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REVIEW PAPER OPEN ACCESS

A comprehensive review on racecadotril drug

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Abstract

Around the globe, diarrhea is a continuing health problem and also a leading cause of sickness and death in both children and adults. It is one of the major causes of morbidity and mortality in developing countries and can be occurred in any age irrespective of the geological location. The chief reason of the deaths is because of electrolytes loss and dehydration by increased intestinal secretions and poor absorption. For this study, previously published papers were reviewed and key words for the search of literature, included: Racecadotril, enkephalinase inhibitor, diarrhea, oral rehydrating solutions, diarrhea treatment, infectious diarrhea, and epidemiology of diarrhea. Oral rehydrating solutions are used to recover water and electrolytes and these are considered as a mainstay of the anti-diarrheal therapy. Inhibition of fluid secretion and stimulation of fluid absorption from the intestinal mucosa is necessary in acute diarrhea, so that the loss of water and electrolytes can be prevented. Racecadotril (acetorphan) belongs to the pharmacological class of enkephalinase inhibitor. Its mechanism of action involves the minimizing of the intestinal secretions by protecting the endogenous enkephalins, which are secreted by the gastrointestinal tract. It is taken orally and proved to be safe and effective for the treatment of diarrhea in both adults and children. Racecadotril has a rapid onset of action and shows greater tolerability than loperamide in patients with acute diarrhea. Racecadotril gives better results in children and infants when taken as an adjuvant to oral rehydrate solutions (ORS) and also cut the overall cost of treatment with better outcomes.

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Introduction

Though diarrhea is a symptom and it has been roughly estimated that per year 25% of US population go through acute diarrheal episodes. While per annum 5% of said population suffers from chronic diarrhea (Schiller *et al.*, 2014). Diarrhea is defined as the abnormal movements of the intestine with increase production of the stool (Fine, 1993). It can be occurred in any age irrespective of the geological location (Mehta, 2012) and worldwide it puts a major health economic burden (Thiagarajah *et al.,* 2015). The self-limiting nature of acute diarrhea usually does not require any pharmacological intervention. However, if patients desire only then necessary symptomatic treatment may be given through OTC medications (Salazar-Lindo, 2011).

In acute diarrhea the only population, which is a matter of concern is pediatric patients. In developing countries, the number of mortalities induced by acute diarrhea has increased since last few years and in developed countries, mortality rate has increased in adult population (particularly older patients) due to visceral failure secondary to dehydration and delaying in start of anti-diarrheal therapy (Archbald-Pannone, 2014). Contaminated food or water with microorganisms cause infection of the gastrointestinal tract and represented as acute diarrhoea. Acute diarrhea remains usually stay self-limiting and can be resolved (Thielman and Guerrant, 2004). Apart from the infection, a very rare genetic atrophic condition of the intestinal epithelial cells in the gut is known as Microvillus Inclusion Disease (MVID) which causes secretory diarrhea that may lead to life threatening dehydration and electrolyte imbalance (Späth *et al.,* 2016). Individuals suffering from chronic diarrhea should seek medical attention from their physician (Schiller *et al.*, 2014). The use of traditional drugs for the treatment of diarrhea has limited scope due to their side effects. Taking an example of the opiate drugs which are agonist of opiate receptors, produce action by increasing the transit times of the colon and caecal part of the gut (Heel *et al.,* 1978; Shook *et al.,* 1989; Sykes, 1996; Turvill and Farthing, 1997). The increase in transit time may also increase the risk of adverse effects of these drugs on the gastrointestinal tract, like fluid accumulation in the distended lumen of the bowel and also enhance the bacterial colonization (DuPont and Hornick, 1973; Brown, 1979; Ruppin, 1987). The use of oral Zinc preparations is recommended by the World Health Organization (WHO) in addition to Oral Rehydration Salts (ORS). In 2008, a joint working group of the European Society for Pediatric Gastroenterology, Hepatolgy and Nutrition (ESPGHAN) and the European Society for Pediatric Infection Diseases (ESPID) had published proved guidelines about use of anti-diarrheal drugs adjuvant to ORS in the treatment of acute diarrhea (Tormo *et al.,* 2008; Gordon *et al.,* 2016). Prior diagnosis to reduce the worsening of sickness (Pessi *et al.,* 2014), new pharmacological therapies and implementation of current interventions is still required to reduce the health burden and with better results (Kotloff *et al.,* 2013; Ashiq *et al.,* 2017). For the present study, previously published papers were reviewed and key words for the search of literature were included: Racecadotril, Enkephalinase inhibitor, diarrhoea, Oral rehydrating solutions, diarrhea treatment, infectious diarrhea, and epidemiology of diarrhea. Databases of the literature search, included: Google Scholar, PubMed, Scopus and MEDLINE (Kanwal *et al.,* 2018; Tanveer *et al.,* 2019).

