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ENHANCEMENT OF ANTIDIARRHOEAL EFFECT OF DIPHENOXYLATE BY PIPERINE

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ABSTRACT: The present study was aimed to evaluate the effect of Piperine on the antidiarrhoeal activity of Diphenoxylate. Antidiarrhoeal effect of Diphenoxylate, Piperine and Diphenoxylate in combination with Piperine was subjected to pharmacological evaluation. Antidiarrhoeal effect was evaluated in castor oil and magnesium sulphate induced diarrhoea model while antimotility and antisecretory effect was evaluated in charcoal meal test and castor oil-induced intestinal secretions in mice. Diphenoxylate at a dose of 1 mg/kg produced 43% and 37.71% inhibition of diarrhoea in castor oil and magnesium sulphate induced diarrhoea model respectively. Diphenoxylate at a dose of 1 mg/kg produced 18.47% antimotility effect and 35.79% antisecretory effect. Piperine at a dose of 10 mg/kg showed 18.89% and 20.72% antidiarrhoeal effect in castor oil and magnesium sulphate induced diarrhoea model respectively. Piperine at a dose of 10 mg/kg produced an 11.55% antimotility effect and 27.65% antisecretory effect. Diphenoxylate (1 mg/kg) with Piperine (10 mg/kg) produced 82.48% and 81.20% inhibition of diarrhoea in castor oil and magnesium sulphate induced diarrhoea model respectively. Diphenoxylate (1 mg/kg) with Piperine (10 mg/kg) produced 42.80% antimotility effect and 73.67% antisecretory effect. The results of the present study indicated that the antidiarrhoeal effect of Diphenoxylate was increased when given with Piperine is because of augmentation of antimotility and antisecretory effect of Diphenoxylate. Enhancement of antidiarrhoeal effect of Diphenoxylate when given with Piperine may be due to the bioenhancing effect of Piperine and thus producing synergism.

INTRODUCTION: Diarrhoea is a frequent medical problem. Intestinal infection is the most common cause of diarrhoea worldwide and is responsible for the deaths of 3-4 million individuals each year, mostly in preschool-age children [1]. Diphenoxylate is an opioid agonist used in the treatment of diarrhoea.

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It acts by reducing intestinal contractions and peristalsis, therefore, allowing the body to remove moisture from the intestinal contents and consolidate waste product into a dense solid form rather than loose and watery as is diarrhoea [2]. An undesirable effect of the Diphenoxylate is nausea, dizziness, drowsiness, restlessness, and abdominal cramps. Higher doses produce respiratory and CNS depression, and prolonged use can potentially lead to opioid dependence [3].

Piperine is an alkaloidal constituent of black pepper recently established as a bioavailability enhancer of drugs and other substances. It stimulates both the digestive and circulatory systems by increase

thermogenesis (the process of generating energy in cells) [4]. The aim of the present study was to evaluate the effect of Piperine on the antidiarrhoeal activity of Diphenoxylate.

MATERIALS AND METHODS:

Drugs: i) Castor oil (refined pure) - Paras Chemical Industries ii) Activated Charcoal - Merck iii) Magnesium sulphate - Merck iv) Diphenoxylate = Sigma Chemicals Ltd. v) Piperine - Sigma Chemicals Ltd.

Animals: Swiss albino mice of either sex, weighing 20-30 gm obtained from VIPER, Pune, were used for the experiments. Mice were kept in standard environmental conditions, fed standard food and water *ad libitum*. All experiments were performed after an overnight fast. The Institutional Animal Ethical Committee of Government College of Pharmacy, Aurangabad, Maharashtra, India (GCPA/IAEC/2011/235), approved the study.

Acute Toxicity Study: Initially, Diphenoxylate and Piperine were studied for acute oral toxicity as per revised OECD guidelines number 423. Diphenoxylate was devoid of any toxicity up to 5 mg/kg in albino mice by oral route. Hence for further studies, 1 to 4 mg/kg dose of Diphenoxylate was used. Piperine was used for the study at the dose of 10 mg/kg because it has not shown any toxicity up to 50 mg/kg. Groups of six mice were used for the study.

