

## Clinical Efficacy of Cefalone-1 (A New Cephalosporin-Fluoroquinolone Antibacterial) in Dogs with Various Respiratory Bacterial Infections

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**Abstract:** A multicentric blind-clinical study, gathering 240 dogs of different breeds, ages and both genders was carried out. All dogs were affected of either one or both these diseases: acute tracheobronchitis and pneumonia. The severity of the respiratory problem was further classified into three categories for each diagnosis (nine categories in all). Dogs were randomly assigned, using an incomplete block design, to one of four treatments to complete 20 patients per grade of respiratory disease or 60 patients per antibacterial. Bacteriological analysis of nasal swabs and respiratory secretions was carried out before treatment and 48 hours after the last injection of the corresponding antibacterial. Independently from classification of the disease, treatments were as follows: group CEA, with cefotaxime 20 mg kg<sup>-1</sup> IM, *bid*; group CEO with cefalone-1 in tablets for oral administration 20 mg kg<sup>-1</sup> *tid*; group ENR with enrofloxacin 10 mg kg<sup>-1</sup> SQ *sid* and group CEIM with the cefalone-1 injected intramuscularly, at a dose of 10 mg kg<sup>-1</sup> *bid*. Tolerance, defined as the absence of clinical adverse reactions and hematological changes, and clinical efficacy, assessed as the absence of clinical signs, were recorded. Overall efficacy was as follows: group CEA: 79.14%; group CEO: 79.76%; group ENR: 70.83% and group CEIM: 93.3%. The total mean number of days needed to clinical cure were: group CEA: 13.3; group CEO: 15.0; group ENR: 15.5, and group CEIM: 11.7. Cefalone-1, injected intramuscularly, stood out in this study as the best choice for bacterial respiratory diseases in dogs.

**Key words:** Clinical efficacy, cefalone-1, cephalosporin-fluoroquinolone, various respiratory, bacterial infections

### Introduction

The so-called cefalones, are a family of antibacterial agents derived from a new chemical moiety that can be named cefaquinolones or cefalones, an original structure that can offer more than 110 possible antibacterial analogs. It basically derives from coupling a 7-aminocephalosporanic moiety to the 3-carboxylic acid group of a fluoroquinolone through a carboxamide linkage, as seen in Fig. 1. *In vitro* studies with one cefalone have shown an outstanding broad spectrum of action and bactericidal potency, similar to third generation cephalosporins (Jhonson *et al.*, 1996; Méndez, 1996 and Carmona, 2002). Acute toxicological studies in rats and mice and subchronic toxicity in rodents and pigs have shown that various of these agents have very low toxicity. Also, excellent clinical efficacy for respiratory diseases has been reported after oral administration in poultry (Sumano *et al.*, 1998) and respiratory problems in dogs (Sumano *et al.*, 1998) and a preliminary trial also suggested good efficacy for empirical treatment of mastitis (Sumano *et al.*, 1996).

Using a sensitive microbiological analytical technique, pharmacokinetics was defined for a cefalone in dogs (Sumano *et al.*, 1996 and Ovalle, 1996). Fast clearance from blood and an extremely high apparent volume of distribution value ( $Vd_{AUC} > 7 \text{ L kg}^{-1}$ ) were reported. This latter pharmacokinetic feature could be interpreted as a demonstration that the cefalone becomes inactivated when entering the blood stream or

else, that it is sequestered in a body compartment, causing that only minor quantities reach the plasma. Conversely, it may be that this cefalone indeed possesses unique penetration into tissues and, consequently, a potentially exceptional biocidal action. Additionally, a dual mechanism of antibacterial action has been proposed for cefalones (Jhonson *et al.*, 1996), hence a potential benefit in using this new antibacterial agent in respiratory bacterial diseases in dogs becomes feasible. Consequently, as part of the pharmaceutical and pharmacological development of this drug, a multicentric clinical trial for the treatment of respiratory diseases in dogs was carried out. Because cefalone possesses both cephalosporanic and fluoroquinolonic groups, treated control groups with cefotaxime and enrofloxacin were included. For ethical reasons an untreated control group was omitted. Cefotaxime is a potent third generation cephalosporin, often successfully used for treatment of infectious diseases in other species and it is reasonable to believe that they may be effective in dogs (Sumano *et al.*, 2004 and Guerrini *et al.*, 1986). Enrofloxacin has become a popular choice among clinicians, because its outstanding activity *in vitro* and because it has been shown to possess potentially good clinical efficacy for the treatment of respiratory infections in dogs (Angus *et al.*, 1997).

