Clinical success of clarithromycin, amoxicillin-clavulanic acid, enrofloxacin and doxycycline in dogs with infectious tracheobronchitis

ABSTRACT

Canine infectious tracheobronchitis (ITB) is a highly contagious disease of dogs expressed with remarkable respiratory signs. Therapy with antibiotics in canine ITB still remains questionable. The purpose of this study was to compare the clinical success of clarithromycin, amoxicillin-clavulanic acid, enrofloxacin and doxycycline in the treatment of canine ITB. Client-owned dogs with canine ITB signs (n=60) were enrolled in this prospective, controlled, and randomized blinded clinical trial. A computer-generated list randomization was employed to assign the dogs equally into the Group CLA: clarithromycin (25 mg/kg, PO), the Group AMX: amoxicillin and clavulanic acid (25 mg/kg, PO), the Group ENR: enrofloxacin (2.5 mg/kg, PO), and the Group DOX: doxycycline (5 mg/kg, PO). The administration of CLA alleviated the cough sign earlier than DOX. The recovery time of oculonasal discharge in group CLA were also earlier compared to the other groups. The tracheal sensitivity also disappeared earlier in the Groups CLA and AMX. In conclusion although there is no always statistically significance between groups, clarithromycin appears to be superior to other antibiotics suggesting that it can be the first antibiotic choice to alleviate the ITB signs in dogs.

Keywords: Antibiotics, dog, infection, tracheobronchitis

INTRODUCTION

Canine infectious tracheobronchitis (ITB) is a highly contagious disease, associated with the respiratory signs, in dogs (Ford, 2012; Hawkins, 2009). In recent literatures, the disease is called as canine respiratory disease complex including multifactorial etiological pathogens such as viruses (adenovirus 2, parainfluenza, coronavirus, influenza, distemper, coronavirus, herpes and reovirus) and bacteria (Mycoplasma spp and Bordetella bronchiseptica) (Hawkins, 2009, Reagan et al., 2020), alone or in combination (Ford, 2012; Kaczorek et al., 2016; Priestnall et al., 2014). Severe clinical signs of the disease can be especially associated with coinfections secondary to multiple pathogens or bacterial agents. While adult dogs may overcome the disease, puppies and young dogs have more severe clinical signs (Hawkins, 2009). Acute honking cough elicited on gently tracheal palpation in canine ITB is remarkable. When the presence of multifactorial pathogens oculonasal discharges also accompany the coughing (Petersen and Kutzler, 2012). Infectious tracheobronchitis is generally self-limiting and outpatient treatment is usually recommended. However, ITB can progress to bronchopneumonia when the immune system is compromised (Hawkings, 2009; Petersen and Kutzler, 2012).

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Research Article

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Antimicrobiotherapy for canine ITB is controversial (Reagan et al., 2020; Köse et al., 2022). Although some reports state that antimicrobials fail to resolve the disease (Hawkings, 2009) several antibiotics including doxycycline, chloramphenicol, enrofloxacine, trimethoprim/sulpha and amoxicillin/clavulanate are often empirically prescribed (Ford, 2012). Empiric antibiotherapy should be based on the most likely agent to be present (Lappin, 2017). Studies cultured the etiological pathogens in dogs with ITB revealed often Bordetella spp. This controlled clinical study was conducted to evaluate clinical responses to various antibiotics in dogs with ITB.

MATERIALS AND METHODS

Study population

Data were collected from 69 dogs including Terrier type (n = 7), German Shepherd (n = 9), Golden Retriever (n = 9), Kangal (n = 4), Cocker (n = 2), Rotweiler (n = 9), Boxer (n = 5) and mixed breed (n = 24). Nine dogs were excluded from the study because of previous antibiotic therapy (Rotweiler, n = 2; mixed breed, n = 2) and concurrent systemic disease including diarrhea and cardiomyopathy (German Shepherd, n = 4; Boxer, n = 1). A total of 60 dogs continued on the study. All dogs had received essential antiparasitic therapy and routine vaccination against infections such as rabies, distemper, hepatitis, parvoviral enteritis and leptospirosis. They were fully vaccinated against these infectious agents every year. The dogs were not in contact with each other and only one dog resided in each household. The dogs did not receive any medication at the time of referral and during diagnostic applications. The inclusion criteria were the presence of ITB signs including spontaneous cough, oculonasal discharge, and retching induced by gentle palpation of the laryngeal and tracheal regions (Ford, 1995; Ford, 1998; Thrusfield et al., 1991). Dogs on antibiotic therapy within 7 days and have exhibited the signs of concurrent systemic disease in their medical history, during clinical examination, or based on their complete blood count were excluded from the study. Written owner consent was also obtained in the study.

