EPIDEMIOLOGICAL AND THERAPEUTICAL STUDIES ON RESPIRATORY DISEASES COMPLEX IN CALVES

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ABSTRACT

During the winter of 1999-2000, in a farm in Gharbia governarate, 425 Calves were examined and noticed for bovine respiratory disease (BRD). The epidemiology of the disease and the efficacy of florfenicol and tilmicosin in treating it were studied. The disease was diagnosed in 104 calves depending on rise of temperature (40.5 °C) accambined with respiratory symptoms. 53 calves were treated twice i/m with florfenicol 20 mg/kg with 48 h intervals, other 51 were injected tilmicosin s/c. once at a dose rate 10 mg/kg. The morbidity rate for the disease were (3.75 %) (33 %) and (6.1%) at age 1-3, 3-6 and 6-18 months respectively. Bacteriological examination revealed isolation of Pasteurella haemolytica, P. multocida and Haemophilus somnus. Florfenicol level in serum was continuo for 48 h after 2nd dose while tilmicosin continuo for 72 h. The response rate for treating were (92.45%) and (78.43%) for florfenicol and tilmicosin respectively.

INTRODUCTION

Bovine respiratory disease (BRD) is the costliest disease affecting the worldwide cattle industry, in terms of both direct costs (deaths, culls, treatment costs) and production costs (lower live weight gains, poor feed conversion) (**John et al, 1998**). It is a multifactorial disease resulting from the complex interaction of bacterial and viral agents, environmental conditions, management factors and the animals (**Yates, 1982**). Common stressors include weaning, shipping commingling, environmental factors (dust, temperature fluctuations), dietary changes fatigue, and processing procedures performed at feedlot (**Roth, 1984**).

Of total feedlot mortalities, those attributed to BRD and associated respiratory tract problems, **Martin (1983)** was reported 45 % ,**Vandankersgoed et al (1994)** was reported 31-71% mortalities and **Vogel and Parrott (1994)** were recorded 37-52%.

Many organsims have been implicated in respiratory diseases including Pasteurella haemolyt-

ica type A1 P. multocida, Haemophilus somnus, Mycoplasma bovis and the viruses, Bovine herpes virus1, Respiratory syncytial virus, Parainfluenza type 3 and bovine adenovirus **(Andrews, 1983 and Musser et al 1996)**. Although the vaccination against respiratory diseases have been applied in most of farms, it can not protect calves completely against this disease as many other stressors may preciptate it, so the need to therapeutical interference still of high value in dealing with the disease.

The selection of an antibiotic is usually based on a combination of susceptibility of causative pathogens, perceived efficacy, cost, ease to administration, availability, toxicity, length of withdrawal time, and its pharmacokinetic properties; mainly its duration of target tissue levels **(Mechor et al,1988 and Watts et al,1994)**.

The aim of this work was :

* Epidemiological studies on respiratory discase in calves.
* Evaluation of field efficacy of florfenicol and tilmicosin (as a recent and specific drugs) for treatment of naturally occurring respiratory disease in calves.
* Determination of the serum concentrations of two drugs to compare its duration of actions.

Materials and Methods

A- Drugs :

1- Florfenicol (Nuflor® 300 mg/ml injectable solution Schering-Plough Animal Health Middle East Africa Operation). It is a structural analog of chloramphenicol but not contain / nitro group, thus aplastic anima has not been associated with its administration **(Bruce et al 1998)**. Florfenicol showing high in vitro potency against pathogenic bacteria mainly those associated with BRD (Pasteurella sp. and Haemophilus somnus) **(Neu and fu 1980 and Syriopoulou et al 1981)**.

2 - Tilmicosin (Micotil® 300 mg/ml injectable solution, Elanco, Animal Health). It is long-acting semisynthetic macrolide, have a good activity against many pathogens commonly associated with respiratory tract infections including Pasteurella and Mycoplasma sp. **(Ose 1987, and Merrill and Tonkinson 1989)**.

B- Animals : Four hundred and fifty two Friesian calves in one of Gharbia governorate farms, 1-18 months were bedded on deep straw in a naturally ventilated open-sided barn with a movable windows. Calves were administered Ivermectin (Ivomec MSD AG-VET) as anthelmintic thera-

py and vaccinated with Cattle Master® 4, Scour Guard 3® (Pfizer, Animal Health. Exton, PA 19341.USA). The calves were noted during the winter of 1999-2000 for respiratory disease symptoms. The case was defined as respiratory disease if there was an elevated rectal temperature (≥40.5°C) associated with respiratory symptoms (dyspnea, nasal discharge, cough, high respiratory rate and abnormal tracheal and lung sound on auscultation) and had no clinical signs attributed to organ other than the respiratory system.

