Rifaximin induces and maintains clinical remission in a dachshund with chronic enteropathy: antibiotic-responsive diarrhoea or inflammatory bowel disease?

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ABSTRACT

A two-year-old male dachshund was presented with a long-term history of chronic small intestine diarrhoea. The dog had been previously treated with several antibiotics, with temporary remission of clinical signs, relapsing each time the therapy was discontinued. On the basis of clinical signs, history and on the investigations performed which failed to detect any other cause of disease, a diagnosis of antibiotic-responsive diarrhoea (ARD) or small intestine bacterial overgrowth secondary to inflammatory bowel disease was made. A three-week antibiotic treatment with rifaximin by oral route was prescribed, achieving a prompt clinical remission but diarrhoea relapsed shortly after the end of drug administration. A continuous therapy with rifaximin was therefore established, allowing to maintain the dog in complete remission, without any side effect. The efficacy shown by rifaximin in this report suggests, for the first time, that this drug could be a good choice for long-term treatment of ARD.

BACKGROUND

Chronic diarrhoea in dogs which responds to antibiotic treatment, if no underlying causes are identified, is defined as antibiotic-responsive diarrhoea (ARD) (German and others 2003). The main clinical sign of the disease is chronic or recur-rent small bowel diarrhoea, sometimes associated with vomit, loss of appetite and weight in the more severe cases(Willard and others 1994). As diarrhoea usually relapses when the therapy is interrupted, long-term or indefinite administration of the antibiotic is usually necessary. For such reason, the insurgence of antibiotic resistance, and the occurrence of side effects are important concerns, which should guide the veterinarian in the choice of the right antimicrobial drug to be used. Moreover, because there is no convincing evidence of a predominant pathogenic role of some bacterial species, but a non-specific dysbiosis or an abnormal immune response to normal intestinal microbiota are probably involved(Hall 2011), broad-spectrum antibiotics are often prescribed, such as amoxicillin/clavulanic

acid, fluoroquinolones or tetracyclines. However, several cases of ARD seem to respond better to metronidazole or tylosin (Westermarck and others 2005), even though the former is active only against anaerobes, while the latter is almost exclusively effective against Gram-positive bacteria. It has been thus hypothesised that the efficacy of these two antibiotics could be due, at least in part, to their immunomodulatory properties (Grove and others 1977, Culić and others 2001). The authors here describe a clinical case of a dachshund with long-lasting chronic diarrhoea, in which rifaximin was effective in achieving and maintaining the clinical remission. Rifaximin, a semisynthetic rifamycin antibiotic not commonly employed for gastrointestinal diseases in dogs, was chosen on the basis of its negligible intestinal absorption (Venturini 1983), broad spectrum of activity and efficacy in humans (Yang and others 2008).

CASE PRESENTATION

A two-year-old male dachshund was referred by a colleague for evaluation because of a long history of persisting gastrointestinal clinical signs. Physical examination showed that the dog was not in good body condition, with a weight of 5.1kg. The severity of gastrointestinal clinical signs was assessed by means of Canine Inflammatory Bowel Disease Activity Index (CIBDAI), a widely accepted scoring method of mucosal inflammation for chronic enteropathies in dogs, ranging from 0 to 18 (Jergens and others 2003), which resulted 11 (severe) (Table1).

CLINICAL HISTORY

Loss of appetite, intermittent diarrhoea, vomit, borborygmi and abdominal pain were the first reported clinical signs, beginning when the dog was seven months old. The dog was previously examined by a colleague, and several exams had been already performed with normal results: complete blood cell count, serum biochemistry, urinalysis, faecal examination for endoparasites, Giardia test, trypsin-like immunoreactivity. Abdominal ultrasonography had been also performed without identifying abnormalities. The dog had been previously treated several times with a commercial oral antibiotic combination of metronidazole/spiramycin, ranitidine, metoclo-pramide and highly digestible and hypoallergenic commercial diet, obtaining the remission of clinical signs, which however relapsed a few days after the therapy was discontinued. In the following months, the clinical signs had worsened progressively, with severe episodes of diarrhoea, melena, prostration, dehydration, abdominal pain, and marked weight loss (from 7 to 5.2kg). The dog was repeatedly treated with different antibiotics (enrofloxacin, amoxicillin/clavulanic acid, metronidazole), antisecretory drugs, and commercial hyper-digestive or hypoallergenic diets with minimal and temporary amelioration of clinical signs. The owner decided also to try homoeopathic remedies, with severe worsening of clinical signs.