### Materials and Methods

This study was carried out in 32 veterinary hospitals

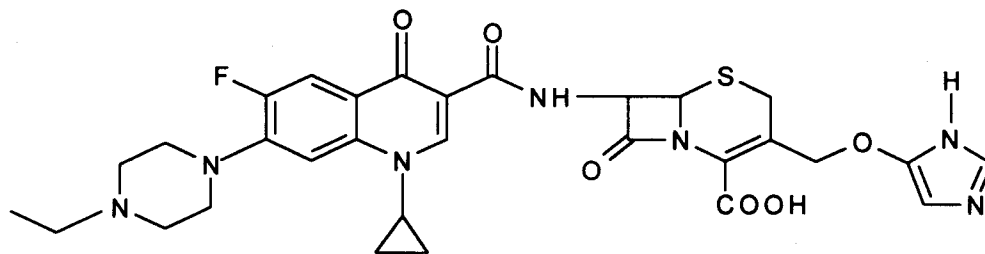


Fig. 1: Structural formula of cefalone-1

Table 1: Signs and laboratory findings used to diagnose ongoing respiratory disease. Severity was further classified as mild, moderately-severe and severe, based on severity of signs and laboratory findings

Clinical Signs and Lab. Findings	Tracheobronchitis	Pneumonia	Tracheobronchitis and Pneumonia
Tachypnea	Rarely or slight	Moderate to severe	Severe
Dyspnea	Rarely present	Often	Almost always
Cough	Almost always	Occasionally	Occasionally
Refusal to efforts	Walking upstairs	Rapid walking	Walking
Bronchovesicular breath sounds	Located in trachea and basal part of thorax	Harsh sounds or absence of breathing sounds in auscultation area	Same plus high pitch sounds in expiration
Fever	Variable but always present	Variable but always present	Variable but always present
Leukocytosis	> 20,000/mm <sup>3</sup>	> 20,000/mm <sup>3</sup>	> 20,000/mm <sup>3</sup>
Radiographic findings	Minimal or none	Consolidation and increased density	Consolidation and increased density
Split in second cardiac sound	No	Some patients	Most patients
Nasal secretion	Almost always	In less than 50% of patients	Almost in all patients

and clinics located in Mexico City during an 8 month period from September 1<sup>st</sup>, 2002 to April 30<sup>th</sup>, 2003. Patients were classified as affected of tracheobronchitis, pneumonia or both, and received no treatment before entering this protocol. Each of these disease entities was diagnosed based on clinical signs and laboratory findings as described in Table 1. Then, animals were further classified into three categories of severity (mild (m), moderately severe (ms) and severe (s)) based on the gravity of clinical signs, as decided by two previously trained, certified clinicians working in each location. Four trained veterinary monitors gathered information from these hospitals and clinics twice a week and made a follow up of cases either in the clinic or at the patient's home, ensuring that medication was properly administered and carrying out clinical evaluations. Only the first twenty cases of each severity grade, for each tested drug, were included in this trial. Table 2 describes the main features of the patients included therein.

**Treatments**. Commercial labels were removed and substituted by codified letters and instructions for use as follows: group CEA: powder cefotaxime (Claforan® 500 mg from Roche, Mexico) was first diluted in its

commercial vehicle, injected intramuscularly at a dose of 20 mg kg<sup>-1</sup> every 12 hours and the remaining solution stored at -4°C for no longer than 48 hs; group CEO: consisting in 50, 100 and 200 mg tablets of cefalone-1 were orally administered at a dose of 20 mg kg<sup>-1</sup> *tid*; group ENR: enrofloxacin solution (Baytril®, Bayer Mexico) was injected SQ once a day at a dose of 10 mg kg<sup>-1</sup>; Group CEIM: powder cefalone (Sumano *et al.*, 1998) was diluted and shaken for no less than two minutes immediately prior to injection and administered via IM at a dose of 10 mg kg<sup>-1</sup> every 12 hours; remnant solution was stored at -4°C not longer than 48 hs. Treatment was concluded when none of the signs listed in Table 1 could be detected.

