CLINICAL AND PULMONARY FUNCTION CHANGES INDUCED BY AEROSOLTHERAPY DURING BOVINE ACUTE RESPIRATORY DISTRESS SYNDROME

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Introduction

Because of the morphological and functional pecularities of their lung, cattle are prone to rapidly develop respiratory failure with a poor prognosis(1). These respiratory diseases induce great financial losses (2,3). Consequently, attention must be payed to new molecules and administration procedures which could reduce the death and enhance the recovery percentages.

As topical administration of therapeutic drugs through the inhaled route offers many advantages, such as the need to administer smaller doses, a quick onset of action and fewer side-effects, the aim of this field investigation was to assess the efficiency of two bronchodilators administered alone or together.

Materials and Methods

Sixty-seven Belgian White and Blue double-muscled calves, struck down by an acute respiratory distress syndrome (A.R.D.S), were involved in this study. These animals weighed 148.3 ± 8.4 kg, ranged from 1 to 36 weeks of age and belonged to 39 breeding units located in the south part of Belgium. As shown in table 1, the animals were randomly divided into three groups, each one being characterized by its treatment.

Table 1. Sample size (n), mean weight and age range of the animals, allocated treatment

Group	n	Weight (Kg)	Age range (Weeks)	Drug	Dosage
A	20	161.0 ± 19.9	2-36	Clenbuterol hydrochlorid	0.075 mg
B	32	128.0 ± 8.9	1-24	Ipratropium bromide	0.6 mg
C	15	171.3 ± 16.7	1-28	Both drugs simultaneously	

Clenbuterol hydrochlorid, a β_2-agonist, and ipratropium bromide, a synthetic cholinergic antagonist with an atropine-like effect on bronchial smooth muscle, were delivered (4 times a day during 3 to 4 days) through two Hudson® 1630 jet nebulizers driven with compressed ambient air (rate : 15 l / min / nebulizer) and connected to a snugly-fitting face mask (Nebul 101™ - Agritronics International S.A., Belgium) which is outlined in figure 1 and which fulfils the conditions required for optimal therapeutic results (4). Each treatment took at about 5 minutes. By the same way, sterile saline water (NaCl 0.9%) was delivered to 3 calves acting as control. For these 3 calves, the parameters, taken into account in this study and measured just before and 1 hour after the inhalation, did not show any significant change.

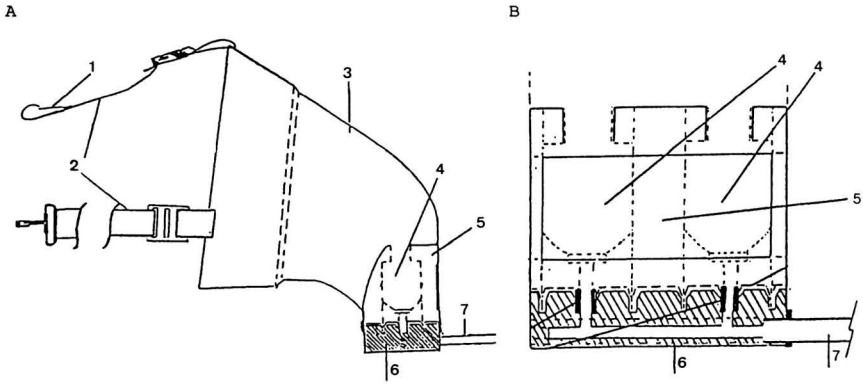
Initiated after the second data collection, an usual antibiotherapy was given during 5 days.

The investigations were carried out just before the first inhalation (0H), 1hour (1H) and 168 hours (168H) after this first inhalation.

Rectal temperature(T°), respiratory(RR) and heart rates(HR), depression or loss of appetite, polypnoea or dyspnoea with or without mouths opening, eventual cough and/or nostrils discharge were recorded. During each investigation, a breathing score was determined. RR and air inhalation route were taken into account in order to determine this score which was recorded as described in table 2. At the same time, the oscillatory resistance (Ros) and the phase angle (Psi) were measured with the monofrequency forced oscillation (MFO) method (5). Ros and Psi allowed the decomposition of the respiratory

system impedance into its real part (Re) and its imaginary part (Im). Arterial blood samples were collected in order to point out the changes concerning the arterial oxygen tension (PaO_2), the alveolar arterial oxygen difference ($A-aDO_2$), the carbon dioxyde tensions ($PaCO_2$) and the arterial pH.

