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Acute intracranial hypertension-induced inhibition of gastric emptying: evaluation in conscious rats

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Abstract

To study the effect of raised intracranial pressure (ICP)-induced alterations in gastric emptying, and their modulation by pharmacological interventions, an experimental model was standardized in rats. A test meal of methylcellulose and phenol red was administered intragastrically. ICP was raised to 40, 60 and 80 mmHg by connecting a buffered saline pressure head to an intracerebroventricular (i.c.v.) cannula. Gastric emptying was estimated after killing the animals, from the residual stomach phenol red content. Inhibition of gastric emptying was observed when ICP was raised, the maximum being at 80 mmHg ICP (percent gastric emptying 26.5% $\pm$ 2.8 vs. 83.4 $\pm$ 4.7 in sham-ICP). Pretreatment with clonidine, prazosin or ondansetron did not modify the raised ICP-induced inhibition of gastric emptying. Cisapride was ineffective at 1 mg/kg but caused a partial reversal at the 5- and 10-mg/kg doses (46.9 $\pm$ 3.1% and 42.6 $\pm$ 4.0%, respectively). Carbachol at a lower dose of 0.1 mg/kg i.p., produced a greater reversal (78.3 $\pm$ 6.0%) than did the high dose (52.8 $\pm$ 4.1). Bretylium partially reversed the inhibition of gastric emptying (45.7 $\pm$ 4.3%). The protective effect of carbachol and cisapride suggests that suppression of vagal activity due to increased ICP may play an important role in the inhibition of gastric emptying due to intracranial hyper-tension.

Keywords: Intracranial pressure; Intracranial hypertension; Vomiting; Gastric emptying

1. Introduction

Increased intracranial pressure (ICP) is known to cause alterations in gastric function. Nausea and vomiting are classical clinical symptoms associated with it (Garrick et al., 1988). Vomiting and possible aspiration are of concern especially when the state of consciousness is altered (Matthews et al., 1988), and can be a cause of death. Moreover, patients often do not tolerate enteral feedings (Hunt et al., 1985) for a period extending up to 15 days after head injury (Norton et al., 1988). This intolerance is manifested by vomiting, diarrhoea, abdominal distension and increased gastric residuals (Ott et al., 1991).

The mechanisms of these gastrointestinal alterations are largely unknown (Garrick et al., 1988). Acute gastric dilatation is a common sequel of head injury (Collins et al., 1979). Impaired smooth muscle motility of the esophagus and the stomach has been implicated in the delayed gastric emptying associated with central nervous system (CNS) insults (Vantrappen et al., 1986).

Thus, normalization of gastric emptying can reduce the morbidity and mortality associated with conditions of raised ICP and thus possibly reduce the complications, and improve recovery.

The purpose of the present study was to standardize an experimental model of changes in gastric emptying due to acute increases in ICP and to study the effect of drugs in this model.

2. Materials and methods

2.1. Animals

Wistar rats of either sex weighing between 200–250 g, inbred in the Central Animal Facility of the All India Institute of Medical Sciences, were used for the study. They were housed for 7 days in the departmental animal house on the natural light–dark cycle, with controlled

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temperature and humidity, as groups of six rats in each cage. Standard rat dry diet and water was allowed ad libitum. Food was withdrawn 24 h before the experiments, however, free access to water was allowed.

2.2. Intracerebroventricular (i.c.v.) cannulation

Scalp vein sets of 20-gauge were used for preparing the i.c.v. cannula. The needle was cut to 5 mm and the edges were smoothed for placement in the lateral cerebral ventricle. The attached plastic tubing was cut 2 cm from the needle end, and a stainless steel connector (16 gauge) was attached between the two cut ends. In ether anaesthetized rats, this cannula was placed in the lateral cerebral ventricle, with the stereotaxic coordinates (0.8 mm caudal, 1.5 mm lateral and 4.5 mm deep to the bregma; Livingston et al., 1991), fixed with dental cement, and secured with an optical screw fixed either side of the skull. The overlying skin was stitched and the animal was allowed to recover from anaesthesia. After 3 days recovery, the cannulated rats were used to study the effect of raised ICP on gastric emptying.