C- **Sampling** : - A deep nasal swabs and lung tissues from dead or emergency slaughtered animals were collected from examined animals for bacteriological examinations according to **Quinn et al (1994)**.

- **B.** Blood samples were collected from 5 calves from each treatment group pre-treatment and at 1,4,8,12 hours and every 24 hours until 6 days post-treatment. Florfenicol and tilmicosin levels in serum were determined using HPLC according to method described by **Modric et al (1998)**.

D- **Treatment** : - The diseased animals were allocated into 2 groups randomly. 53 calves were treated with florfenicol i/m. at a dose rate of 20 mg / kg b. wt. Twice with 48 hour apart and 51were treated with tilmicosin once at a dose rate of 10 mg /kg b. wt. s/c. (None of treated calves had previously been treated for BRD).

Rectal temperatures were evaluated daily in treated animals until 24h. after therapeutic blood levels were assumed to have subsided, which was 48h after the 2nd treatment with florfenicol and 72h after treatment with tilmicosin. Clinical measuments of efficacy included mortality, rectal temperature, number of treatment failures and number of relapses.

A calf was defined as a treatment failure if died or if on last day of monitoring, it had a temperature > 40°C. A relapse was defined as a calf that had respond to treatment (temperature < 39°C with improvement of its general conditions) and diagnosesd with respiratory diseasse at a later date. Calves that relapsed during first 3 weeks of trials were treated with the same antibiotic that was originally administered for a maximum of 2 relapses. If a calf relapsed a 3rd time, it was deemed to be chronic and treated with anther antibacterial (neither florfenicol nor Tilmicosin). Calves were monitored for treatment failure, relapse and mortality for 28 days.

Results & Discussion

The epidemiological failures of BRD in investigated farms were summarized in table (1). Con-

cerning the results of treatment trials it was found that the BRD mortality and second relapse were significantly lower in florfenicol group than in tilmicosin group as reported in table (2). There were fewer treatment failures in florfenicol treated calves 2 / 53 (3.8 %) versus 4 /51 (7.8%). Also treatment response was significantly higher in florfenicol group (92.45 %) versus (78.43%) in tilmicosin group. Average daily gains was 0.94 kg / day and 0.89 kg /day for florfenicol and tilmicosin groups respectively, while the average daily gain for healthy calves (as a control group) was 1.028 kg /day.

Daily mean rectal temperatures of each group are shown in figure (1). There was no significant difference in the degree of temperature changes between the groups.

The isolated bacteria were Pasteurella haemolytica , P. multocida and Haemophilus somnus as shown in table (3).

The mean blood levels of florfenicol and tilmicosin were illustrated in table (4).

The present investigation showed that, the incidence of respiratory disease in calves was 23 % while **Waltner et al (1986) and Curtis et al (1988)** reported only 22.4 % incidence of respiratory disease in calves until weaning (90 day). On the other hand, **Musser et al (1996) and Selim et al (1998)** recorded higher percentage (51 % and 69.34 % respectively). The present study revealed that, the highest incidence of respiratory disease was recorded at 3-6 months (33 %) while on other extreme it was 3.75 % and 6.1 % in age group 1-3 & 6-18 months respectively. Nearly similar results were recorded by **Gourlary et al (1989), Douglas et al (1993) and Bruce et al (1998)**. On the other hand, **Breeze et al (1982), Kelly (1984) and Peters (1985)** mentioned that, the epidemic curves of mortality and morbidity reach their peak levels in first few weeks of calf's life, and **Byson (1985)** recorded a peak occurrence of respiratory disease in calves at 6-8 weeks. While **Selim et al (1998)** recorded its occurrence at 6-10 months and **Kee jim et al (1999)** recorded at 7-10 months. These difference in time of occurrence the peak of respiratory disease may be contributed to timing of exposure to the stress factors on calves, specially temperature fluctuations at climatic changes, calves transportation, and dietary changes at the feed lot.