A one way analysis of variance was used to assess (1°) whether the parameters changed significantly within the period of the study, (2°) whether the three groups were similar for each parameter. A significance level of 0.05 was used. Data are displayed as mean ± SEM.



1 = Clip; 2 = Strap to attach the mask; 3 = Face mask; 4 = Jet nebulizer; 5 = Aerosol generating chamber; 6 = Nebulizer supporting plate; 7 = Feeder pipe of compressed air.

Fig. 1. Sagittal section of the face mask (A) and transverse section of the aerosol generating chamber (B)

Table 2. Breathing scores recorded before (0 hour), during and after treatment (1 hour, 168 hours)

Elapsed time	0H	1H	168H
I	0	0	0
II	0.50	0.50	2.00
III	1.00	1.00	4.00
IV	2.00	2.00	8.00

I.= Normal breathing; II = Polypnoea (respiratory rate more than $50.min^{-1}$); III = Dyspnoea and nasal breathing; IV = Dyspnoea and mouth opening

Results

Results are presented in table 3, figures 2 to 4 and table 4.

For each group, a significant reduction of the breathing score was registered both 1H and 168H after the first inhalation.

In groups B and C, Re registered at the end of this investigation (168H) was significantly lower than baseline values.

One hour (1H) after the first inhalation, a significant improvement of $Pa0_2$ was registered in animals which inhaled the two drugs (group C). Such an improvement was registered in each group, 168H after the start of treatment.

Table 3. Death, non recovery and recovery (%) registered in group A, B and C

Group	Death	Non recovery	Recovery
A	20	15	65
B	6	3	91
C	0	0	100

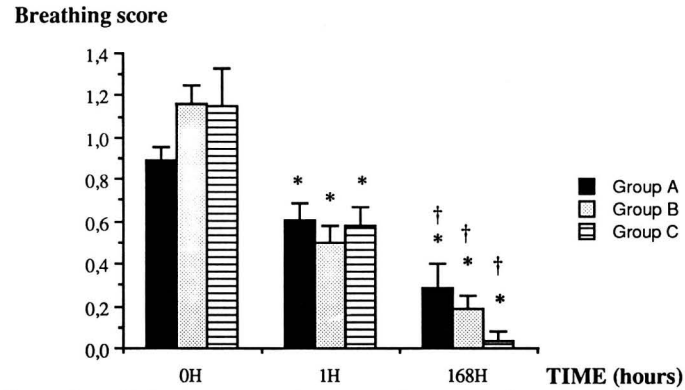


Fig. 2. **Breathing score changes observed in each group during the investigation** (* significantly different from baseline values; † significantly different from data collected 1 hour (1H) after the first inhalation)

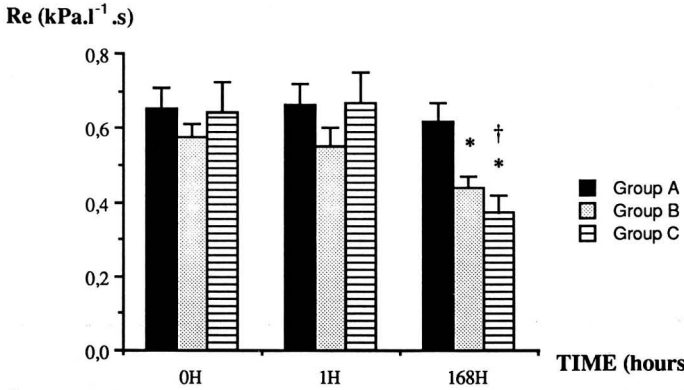


Fig. 3. **Real part (Re) of the respiratory system impedance. Changes observed in each group during the investigation period** (For keys : see figure 2).

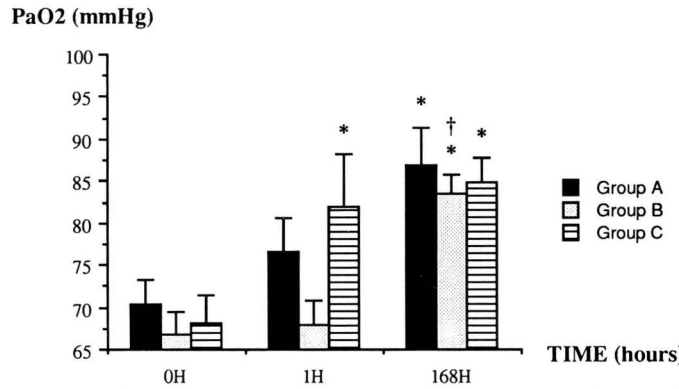


Fig. 4. **Arterial oxygen tension (PaO_2) changes observed in each group during the investigation period** (For keys : see figure 2)

