los animales testigo.

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