Polish Journal of Veterinary Sciences Vol. 16, No. 1 (2013), 193–197

DOI 10.2478/pjvs-2013-0028

Review

Proper use of Quinolones for canine colitis ambulatory treatment: literature review and REQUEST guidelines

R. Lechowski[1], J.P. Cotard[2], H.J. Boulouis[3], M. Kietzman[4], A.M. Farca[5], J. Fontaine[6], S. Caney[7], G. Dupree[8] REQUEST Group

[1] Faculty o Veterinary Medicine, University of Life Science, Nowoursynowska 166, 02-776 Warsaw, Poland
[2] former prof. Ecole Nationale Veterinaire d'Alort, Paris, France
[3] Ecole Nationale Veterinaire d'Alort, Paris, France
[4]Institut fur Pharmacologie, Toxicologie und Pharmazie, Tierartzliche Hochshule, Hannover, Germany
[5] Departement of Animal Pathology, Faculty of Veterinary Medicine, Turin, Italy
[6] Facuulte Veterinaire, Universite de Liege, Belgium
[7] Vet Professionals Ltd, Midlothian Innovation Centre, Pentlandfield Roslin Midlothian, United Kingdom
[8] Klinik fur Kleintierchirurgie, VetMed Universitat Vienne, Austria

Abstract

The literature analysed by REQUEST (**RE**assesing **QU**inolone **E**uropean **ST**andard) using inclusion and exclusion criteria allows to make the conclusion that the proper use of fluoroquinolones (FQ) in canine colitis requires rigorously performed qualification to specific antimicrobial treatment. An infectious agent responsive to FQ therapy plays an integral role in the clinical manifestation of canine colitis, especially histiocytic ulcerative colitis (HUC) in young Boxer dogs. This supports the use of FQ in these cases. The Request guidelines for proper use of FQ in canine colitis is established, according to the available literature data.

Key words: dog, quinolones, colitis, REQUEST, gudelines

Colonic inflamatory diseases (colitis) in dogs are the main causes of large bowell diarrhea which may be of dietary, parasitic, traumatic, infectious, immune or idiopatic origin. Other causes are very rare and like irritable colitis or fibre responsive colitis are more frequently diagnosed than actually occuring.

Classical approach to the patient with colitis includes firstly dietary modification and anti-parasitic medication despite any previous treatment of this sort. The second step includes antibacterial therapy depending on specific breed and age of ill dog.

The guidelines for treatment of colitis in dogs is, in many cases, adapted from human medicine or based on clinical cases report. Several chronic granulomatous diseases that were once thought to be intractable now yield to long term antibiotic treatment (Van Kruiningen 1995). One of the specific condition is granulomatous colitis (GC), rare and breed specific

Correspondence to: R. Lechowski, e-mail: romanlechowski@hot.pl

Table 1. The grading recommendations by Request.

Grade	Significance
A	High quality evidence with coherence between pharmacokinetic, pharmacodynamic and clinical data which makes this kind of recommendation a **mandatory proper usage** of fluoroquinolones among companion animals or specific species.
B	High or good quality evidence with coherence between pharmacokinetic, pharmacodynamic and clinical data despite the fact that some data are missing which makes this kind of recommendation a **relevant proper usage** of fluoroquinolones among companion animals or specific species until additional data are available.
C	High or good quality evidence with possible discrepancy between pharmacokinetic, pharmacodynamic and clinical data (whether missing or not) which makes this kind of recommendation a **current possible usage** of fluoroquinolones among companion animals or specific species until additional data are available.
D	Insufficient or poor quality evidence despite consensus among experts that make this kind of recommendation a **cautious usage** of fluoroquinolones among companion animals or specific species. Requires that veterinary schools, and/or pharmaceutical companies, conduct specific research and publish related results in order to reassess the recommendation as soon as possible.
E	High or good quality evidence with possible discrepancy between pharmacokinetic, pharmacodynamic and clinical data (whether missing or not) that **recommends not to use** fluoroquinolones among companion animals or specific species until additional data are available.
F	**Absence of evidence** to use fluoroquinolones among companion animals or specific species. Requires that veterinary schools, and/or pharmaceutical companies, conduct specific research and publish related results in order to reassess the recommendation as soon as possible.

bowel disease in Boxer dogs, especially young (Craven et al. 2011).