INVESTIGATIONS

Complete blood cell count, serum and urine biochemistry, multiple faecal examination and trypsin-like immunoreactivity were repeated showing normal results, apart from a mild decrease in folate and vitamin B12. Since the dog had never been previously submitted to endoscopic exams, a gastro-duodenoscopy and a colonoscopy were performed, with subsequent histologic evaluation of multiple biopsies. The endoscopies evidenced features of moderate gastritis with increase of mucosal thickness (Fig 1). Duodenum had markedly hyperaemic, oedematous and friable mucosa,

with numerous large erosions (Fig 2); colon appeared normal (Fig 3). Histologic evaluation evidenced mild chronic gastritis and a moderate enterocolitis with prevalent lympho-plasmacellular infiltrate (Fig 4).

DIFFERENTIAL DIAGNOSIS

On the basis of physical, endoscopic and histological evaluation, and of clinical history of amelioration after the administration of antibiotics, a diagnosis of ARD was made, even if inflammatory bowel disease (IBD) with secondary small intestine bacterial overgrowth (SIBO) could not be ruled out. Other possible aetiologies of chronic diarrhoea, such as endoparasitic infestations, lymphangiectasis, pancreatic insufficiency, neoplastic disease or food allergies, were excluded by means of previous Investigations.

TREATMENT

An oral antibiotic therapy with rifaximin, a non-absorbable broad-spectrum antibiotic commonly Employed for the treatment of diarrhoea in human patients, was prescribed (Yang and others 2008). The therapeutic protocol was the following: 20mg/kg rifaximin (Rifacol 2 per cent oral suspension) every 12 hours for 21days; ranitidine (2mg/kg every 12 hours) and metoclopramide (0.3mg/kg every 12 hours) for 15 days. A supplement of vitamin B12 (cyanocobalamin 250µg intramuscularly) was administered once a week. An easily digestible home-made diet which consisted exclusively of boiled chicken meat and rice was prescribed for 21 days.

OUTCOME AND FOLLOW-UP

After few days of therapy, the clinical signs were markedly ameliorated: the appetite was normal, the dog was lively, gained weight, no vomiting episodes were observed and the faeces appeared normal. At the end of 21days antibiotic treatment period, the dog was evaluated again for CIBDAI score which resulted 0.The body condition of the dog was good, and the weight was 7.2kg. After a few days, however, the clinical signs relapsed. Two further 21-day treatments with rifaximin were thus prescribed, each time with complete remission of clinical signs, followed by a relapse shortly after the end of the therapy. ARD was therefore suspected, and, since this antibacterial drug has a good safety profile (Menees and others 2012), a maintenance therapy with 20mg/kgrifaximin every 12 hours was prescribed. Up to this date, the dog has been under monotherapy with rifaximin for 18 months, and is in complete remission of the disease. The dog has progressively returned to his previous usual diet. No side effects have been reported by the owner during this period.

DISCUSSION

ARD is the term used to define a clinical form of chronic diarrhoea in dogs, which responds positively to the administration of antibiotic drugs, and it is at present preferred to the previously used acronym SIBO. Indeed, it is now generally accepted that the actual increase of bacteria number in small intestinal lumen observed in human SIBO (>105colony-forming units per ml) is

not a reliable index of disease in dogs or cats, where higher number of bacteria are often detected in healthy subjects(Johnston and others 1993, Willard and others 1994).ARD is generally diagnosed in large or giant dog breeds, among which German Shepherds seem to be particularly predisposed (Batt and others 1983). The present report describes a chronic diarrhoea, responding to antibiotic treatment, in a small dog breed (dachshund), successfully controlled with oral administration of rifaximin. Even though the remission obtained and maintained only with continuous antibiotic treatment is suggestive of ARD, the histologic features of gastrointestinal biopsies do not allow to exclude an IBD with a secondary SIBO, as histologic changes induced by ARD are usually minimal (Hall 2011). The diagnosis of idiopathic ARD is indeed controversial, as it may be problematic to discriminate between this disease and a SIBO secondary to IBD or other chronic enteropathies. In this clinical case, however, food allergy and other common causes of chronic enteropathy were excluded by performed investigations, and the prompt remission achieved and maintained with rifaximin suggests that intestinal bacteria are the main cause of the disease. Anyway, from a practical point of view, in this specific case the differential diagnosis between idiopathic ARD and an 'antibiotic-responsive' IBD(which is also considered idiopathic) seems to have little clinical or therapeutic relevance.