**Laboratory evaluations.** Bacteriological analysis of nasal swabs and respiratory secretions was carried out before treatment and 48 hours after the last injection of the corresponding antibacterial. Samples were sent to reference laboratory in an ice-chilled box and processed as customary for identification of possible etiology, under standard laboratory procedures. Then, an antibiogram using the Kirby-Bauer method under NCCLS standards was carried out for each isolate, using 30 µg/disk of cefotaxime and cefalone-1. Also,

Table 2: General characteristics of patients affected of respiratory diseases and treated with: cefotaxime (CEA) 20 mg kg<sup>-1</sup> IM, *bid*; cefalone-1 tablets for oral administration (CEO) 20 mg kg<sup>-1</sup> *tid*; enrofloxacin (ENR) 10 mg kg<sup>-1</sup> SC *sid* or cefalone-1 for IM administration (CEIM) 10 mg kg<sup>-1</sup> *bid*

Group	Disease	Sex		Age (X ± SD)	Severity grading		
		Male	female		Mild	Moderately severe	Severe
CEA	Tb	8	12	3.2 ± 1.4	8	7	5
	Pn	7	13	5.2 ± 1.8	4	6	10
	Tb/Pn	9	11	6.9 ± 2.2	3	3	14
CEO	Tb	13	7	2.8 ± 1.8	8	6	6
	Pn	11	9	5.6 ± 2.4	3	5	12
	Tb/Pn	6	14	7.2 ± 1.8	2	4	14
ENR	Tb	8	12	3.0 ± 1.0	7	7	6
	Pn	7	13	5.8 ± 2.4	4	4	12
	Tb/Pn	12	8	7.2 ± 2.6	2	2	16
CEIM	Tb	9	11	4.2 ± 1.6	9	5	6
	Pn	12	8	6.2 ± 1.8	5	4	11
	Tb/Pn	8	12	7.8 ± 2.8	3	2	15

Table 3: Summary of relevant data obtained in patients affected of respiratory diseases and treated with: cefotaxime (CEA) 20 mg kg<sup>-1</sup> IM, *bid*; cefalone-1 tablets for oral administration (CEO) 20 mg kg<sup>-1</sup> *tid*; enrofloxacin (ENR) 10 mg kg<sup>-1</sup> SC *sid* or cefalone-1 for IM administration (CEIM) 10 mg kg<sup>-1</sup> *bid*

Severity	Diagnosis/no.Of Patients			Days to Clinical Cure			Total	Cure Rate(%)*				Not Cured/Relapses**			
	Tb	Pn	Tb/Pn	Tb	Pn	Tb/Pn		Tb	Pn	Tb/Pn	Total	Tb	Pn	Tb/Pn	
CEA	Mild	8	4	3	4.14	13.0	14.0	100	66	66		0/0	1/0	1/0	
	Moderately severe	7	6	3	6.0	16.0	17.6	13.3	100	100	100	79.14	0/0	0/0	0/0
	Severe	5	10	14	7.2	19.0	23.4		100	71.4	71.42		0/0	4/1	4/1
CEO	Mild	8	3	2	4.0	14.3	16.5	15.0	100	100	100	79.76	0/0	0/0	0/0
	Moderately severe	6	5	4	6.0	19.2	20.0		100	100	75.0		0/0	0/1	1/0
	Severe	6	12	14	8.6	22.2	24.4		100	66.6	64.28		0/0	4/0	5/0
ENR	Mild	7	4	2	6.5	15.5	13.0	15.5	100	100	100	70.83	0/0	0/0	0/0
	Moderately severe	7	4	2	9.1	23.0	12.0		100	75.0	50		0/0	1/1	1/0
	Severe	6	12	16	11.33	25.0	23.8		100	66.6	62.5		0/0	4/0	6/0
CEIM	Mild	9	5	3	3.5	13.0	12.0	11.7	100	100	100	93.3	0/0	0/0	0/0
	Moderately severe	5	4	2	4.0	14.0	13.5		100	100	100		0/0	0/0	0/0
	Severe	6	11	15	6.8	18.4	20.2		100	81.8	80.0		0/0	2/0	3/0

\*No deaths were recorded and patients that were classified as not cured, were transferred to a different treatment-protocol. \*\*Relapses were recorded within 1 month after the patient was regarded as cured. Tb = tracheobronchitis; Pn = pneumonia; Tb/Pn = tracheobronchitis and pneumonia.

pre- and post-treatment values for aspartate amino transferase (ASP), alanine amino transferase (ALT), urea, creatinine and blood hematologic values were measured by a reference laboratory and using standard techniques.

The following variables were recorded: number of patients treated/number cured. A given patient was regarded as clinically cured if none of the clinical signs listed in Table 1 were detected by both the monitor and the clinician. A not-cured patient was that individual whose clinical signs remained unchanged or with little improvement. Number of days of treatment needed to achieve clinical cure and relapses within the next month, were recorded. Also an alert call to monitors was established to verify and collect any systemic

adverse drug reactions and local tissue reactions. Statistical analysis included Ji<sup>2</sup>, Kappa analysis, as well as analysis of variance followed by Bonferroni *t* test for efficacy and number of days to cure.