Specific role in canine colitis is played by mucosa-associated microflora that is considered to play a pivotal role in the pathogenesis of inflammatory bowel disease. This phenomenon is supported by recent studies that have revealed a genetic susceptibility to defective bacterial clearance in Boxer dogs with GC. Differential expression of pathogen recognition receptors were identified in dogs with enteropathies (Suchodolski 2011). In boxer dogs with large bowel diarrhea the macrophages in the lamina propria and submucosa, as well as these aggregates in regional lymph nodes showed immunoreactivity with polyclonal E. coli antibody. This makes the identification of causative agent of granulomatous disease in Boxer dogs possible (Van Kruiningen et al. 2005). Culture-independent molecular analysis has transferred therapy and prognosis by uncovering a correlation between granulomatous colitis and E.coli invasion within colonic mucosal macrophages (Craven et al. 2010) Simpson et al. (2006) showed that in Boxers colitis in 100% samples intramucosal Gram-negative coccobacilli were present and that Boxer colitis is associated with selective intramucosal colonization by E. coli that have an adherent and invasive phenotype (Simpson et al. 2006).

Findings observed in Boxer dogs are similar to these documented in human inflamatory bowel disease, especially ulcerative colitis, and according to some authors (German et al. 2000) suggest an important role for the mucosal immune system in the pathogenesis of canine histiocytic ulcerative colitis.

Several investigations showed that E. coli as a pathogen in inflammatory bowel disease (IBD) has invasive and adherent properties in humans and similar organisms have also been found to be universally present in the granuloma tissue from Boxer dogs with colitis (Simpson et al. 2006, Hansen et al. 2010) especially histiocytic ulcerative colitis. However, although HUC displays a higher predisposition in Boxers (Hill and Sulivan 1978, German et al. 2000, Davies et al. 2004, Mansfielt et al. 2009) it has also been described in other breeds, such as French bulldog, Doberman pincher, Mastiff and Alaskan malamute (Stokes et al. 2001, Tanaka et al. 2003, Hostutler et al. 2004, Cerquetella et al. 2010).

Bacterial infection as a cause of canine, especially Boxer, colitis, previously considered as a immune-mediated disease, changed the treatment principles from immunosuppressive to antimicrobial treatment.

Taking this into consideration and according to the principles of Evidence Based Medicine, the group of experts founded the international group REQUEST (**RE**assesing **QU**inolone **E**uropean **ST**andard) during a meeting in Lyon, France in 2008 and decided to establish the proper and judicious use of very popular and frequently used group of antimicrobial agents in canine and feline practice – fluoroquinolones. Request members came to the conclusion that formulation of Evidence Based Usage of Quinolones among Companion Animals must be elaborated according to specific grading scales of pharmacokinetic, pharmacodynamic and clinical publications using the methodology worked out by REQUEST. The evidence selection process has been performed according to inclusion and exclusion criteria. Inclusion criteria were a detailed description of pharmacokinetic studies performed with groups of dogs and cats (no single case studies), established or validated analytical methods and pharmacokinetic calculations using generally accepted methods. Exclusion criteria were the inability to meet the international Guiding Principles for Biomedical Research Involving Animals Welfare Act, US Public Health Service Policy on the Human Care and Use of Laboratory Animals, NRC Guide for the Care and Use of Laboratory Animals. The paper containing information which suggested that animals were subjected to adverse, stressful or harsh conditions or treatments was excluded unless clear demonstration that the knowledge gained was of sufficient value to justify these conditions or treatments. The papers were classified using the appropriate criteria and on this basis the grading scale from A to D was established (Table 1). On this basis the guidelines for proper use of FQ were determined in selected diseases including colitis in dogs. In detail the goal of Reguest is to define guidelines for the correct and appropriate prescription of FQ among dogs and cats, and to publish recommendations which will help the veterinary practitioners in every situation.

The research of Request Group is based on the three steps activity program. The first step comprised targeted review of the literature, with the aim of providing background knowledge and evidence, necessary for veterinary clinicians to be informed and to advocate judicious use of fluoroquinolones in everyday situations. The second step resulted in recommendations based on literature analysis and experts opinions following a rigorous Peer Reviewed Evidence methodology. The third step will require specific studies identified and promoted by the expert group in a collaborative manner with the pharmaceutical industry and/or veterinary schools in order to validate and/or refine the intermediate recommendations made in this publication.

When performing the first step of the three steps program of REQUEST the members reviewed the literature with the aim of providing background knowledge and evidence necessary for veterinary practitioners. The results of the literature review and classification according the Request scale (Table 1) concerning canine colitis revealed that FQ may be used in these cases that are caused by infectious agent especially E. coli (Cummings et al. 2003, Balfour Satrtor 2008, Hansen et al. 2010).