Bacteriological examination of nasal swabs and lung tissue showed that, the main isolates were P. haemolytica , P. multocida and Haemophilus Somnus, nearly similar results were reported by **Paul et al (1990) Musser et al (1996), Bruce et al (1998) and Selim et al (1998).**

The Serum level of florfenicol was still for 72 hour after 2nd dose which given after 48 hour (sum =120hour) (the minimum inhibitory concentration (MIC = 0.125-1.0ug/ml) which recorded for pathogenic bacteria (Pasteurella and Haemophilus sp) isolated from respiratory infection in calves by **Bruce et al (1998). Varma (1994) and De Haas et al (1995)** concluded that, the level

of florfenicol in lung tissues and bronchial secretion has been several times higher than that present in serum, so all these results have been illustrated the recorded high efficacy of florfenicol in treating BRD. Further more, **Neu and Fu (1980) and Syriopoulou et al (1981)** mentioned that, florfenicol showing high in vitro activity against pathogenic bacteria isolated from BRD. Also **Varma (1994)** concluded that, the highest concentrations of florfenicol in bronchial secretions make it a reasonable choice for treatment of BRD.

The efficacy of tilmicosin in treatment of pulmonary infections may be contributed to its high efficacy on bacteria that cause the pulmonary infections specially Pasteurella and Mycoplasma sp. **(Ose and Tonkinson, 1988, and Crosier et al 1996)**. Also **Gourlay et al (1989)** recorded the mean concentration of tilmicosin in lung was 0.46 ug /gm after 6 days from its once administration (10mg/kg) compared with serum level at that time 0.02 ug /ml (ratio 23: 1)

The results of this study in favor of florfenicol versus tilmicosin in treating of BRD in calves due to its high treatment response and daily weight gain as well as lower chronicity, BRD mortality and treatment failure. Similar results to this study with comparative therapeutic efficacy were reported by **Bruce et al (1998) and Kee Jim et al (1999)**. The higher efficacy of florfenicol than tilmicosin may contributed to its slow release and absorption from injection site, its half-life was 44 hour and as drug injected two times, so its half-life continue for about 48 hour after second dose and tmax was 3.0 hour). Similar results were recorded by **Lobell et al (1994) and Craene et al (1997)**. But tilmicosin have a fast absorption rate from injection site, its half-life was 30 hour and tmax was 0.5hour. Similar results were recorded by **Ziv et al (1995)**. On the other hand, the efficacy of tilmicosin on Haemophilus somnus is doubtful and if present, needs a high MIC 6.25ug/ ml **(Bruce et al, 1998)**.

Finally it could be concluded from this study that, the highest incidence of BRD predicted among age group of 3-6 months requiring special careful management at that period. In additions florfenicol and tilmicosin were highly effective in treeing respiratory disease in calves, reduction of reduction of body temperature within 24 hour and in reducing BRD mortality with special superiority to florfenicol.

Table 1 : The epidemiological results of BRD in the farm.

Age group	animal			Morbidity rate	Mortality rate
	Exmined	diseased	died		
1-3 months	80	3	1	3.75%	1.25%
3-6 months	290	96	4	33%	1.38%
6-18 months	82	5	0	6.1%	0
Total	452	104	5	23%	1.11%

$P \leq 0.001$

Table 2 : Results of trail comparing florfenicol with tilmicosin for treatment of BRD.

Age group	Tilmicosin group	Tilmicosin group	P. value
Number of trial	53	51	0.64
Treatment failure	2 (3.77%)	4 (7.84%)	0.047
BRD moratality	1 (1.89%)	4 (7.84%)	0.73
1st relapse	13 924.53%)	15 (29.4%)	0.037
2nd relapse	3 (5.66%)	11 (21.57%)	0.58
chronicity	1 (1.89%)	3 (5.88%)	0.049
treatment response	49 (92.45%)	40 (78.43%)	0.82
Average daily gain (kg / d)*	0.94	0.89	

* Average daily gain for healthy calves (control) = 1.028 kg/day.

Table 3 : Bacterial Isolations from nasal swabs awabs and lung tissue.

Isolated organisms				
	Florfenicol group	Tilmicosin group	Florfenicol group	Tilmicosin group
Number of isolates	26	30	1	4
Pasteraulla haemolytica	10	14	1	-
Pasteraulla multocida	11	8	-	1
Haemophilus somnus	4	6	-	2
P. haemolytica + P. multocida	1	2	-	1

Table 4 : The mean blood levels (ug/ml) of florfenicol and tilmicosin. (n = 5).