Table 4. Effects of three different treatments on clinical and pulmonary function values (For keys : see figure 2 - N.D. = not determined - °n = number of available data)

	Units	A0H	A1H	A168H	B0H	B1H	B168H	C0H	C1H	C168H
RR	Breath.min^{-1}	70.3 ±3.8 12°	65.3 ±3.1 12	56.2* ±6.1 12	72.2 ±5.4 16	62.7 ±4.6 16	47.3*† ±4.0 16	69.9 ±7.7 14	72.4 ±10.4 14	45.4*† ±4.4 14
HR	Beat.min^{-1}	118.2 ±8.8 6	108 ±9.7 6	97.0 ±9.0 4	112.5 ±4.3 29	106.9 ±6.3 18	102.9*† ±3.6 29	ND ND ND	ND ND ND	ND ND ND
T°	°C	39.6 ±0.1 11	39.7 ±0.2 11	39.1*† ±0.1 11	39.7 ±0.2 14	39.5 ±0.2 14	39.0*† ±0.2 14	39.9 ±0.3 13	39.9 ±0.3 13	38.7*† ±0.1 13
AaDO2	mmHg	45.4 ±3.3 8	42.6 ±3.7 8	28.3* ±3.3 5	53.4 ±2.3 9	53.9 ±2.7 6	31.8*† ±2.1 9	48.5 ±3.9 9	35.9* ±5.3 9	25.2* ±1.7 6
PaCO2	mmHg	47.5 ±4.6 8	44.7 ±2.2 8	44.9 ±0.5 5	45.8 ±1.6 10	44.0 ±2.5 6	43.1 ±5.2 10	49.6 ±3.4 8	48.0 ±3.2 8	48.1 ±3.6 6
pH		7.369 ±0.025 9	7.380 ±0.025 9	7.396 ±0.008 6	7.366 ±0.012 9	7.389* ±0.013 6	7.384 ±0.014 9	7.359 ±0.024 10	7.393* ±0.018 10	7.383 ±0.020 7
Ros	kPa.l^{-1}.s	0.574 ±0.041 11	0.572 ±0.034 11	0.563 ±0.044 11	0.509 ±0.016 19	0.472 ±0.015 19	0.414* ±0.028 16	0.491 ±0.024 11	0.509 ±0.018 11	0.403*† ±0.020 11
Im	kPa.l^{-1}.s	-0.299 ±0.024 11	-0.302 ±0.019 11	-0.284 ±0.025 11	-0.28 ±0.013 19	-0.25 ±0.014 16	-0.155*† ±0.014 19	-0.244 ±0.037 10	-0.267 ±0.030 10	-0.166*† ±0.029 10

Discussion

On the basis of both clinical and ventilatory function parameters used in this study, the animals treated either with the association (group C) or with the anticholinergic substance (group B) showed a better improvement than the animals treated with the β_2 adrenergic substance. This is in agreement with

in vitro studies and could be explained by the fact that, in the airways of Belgian White and Blue double-muscled calves, the density of muscarinic receptors is higher than in Friesian calves (Roets, personal communication). Furthermore, following the results of our study (Fig. 3, Table 4), we may ascertain that, during a natural outbreak of A.R.D.S., most of the double-muscled calves are struck down by a severe constriction of the lower respiratory tract.

The death, non recovery and recovery percentages (Table 3) registered during this trial let us think that the inhalation of $ß_2$ agonist and/or anticholinergic substances may reduce the economic losses due to the acute respiratory distress syndrome. In fact, during an earlier field trial relative to two marketed drugs which have to be injected (unpublished data), the death percentage reached at least 20 %.

Even if the inhalation of drugs, used to inhibit effects of parasympathetic nervous system and/or to stimulate the sympathetic nervous system, does enhance the probability of recovery in calves struck down by A.R.D.S., this route of drug administration has some disadvantages. The inhalation requires to contain the animals during a few minutes, to use an equipment which is adapted to the physiological requirements of calves and to avoid the inhalation of drug by the therapist. Furthermore, the inhaled drugs have to be administered more frequently than drugs allocated by injection. This is due to the short-term action of these drugs and could be solved by the development of new long-term bronchodilators (6).

We may conclude that (1°) the inhaled route may offer a quick onset of action and is highly efficient in the treatment of A.R.D.S. in calves, and (2°) the $ß_2$-adrenergic and the anticholinergic substances, used in this study, are more effective when they are inhaled in a conbination regimen than alone.

Summary.

