Original Research

Effect of antiemetic drugs on decrease in gastric emptying in experimental model of motion sickness in rats

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KEY WORDS gastric emptying; motion sickness; cisapride; scopolamine; propranolol; mepyramine; rats

ABSTRACT

AIM: To study the effect of pretreatment with different antiemetic drugs on the motion sickness-induced inhibition in gastric emptying. **METHODS:** The rats were rotated for a period of 45 min at the rate of 30 rotations per min. **RESULTS:** Rotating the rats caused a significant decrease in gastric emptying as compared to the non-rotated group. Pretreatment with scopolamine (5 mg/kg, ip) did not reverse the delay in gastric emptying, while it *per se* caused inhibition of gastric emptying in the non-rotated group. Similarly other drugs mepyramine, cisapride, and granisetron did not have any effect on delay in gastric emptying caused by rotation. However beta blocker propranolol could partially but significantly reverse the decrease in gastric emptying. **CONCLUSION:** The present study demonstrated the potential use of propranolol as adjuvant with conventional antiemetics for motion sickness to combat associated secondary symptoms.

INTRODUCTION

Motion sickness is malady characterized by a combination of signs and symptoms that accompany movement or perceived movement in the environment. Many different circumstances can elicit motion sickness like travel in automobiles particularly on mountainous tracks, aircraft, spacecraft, boats, elevators and exposure to moving visual scenes[1] *etc*.

The most critical comes from the vestibular system which than goes to the vestibular nuclei and from the nuclei to the vomiting center leading to nausea and vomiting, the cardinal features of motion sickness[2].

A number of neurotransmitters and neuro-modulators have been shown to influence the activity of vestibular nucleus neurons, viz acetylcholine, glutamate, GABA, histamine, norepinephrine, dopamine, serotonin, ACTH *etc*[3]. Accordingly, a large number of pharmacological agents, eg, antihistamines, anticholinergics, antidopaminergics have been tried against motion sickness.

The secondary symptoms that accompany motion sickness are slowing of brain waves, loss of performance, and inhibition of gastric emptying. The inhibition of gastric emptying in the patients of motion sickness may be a result of reductions in gastric tone and motility and changes in the gastric myoelectric activity [2]. The present study was conducted to investigate whether these antiemetics have effects on the gastric emptying which is seen as a secondary symptom of motion sickness in rats. Since increased sympathetic discharge has been reported in the literature dur-

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Received 2002-02-27 Accepted 2002-12-20

ing motion sickness[4], which may lead to the inhibition of gastric motility, it was also considered worthwhile to study the effect of propranolol in the present study.

MATERIALS AND METHODS

Animals Adult male Wistar rats weighing 200-250 g were used for the study. The animals were procured from the central animal house facility at All India Institute of Medical Sciences, New Delhi. The rats were group housed in polypropylene cages (38 cm×23 cm×10 cm) with not more than 5 animals per cage and maintained under standard laboratory conditions with natural dark and light cycle (14 h±1 h light; 10 h±1 h dark). The animals were deprived of food 24 h prior to the experiment but allowed free access to water until 2 h before the experiment. A wire mesh was placed at the bottom of the cage to prevent coprophagy during the fasting period. All procedures described were reviewed and approved by the Institutional Animal Ethics Committee.

Drugs and chemicals Scopolamine, granisetron, propranolol (Sigma Chemical Co, St Louis, MO, USA), mepyramine, cisapride, (courtesy, Intas India Ltd) were dissolved in distilled water and administered intraperitoneally. All the drugs were prepared freshly and administered using a 26-gauge needle in a volume not exceeding 1 mL/kg. The doses used in the study were chosen on the basis of the dose used in the rats by other researchers.

Method for surrogate model of motion sickness The rats were placed individually in a specifically designed perspex restrainers of (20 cm long and 5 cm diameter) with a sliding door at one end to adjust the rat size and holes for adequate ventilation. With the help of a hook in the middle, the restrainers were hanged to the shaft of the blade of the ceiling. The hanging rope was only 20 cm long so as to minimize the centrifugal effect. The distance at the shaft of the fan was kept such that the diameter of rotation is fixed at 35 cm. The fan was run at a speed so as to get rotations of 30 per min. The rats were rotated in a group of 3 each (1 hanged on each blade) for 45 min. The 45-min time of rotation was chosen because in our standardization experiments significant pica behavior (kaolin consumption) was observed (1.2±0.3) g in 45-min rotated rats as compared to (0.60±0.15) g and (0.32±0.11) g in 15-min rotated group and the control group, respectively. Also a significant inhibition of gastric emptying was observed in the group rotated for 45 min after meal administration.