Clinical properties of an ideal anti-diarrheal agent

American Journal of Medicine published a paper in 1985 which mentioned the ideal characteristics of a drug (Table 1) used for the infectious diarrhoea treatment (Edelman, 1985).

Racecadotril as drug of choice

According to the several guidelines, concomitant use of Racecadotril with oral rehydration solution may be recommended for the treatment of acute diarrhea in children (Eberlin *et al.,* 2012). Racecadotril has a greater tolerability than loperamide in patients with acute diarrhea (Fischbach *et al.,* 2016). Racecadotril, (±)-benzyl2-(2-(acetylthiomethyl)-2-methyl-3 phenylpropanamido) acetate (Fig. 1) is a new anti-diarrheal drug (Matheson and Noble, 2000).

Enkephalinase discovered in 1975 and showed a major role in gastrointestinal secretions (Schwartz, 2000). Racecadotril is a potent, orally active drug (Prado, 2002) that inhibits the enkephalinase enzyme activity and preventing the degradation of enkephalins which are abundant in the intestinal villi (Pollard *et al.,* 1991; Vishwakarma, 2018). Enkephalins have an antisecretory effect (Vetel *et al.,* 1999) by inhibiting cyclic adenosine monophosphate (cAMP) (Huijghebaert *et al.,* 2003; Wang *et al.,* 2005). Inhibition of enzyme enkephalinase takes place when parent drug (Racecadotril) is converted to its metabolite thiorphan, in peripheral tissue membranes. The concentration level of Enkephalin is increased due to opioid receptors activation which results in cAMP level reduction. Ultimately, electrolytes and water secretion reduced into the intestinal lumen (Matheson and Noble, 2000; Kozuch and Hanauer, 2008; Basniwal *et al.,* 2008). Maximum absorption occurs when the drug is administered orally at different doses and C_{max} is achieved within 1 hour. According to the BCS,

Racecadotril belongs to Class-II drug (high permeability, low solubility). Class-II drugs (BCS) are further classified on the basis of pKa as a Class IIa (pKa<5), Class IIb (pKa>6.5) and Class IIc (Neutral Drug).

Table 1. Clinical properties of ideal drug for infectious diarrhea treatment.

i	Inhibition fluid secretion and stimulation of liquid absorption through intestinal mucosa
ii	Short onset of action
iii	Constipating effects must be limited to avoid fluid pooling in bloated intestinal lumen
iv	Enhancement of bacterial colonization of the upper bowel Invasion by Shigella
v	Must not obstruct the local function of bowel recovery
vi	Effects on central nervous system should be less with greater therapeutic index.
vii	Abuse potential must be low.

The pKa of Racecadotril is 12.6 which mean that drug falls in BCS Class IIb and can be predicted to have high solubility and dissolution rates at acidic pH in the stomach. Racecadotril bioavailability is not affected by food and rapidly converted to its active metabolite. Thiorphan inhibit the enkephainase enzyme activity and decreases the production of secretions. In addition, oral administration of Racecadotril does not cross blood–brain barrier (Eberlin *et al.,* 2012). Racecadotril and its active metabolite, thiorphan can be analyzed by liquid chromatography and detected by UV in human plasma after extraction of solid-phase.

Preclinical studies interprets that in experimental models, the drug (Racecadotril) is active in hypersecretory diarrhea (Marcais-Collado *et al.,* 1987; Primi *et al.,* 1999). These studies proved that in the small intestine, gastrointestinal transit time of Racecadotril does not increase or effect bacterial over growth (Duval-Iflah *et al.,* 1999).

Racecadotril prevents intestinal fluid secretion

Acute diarrhea is a major cause of hyper-secretion that results in water and electrolyte loss in the body (Edelman, 1985). To treat the diarrhea, inhibition of fluid secretion and stimulation of fluid absorption is necessary by the mucosa of the intestine (Wingate, 2001). Racecadotril secretions prevention action in experimental animal models has been verified in a research (Marcais-Collado *et al.,* 1987; Duval-Iflah *et al.,* 1999). In a study, six healthy volunteers were examined to study the influence of cholera-induced hyper secretion and Racecadotril in the jejunum. A small section of the jejunum (approximately 30cm) was perfused in an electrolyte solution with the same concentration as plasma and cholera toxin effect (a 6.25 mg intra-jejunal bolus) was measured with and without oral administration of the drug (3× 100 mg capsules). Cholera toxin caused the net secretion of water. However, Cholera toxin effect was inhibited significantly (PB 0.05) by Racecadotril administration, that altered the net effect of