The literature analysed by REQUEST using inclusion and exclusion criteria allows to make the conclusion that the proper use of FQ in canine colitis needs rigorously performed qualification to specific antimicrobial treatment. Succeful treatment of GC requires antimicrobials that are effective against E. coli and penetrate intracellularly (Gaschen 2007, Craven et al. 2011).

The papers of Hostutler et al. (2004) and Mansfielt et al. (2009) show that Boxer's HUC is the main indication for use of antimicrobials among which the FQ are the most appreciated. An infectious agent responsive to FQ therapy plays an integral role in the clinical manifestation of canine colitis, especially HUC and supports the use of FQ (Hansen et al. 2010). Although the correlation between clinical remission and eradication of mucousally invasive E. coli during the treatment with enrofloxacine supports the causal involvement of E. coli in the development of HUC in susceptible Boxer dogs, the poor response to enrofloxacin treatment in granulomatous colitis might be due to colonisation with enrofloxacin-resistant E. coli (Mansfielt et al. 2009). Fluoroquinolone resistance is an emerging problem in companion animal practice (Gibson et al. 2010). The studies of Craven et al. (2010) performed to determine susceptibility profiles of E. coli strains from GC and healthy dogs revealed that enrofloxacin resistant E. coli were isolated in 42% of cases from a group of 14 dogs with GC. This allows to make the conclusion that antimicrobial resistance is common among GC-associated E. coli and influence the clinical improvement. The authors have concluded that antimicrobial therapy should be guided by mucosal culture and antimicrobial susceptibility testing rather than the empirical knowledge. The same authors, one year later, indicated in the review paper, that enrofloxacin is regarded as the antibiotic of choice in the treatment of GC in dogs (Craven et al. 2011).

Table 2. When intending to prescribe Fluoroquinolones among dogs with typical signs of acute and/or chronic colitis the REQUEST recommends:

Indication	Recommendation	Grade
Young boxer colitis	– institution of conservative dietary and anti-parasitic therapy – fluoroquinolones for 8 weeks – reasesemment of prescription after 2 weeks if clinical signs don't change or after temporary remission if clinical signs relapse	A
Other predisposed breed*)	– institution of conservative dietary and anti-parasitic therapy – fluoroquinolones for 2 weeks – reasesemment of prescription after 2 weeks if clinical signs don't change or after temporary remission if clinical signs relapse	D
Colitis (other than boxer or predisposed breed) in case of recurrent relapse or chronic	– institution of conservative dietary and anti-parasitic therapy – fluoroquinolones for 7-14 days – reasessment of prescription after 7 days if clinical signs don't change or after temporary remission if clinical signs relapse	D

* English bulldog, French bullgog, Doberman pincher, Mastiff, Alaskan Malamute

Table 3. REQUEST choice of Fluoroquinolones according to available data and clinical experience.

Drug	Indication	Dose (mg/kg)	Route	Interval (h)	Request choice
Enrofloxacin	Yes	5-10	*Per os*	12	+++
Enrofloxacin	Yes	10-15	*Per os*	24	++++
Marbofloxacin	Yes	2-2.5	*Per os*	24	+++

The second step resulted in recommendation based on literature analysis and expert opinions according to Peer Reviewed Evidence Based methodology. The Request qualification guidelines for the proper use of FQ in canine colitis is shown in Table 2. The recommendation grade A was selected for the young Boxer dogs, which have a great predisposition to form of colitis – HUC. In other breeds with or without predisposition to colitis, the REQUEST recommendation is grade D with differences concerning the duration of therapy before other, more specific diagnostic procedures will be performed.

The dosage and administration of FQ in canine colitis recommended by REQUEST is shown in Table 3. Dogs with colitis are treated preferentially per os, less frequently parenterally. Enrofloxacin is the main FQ described in the literature (Hill and Sulivan 1978, Davies et al. 2004, Hostutler et al. 2004) and both oral and subcutaneous route of administration are acceptable with high degree of bioaviability It has been concluded, using an animal model of colitis (rat, mouse), that one of the FQ – ciprofloxacin – is effective against bacterial colitis especially against Gram-negative microorganisms (Cummings et al. 2003). However ciprofloxacin when combined with metronidazole and clindamycin is most consistently effective if given before the onset of colitis (Cummings et al. 2003). There is no information in the literature on efficacy and safety of use of ciprofloxacin or pradofloxacin in canine colitis in contrast to enrofloxacine (Mansfielt et al. 2009), so in the REQUEST guidelines these FQ are not included.