Time of sampling	Florfenicol (mean ± SD)	Tilmicosin (mean ± SD)
Pre-treatment	0	0
1 hour	8.67 ± 0.48	2.21 ± 0.26
4 hour	8.22 ± 0.68	0.49 ± 0.23
8 hour	7.32 ± 0.41	0.82 ± 0.19
12 hour	4.2 ± 0.27	0.6 ± 0.11
1 day*	2.61 ± 0.39	0.38 ± 0.04
2 day	0.81 ± 0.16	0.17 ± 0.03
3 day	0.49 ± 0.04	0.085 ± 0.006
4 day	0.37 ± 0.04	0.066 ± 0.01
5 day	0.26 ± 0.08	0.025 ± 0.005
6 day	ND	ND
T max (h)	3	0.5
T1/2 = (h)	44	30

* 1day after 2nd dose in florfenicol treated group.

ND = not detected.

T_{max} = time at which drug reaches to maximum concentration.

$T_{1/2}$ = time at which drug reaches to its half concentration.

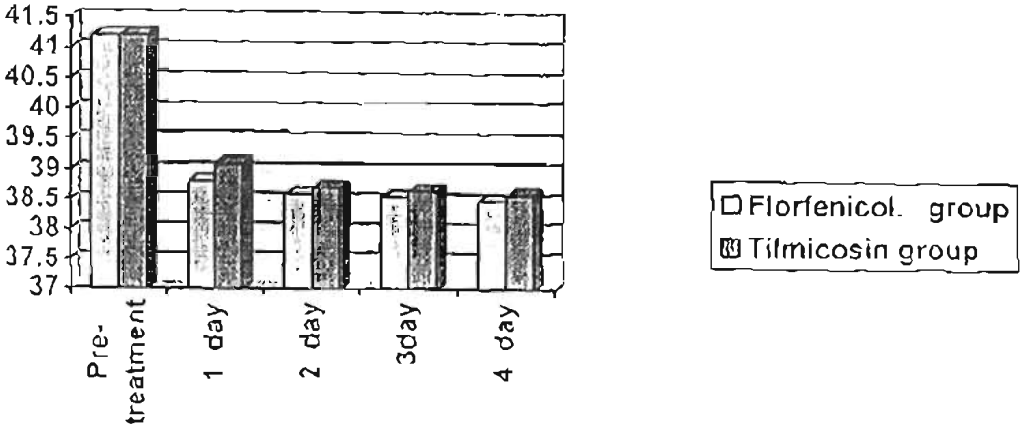

Fig. 1 : The main daily reduction of rectal temperature

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الملخص العربى

دراسات وبائية وعلاجية على الأمراض التنفسية فى العجول

المشتركون فى البحث

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- أجريت هذه التجربة فى إحدى مزارع محافظة الغربية على ٤٥٢ عجل تتراوح أعمارهم من ١-١٨ شهر وذلك خلال شتاء عام ١٩٩٩-٢٠٠٠ وذلك لدراسة وبائية المرض وتقييم كفاءة عقارى الفلورفينيكرل والتلموكوزين فى السيطرة على المرض.
- تم تشخيص المرض فى ١٠٤ عجل على أساس إرتفاع درجة الحرارة ≥ ٥ر٤٠م مع ظهور أعراض تنفسية وتم علاج ٥٣ عجل بحقن جرعتين من الفلورفينيكول فى العضل ٢٠مجم / كيلوجرام بينهم ٤٨ ساعة وعلاج ٥١ عجل بحقن تلموكوزين تحت الجلد جرعة واحدة بمعدل ١٠ مجم / كيلو جرام من وزن العجل وقد تم متابعة العجول المعالجة لمدة ٢٨ يوم وتم أخذ مسحات من العجول المصابة وعينات من الرئتين من تلك التى نفقت أو ذبحت إضطرارياً خلال الدراسة وذلك لعزل المكروب المسبب كما تم أخذ عينات دم من خمسة عجول من كل مجموعة علاجية لقياس مستوى كل من الدوائين ومداه العلاجى.
- أظهرت النتائج أن أعلى نسبة إصابة فى العجول كانت فى المرحلة السنية من ٣-٦ شهور وأن الميكروب المسبب للمرض الذى تم عزله هو الباستريلا والهيموفولس وأن مستوى الفلورفينيكول فى الدم يستمر لمدة ٤٨ ساعة من ثانى جرعة بينما يستمر مستوى التلموكوزين ٧٢ ساعة. كما أظهرت النتائج كفاءة كل من العقارين فى علاج المرض وخفض درجة الحرارة خلال ٢٤ ساعة من بدء العلاج وكانت نسبة الإستجابة فى العجول التى عولجت بفلورفينيكول (٤٥ر٩٢٪) وتلك التى عولجت بتلموكوزين (٤٣ر٧٨٪).