Experimental Procedures for Antidiarrhoeal Activity:

Castor oil Induced Diarrhoea: (Effect of diphenoxylate, piperine and diphenoxylate with piperine on castor oil-induced diarrhoea)

Group 1 (Control Group): Distilled water 7 ml/kg, p.o.

Group 2 (Standard Group): Diphenoxylate 1, 2, 4 mg/kg, p.o.

Group 3 (Test Group): Piperine 10 mg/kg, p.o.

Group 4 (Test Group): Diphenoxylate (1 mg/kg, p.o.) with Piperine (10 mg/kg, p.o.)

Castor oil (0.2 ml/mouse) was administered to each mouse after 30 min of above treatment. Animals were then placed on the floor lined with blotting paper, under separate glass funnels, for observation for 4 h. The parameters observed were: onset of diarrhoea, total number of faecal output, and number of wet faeces [5].

Magnesium Sulfate Induced Diarrhoea: (Effect of Diphenoxylate, Piperine and Diphenoxylate with Piperine on magnesium sulfate induced diarrhoea)

Group 1 (Control Group): Distilled water 7 ml/kg, p.o.

Group 2 (Standard Group): Diphenoxylate 1, 2, 4 mg/kg, p.o.

Group 3 (Test Group): Piperine 10 mg/kg, p.o.

Group 4 (Test Group): Diphenoxylate (1 mg/kg, p.o.) with Piperine (10 mg/kg, p.o.).

Magnesium sulfate was given in the dose of 2 g/kg to the animals 30 min after the above treatment, and a similar protocol used for castor oil-induced diarrhoea was followed [6, 7].

Gastrointestinal Motility by Charcoal Meal: (Effect of Diphenoxylate, Piperine, and Diphenoxylate with Piperine on castor oil-induced gastrointestinal motility):

Group 1 (Control Group): Distilled water 7 ml/kg, p.o.

Group 2 (Standard Group): Diphenoxylate 1, 2, 4 mg/kg, p.o.

Group 3 (Test Group): Piperine 10 mg/kg, p.o.

Group 4 (Test Group): Diphenoxylate (1 mg/kg, p.o.) with Piperine (10 mg/kg, p.o.).

After 30 min of the above treatment, each animal was given castor oil (0.2 ml/mouse, p.o.). 0.2 ml of charcoal meal (3% charcoal in 5 % gum acacia) was given to each animal orally, 30 min after castor oil administration. After 30 min of charcoal meal administration, animals were sacrificed, and the small intestine was immediately isolated. Peristaltic index for every mouse was expressed as percentage of the distance travelled by the charcoal meal relative to the total length of the small intestine [8].

Small Intestinal Secretions: (Effect of Diphenoxylate, Piperine and Diphenoxylate with

Piperine on castor oil-induced small intestinal secretions):

Group 1 (Control Group): Distilled water 7 ml/kg, p.o.

Group 2 (Standard Group): Diphenoxylate 1, 2, 4 mg/kg, p.o.

Group 3 (Test Group): Piperine 10 mg/kg, p.o.

Group 4 (Test Group): Diphenoxylate (1 mg/kg, p.o.) with Piperine (10 mg/kg, p.o.)

Castor oil (0.2 ml/mouse) was administered to each mouse after 30 min of the above treatment, and they were sacrificed 30 min after castor oil administration. The entire small intestine isolated from each animal was weighed, and their group average was calculated. The difference in the weight of the intestine in the castor oil-treated group and control was considered as the castor oil-induced accumulation of intestinal fluid [9, 10].

Statistics: The results of all experiments were reported as mean ± S.E.M. Statistical analysis was carried out using Student's 't'-test. A level of significance of $P < 0.05$ was regarded as statistically significant.

RESULTS: According to this study, antidiarrhoeal effect of Diphenoxylate was potentiated when given with Piperine in mice in castor oil-induced diarrhoea model, magnesium sulphate induced diarrhoea model, antimotility model, and intestinal secretion model.