2.3. Preparation of the test meal

The methodology used to measure gastric emptying was as described by Scarpignato et al. (1980) using a methylcellulose test meal. Methylcellulose was dispersed in water at 80°C at a concentration of 1.5% under continuous stirring. The solution was allowed to cool to 37°C, then phenol red (50 mg/100 ml), used as non-absorbable marker, was added. This mixture was kept under constant intensity of agitation and temperature (37°C) for 4 h, before feeding to the rats, to ensure constant viscosity. The phenol red–methylcellulose meal was freshly made each day.

2.4. Measurement of gastric emptying after increasing intracranial pressure

In i.c.v. cannulated conscious rats, a volume of 1.5 ml of the methylcellulose–phenol red meal was fed intragastrically through a stainless-steel feeding tube.

Immediately after the delivery of the test meal, the i.c.v. cannula was connected through the infusion tubing to a pressure head, prepared with a 20-ml vial filled with buffered saline. The vial was hung on a stand and its height could be adjusted appropriately with a cord and pulley system to obtain the desired level of ICP. In one set of experiments, the ICP raised with this system was checked by placing another cannula in the contralateral ventricle and monitoring the ICP with the help of a pressure transducer and advanced Codas Videograph (M/s. Coulbourn Instruments, USA). The actual level of ICP attained by adjusting the height of the pressure head did not vary by more than ± 2 mmHg. The baseline ICP, as has also been reported previously (Barth et al., 1991), was up to 1 mmHg.

In preliminary experiments, normal gastric emptying was estimated by killing the animals at different time intervals, i.e., 15, 30 and 45 min after test meal administration. Based on previous reports (Garrick et al., 1988; Ott et al., 1991) inhibition of gastric emptying with raised ICP could be expected. In these experiments, very low concentrations (48.6 ± 11.6 μg) of phenol red could be recovered from stomachs of rats dissected 45 min after the test meal. Thus, a duration of 30 min for increasing ICP was selected for further experimentation.

In different groups of experiments ($n = 6$ each), ICP was raised to different levels, i.e., 40, 60 and 80 mmHg for 30-min duration. At 30 min, the pressure head was disconnected from the i.c.v. cannula and the animals were immediately decapitated. After the abdominal wall was cut through, the stomach was clamped at the pyloric and cardiac ends, dissected out, removed, and rinsed in 0.9% saline. The stomachs were then placed in 100 ml of 0.1 N NaOH, cut into small pieces, and homogenized for 30 s. The suspension was allowed to settle for 60 min at room temperature, and 5 ml of supernatant was added to 0.5 ml of trichloroacetic acid (20% wt.:vol.). After centrifugation at 2800 rpm for 20 min, the supernatant was added to 4 ml of 0.5 N NaOH, and absorbance of the sample was read at a wavelength of 560 nm.

The gastric emptying for each rat was calculated according to the following formula:

$$\text{Percent gastric emptying} = 1 - \frac{\text{Amount of phenol red recovered from test stomach}}{\text{Average amount of phenol red recovered from standard stomachs}} \times 100.$$

Phenol red recovered in the stomachs of rats decapitated immediately after intragastric delivery of the meal served as ‘standard stomachs’. Experiments were also conducted in sham-operated rats (sham-ICP) in which i.c.v. cannulation was done, the cannula was connected to the device used for increasing ICP, but the pressure was not increased. The rats were given the test meal and were killed 30 min later.

2.5. Drug pretreatments

Since an ICP of 80 mmHg produced the most consistent and reproducible inhibition of gastric emptying, the effects of drug pretreatment on alterations in gastric emptying induced by increased ICP was studied at this level.

Drug pretreatment was undertaken in both sham-operated (sham-ICP) and raised ICP (80 mmHg) groups ($n = 6$ each). The drugs and the doses used are given in Table 1.

I.p. administration of the drugs was done 45 min before, while central administration was done 15 min prior to, the test meal delivery. However, clonidine (i.p.) was administered 30 min before and bretylium 1 h before test meal delivery, based on the studies of Lenz (1989) and Tadano et al. (1992), respectively.