Measurement of gastric emptying The rate of gastric emptying of non-nutrient solution was determined according to the method described by Scarpignato *et al*, 1980[5]. Briefly, a test meal (0.05 % phenol red in a 1.5 % aqueous methylcellulose solution) of 1.5 mL per rat was given by an intragastric tube. Forty-five minutes after the meal, the animals were sacrificed. The stomach was removed and homogenized in 100 mL of NaOH 0.1 mol/L. Stomach tissue proteins (in 5 mL homogenate) were precipitated with 0.5 mL of trichloroacetic acid (20 % w/v) and centrifuged out. The supernatant was mixed with 4 mL of NaOH 0.5 mol/L and absorbance of the sample was read at a wavelength of 560 nm. Phenol red recovered from the stomach of rats sacrificed immediately after administration of methyl cellulose meal served as standard. The percentage gastric emptying of each rat was calculated from the following formula:

Gastric emptying (%)=

$$1-C_{\text{phenol red (test stomach)}}/C_{\text{phenol red (standard stomach)}}\times 100.$$

Experimental protocol Rats were divided into different groups with 9 animals each. One group of rats were sacrificed instantaneously after administration of test meal by cervical dislocation, which severed as standard for the measurement of percent gastric emptying. Tab 1 describes the drugs administered, their pretreatment time and the time after which the rats were sacrificed after administration of test meal in different groups.

Statistical analysis The results are expressed as mean±SEM. The values were compared using one way ANOVA with *post hoc* comparison (*Bonferroni*) among all the groups. $P<0.05$ was taken as level of significance.

RESULTS

The percent gastric emptying of the rats that were sacrificed immediately after intragastric test meal was taken as 0 %. When the rats were sacrificed after 45 min of meal administration a significant gastric emptying was observed. The value was 88 %±10 %.

In the rats rotated for a period of 45 min after administration of test meal there was almost complete inhibition of gastric emptying as compared to the non rotated group. The value was 3.0 %±0.5% ($P<0.05$).

In the rats treated with scopolamine (5 mg/kg, ip) 30 min prior to the test meal and sacrificed 45 min after administration of meal it was observed that scopolamine per se caused a significant inhibition in the gastric

Tab 1. Protocal of drug administration.

Groups	Drug treatment	Drug treatment time before test meal/min	Period after which the rats were sacrificed/min	
			Rats not subjected to rotation	Rats subjected to rotation
1	Standard		0	
2a.	Control	-	45	
2b.	Control	-		45
3a.	Scopolamine (5 mg/kg, ip)	30	45	
3b.	Scopolamine (5 mg/kg, ip)	30		45
4a.	Cisapride (10 mg/kg, ip)	45	45	
4b.	Cisapride (10 mg/kg, ip)	45		45
5a.	Granisetron (5 mg/kg, ip)	45	45	
5b.	Granisetron (5 mg/kg, ip)	45		45
6a.	Mepyramine (10 mg/kg, ip)	45	45	
6b.	Mepyramine (10 mg/kg, ip)	45		45
7a.	Propranolol (10 mg/kg, ip)	45	45	
7b.	Propranolol (10 mg/kg, ip)	45		45

emptying. The % gastric emptying in this group was (2.3 %±0.4 %) (P<0.05) as compared to the control non-rotated group. Further the pretreatment with scopolamine did not effect the inhibition in gastric emptying caused by rotation. The % gastric emptying in this group was 2.0 %±0.6 %.

Administration of cisapride (10 mg/kg, ip) *per se* did not have any significant effect on the gastric emptying in the non-rotated group. The % gastric emptying in this group was 77 %±8 %. However pretreatment with cisapride could not reverse the inhibition of gastric emptying due to rotation. The percent gastric emptying in this group was 3 %±1 % .

When the rats were pretreated with 5HT3 receptor antagonist granisetron (5 mg/kg, ip) 30 min prior to administration of test meal and sacrificed after 45 min there was no significant difference in the gastric emptying (84 %±13 %) as compared to control. In the group which was rotated after administration of test

Tab 2. Effect of pretreatment with different drugs on gastric emptying in rats. [b]P<0.05 *vs* control (non-rotated group). [e]P<0.05 *vs* control (rotated group).

Drug	Percentage of gastric emptying/%[1)]	
	Non-rotated rats	Rotated rats
Standard[2)]	0	
Control	88±10	3.0±0.5
Scopolamine 5 mg/kg, ip	2.3±0.4[b]	2.0±0.6[b]
Cisapride 10 mg/kg, ip	77±8[e]	3.1±1.0[b]
Granisetron 5 mg/kg, ip	84±13[e]	2.0±0.5[b]
Mepyramine 5 mg/kg, ip	90±18[e]	1.0±0.3[b]
Propranolol 10 mg/kg, ip	89±13[e]	32±5[be]

[1)] Percentage of gastric emptying was measured at 45 min of test meal administration.

