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Original Article

AN INVESTIGATION INTO THE ANTI-DIARRHEAL PROPERTY OF MONTELEUKAST

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ABSTRACT

Diarrhea is an increase in the frequency, fluidity or volume of bowel movements. Diarrhea refers to frequent defecation of liquid feces. It is caused by increased motility and decreased absorption by the intestines. When chyme passes too quickly through the large intestine, there is not enough time left for absorption. Diarrhea can result in dehydration and electrolyte imbalance. Monteleukast is a leukotriene antagonist and is used in the treatment of Asthma. An excess secretion of leukotrienes and prostaglandins in our gastrointestinal tract results in diarrhea.This leukotriene antagonizing property of monteleukast has been exploited in the present investigation to determine whether monteleukast has any antidiarrheal property.This study was undertaken to evaluate the antidiarrheal effect of monteleukast in a dose of 10 mg/kg by using magnesium sulphate induced diarrhea model. It was found that therapeutic dose of monteleukast showed significant reduction of stools which might be due to, inhibition of synthesis of prostaglandins which are responsible for diarrhea. Monteleukast was administered at a dose of 10 mg/kg and reduced the total weight of feaces in 4 hrs, (11.0g±1.2**) and total number of wet feces in 4 hrs. (10.0g ±1.4**). This was compared to control group (16.0g ± 0.56 and 15.0g ± 0.98). Also monteleukast at a dose of 10 mg/kg showed more significant reduction in the mean weight of feces compared to control group and percentage inhibition of defecation by monteleukast at a dose 10 mg/kg was 31.25% as compared to control group. While loperamide at a dose 2 mg/kg showed 54.37% inhibition of diarrhea. These results suggest that monteleukast possesses antidiarrheal efficacy which may be due to its antimotility and antisecretory actions.

Keywords: Monteleukast, Loperamide, Magnesium sulphate induced diarrhea.

INTRODUCTION

Diarrhea is discharge of semisolid or watery fecal matter from the bowel three or more times in a day.[1-5] Diarrhea includes loss of electrolytes and water and decreased absorption of fluid from our gastrointestinal tract [6,7].Diarrhea is defined as an increase in the frequency, fluidity or volume of bowel movements[8].It is often accompanied by pain, urgency, perianal discomfort and incontinence. Low volume, painful bloody diarrhea is known as dysentery [9] Diarrhea has been traditionally linked to the gastrointestinal tract. Antidiarrheal drugs are classified into two types. First type includes specific antimicrobial drugs like tetracycline, norfloxacin, ciprofloxacin, erythromycin, metronidazole and tinidazole. And second type are nonspecific anti-diarrheal drugs like isphaghula, psyllium, bismuth subsalicylate, atropine, diphenoxylate, loperamide [10] etc.Loperamide (2 mg/kg oral) was used as a standard drug in our experimental studies. Loperamide is an opioid-receptor agonist and acts on the μ-opioid receptors in the myenteric plexus of the large intestine, affecting water and electrolyte movement through the bowel[11,12]. Monteleukast is a drug which is routinely used in the treatment of asthma and to relieve symptoms of seasonal allergies, wheezing and intestinal pain[13]

MATERIALS AND METHOD

Monteleukast was obtained as a gift sample from cipla pharmaceuticals Ltd, Mumbai.

Experimental animals

The study was approved by Institutional animal ethical committee for animal experimentation (IAEC/RAP/3961), of Rajiv Academy for pharmacy,Mathura,U.P. Healthy albino wistar rats weighing 200-250 gm were kept in animal house of Rajiv academy for pharmacy, Mathura and maintained on food and water ad libitum.

Chemicals/ Drugs

Monteleukast(Cipla pharmaceuticals Ltd.,Mumbai), loperamide (Cipla pharmaceuticals Ltd.,Mumbai), magnesium sulphate (Central drug house pvt. Ltd, New Delhi).