Table 1
Routes of administration and doses of the drugs used for pretreatment

Drug	Route	Dose
Clonidine	i.c.v.	20 μg[a]
	i.p.	100 μg/kg[b]
Prazosin	i.c.v.	40 μg[c]
	i.p.	2 mg/kg[d]
Bretylium	i.p.	25 mg/kg[e]
Ondansetron	i.p.	3 mg/kg[f]
Cisapride	i.p.	1 mg/kg[g]
		5 mg/kg
		10 mg/kg
Carbachol	i.p.	0.1 mg/kg[h]
	i.p.	0.5 mg/kg

[a and b]Tadano et al. (1992); [c]Borisova and Kadar (1993); [d]Heal et al. (1995); [e]Lenz (1989); [f]Filip et al. (1992); [g]Zuccato et al. (1992); [h]Lu and Owyang (1995).

Clonidine, ondansetron, carbachol and bretylium were dissolved in 0.9% normal saline which had a pH of 7.4. Cisapride was freshly suspended in 0.9% normal saline, immediately prior to its injection. Prazosin was dissolved in 10% propylene glycol and the pH was adjusted to 7.4 with 0.1 N NaOH.

2.6. Statistical analysis

The results are expressed as means ± S.E.M. of percent gastric emptying. The data were analysed by means of the Kruskal–Wallis analysis of variance and statistical comparisons were done with Duncan's non-parametric multiple range test. A *P*-value of less than 0.05 was considered as statistically significant.

3. Results

3.1. Normal gastric emptying

The mean recovery of phenol red in standard stomachs, taken from rats who were killed immediately after test meal delivery, was 623.8 ± 15.9 μg (83.0 ± 2.0%), from a total amount of 750 μg administered to each rat. Normal rats, not i.c.v. cannulated, showed a time-dependent increase in percent gastric emptying.

At 15, 30 and 45 min, gastric emptying was 51.2 ± 3.0%, 87.3 ± 2.9% and 91.8 ± 2.0%, respectively. The values at 30 and 45 min did not differ significantly ($P > 0.05$). However, both values were significantly higher than the value at 15 min ($P < 0.05$; Fig. 1).

3.2. Effect of increased intracranial pressure on gastric emptying

The procedure of i.c.v. cannulation did not produce any significant change in gastric emptying at 30 min (83.4 ± 4.7% in sham-ICP animals), compared to that seen in normal animals (87.3 ± 2.9%).

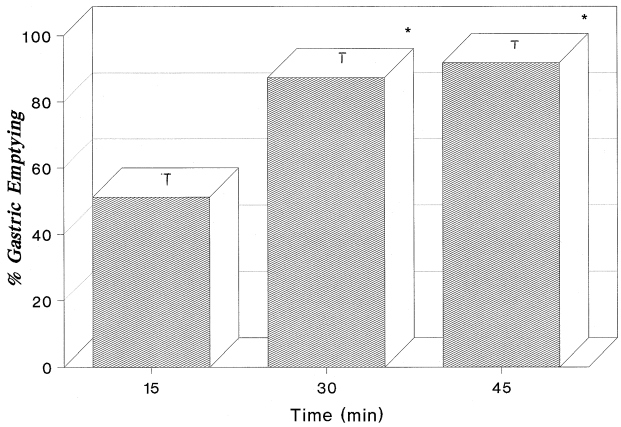

Fig. 1. Normal gastric emptying in rats killed 15, 30 and 45 min after administration of methylcellulose–phenol red test meal ($n = 6$). Gastric emptying at 30 and 45 min was significantly greater than at 15 min. * $P < 0.05$. Results are expressed as means ± S.E.M. of percent gastric emptying.

Increasing the ICP caused a significant inhibition of gastric emptying. At 40, 60 and 80 mmHg, gastric emptying was reduced to 54.8 ± 7.1%, 30.5 ± 4.6% and 26.5 ± 2.8%, respectively ($P < 0.05$ compared to sham-ICP; Fig. 2). Experiments at 80 mmHg ICP were carried out to study the protective effect of different drug treatments on inhibition of gastric emptying due to increased ICP.