This study aimed to assess the efficiency of a $ß_2$-adrenergic (clenbuterol hydrochlorid) and an anticholinergic (ipratropium bromide) substance inhaled alone or simultaneously during a natural outbreak of acute respiratory distress syndrome in calves.

Sixty-seven Belgian White and Blue double-muscled calves (body weight : 148.3 ± 8.4 kg, age ranging from 1 to 36 weeks) inhaled (4 times a day during 3 to 4 days) clenbuterol hydrochlorid (0.075 mg - group A - n = 20), ipratropium bromide (0.6 mg - group B - n = 32) or these 2 drugs simultaneously (group C - n = 15). Clinical parameters, pulmonary function data issued from the Monofrequency Forced Oscillation (MFO) technique, arterial blood gases parameters were recorded at each step of this field investigation, i.e. before (0H), 1 hour (1H) and 168 hours (168H) after the first inhalation.

Following the results, the best improvements were obtained in group C. It was concluded that (1°) the inhaled route may offer a quick onset of action and is highly efficient in the treatment of A.R.D.S. in calves, (2°) the $ß_2$-adrenergic and the anticholinergic substances, used in this study, are more effective when they are inhaled in a conbination regimen than alone.

Résumé

Le but de cette étude fut de tester l'efficacité thérapeutique d'un $ß_2$-agoniste (clenbuterol hydrochlorid) et d'un anticholinergique (ipratropium bromide) inhalés, seuls ou en association, par des veaux atteints d'un Syndrome de Détresse Respiratoire Aiguë (SDRA).

Soixante-sept veaux de race Blanc Bleu Belge (Poids : 148,3 ± 8,4 kg; Age : 1 à 36 semaines) furent traités par inhalations de clenbutérol (0,075 mg - groupe A - n = 20), de bromure d'ipratropium (0,6 mg - groupe B - n = 32) ou de ces 2 substances administrées en association (groupe C).

Des paramètres cliniques, des paramètres de la fonction pulmonaire obtenus par la technique des oscillations forcées monofréquentielles, divers paramètres issus d'analyses du sang artériel ont été déterminés à chaque étape

de l'investigation, à savoir avant (OH), 1 heure (1H) et 168 heures (168H) après la première inhalation.

Les meilleurs résultats thérapeutiques ont été obtenus chez les animaux du groupe C. En conclusion,, chez les veaux atteints d'un SDRA, (1°) l'inhalation permet d'obtenir des résultats thérapeutiques optimaux caractérisés par un temps de latence très court, (2°) le $ß_2$–agoniste et l'anticholinergique administrés en association sont plus efficaces que ne le sont ces 2 substances administrées séparément.

Zusammenfassung

Während eines natürlichen Ausbruches des akuten Respiratorischen Distress Syndroms (RDS) bei Kälbern wurde die Wirksamkeit eines $ß_2$-Agonisten (Clenbuterol Hydrochlorid) und eines Parasympathikolytikums (Ipratropium Bromid) geprüft.

Dieser Versuch wurde mit 67 Kälbern (148,3 ± 8,4 kg schwer; 1 bis 36 Wochen alt) der Weiß-Blauen Belgischen Rasse durchgeführt, die in drei Gruppen eingeteilt waren. Die erste Kälbergruppe (Gruppe A - n = 20) wurde mit Clenbuterol (0,075 mg), die zweite (Gruppe B - n = 32) mit Ipratropium Bromid (0,6 mg) und die dritte (Gruppe C - n = 15) mit beiden Mitteln behandelt. Die Behandlung erfolgte per Inhalationem 4 mal täglich über 3 - 4 Tage.

Klinische Befunde, Blutgasuntersuchungen und mit Hilfe der monofrequenten Oszillationstechnik (MFO) ermittelte Parameter der Lungenfunktion wurden vor (0H), 1 Stunde (1H) und 168 Stunden (168H) nach der ersten Inhalation ermittelt.

Die besten Erfolge wurden in Gruppe C erzielt. Aus den Ergebnissen wird folgendes geschlußfolgert : (1°) Die Inhalation von Medikamenten stellt eine sehr schnell und mit hoher Wirksamkeit einsetzende Therapieform zur Behandlung akuter respiratorischer Erkrankungen der Kälber dar. (2°) Die Kombination von $ß_2$-Adrenergika und Anticholinergika ist therapeutischer wirksamer als die alleinige Inhalation eine der beiden Substanzen.

Acknowledgements

This work was supported by the "Ministère de la Région Wallonne". The drugs were supplied by Boehringer Ingelheim.

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