However, the long term therapy (Van Kruiningen 1995), especially in young Boxer dogs, makes parenteral administration of drug less convenient, so the first REQUEST choice is enrofloxacin administered orally once a day for minimum 6 to 8 weeks (Table 3).

References

Cerquetella M, Spaterna A, Laus F, Tesei B, Rossi G, Antonelli E, Villanaci V, Bassotti G (**2010**) Inflamatory bowel disease in the dog: differences and similarities with human. World J Gastroenterol 16: 1050-1056.

Craven M , Dogan B, Schukhen A, Volkman M, Chandler A, McDonough PL, Simpson KW (**2010**) Antimicrobial resistance impact clinical outcome of granulomatous colitis in boxer dogs. Journal of Veterinary Internal Medicine 24: 819-824.

Craven M, Mansfield CS, Simpson KW (**2011**) Granulomatous colitis of boxer dogs. Vet Clin North Am Small Anim Pract 41: 433-445.

Cummings JH, Macfarlane GT, Macfarlane S (**2003**) Intestinal bacteria and ulcerative colitis Curr Issues Intest Microbiol 4: 9-20.

Davies DR, O'Hara AJ, Irwin PJ, Guilford WG (**2004**) Successful management of histiocytic ulcerative colitis with enrofloxacin in two boxer dogs. Aust Vet J 82: 58-61.

Gaschen FP (**2007**) Bacteria and the canine and feline gut: the good, the bad and the ugly, The North American Veterinary Conference 419-421.

German AJ, Hall EJ, Kelly DF, Watson AD, Day MJ (**2000**) An immunohistochemical study of histiocytic ulcerative colitis in boxer dogs. J Comp Path 122: 163-175.

Gibson JS, Cobbold RN, Kyaw-Tanner MT, Heisig P, Trott DJ (**2010**) Fluoroquinolone resistance mechanisms in multidrug-resistant Escherichia coli isolated from extraintestinal infections in dogs. Vet Microbiol 146: 161-166.

Hansen R, Thompson JM, El-Omar EM, Hold GL (**2010**) The role of infection in the aetiology of inflamatory bowel disease, J Gastroenterol 45: 266-276.

Hill FWG, Sulivan ND (**1978**) Histiocytic ulcerative colitis in a boxer dog. Aust Vet J 54: 447-479.

Hostutler RA, Luria BJ, Johnson SE, Weisbrode SE, Sherding RG, Jaeger JQ, Guilford WG (**2004**) Antibiotic-responsive histiocytic ulcerative colitis in 9 dogs. J Vet Inter Med 18: 499-504.

Mansfielt C.S. James FE., Craven M., Davies DR., O'Hara AJ., Nicholls PK., Dogan B., MacDonough SP., Simpson KW. Remission of histiocytic ulcerative colitis in Boxer dogs correlate with eradication of invasive intramucosal E.col. Journal of Veterinary Internal Medicine 23: 965-969.

Satrtor RB (**2008**) Microbial influences in inflamatory bowel disease. Gastroenterology 134: 577-594.

Simpson KW, Dogan B, Rishniw M, Goldstein RE, Kleasig S, McDonough PL. German AJ, Yates RM, Russel DG, Johnson SE, Berg DE, Harel J. Bruand G. McDonough SP. Schukken YH (**2006**) Adherent and invasive E. coli is associated with granulomatous colitis in boxer dogs. Infect Immun 74: 4778-4792.

Stokes JE. Kruger JM. Mullaney T. Holan K. Schall W (**2001**) Histiocytic ulcerative colitis in three non-boxer dogs. J Am Anim Hosp Assoc 37: 461-465.

Suchodolski JS (**2011**) Companion animals symposium: Microbes and gastrointestinal health of dogs and cats. J Anim Sci 89: 1520-1530.

Tanaka H, Nakayama M, Takase K (**2003**) Histiocytic ulcerative colitis in a French bulldog. J Vet Med Sci 65: 431-433.

Van Kruiningen HJ (**1995**) On use of antibiotics in Crohn's disease. J Clin Gastroenterol 20: 310-316.

Van Kruiningen HJ, Civco IC, Cartun RW (**2005**) The comparative importance of Escherichia coli antigen in granulomatous colitis of boxer dogs. APMIS 113: 420-425.