Signs of discomfort and behavioral alterations were evident in all the animals during the increase in ICP. With the ICP of 80 mmHg, an initial phase of restlessness (exploratory behavior) was seen in all the animals after ICP was raised. This was followed by an increase in respiratory rate (6/6), depressed activity (withdrawal; 5/6), unsteady gait or loss of posture (4/6), labored

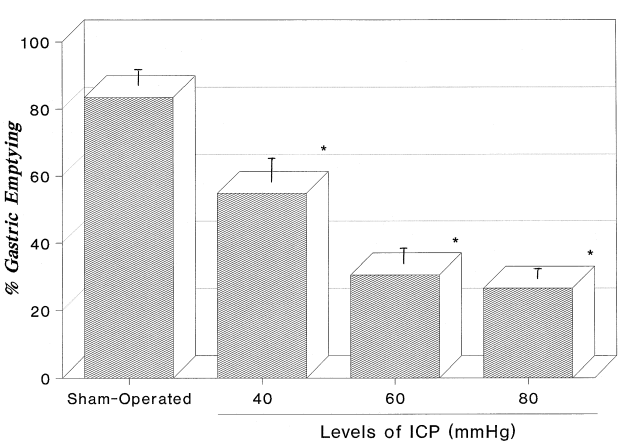

Fig. 2. Effect of i.c.v. cannulation (sham-ICP) and of increasing ICP to 40, 60 and 80 mmHg in i.c.v. cannulated rats, killed 30 min after administration of methylcellulose–phenol red test meal ($n = 6$). Gastric emptying with ICP of 40, 60 and 80 mmHg was significantly less than that in sham-ICP animals. * $P < 0.05$. Results are expressed as means ± S.E.M. of percent gastric emptying.

Table 2
Incidence of different behavioral alterations seen at 80 mmHg ICP ($n = 6$)

Behavioral effect	Incidence
Restlessness	6/6
Increased rate of respiration	6/6
Depressed activity	5/6
Unsteady gait/loss of posture	4/6
Labored breathing	2/6
Jerking	5/6
Bulging of eyeballs	1/6

breathing (2/6) and jerking (5/6). In one animal, bulging of eyes was also seen (Table 2).

3.3. Effect of drug treatment on gastric emptying

3.3.1. Effect of clonidine

Clonidine 20 μg i.c.v. was administered 15 min before test meal in sham-ICP and ICP 80 mmHg groups ($n = 6$ for each). Per se, clonidine had a significant inhibitory effect on gastric emptying. In sham-ICP animals it reduced the percent gastric emptying to 26.6 ± 3.6, as compared to control ($83.4 \pm 4.7\%$; $P < 0.05$). However, clonidine, as pretreatment in ICP 80 mmHg rats, did not modify the inhibition of gastric emptying seen with the ICP of 80 mmHg ($29.4 \pm 2.7\%$ in clonidine group vs. $26.5 \pm 2.8\%$ in ICP control group; Fig. 3).

Clonidine 100 μg also was given i.p. in both sham-ICP and ICP 80 mmHg groups ($n = 6$ each). Like i.c.v. clonidine, peripheral administration of clonidine also had a significant per se inhibitory effect, which, however, was not as marked as with central administration ($52.6 \pm 4.4\%$ compared to $26.6 \pm 3.6\%$ in clonidine i.c.v. and $83.4 \pm 4.7\%$ in sham-ICP; $P < 0.05$ compared to sham-ICP). Similarly, clonidine also failed to alter the inhibitory effect of 80 mmHg ICP on gastric emptying ($31.3 \pm 3.9\%$, compared to $26.5 \pm 2.8\%$ in ICP control group; Fig. 3).

3.3.2. Effect of prazosin

Central administration of prazosin 40 μg did not modify gastric emptying in sham-ICP animals ($77.2 \pm 6.0\%$ vs. $83.4 \pm 4.7\%$ in sham-ICP). When it was administered by the i.p. route (2 mg/kg) as 45 min pretreatment, a significant though variable, decrease in gastric emptying was observed ($53.8 \pm 7.4\%$ vs. $83.4 \pm 4.7\%$ in control; $P < 0.05$). Neither i.c.v. nor i.p. administration of prazosin produced any significant alteration in the inhibition of gastric emptying due to 80 mmHg ICP ($28.7 \pm 4.1\%$ and $25.7 \pm 3.8\%$, respectively, compared to $26.5 \pm 2.8\%$ in ICP control group; Fig. 4).