Since diarrhoea usually relapses after discontinuation of therapy in ARD-affected dogs, the choice of an effective antimicrobial drug, also having a good safety profile, is of paramount relevance. Rifaximin, commonly prescribed against traveller's diarrhoea in humans, was also proven to be effective in several chronic intestinal diseases in human patients, such as IBD and irritable bowel syndrome associated with bacterial over-growth(Huang and DuPont 2005, Majewski and others 2007, Pimentel et al., 2011). Moreover, a recent clinical trial has been published, showing that rifaximin is effective as metronidazole in inducing the clinical remission in dogs with chronic enteropathy (Menozzi et al., 2016). As bacterial overgrowth is not considered crucial in the pathogenesis of ARD in dogs, other mechanisms seem to be important for the development of the disease, such as dysbiosis, alterations in bacteria metabolismand abnormal immune response to antigens of microbiota (Hall, 2011). Rifaximin seems to be of benefit against the majority of these phenomena; it was in fact shown in previous studies that rifaximin is able to modify metabolites of bacterial origin(Bajaj and others 2013)and reduce virulence of enterobacteria without significantly decreasing their number(Jiang et al., 2010,Kang and others 2016,Sartor, 2016). Furthermore, it was proven that rifaximin, by activating pregnane-X receptor, reduces the expression of proinflammatory cytokines (eg, tumour necrosis factor-α or interleukin-1β); thus this antibiotic could be effective also because of its anti-inflammatory properties (Cheng and others 2010)and blunting of the immune response against bacterial antigens in the gut lumen.

In the present case report, after more than 18 months of continuing administration of rifaximin, no side effects were observed. The safety of rifaximin has been previously demonstrated in humans, and it may be explained by its negligible absorption by oral route (Venturini 1983, Jiang and others 2000); conversely, other antimicrobial drugs commonly used for the treatment of ARD are known to cause nephrotoxicity, ototoxicity and peripheral neuropathy (Dow and others 1989). Moreover, long-term treatment with an antibiotic drug might easily induce bacterial resistance, and it was observed, for example, that ampicillin, trimethoprim-sulfamethoxazole, and ciprofloxacin are already practically ineffective against traveller's diarrhoea in humans (Kuschner and others 1995, Huang and DuPont 2005). By contrast, rifaximin is considered to bear a very low risk of causing bacterial resistance (Saadi and McCallum 2013), possibly because of its minimal systemic bioavailability along with its bactericidal mechanism of action.

LIMITATION OF THE STUDY

A limitation of the present study could be represented by the beneficial effect due to diet modification, or to antiemetic and antisecretive drugs administration. However, these drugs and hyperdigestive diet had been already previously prescribed without significant amelioration, so their contribution to remission is likely minimal; furthermore, the dog has been in complete remission with only rifaximin for 18 months. In conclusion, the case here presented, while documenting a possible uncommon clinical form of ARD in a dachshund, provides novel information about the therapeutic potential of rifaximin in the treatment of chronic enteropathies with paramount pathogenetic role of intestinal microbiome in dogs, even though a broader clinical trial would be needed in order to support the clinical efficacy of this antibiotic.

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TABLE 1. *Assessment of CIBDAI (Canine Inflammatory Bowel Disease Activity Index) score at T0 (before treatment) and T21 (after 21 days of rifaximin administration).*

	Attitude/activity (0-3)	**Appetite (0-3)**	**Vomiting (0-3)**	**Stool consistency (0-3)**	**Stool frequency (0-3)**	**Weight loss (0-3)**	**Total**
TO	2	3	1	2	1	2	11
T21	0	0	0	0	0	0	0

0 = normal; 1 = mild change; 2 = moderate change; 3 = severe change