Study design

In this prospective randomized trial, all dogs were examined by a standardized protocol including clinical examination (fever, appetite, weight, mucosal color, capillary refill time, lung and heart auscultation, lymph nodes, abdominal palpation), blood analysis (complete blood count and, serum profiles including urea, creatinine, total bilirubin, albumin, alanine aminotranspherase, aspartat aminotranspherase, alkaline phosphatase, gama glutamil transpherase and creatine kinase using Exigo Eos Vet Hematology Analyzer USA and Erba XL 600 Biochemical Analyzer, Russia) , and thoracic radiography (VD/LL). Blood samples were collected from the cephalic vein into EDTA tubes. Complete laryngopharyngeal diagnostic workup using a video endoscope (Video endoscopy system, Eickemeyer, Germany) was also performed in all dogs. Using a computer-generated list randomization (Microsoft Excell, 2016), dogs were divided into 4 treatment groups: Group CLA (n = 15): clarithromycin (25 mg/kg, PO), Group AMX (n = 15): amoxicillin and clavulanic acid (25 mg/kg, PO), Group ENR (n = 15): enrofloxacin (2.5 mg/kg, PO) and Group DOX (n = 15): doxycycline (5 mg/kg, PO). All prescribed therapies are administered twice daily for one week. Alleviation in clinical signs (cough, oculonasal discharge and tracheal sensitivity) was evaluated daily by a physician who was blind to the treatments. Termination of oculonasal discharge and tracheal sensitivity confirmed upon physical examination. Termination of cough was also based on the owner's information.

Statistical analysis

Kaplan Meier survival analysis was used to calculate mean recovery times and life curves. To

test the difference between the life curves, Breslow test was used. Pairwise comparisons were done using Wilcoxon test. P<0.05 was considered as significant in all analyses. All statistical analysis were performed by using SPSS 14.01 (SPSS Inc., Chicago) package programme for Windows.

RESULTS

The mean age of the dogs enrolled in the study was 3.03 ± 0.13. The mean age as well as gender and breed distributions did not vary among the groups. The cough recovery times for dogs in Group CLA, ENR, AMX and DOX were 3.73 ± 0.48 d, 4.33 ± 0.39 d, 4.60 ± 0.45 d and 5.66 ± 0.37 d, respectively (Table 1, Figure 1).

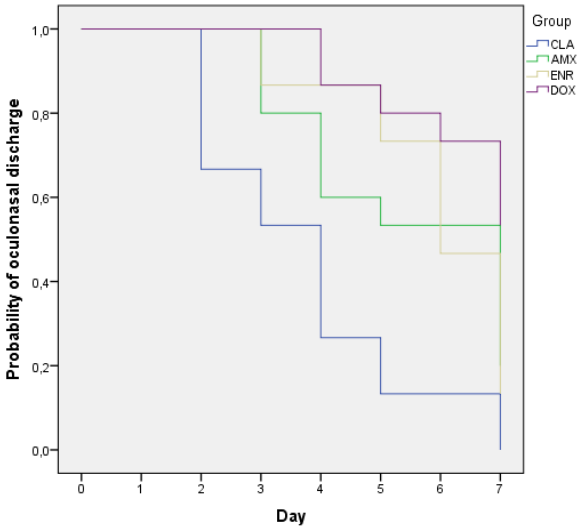

Figure 1. Probability of coughing after treatment of each antibiotics.