3.3.3. Effect of bretylium

Bretylium (25 mg/kg) was administered i.p. 1 h before test meal. In sham-ICP animals, it did not cause any alteration in gastric emptying at 30 min ($78.4 \pm 2.7\%$ vs. $83.4 \pm 4.7\%$ in sham-ICP control group). In contrast, bretylium did induce a partial but significant reversal of the inhibitory effect of 80 mmHg ICP on gastric emptying. In ICP control animals, gastric emptying was $26.5 \pm 2.8\%$ which was increased to $45.7 \pm 4.3\%$ in the bretylium treated group ($P < 0.05$; Fig. 5).

3.3.4. Effect of ondansetron

Ondansetron, 3 mg/kg, as pretreatment, did not have any significant effect on gastric emptying in sham-ICP animals ($66.2 \pm 15.3\%$ vs. $83.4 \pm 4.7\%$ in sham-ICP). It also did not modify the effect of 80 mmHg ICP on gastric emptying ($30.5 \pm 4.4\%$ vs. $26.5 \pm 2.8\%$ in ICP control group; Fig. 6).

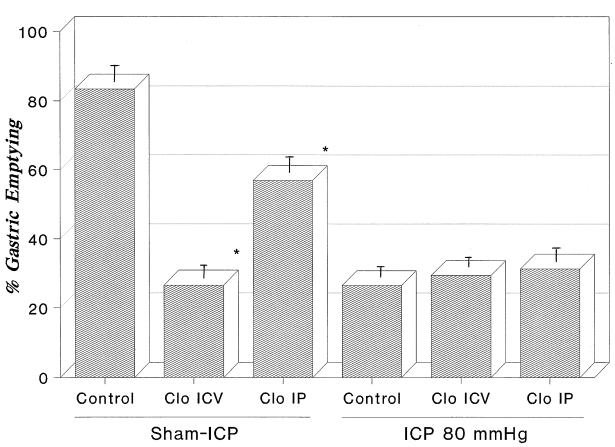

Fig. 3. Effect of clonidine (Clo) 20 μg i.c.v. 15-min pretreatment and 100 μg/kg i.p. 45-min pretreatment on gastric emptying in sham-ICP and ICP 80 mmHg groups of rats ($n = 6$). Inhibition of gastric emptying with clonidine per se was significant as compared to that in untreated animals. * $P < 0.05$. Results are expressed as means ± S.E.M. of percent gastric emptying.

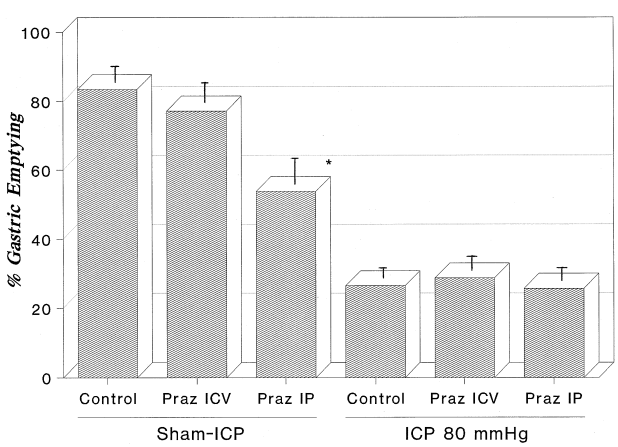

Fig. 4. Effect of prazosin (Praz) on gastric emptying in sham-ICP and ICP 80 mmHg groups. Prazosin was given in the doses of 20 μg i.c.v. 15-min pretreatment and 2 mg/kg i.p. 45-min pretreatment. Prazosin 2 mg/kg caused a significant decrease in gastric emptying in sham-operated animals. * $P < 0.05$. Results are expressed as means ± S.E.M. of percent gastric emptying.