### Results

In all, 130 bitches and 110 male-dogs were included in this trial. Ages ranged from 4 months to 12 years old. Table 3 shows the clinical response observed for the 60 patients per antibacterial and for the four antibacterial agents, the number of days required for clinical cure. Overall efficacy was as follows: group CEA: 79.14%; group CEO: 79.76%; group ENR: 70.83% and group CEIM: 93.3%. The total mean number of days needed to clinical cure were: group

CEA: 13.3 ; group CEO: 15.0; group ENR: 15.5, and group CEIM: 11.7. Although the number of dogs that reached clinical cure was greater in the CEIM group, a  $J_i^2$  and a *Kappa* analysis revealed lack of statistically significant differences among groups ( $P > 0.05$ ). However, an ANOVA test and Bonferroni "t" test showed some statistically significant differences *i.e.*, CEA and CEO groups had similar efficacies, ENR had the lowest efficacy in this study and the CEIM the best. The same differences are observed for the number of days needed for clinical cure. Again, group CEIM required less number of days to achieve clinical cure. Dogs that did not experience clinical improvement when treated with the antibacterial alone were regarded as treatment-failure and were then handled successfully, out of protocol, with a double scheme of antibacterials including gentamicin and the formerly utilized antibacterial plus antifungal therapy with fluconazole. Additionally, non salicilate

antiinflammatory agents (carprofen or zafyrlukat); supplementary oxygen tips; mucolytics (ambroxol or bromhexine); bronchodilator agents (salbutamol or clenbuterol) and 80 ml  $kg^{-1} day^{-1}$  of Hartmann solution were discretionally administered. Hematologic and biochemical values did not show appreciable differences excepting the leukocyte counts (Table 4). All successfully treated animals completed their antibacterial treatment-scheme, and no side effects were reported or detected.

Bacteriological analysis revealed that before treatment, the main aetiological agent were *Staphylococcus sp.* (21.66%); *Escherichia coli* (13.75) and *Bordetella sp.* (12.50%). Some samples gave negative to bacterial growth *Escherichia coli* (11.5%) and *Haemophilus sp* (8.5%). The complete list of bacteria involved in these respiratory problems is presented in table 5. Bacteria were recovered from clinically cured animals in almost 40% of the cases.

Table 4: Mean values for some blood chemistry and haematological measurements in dogs affected with various respiratory bacterial disease, before and after completion of the treatment with one of the following antibacterials: cefotaxime (CEA) 20 mg  $kg^{-1}$  IM, *bid*; cefalone-1 tablets for oral administration (CEO) 20 mg  $kg^{-1}$  *tid*; enrofloxacin (ENR) 10 mg  $kg^{-1}$  SC *sid* or cefalone-1 for IM administration (CEIM) 10 mg  $kg^{-1}$  *bid*

Group Blood chemistry	CEA		CEO		ENR		CEIM	
	Before	After	Before	After	Before	After	Before	After
ASP	11.47	12.11	9.38	9.98	11.25	12.12	11.45	10.65
ALT	6.28	7.03	5.95	5.84	6.40	7.33	7.33	6.50
Urea	0.08	0.07	0.41	0.35	0.1	0.23	0.32	0.14
Creatinine	1.21	1.33	1.01	1.21	1.0	1.22	1.05	0.98
Haematology	Before	After	Before	After	Before	After	Before	After
Total leukocytes $\times 10^9/\mu l$	22.29	9.52	32.33	12.01	33.12	10.2	30.5	9.12
Neutrophiles %	69.55	67.84	68.21	65.79	70.21	68.56	69.21	68.35
Lymphocytes %	2.46	2.38	3.05	3.29	4.2	4.6	4.8	3.8
Erythrocytes x $10^{12}/\mu l$	6.39	6.41	7.83	7.31	5.84	6.21	6.12	6.02
Plateletes x $10^9/\mu l$	409	390	498	489	459	489	467	465
Plasma protein $g dl^{-1}$	7.81	7.77	8.35	7.80	7.98	7.68	8.02	8.06