Effect of Diphenoxylate, Piperine and Diphenoxylate with Piperine on Castor Oil Induced Diarrhoea in Mice: During the course of observation for 4 h after castor oil administration, all the mice in control group produced copious diarrhoea. Diphenoxylate showed a significant dose-dependent delay in the onset of diarrhoea, decrease in the frequency of purging (reduction of a number of wet stools and total no of stools) as shown in **Table 1**. Diphenoxylate showed 43%, 68.93%, 85.15% inhibition of diarrhoea at doses of 1 mg/kg, 2 mg/kg and 4 mg/kg, respectively. Piperine showed 18.89%, inhibition of diarrhoea at dose of 10 mg/kg. Diphenoxylate (1 mg/kg) with Piperine (10 mg/kg) showed 82.48% inhibition of diarrhoea.

TABLE 1: EFFECT OF DIPHENOXYLATE, PIPERINE AND DIPHENOXYLATE WITH PIPERINE ON CASTOR OIL (0.2 ml) INDUCED DIARRHOEA IN MICE

Group	Dose (mg/kg)	Onset of diarrhoea (min)	Total number of stools	Number of wet stools	% Inhibition
Control		56 ± 2.28	14.5 ± 0.40	12.33 ± 0.30	
Diphenoxylate	1	72 ± 2.54	8.5 ± 0.36	7.00 ±0.25	43
Diphenoxylate	2	104 ± 3.78	4.66 ± 0.30	3.83 ± 0.30	68.93
Diphenoxylate	4	170 ± 4.82	2.00 ± 0.211	1.83 ± 0.16	85.15
Piperine	10	61 ± 2.37	13.00 ± 0.33	10.00 ± 0.49	18.89
Diphenoxylate + Piperine	1 ± 10	163 ± 4.68	2.66 ± 0.16	2.16 ± 0.22	82.48

Values are mean ± standard error of mean. Each value represents average of six determinations. $P < 0.05$ vs. control, student's '*t*' test.

TABLE 2: EFFECT OF DIPHENOXYLATE, PIPERINE AND DIPHENOXYLATE WITH PIPERINE ON MAGNESIUM SULPHATE (2 g/kg) INDUCED DIARRHOEA IN MICE

Group	Dose (mg/kg)	Onset of diarrhoea (min)	Total number of stools	Number of wet stools	% Inhibition
Control		48 ± 2.37	12.00 ± 0.36	8.83 ± 0.49	
Diphenoxylate	1	79 ± 3.15	7.66 ± 0.30	5.5 ± 0.33	37.71
Diphenoxylate	2	92 ± 4.35	4.5 ± 0.33	3.33 ± 0.30	62.28
Diphenoxylate	4	217 ± 6.71	1.00 ± 0.21	0.83 ± 0.16	90.60
Piperine	10	61 ± 2.39	9.83 ± 0.42	7.00 ± 0.47	20.72
Diphenoxylate + Piperine	1 + 10	172 ± 3.84	2.16 ± 0.22	1.66 ± 0.21	81.20

Values are mean ± standard error of mean. Each value represents average of six determinations. $P < 0.05$ vs. control, student's '*t*' test.

Effect of Diphenoxylate, Piperine and Diphenoxylate with Piperine on Magnesium Sulphate induced Diarrhoea in Mice: Administration of magnesium sulphate to the mice in control group produced diarrhoea during the observation period of 4 h. Pretreatment of mice with the different doses of Diphenoxylate caused a significant dose-dependent delay in the onset of

copious diarrhoea, decrease in the frequency of purging (reduction of number of wet stools and total no of stools) as shown in **Table 2**. Diphenoxylate produced 37.71%, 62.28%, 90.60% inhibition of diarrhoea at doses of 1 mg/kg, 2 mg/kg and 4 mg/kg, respectively. Piperine produced 20.72%, inhibition of diarrhoea at a dose of 10 mg/kg. Diphenoxylate (1 mg/kg) with Piperine (10 mg/kg) produced 81.20% inhibition of diarrhoea.