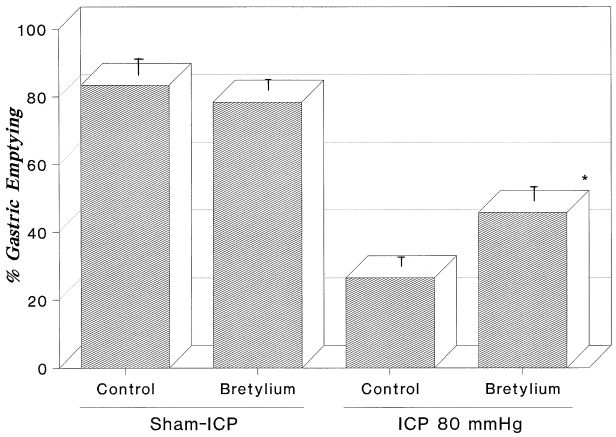

Fig. 5. Effect of bretylium on gastric emptying in sham-ICP and ICP 80 mmHg groups. Bretylium was given in a dose of 25 mg/kg i.p. as 1-h pretreatment. Bretylium had a partially protective effect against inhibition of gastric emptying due to ICP 80 mmHg. $^{*}P < 0.05$. Results are expressed as means ± S.E.M. of percent gastric emptying.

3.3.5. Effect of cisapride

Cisapride was administered i.p. at three different doses (1, 5 and 10 mg/kg as 45 min pretreatment) in different sets of animals, both in sham-ICP and ICP 80 mmHg groups.

With the 1 mg/kg dose of cisapride, there appeared to be a small reduction in gastric emptying in sham-operated animals compared to the control (61.2 ± 4.1% vs. 83.4 ± 4.7% in sham-ICP; $P < 0.05$). It also failed to reverse the inhibition of gastric emptying due to raised ICP (30.5 ± 4.7%) (Fig. 7).

Cisapride 5 mg/kg did not cause any per se inhibition of gastric emptying in sham-ICP animals (67.3 ± 2.4% vs. 83.4 ± 4.7% in sham-ICP control animals). However, it did cause partial reversal of the inhibitory effect of 80 mmHg ICP on gastric emptying. Gastric emptying was significantly increased to 46.9 ± 3.1% compared to that in ICP control of 26.5 ± 2.8% ($P < 0.05$; Fig. 7).

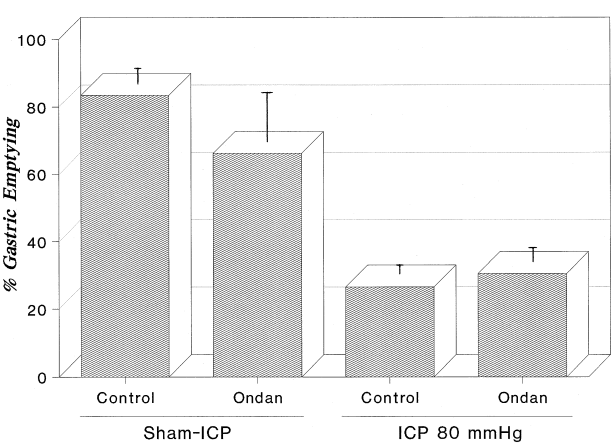

Fig. 6. Effect of ondansetron on gastric emptying in sham-ICP and ICP 80 mm Hg groups. Ondansetron was given in a dose of 3 mg/kg i.p. as 45-min pretreatment. Results are expressed as means ± S.E.M. of percent gastric emptying.