[2)] Rats in standard group were sacrificed immediately after the administration of test meal. The values have been taken as zero.

meal granisetron pretreatment also did not reverse the inhibition of gastric emptying. The % gastric emptying was 2.0 %±0.5 %. Pretreatment with histamine H_1 receptor blocker mepyramine (5 mg/kg, ip) per se did not have any effect on the gastric emptying in the rats which were scarified 45 min after test meal without rotating. The percent gastric emptying value was 90 %±18 % and 88 %±10 %, respectively. Mepyramine pretreatment could not reverse the rotation-induced inhibition in gastric emptying as compared to control. The gastric emptying was 1.0 %±0.3 % as compared to 3.0 %± 0.5 % in the rotation control group.

When the rats were pretreated with propranolol (10 mg/kg, ip), the gastric emptying was 89.3±13% in the non-rotated group and was insignificant as compared to the control non-rotated group. Interestingly, pretreatment with propranolol could significantly reverse the decrease in gastric emptying by rotation. The gastric emptying was 32 %±5 % as compared to 3 %± 0.5 % in the rotation control group.

Thus, among all the drugs used (scopolamine, granisetron, mepyramine, cisapride and propranolol) in the present study only propranolol could partially but significantly reverse the inhibition of gastric emptying by rotation.

DISCUSSION

Motion sickness occurs when sensory inputs regarding body position in space are different from those predicted from experience. Signals from the vestibular

system are essential for triggering motion sickness[2]. Effective drugs for combating motion sickness include antihistaminics, antimuscarinics, serotoninergic receptor agonists *etc*, however complete information concerning physiological basis of motion sickness is still poorly known and requires further research using animal models[6]. Although the commonly used animals for motion sickness are monkey, cat, suncus murinus and dog, the pica behavior (ingestion of non-nutritive substances) in rodents which lack emetic reflex is analogous to vomiting in other species and is mediated by the same mechanisms as vomiting. Pica behavior has been demonstrated after administration of cisplatin, a highly emetic cancer chemotherapeutic agent[7,8]. Inhibition of gastric emptying as a secondary symptom is associated in patients with motion sickness[9]. We have also demonstrated the delay in gastric emptying after cancer chemotherapeutic agents known to cause vomiting and the effect being reversed by antiemetics[10]. The antiemetics usually prescribed and effective for motion sickness are known to relieve vomiting, however whether they also reverse the associated decrease in gastrointestinal emptying is not known. This becomes important to know because anticholinergics themselves can cause gastric stasis.

The present study was therefore conducted to see the effect of commonly used antiemetic drugs on gastric emptying in an experimental model simulating motion sickness in rats.

It was observed that rotating the rats in a horizontal plane at a speed of 30 rpm for 45 min almost completely inhibited gastric emptying. This is similar to the reported motion sickness associated gastric stasis in humans[2]. When the rats were pretreated with antimotion sickness drug scopolamine, it was observed that there was no effect on the gastric stasis. On the other hand, scopolamine per se caused decrease in gastric emptying in the non-rotated group. This is because scopolamine would be blocking the peripheral muscarinic receptors thus antagonizing the gastrokinetic mechanism of the cholinergic system. The antihistaminic agent mepyramine also could not reverse the gastric stasis. It could be because of the blocking effect of mepyramine on the histamine receptors as well as cholinergic receptor in the periphery which otherwise increase the gastric motility.

Interestingly, prokinetic agent cisapride also failed to reverse rotation-induced decrease in gastric emptying. Since during motion sickness central nervous system pathways evoke gastric dysrythmias leading to gastric inhibition[11,12], this central component would be overcoming the peripherally mediated beneficial effects of this drug. Similarly granisetron which has been found to be highly effective in cancer chemotherapy-induced emesis could not affect the gastric stasis in the rotated rats. During motion sickness there is release of stress hormones, eg, ACTH, epinephrine, norepinehrine[13]. Moreover it has been seen that there are changes in autonomic nervous system activity during motion sickness[14]. It was seen in our experiments that only the beta-blocker propranolol partially but significantly reversed the inhibition of gastric emptying. That during motion sickness there is an increase in the sympathetic discharge to the gastrointestinal tract is well established[4]. Moreover it has been reported that motion sickness is invariably associated with stress and that stress itself causes changes in gastric motility[15]. In the present study propranolol would have countered the sympathetic as well as the stressor effect on gastric emptying and therefore was partially effective.

From the results it can be postulated that beta blocking agents, eg, propranolol in combination with conventional antiemetic, eg, anticholinergics may offer an added advantage of alleviating the secondary symptoms of motion sickness like delayed gastric emptying. However more studies are required in this direction to reach any conclusion.

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