TABLE 3: EFFECT OF DIPHENOXYLATE, PIPERINE AND DIPHENOXYLATE WITH PIPERINE ON CASTOR OIL (0.2 ml) INDUCED INTESTINAL TRANSIT IN MICE

Group	Dose (mg/kg)	Percent intestinal transit	% Inhibition
Control		85.16 ± 2.24	
Diphenoxylate	1	69.43 ± 2.08	18.47
Diphenoxylate	2	56.28 ± 1.97	33.91
Diphenoxylate	4	45.25 ± 1.65	46.86
Piperine	10	75.32 ± 2.33	11.55
Diphenoxylate + Piperine	1 ± 10	48.71 ± 1.76	42.80

Values are mean ± standard error of mean. Each value represents average of six determinations. $P < 0.05$ vs. control, student's '*t*' test.

Effect of Diphenoxylate, Piperine and Diphenoxylate with Piperine on Castor Oil induced Small Intestinal Transit in Mice: The results revealed that Diphenoxylate significantly inhibited the castor oil-induced gastrointestinal transit of charcoal in mice, as shown in **Table 3**. Diphenoxylate inhibited the castor oil-induced gastrointestinal transit of charcoal in mice by 18.47%, 33.91%, and 46.86% at doses of 1 mg/kg, 2 mg/kg, and 4 mg/kg, respectively. Piperine inhibited the castor oil-induced gastrointestinal transit of charcoal in mice by 11.55%, at a dose 10 mg/kg. Diphenoxylate (1 mg/kg) with Piperine (10 mg/kg) showed 42.80% inhibition of gastrointestinal transit.

Effect of Diphenoxylate, Piperine and Diphenoxylate with Piperine on Castor Oil induced Small Intestinal Secretion in Mice: Diphenoxylate showed the inhibition of castor oil-induced intraluminal accumulation of fluid as shown in **Table 4**. Diphenoxylate inhibited the castor oil-induced intraluminal accumulation of fluid by 35.79%, 60.98%, and 77.08% at doses of 1 mg/kg, 2 mg/kg and 4 mg/kg, respectively. Piperine inhibited the castor oil-induced intraluminal accumulation of fluid by 27.65%, at a dose of 10 mg/kg, respectively. Diphenoxylate (1 mg/kg) with Piperine (10 mg/kg) showed 73.67% inhibition of castor oil-induced intraluminal accumulation of fluid.

TABLE 4: EFFECT OF DIPHENOXYLATE, PIPERINE AND DIPHENOXYLATE WITH PIPERINE ON CASTOR OIL (0.2 ml) INDUCED INTRALUMINAL FLUID ACCUMULATION IN MICE

Experimental Group	Dose (mg/kg)	Weight of small intestine (mg)	Castor oil induced intraluminal fluid (mg)	% Inhibition
Normal		1059 ± 24		
Control		1587 ± 37	528 ± 21	
Diphenoxylate	1	1398 ± 31	339 ± 18	35.79
Diphenoxylate	2	1265 ± 25	206 ± 15	60.98
Diphenoxylate	4	1180 ± 24	121 ± 08	77.08
Piperine	10	1441 ± 26	382 ± 13	27.65
Diphenoxylate + Piperine	1 ± 10	1198 ± 22	139 ± 11	73.67

Values are mean ± standard error of mean. Each value represents average of six determinations. $P < 0.05$ vs. control, student's '*t*' test.

DISCUSSION: World Health Organization defines diarrhoea as the "passage of loose or watery stools at least three times in a 24 h period". In diarrhoea increase in the motility of the gastrointestinal tract, along with increased secretion and a decrease in the absorption of fluid causes significant loss of electrolytes and water and thus produces dehydration, which can be life-threatening if untreated [11, 12]. Diphenoxylate is an effective antidiarrhoeal agent act by increasing the intestinal tone and decreasing the propulsive movements of the bowel. Diphenoxylate is a piperidine derivatives, extensively absorbed after oral administration, with peak levels achieved within 1 to 2 h. It can produce CNS effects when used in higher doses and thus have a potential for abuse or addiction [13].