Table 1. Means for recovery time of coughing

Groups	Mean			
	Day	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
CLA [a]	3.733	0.485	2.783	4.684
AMX [ab]	4.600	0.450	3.718	5.482
ENR [a]	4.333	0.396	3.557	5.110
DOX [b]	5.667	0.373	4.935	6.398

[a,b]: Different lower cases indicate statistical differences (Wilcoxon test). (Kaplan-Meier, Breslow test, P=0.032) Significance levels are P<0.05. DOX: Doxycycline, CLA: Clarithromycin; AMX: Amoxicillin clavulanic acid; ENR: Enrofloxacin.

The recovery times of oculonasal discharge and tracheal sensitivity were also shown in Table 2 and Table 3 (Figure 2, Figure 3), respectively.

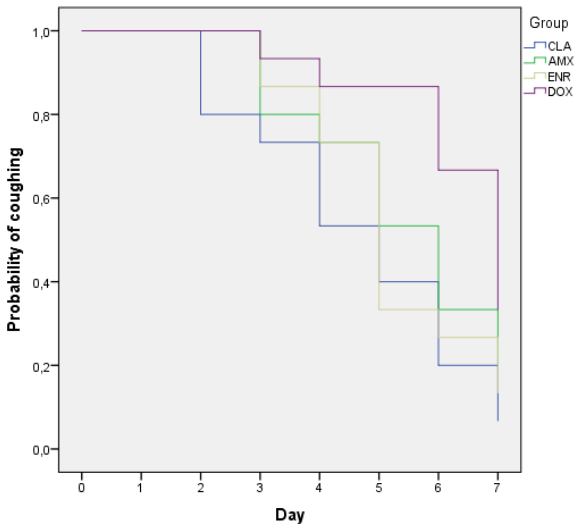

Figure 2. Probability of oculonasal discharge after treatment of each antibiotics.

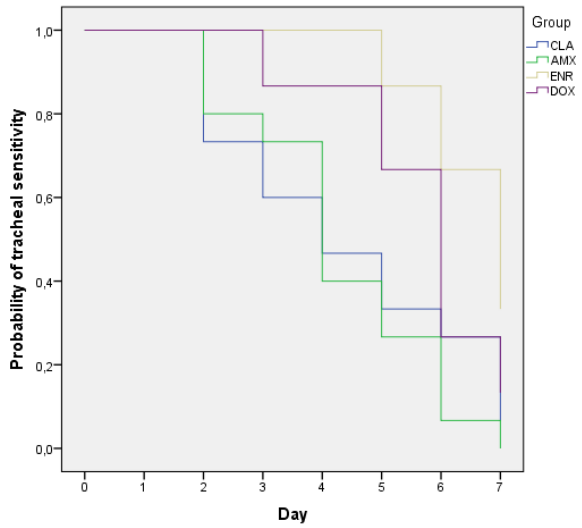

Figure 3. Probability of tracheal sensitivity after treatment of each antibiotics.

DISCUSSION

Affected dogs with ITB have the clinical signs of oculonasal discharge and paroxysmal cough induced by gentle palpation of the tracheal region.

Although ITB in adult dogs considered as self-limiting and non-systemic disease, it can progress to more severe systemic clinical signs including weight loss, persistent anorexia, fever, diarrhea, retinitis or seizures in puppies and immunocompromised dogs (Hawkins, 2009; Nelson and Couto, 2009). Dogs with only non-systemic clinical signs of ITB and normal reference ranges in complete blood counts enrolled in the study. They had been immunized against the infections of rabies, distemper, hepatitis, parvoviral enteritis and leptospirosis. The diagnosis of ITB in dogs is based on typically clinical signs and the history of the exposure to other dogs (Ford, 2012; Petersen and Kutzler, 2012). Although it has been reported that additional diagnostic applications including thoracic radiography and culture of the airway fluids are not indicated, remarkable and necessary in uncomplicated cases (Ettinger and Kantrowitz, 2012; Petersen and Kutzler, 2012), possible role of congenital respiratory problems were also ruled out by the thoracic radiography in this study. The culture of the airway fluids has not been performed. The usage of antimicrobials in dogs with ITB is still questionable. While some literatures (Hawkins, 2009) regarding the usage of antibiotics have described the resolving of the ITB spontaneously regardless of any specific treatment implemented, some of them (Ford, 2012) have justified the usage of empiric antimicrobial therapy before the complication by overt bacterial pneumonia in dogs with ITB. In various studies considering the antimicrobial sensitivities of *Bordetella bronchiseptica*, isolates have been reported as susceptible to tetracycline, DOX, AMX, and ENR (Angus et al., 1997; Speakman et al., 2000). However, the usage of CLA to alleviate the clinical signs in dogs with ITB have not been previously defined. The purpose of the current study was to compare the effectiveness of CLA, AMX, ENR and DOX in treatment of canine ITB. CLA is a broad-spectrum macrolide using in respiratory tract infections in human medicine (Evangelos et al., 2008; Langtry and Brogden, 1997). It is also safe and suitable for therapeutic use in dogs (Vilmgnyi et al., 1995). In this study CLA was well tolerated and no side effects were noted in dogs with ITB as well.