absorption of water. Transport of electrolyte in the intestine was also changed significantly with respect to absorption (Wang *et al.,* 2005). Another study was conducted on the healthy volunteers and diarrhea was induced by the castor oil and the action of Racecadotril was measured, it is also known as a model of hypersecretory diarrhea. Six healthy volunteers were pretreated with and without oral administration of Racecadotril (10 mg/kg) before 45 min of taking castor oil (30 g). Both treatments were given to all the subjects. The cumulative weight of stool was reduced significantly (PB0.001) with administration of Racecadotril as compared to the placebo. Further, a delayed onset of diarrhoea was seen by the effect of the drug (Baumer *et al.,* 1992).

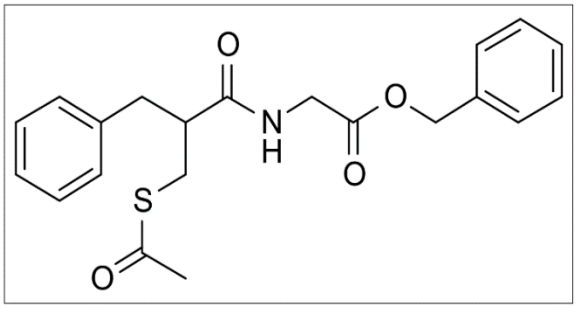

Fig. 1. Chemical structure of Racecadotril.

Racecadotril shows fast onset of action

Onset of action must be rapid for those drugs used for the treatment of diarrhea (Prado, 2002). The studies showed that Racecadotril has rapid onset of action in healthy subjects as well as on the patients that were suffering from diarrhea (Lecomte, 2000; Matheson and Noble, 2000). Effect of plasma enkephalin enzyme was determined in eight healthy volunteers after oral administration of a single dose of Racecadotril (100 mg). Significant inhibition of plasma enkephalin enzyme (PB0.01) was demonstrated after first 30 min of drug administration and maximum inhibition was produced after 1 hour. A double-blind, randomized and parallel-group study shows the rapid onset of action of drug. Racecadotril (100 mg) three times daily was given to adult patients (32 patients, 32 placebo) of acute diarrhea for 7 days. Stool weight was measured to demonstrate the anti-secretory effect of drug, Racecadotril showed a significant, 28.9% reduction (P=0.025) in weight of stool after first 24 hours of treatment, as compared with placebo drug. Significantly less diarrheic stools was associated with Racecadotril than placebo drug (P=0.027) (Hamza *et al.,* 1999).

Racecadotril does not produced adverse gastrointestinal effects

Racecadotril absorbed the fluid from the gastrointestinal tract without causing any harmful effects (Schwartz, 2000). It was proved in a randomized, crossover, double-blind, placebo-controlled study. An investigation was conducted on 12 healthy volunteers to demonstrate the action of Racecadotril on transit time of GIT. Biotransformation of sulphasalazine to active metabolite and sulphapyridine was used to access oro-caecal transit time. Racecadotril (100 mg) or placebo drug was given daily (3 times) to the patients for 7 days. On 7th day, each subject received sulphasalazine (2g) with a standardized breakfast and samples of blood were taken after every thirty minutes over a period of eight hours. The presence of sulphapyridine in the plasma shows the oro-caecal transit time. No substantial effect was seen on mean (9SEM) oro-caecal transit time by the administration of Racecadotril. The transit time of colon was also measured by oral ingestion of radio-opaque markers in first 5 days after starting the treatment of the drug. In colon the number of markers, was counted by X-ray on the 6thday of drug administration. No significant effect of Racecadotril was determined at mean (9SEM) colonic transit time (Racecadotril 31.395.6 h vs. placebo 25.895.8 h). Racecadotril has no effect on transit time of GIT have been confirmed in patients that suffering from acute diarrhoea (Bergmann *et al.,* 1992). Clinical research has been conducted for comparison of Racecadotril and placebo drug to show the occurrence of constipation during the treatment treated 193 patients who had acute diarrhea with Racecadotril (n=95) or placebo (n=98) for a maximum of 10 days. The occurrence of constipation was low in both groups; only four patients receiving Racecadotril, suffered from constipation and two on placebo. The frequency of both abdominal distension and abdominal pain was