A current area of basic research is the activity of Piperine as a vanilloid agonist to treat gastrointestinal disorders such as irritable bowel syndrome and diarrhoea. Since piperine has been used to stimulate the gastrointestinal tract, it could be helpful for conditions such as diarrhoea and irritable bowel syndrome, which are not easily managed by standard care [14]. The present study was

conducted to investigate the enhancement of the efficacy of Diphenoxylate by Piperine in the treatment of diarrhoea. Integrated effect of Diphenoxylate and Piperine was studied in mice in diarrhoea induced by castor oil model, magnesium sulphate induced diarrhoea model, Charcoal meal test for intestinal motility model, and castor oil-induced intraluminal fluid accumulation test model.

The castor oil-induced diarrhoea demonstrates secretory diarrhoea, since it induces diarrhoea by causing increased secretion of fluid and electrolytes into the lumen of the bowel by intestinal mucosa, resulting in fluid accumulation and a watery luminal content that flows rapidly through the small and large intestines [15]. This is brought about by the irritant effect of ricinoleic acid liberated by pancreatic lipases, which hydrolyze the oil derived from the seeds of *Ricinus communis* [16]. As Diphenoxylate successfully inhibited the castor oil-induced diarrhoea, it can be assumed that the antidiarrhoeal action was exerted by antisecretory mechanism. This was also evident from the reduction of the total number of wet faeces in the test groups in the experiment. Antidiarrhoeal effect of Piperine was very less as compared to Diphenoxylate but Piperine has shown to increase the antidiarrhoeal effect of Diphenoxylate significantly by enhancing the antisecretory activity of Diphenoxylate.

Magnesium sulphate produces the diarrhoea by osmotic properties, preventing reabsorption of water ions, leading to an increase in the volume of the intestinal content. It promotes the liberation of cholecystokinin from the duodenal mucosa, which increases the secretion and motility of the small intestine and thereby prevents the reabsorption of sodium chloride and water [17]. Diphenoxylate reduced the diarrhoea in this model due to increase in the absorption of water and electrolyte from the gastrointestinal tract. Antidiarrhoeal effect of Piperine was less potent as compared to Diphenoxylate. Significant increase in the antidiarrhoeal activity of Diphenoxylate when given with Piperine may be due to increase in the absorption of water and electrolyte from the gastrointestinal tract.

Gastrointestinal motility describes the contraction of the muscles that mix and propel contents in the gastrointestinal tract. Usually, the diarrhoea is considered a consequence of altered motility and fluid accumulation in the intestinal tract. Charcoal meal test in mice is a method used to study the effect of drugs on the motility of the intestine [18]. Diphenoxylate was found to be an inhibitor of intestinal motility. Antimotility effect of Piperine was less as compared to Diphenoxylate but the antimotility effect of Diphenoxylate was enhanced when given with Piperine.

Diarrhoea occurs when the bowels secrete more electrolytes and water than they absorb. Causes of increased secretions include infections like gastroenteritis, unabsorbed fats, certain drugs, and various intrinsic and extrinsic secretagogues [19]. Permeability changes produced by castor oil in the intestinal mucosa membrane cause intraluminal fluid accumulation [20, 21]. The intestinal secretions were blocked by Diphenoxylate. The antisecretory effect of Piperine was less potent as compared to Diphenoxylate. Antisecretory effect of Diphenoxylate was significantly increased when given with Piperine.

CONCLUSION: Piperine showed an increase in the antidiarrhoeal effect of Diphenoxylate in castor oil and magnesium sulphate induced diarrhoea in mice. Piperine enhanced the antimotility effect of Diphenoxylate in mice. The inhibitory effect of Diphenoxylate on intraluminal fluid accumulation induced by castor oil in mice was potentiated by Piperine. Thus the results of the present study indicated that the antidiarrhoeal, antimotility and antisecretory effect of Diphenoxylate was increased when given with Piperine which leads to a decrease in the effective antidiarrhoeal dose of Diphenoxylate. A decrease in the effective antidiarrhoeal dose of Diphenoxylate may results in a decrease in the dose-dependent side effects of the Diphenoxy-late while using as antidiarrhoeal agent, which makes the Diphenoxylate suitable for the treatment of acute as well as chronic diarrhoea. Enhancement of anti-diarrhoeal effect of Diphenoxylate, when given with Piperine, may be due to the bio enhancing effect of Piperine and thus producing synergism.

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CONFLICTS OF INTEREST: Nil

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