Table 5: Bacterial isolates from dogs affected of an airway bacterial infection (tracheobronchitis, pneumonia, and tracheobronchitis with pneumonia) treated with one of the following antibacterials: cefotaxime (CEA) 20 mg  $kg^{-1}$  IM, *bid*; cefalone-1 tablets for oral administration (CEO) 20 mg  $kg^{-1}$  *tid*; enrofloxacin (ENR) 10 mg  $kg^{-1}$  SC *sid* or cefalone-1 for IM administration (CEIM) 10 mg  $kg^{-1}$  *bid*

Bacteria	No. of isolates		No. of cases not cured
	Before	After	
<i>Staphylococcus sp.</i>	42	23	3 CEA; 2 CEO; 4 ENR; 1 CEIM
<i>Streptococcus sp.</i>	23	12	1 CEA; 1 CEO; 2 ENR
<i>Escherichia coli</i>	18	15	1 CEO
<i>Pseudomona sp.</i>	8	4	2 CEA; 3 CEO; 1 ENR; 2 CEIM
<i>Klebsiella sp.</i>	12	3	1 CEA; 1 CEO; 1 ENR
<i>Pasteurella sp.</i>	16	7	
<i>Bacillus sp.</i>	23	12	2 CEA; 2 ENR
<i>Bordetella sp.</i>	28	11	
<i>Proteus sp.</i>	8	0	1 CEA; 2 CEO; 2 ENR; 1 CEIM

## Discussion

Due to the unfavorable cost:benefit ratio derived from developing new antibacterials for veterinary medicine, research on this field tends to focus on agents for human medicine. Hence, no new antibacterials agents have been introduced for small animal clinic in a long time, and it is unlikely to think that in the foreseeable future a new antibacterial drug, other than cefalone, will be available for this sector. However, if this drug proves to possess low toxicity as well in human beings, it may encounter better perspectives in this area of medicine. In either case, the drug must not be regarded as a new cephalosporin neither as a different fluorquinolone because it appears to possess unique pharmacological and clinical properties. At least this cefalone acts as a new entity and according to unpublished data its biotransformation appears to be minimal or non-existent.

It has been stated in previous studies with dogs that a cefalone exhibited an unusual high apparent volume of distribution ( $V_{dAUC} > 7 \text{ L kg}^{-1}$ ) and a rapid clearance value. The former feature could explain the outstanding efficacy observed in this trial, while the latter may be a disadvantage that would require shortening of dosing intervals or re-designing the pharmaceutical formulation of most cefalones, perhaps utilizing a vehicle capable of prolonging its plasma concentrations.

Efficacy observed in this trial can not be explained only in terms of tissue distribution. Enrofloxacin also possesses high apparent volume of distribution in dogs (Küng *et al.*, 1983), but efficacy with this agent appears to be lower than the one observed for cefalone. In contrast, cefotaxime has a lower apparent volume of distribution at steady state ( $0.48 \text{ L kg}^{-1}$ ) (Guerrini *et al.*, 1986) and yet its clinical efficacy was somewhat comparable to that of enrofloxacin. Other variables must be taken into account, such as the biocide activity of these antimicrobial agents in the milieu generated by bacterial respiratory infections. It has been shown that biological fluids can affect the antibacterial action of many agents (Fang and Vikerpuur, 1995), a factor rarely assessed *in vitro* under standard conditions. For many antibacterial drugs, it appears that minimal inhibitory concentrations obtained *in vitro* are only a relative reference for antibacterial activity *in vivo*. In contrast, the clinical efficacy obtained in this multi-center trial, is necessarily confronted with these factors. From such a perspective, these results comply well with the idea that cefalone-1 has a potent biocide capability and that it is not altered in the media generated by a bacterial respiratory infection. However, due to the clinical nature of this trial, lung and sputum samples to determine concentrations of these antibacterial agents could not be done, and therefore, speculation on the pulmonary diffusion vs. biocide activity of these agents *in vivo*, awaits confirmation.

The rapid clinical improvement and the lack of adverse

drug reactions with this cefalone-1, as assessed through the hematologic tests and clinical evaluations, suggests that this new antibacterial could be safely used in dogs, at least in dosing schedules no longer than 21 days. An important feature of this agent is that no signs of arthralgia, as part of the clinical signs of cartilage erosion, were observed, a feature closely related to fluoroquinolones (Egerbacher *et al.*, 2001 and Burkhardt *et al.*, 1990). However, it would also be necessary to confirm for cefalone-1, the apparent lack of this side effect. In summary, results obtained could be taken to indicate that this drug is potentially useful in dogs for the treatment of respiratory infections. Also, data here presented may be taken as a step in the pharmacological development of cefalones for use in bacterial diseases in human beings.

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