considerably (PB 0.05) lesser than the Racecadotril; at the end of investigation out of 18 (20.5%) patients on placebo eight patients (9.6%) had abdominal pain, and 13 (18.3%) had abdominal distension at the end of the analysis compared with 26 (34.7%) on placebo (Baumer *et al.,* 1992). In a double blind trial, two groups of adult patients with acute diarrhea were compared to observe the effects of placebo and Racecadotril. It was reported that there is no significance variance in weight of stool when diarrhea had resolved. The study also showed the lack of constipation with Racecadotril. At the consultation on a second patient on day four the frequency of distension in the abdomen was reported to be 18.2% with placebo as compared to 5.6% with Racecadotril (Hamza *et al.,* 1999). In a double-blind study, which was carried out on patients with acute diarrhea has compared the effects of loperamide (n=32 with a dose of 1.33mg) with Racecadotril (n=37, with a dose of 100mg) at a frequency of 3 times daily for 7 days continuous treatment. When the diarrhea got cured, 31.3% patients treated with loperamide and 8.1% patients who received Racecadotril complained recurrence of constipation (PB 0.02). While abdominal distension was also reported by 50% and 27% of the treated patients with loperamide and Racecadotril, respectively (PB 0.05), in addition to this, 40.5% of patients on Racecadotril reported abdominal pain more than 1 day during the period of treatment as compared 59.4% to patients treated with loperamide reported the same (Roge *et al.,* 1993). A study carried out also endorsed that the frequency of recurrence constipation is lower with Racecadotril than loperamide (Vetel *et al.,* 1999) and showed better tolerability than loperamide in children and adults with diarrhea (Metheson and Noble, 2000).

Racecadotril is drug of high therapeutic index

The medicines used for the cure and management of diarrhea must have a high therapeutic index (Singh and Narayan, 2008). The safety profile of a medication depends upon the therapeutic index (Lecomate, 2000). Pharmacological studies of Racecadotril showed that no toxic effects were observed when it is administered in primates, up to 100 times of the therapeutic dose for the period of 12 months. In human beings, a single dose of two grams that is equivalent to more than 20 times of its therapeutic dose was orally given to healthy volunteers that cause no adverse effects. In a study, clinical trials have been conducted on 1883 patients, treated with Racecadotril, 100 patients was given the drug for at least 90 days. A clinical trial has shown that the safety profile and tolerability of Racecadotril is similar to the placebo drug and highly favorable than loperamide (opiate receptor agonist). Baumer and co-authors, in their research on 193 patients with acute diarrhea, interpreted the occurrence, nature, and severity of adverse effects was same for Racecadotril as well as placebo drug. Global analysis by both physician and patient confirmed the safety and fair tolerability of Racecadotril (Baumer *et al.,* 1992). A study evaluated that 3.1% of patients receiving Racecadotril described adverse events at the second physician consultation on the 4th day when compared with 5.3% of those taking placebo drug (Hamza *et al.,* 1999). The two double-blind relative studies also confirmed that Racecadotril is safe and well tolerated as compared to the loperamide (Roge *et al.,* 1993; Vetel *et al.,* 1999).

Racecadotril has no side effects on the central nervous system

The drugs used for the treatment of diarrhea must have minimal effects on central nervous system and misuse potential should be low (Duval-Iflah *et al.,* 1999). The ability of drug to cross the blood brain barrier was determined by relating the enkephalin enzyme activity in plasma and cerebrospinal fluid when given orally. Two patients undergo myelography had been hospitalized and to them Racecadotril (dose 20 mg/kg) was given orally. Enkephalin enzyme activity in the plasma had reduced to minimum level within 30 minutes that showed maximum inhibition of enzyme by Racecadotril. In contrast, effect of the enzyme in cerebrospinal fluid did not alter, which indicated that Racecadotril has no ability to cross the blood–brain barrier. A double-blind, crossover and randomized study conducted on 12 healthy volunteers confirmed

that Racecadotril has no effect on the central nervous system. Racecadotril placebo (300 mg/day) was given to each subject for 3 days, and a psychometric tests battery was conducted to evaluate the vigilance before and after treatment. Both treatments were given to all subjects and the results demonstrated that vigilance was not impaired by Racecadotril.

The studies conducted in monkeys and rats also revealed a lack of potential for abuse with Racecadotril (Kachel *et al.,* 1986).

Conclusion

Diarrhea is a common symptom which is associated with many pathological conditions. It causes increased mortality and morbidity among children and adults, especially in lower income countries and put a high cost burden of the treatment on health budgets. Racecadotril is a new drug of choice for the treatment of diarrhea with proven clinical efficacy.

It shows a rapid onset of action and has a high therapeutic index combined with the lack of side effects on the gastrointestinal tract and central nervous system. It is concluded from the current study that Racecadotril offers a new approach for the treatment of diarrhea by inhibiting the enzyme enkephalinase and by reducing the GIT secretions. However, there is a need to carry out further research so that reliable conclusions can be measured for the treatment of diarrhea with Racecadotril.

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