Anti-diarrheal activity study by magnesium sulphate induced diarrhea

Rats were fasted for 18 hrs prior to experimentation and were divided into three groups control, standard and test as indicated in Table No-1.Each group contained six rats. Control group received vehicle, i.e, and 2 ml (per oral) of distilled water. Standard group received loperamide at a dose of (2 mg/kg, p.o.) and test group received monteleukast (10 mg/kg, p.o.).

After 30 min of administration of these drugs, diarrhea was induced by oral administration of magnesium sulphate at a dose of 2 g/kg to each rat. Each rat was placed in an individual cage, the floor of which was lined with blotting paper. During an observation period of 4 hours the percentage inhibition of diarrhea was determined by taking into account the weight of the total fecal output and this was compared with that of the control group [14]

Calculation of percentage Inhibition of diarrhea- % Inhibition = [control mean – treated (test) mean]× 100 [control mean]

Statistical analysis

Values were Mean ± SEM (n=6); P values: *< 0.05;** < 0.001; *** < 0.0001 showed significant inhibition of total fecal output as compared with the control. Inter group comparison were made using one- way ANOVA followed by Dunnett's test.

RESULTS AND DISCUSSION

This study was undertaken to evaluate the antidiarrheal property of monteleukast at a dose of 10 mg/kg by using magnesium sulphate induced diarrhea model. It was found that therapeutic dose of monteleukast showed significant reduction of stools which might be due to, inhibition of synthesis of prostaglandins, which are responsible for diarrhea. Monteleukast was administered at a dose of 10 mg/kg and reduced the total weight of feces in 4 hrs (11.0g±1.2**) and total number of wet feces in 4 hrs. (10.0g ±1.4**). This was compared to control group (16.0g ± 0.56 and 15.0g ± 0.98) respectively. Also monteleukast showed more significant reduction in the mean weight of feces compared to that of control group.

Percentage inhibition of total fecal output at a dose of 10 mg/kg of monteleukast was 31.25% while loperamide at a dose of 2 mg/kg showed 54.37%.Evaluation of antidiarrheal activity of monteleukast by magnesium sulphate induced diarrhea is given in Table No. 1.

Table 1: Effect of Magnesium sulphate induced diarrhea in rats

S. No.	Treatment	Dose (mg/kg)	Mean weight of feces in 4 hrs (gm)	Mean number of wet feces in 4 hrs (gm)	% Inhibition
1.	Control (water)	2ml	16.0 ± 0.56	15.0 ± 0.98	-
2.	Standard (Loperamide)	2mg/kg	7.3 ± 0.59**	6.6 ± 0.99**	31.25
3.	Test (Monteleukast)	10mg/kg	11.0 ± 1.2**	10.0 ± 1.4**	54.37

Values are Mean ± SEM (n=6); P values: *< 0.05;** < 0.001; *** < 0.0001, showed significant reduction of fecal output as compared with control. Inter group comparison were made using one- way ANOVA followed by Dunnett's test Diarrhea results from an imbalance between the absorptive and secretory mechanisms in the intestinal tract, accompanied by intestinal hurry, resulting in an excess loss of fluid in the faeces[15] These observations suggest that antidiarrheal effect of monteleukast may be due to the inhibition of the release of prostaglandins and leukotrienes.These conditions aim to suggest that monteleukast reduces diarrhea by increasing reabsorption of electrolytes and water and inhibiting intestinal accumulation of fluid as in the case of loperamide. Monteleukast has also showed decrease in hypermotility and hypersecretion of intestinal fluid in experimental animal models.[16] In the above experiments loperamide was used as standard drug and it acted by slowing intestinal motility and thereby reducing water and electrolyte movement through the bowel. Loperamide does not have opioid effects in the central nervous system as it does not cross the blood–brain barrier in significant amounts. Magnesium sulphate produces diarrhea by osmotic properties, preventing reabsorption of water and ions, leading to an increase in the volume of the intestinal content. It has also been proved that magnesium sulphate promotes the release of cholecystokinin from the duodenal mucosa, which increases the secretion and motility of the small intestine, thereby preventing the reabsorption of sodium chloride and water[17,18].

CONCLUSION

The results of this investigation revealed that monteleukast has signifiant antidiarrheal property and further studies are required to test its efficacy in human subjects.

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