Table 2. Means for recovery time of oculonasal discharge

Groups	Mean			
	Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
CLA [a]	2.733	0.441	1.868	3.599
AMX [b]	4.667	0.496	3.695	5.639
ENR [bc]	5.067	0.383	4.317	5.817
DOX [c]	5.933	0.371	5.207	6.660

[a,b,c]**:** Different lower cases indicate statistical differences. (Wilcoxon test). (Kaplan-Meier, Breslow test, P<0.001), DOX: Doxycycline, CLA: Clarithromycin; AMX: Amoxicillin clavulanic acid; ENR: Enrofloxacin.

Table 3. Means for recovery time of tracheal sensitivity

Grup	Mean			
	Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
CLA [a]	3.467	0.532	2.424	4.510
AMX [a]	3.267	0.408	2.467	4.066
ENR [c]	5.867	0.264	5.348	6.385
DOX [b]	4.800	0.368	4.080	5.520

[a,b,c]**:** Different lower cases indicate statistical differences. (Wilcoxon test). (Kaplan-Meier, Breslow test, P<0.001), DOX: Doxycycline, CLA: Clarithromycin; AMX: Amoxicillin clavulanic acid; ENR: Enrofloxacin.

If fever, lethargy and anorexia without clinical evidence of pneumonia are present, the working group about the antimicrobial use guidelines for treatment of canine ITB recommends administration of DOX for 7-10 d as the first-line antibiotic (Lappin et al., 2017). Although it is difficult to compare this study with the present one, contrary to suggestions of working group (Lappin et al., 2017) cough recovery time at the end of the treatment was earlier in group CLA compared to other groups. Oculonasal discharge recovery time was also very late in group DOX at the end of the treatment. The same working group has also recommended the usage of AMX to be alternate first-line antibiotic in failure of DOX. Compared to group CLA, cough and oculonasal discharge recovery times were later at the end of the treatment in groups AMX. Working group (Hawkins, 2009; Lappin et al., 2017) has not also recommended the usage of fluoroquinolones even if the choice of DOX and AMX is ineffective. In this study, treatment with ENR was more effective to alleviate the signs of cough and oculonasal discharge compared to DOX. This may be related to the number of cases in the presented study. In a study from England revealed significant decrease in coughing in canine ITB with the use of AMX (Thrusfield, 1991). They (Thrusfield, 1991) also used some other drugs including ampicillin/amoxicillin-corticosteroid or trimethoprim/sulphonamide-corticosteroid combinations. Although comparison of the studies are difficult, in the study presented here cough recovery times were later in Groups AMX (4.6±0.45), ENR (4.33±0.39) and DOX (5.6±0.37) compared to Group CLA (3.7±0.48). In this study, we use only relevant antibiotics without other medications including corticosteroids. So significant decrease of coughing in the study of Thrusfield, (1991) could be associated the effect of corticosteroids. The lack of pre- and post-treatment culture results of pathogens isolated from airway fluids was a limitation of the current study. We did not also detect antibiotic resistance in the study.

CONCLUSION

In conclusion, it appears that CLA is considered as the first-line antibiotic to alleviate the ITB signs in dogs.

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Conflict of interest: The authors declared that there is no conflict of interest.

Ethical statement: Written owner consent was obtained from the owners.

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