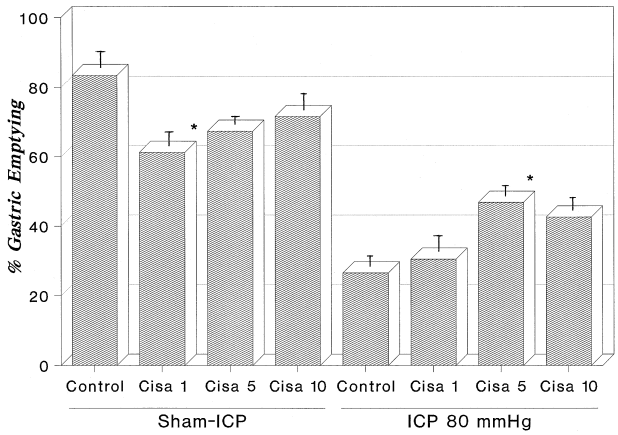

Fig. 7. Effect of cisapride on gastric emptying in sham-ICP and ICP 80 mmHg groups. Cisapride was administered in doses of 1, 5 and 10 mg/kg i.p. in different sets of experiments, all as 45-min pretreatment. The 5 and 10 mg/kg dose of cisapride caused a partial reversal of the inhibitory effect of 80 mmHg ICP on gastric emptying, which was significant with the 5 mg/kg dose. $^{*}P < 0.05$. Results are expressed as means ± S.E.M. of percent gastric emptying.

The 10 mg/kg dose of cisapride had a similar effect. There was no significant effect of the drug on gastric emptying in sham-ICP animals (71.6 ± 4.8%). Also there was a partial reversal of the inhibition of gastric emptying due to 80 mmHg ICP (42.6 ± 4.0% vs. 26.5 ± 2.8% in ICP control), though not to the same extent as with the 5 mg/kg dose (Fig. 7).

3.3.6. Effect of carbachol

With carbachol 0.1 and 0.5 mg/kg i.p. as 45-min pretreatment gastric emptying was 93.5 ± 3.2% and 86.8 ± 10.9%, respectively. This was not significantly different from that seen in sham control animals ($P > 0.05$). Both these doses of carbachol significantly reversed the inhibi-

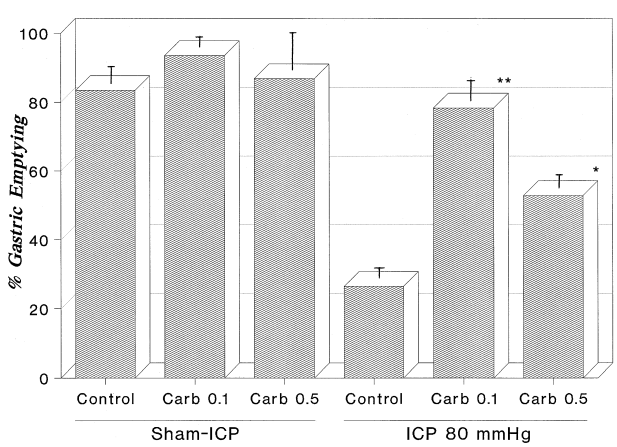

Fig. 8. Effect of carbachol on gastric emptying in sham-ICP and ICP 80 mm Hg groups. Carbachol was given in doses of 0.1 mg/kg (Carb 0.1) and 0.5 mg/kg (Carb 0.5) i.p. as 45-min pretreatment. Carbachol had a protective effect against inhibition of gastric emptying due to 80 mmHg ICP, more so at the lower doses. $^{**}P < 0.01$; $^{*}P < 0.05$. Results are expressed as means ± S.E.M. of percent gastric emptying.

tion of gastric emptying due to 80 mmHg ICP. Interestingly, the reversal by carbachol was more marked at the lower dose of 0.1 mg/kg ($78.3 \pm 6.0\%$; $P < 0.01$) than at the higher dose of 0.5 mg/kg ($52.8 \pm 4.1\%$; $P < 0.05$; Fig. 8).

4. Discussion

Head trauma patients with elevated ICP frequently suffer from gastrointestinal tract complications. The earliest manifestations of the intracranial hypertension are nausea and vomiting (Livingston et al., 1991). These patients are also often intolerant to enteral feedings (Ott et al., 1991), and require increased amounts of nutrients since they are hypermetabolic and hypercatabolic (Clifton et al., 1984; Young et al., 1985; McClain et al., 1986). Infection is a common finding in these patients, which prolongs their rehabilitative process (Antonacci, 1986). Adequate nutritional support may improve patient outcome and recovery due to decreased susceptibility to sepsis (Rapp et al., 1983) and enhanced immunocompetence (Rapp et al., 1983; Young et al., 1987). Thus, acute gastric dilatation (Collins et al., 1979) and delayed gastric emptying (Ott et al., 1991) may be of pathophysiological relevance in patients with head injury. Normalization of these aspects may be useful for improving the outcome and recovery of the patients from CNS insults. However, the mechanisms of these gastrointestinal alterations are still poorly understood (Garrick et al., 1988), and studies with drug treatments in such critically ill patients are few.

