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## The use of racecadotril as an effective adjunct therapeutic measure in the management of diarrhea



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**Abstract**

Most of the episodes of diarrhea are self-limiting and should be managed without the indiscriminate use of antibiotics. A variety of anti-secretory agents have been subjected to countless investigations including racecadotril as an adjunct therapy. The present study was conducted to study the efficacy of racecadotril in the management of diarrhea in dogs. A total of eleven dogs suffering from non-hemorrhagic diarrhea were included in the study. Animals were divided into two groups, group I (n=6) was treated with conventional antibiotic therapy and group II with Racecadotril (n=5). The groups were evaluated based on duration of clinical recovery and improvement in the faecal score. The ameliorative action of racecadotril, an enkephalinase inhibitor is attributed to selective anti-secretory activity via protecting endogenous enkephalin degradation which induces a selective increase in chloride absorption. The drug holds an effective alternative promise in management of diarrhea without inappropriate antibiotic use.

**Keywords:** diarrhea, racecadotril, enkephalinase inhibitor, antibiotic resistance

**1. Introduction**

Diarrheal disease is the second leading cause of death in children younger than 5 years of age, and the most common cause of acute watery diarrhea in young children worldwide (Bui *et al.*, 2017) [1]. Clinical management of diarrhoea poses a serious challenge to medical practitioners. An improved understanding of the patho-physiology of diarrhoea has provided basis for a more rational therapeutic approach. Although diseases leading to an acute diarrhoeal illness are often self-limiting, shortening of the illness duration can have significant benefits with regard to hydration and subsequent morbidity. In addition to rehydration therapy which constitutes the foundation stone in the treatment of diarrhoea, the use of anti-diarrheal therapy reduces the convalescence time in acute diarrhoea (Sreenivas *et al.*, 2017) [2] and is a promising option to reduce the indiscriminate use of antimicrobials often initiated in acute gastrointestinal diseases.

There is mounting need for the judicious use of antibiotics since their widespread use plays a major role in the emerging public health crisis of antibiotic resistance. The indiscriminate antibiotic use has led to the development of resistant strains with significant public health relevance (WHO, 2014) [3]. A significant association exists between the prevalence of animal-associated antimicrobial-resistant bacteria in animals and in humans, as well as between the levels of antimicrobial use in animals at a population level, and the prevalence of antimicrobial-resistant bacteria in humans (Vieira *et al.*, 2011) [4]. Antimicrobial-resistant bacteria of animal origin can be transmitted to humans through the environment (Graham *et al.*, 2009) [5] or food products (Price *et al.*, 2005) [6] and to agricultural workers by direct contact (Smith *et al.*, 2013) [7]. The use of antibiotics for diarrhea adds to this problem, as these drugs increase the risk of infections by drug-resistant bacteria, in addition to causing long-lasting changes in the intestinal microbiota (Sullivan *et al.*, 2001) [8]. Therefore, treating diarrhoea with antibiotics is not encouraged. Therefore research needs to be directed towards the use of non-antibiotic drugs with effects on the gastrointestinal function.

Enkephalins (Endogenous Opioids) secreted by gut epithelium have marked pro-absorptive activity and are inactivated by enzyme enkephalinase. Racecadotril, (acetorphane: N((R, S)-3-acetylmercapto-2benzylpropanoyl)-glycine, benzyl ester) is an enkephalinase inhibitor augmenting the anti-secretory action of enkephalin in the submucous myenteric neurons. Once absorbed after oral administration, it is converted to its parent compound (thiorphane) which acts to increase the half-life of enterocyte methionine-enkephalin (Christophe, 2013) [9] and

Thus prevents the degradation of endogenous opioids (Enkephalins) responsible for hypersecretion of water and electrolytes into intestinal lumen. This decreases the stool output without disturbing the intestinal transit time (Singh *et al.*, 2016) [10].

As such the present study was undertaken in canines to evaluate the potential efficacy of racecadotril as a therapeutic tool in simplifying the management of diarrhea so as to strengthen the disease control strategy.

## 2. Material and Methods

The study was carried out on dogs presented at Teaching Veterinary Clinical Complex of the Faculty of Veterinary Science and Animal Husbandry, Sher-e-Kashmir University of Agricultural Sciences and Technology – Jammu presented

with history of diarrhea. A total of eleven cases exhibiting non-haemorrhagic diarrhoea were included in this study. Inclusion criteria included non-haemorrhagic diarrhoea and no history of previous treatment with antimicrobials/anti-motility drugs/anti-diarrhoeals within the preceding 7 days. Among them six dogs were included in the first group and prescribed an antibiotic while five were included in the second group and prescribed Racecadotril powder, Enuff-10 @ 1mg/kg t.i.d (Hetero Labs Limited). The groups were evaluated based on the number of days taken for the resolution of clinical signs. In addition, the severity of diarrhoea was keenly observed and graded on the basis of a faecal scoring system for dogs and cats (Moxham, 2001) [11] (Table 1).

**Table 1:** Scoring system for assessment of clinical score. (Waltham faecal scoring system).

Grade	Interpretation
1	Hard, dry and crumbly; “bullet like”
2	Well formed: does not leave a mark when picked up; “kickable”
3	Moist beginning to lose form, leaving a definite mark when picked up
4	The majority, if not all form is lost; poor consistency; viscous
5	Watery diarrhoea

## 3. Results and Discussions

The mean faecal score in group B was lower ( $2.70 \pm 0.24$ ) as compared to group A ( $3.80 \pm 0.22$ ) which was prescribed

antibiotic (Table 2). In addition, the mean number of days taken for the resolution of clinical signs was lower in group B as compared to group A (Table 3).

**Table 2:** Mean faecal grade

Mean faecal grade	
Group A (n=6)	$3.80 \pm 0.22$
Group B (n=5)	$2.70 \pm 0.24$

**Table 3:** Mean minimum days for the resolution of clinical signs

Mean minimum days for the resolution of clinical signs	
Group A (n=6)	$2.0 \pm 0.44$
Group B (n=5)	$1.5 \pm 0.25$

In the present study, Racecadotril was found to be effective in dogs to be used as an anti-diarrhoeal in treating diarrhoea. Racecadotril exhibits selective anti-secretory activity without affecting the intestinal motility by inhibition of enkephalinase and thereby protecting endogenous kephalins from degrading which in turn mediate their effect and induce a selective increase in chloride absorption (Primi *et al.*, 1999) [12]. In addition, the use of Racecadotril has been associated with a lower incidence of reactive constipation (Wang *et al.*, 2005) [13]. A number of studies have assessed the efficacy of its use in children and infants with racecadotril having shown to have a clinically relevant effect in reducing diarrhoea (duration, stool output and stool number), irrespective of baseline conditions (dehydration, Rotavirus or age), treatment conditions (inpatient or outpatient studies) or cultural environment (Lehert *et al.*, 2011) [14]. Our study signifies its potential use as an anti-diarrhoeal in the management of canine diarrhea. Keeping in view the findings of our study, racecadotril can be used as an adjunct therapy in the treatment of diarrhea, the conclusion being supported by the lower fecal-consistency scores and the shorter duration of diarrhea. Further work is suggested to conduct larger trials so as to detect a significant difference in diarrheal duration and its morbidity in different types and severity of diarrhea.

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