In the present study, we standardized an experimental model to investigate the effect of increased ICP on gastric emptying in conscious rats. The method used to estimate gastric emptying is a standard procedure used in earlier studies (Scarpignato et al., 1980; Tache et al., 1987). Surgical procedures and anaesthetic agents are known to have an inhibitory effect on gastric motility and emptying (Ogilvy and Smith, 1995). Therefore, in our study, experiments were designed to use chronically i.c.v. cannulated conscious rats. Mechanical damage due to i.c.v. cannulation was restricted to the area of the ventricles and it did not interfere with the study. The absence of any alteration in gastric emptying in sham-operated animals further indicated that the presence of the i.c.v. cannula had no effect.

Increases in ICP induce a massive increase in sympathetic nerve activity, which is responsible for many of the peripheral symptoms of head injury (Rosner et al., 1984; Soblosky et al., 1992). This enhancement of sympathetic discharge has been shown to be reduced by the α2-adrenoceptor agonist, clonidine, through a central action (Payen et al., 1990). At the same time, clonidine has also been shown to inhibit small intestine transit, after both central and peripheral administration, an effect which is vagus-dependent (Tadano et al., 1992). In the present study also, clonidine, per se, had an inhibitory effect on gastric emptying. Further, it did not modify the inhibition of gastric emptying due to increased ICP. The reversal of sympathoadrenal discharge due to increased ICP in the brain may have been inadequate or the vagus-mediated effect of clonidine itself countered it (Payen et al., 1990; Tadano et al., 1992).

Sympathetic stimulation has been shown to produce an inhibitory effect on gastric motility (Abrahamsson and Glise, 1984), mediated by α-adrenoceptors present presynaptically on the intramural cholinergic neurons (Gillespie and Khoyi, 1977). α1-Adrenoceptors have also been demonstrated centrally in the chemoreceptor trigger zone and their blockade has been shown to prevent noradrenaline-induced emesis (Jenkins and Lahay, 1971). We observed earlier (Kacker and Gupta, 1996) that prazosin reduces the incidence of retching and vomiting due to raised ICP in conscious dogs. Such an effect was observed after both central and peripheral administration, though it was more marked when the drug was given i.c.v. Since it has been observed that many of the emetogenic stimuli also cause an inhibition of gastric emptying besides causing vomiting, we aimed to investigate the effect of prazosin on the inhibition of gastric emptying induced by increased ICP, vis-a-vis its efficacy against vomiting induced by the same stimulus. However, neither central nor peripheral administration of prazosin protected against raised ICP-induced inhibition of gastric emptying. On the other hand, bretylium, which is a specific noradrenergic neuron blocker, produced a partial reversal of the inhibitory effect of increased ICP on gastric emptying. This indicates that increased sympathetic activity may be, at least in part, responsible for the inhibition of gastric emptying. But since prazosin was ineffective to protect, this effect may be mediated through β-adrenergic receptors.

5-HT_3 receptor antagonists such as ondansetron, granisetron and tropisetron are effective antiemetics for chemotherapy-induced vomiting (Bhandari et al., 1989; Milne and Heel, 1991) and postoperative nausea and vomiting (Russell and Kenny, 1992). Several of these compounds have been shown to possess gastrokinetic effects (Schiavone et al., 1990). However, in the present study, pretreatment with ondansetron did not reverse the inhibition of gastric emptying due to raised ICP, indicating that 5-HT_3 receptors are not involved.

Cisapride is an effective prokinetic agent which is used clinically for reflux esophagitis, gastroparesis, non-ulcer dyspepsia, etc. (Gwee and Read, 1994). The mechanism of action of cisapride is believed to be enhancement of cholinergic activity (Tonini et al., 1991; Onat et al., 1994), which may be mediated by 5-HT_4 receptors (Bockaert et al., 1992). Interestingly, in our study, cisapride did partially reverse the intracranial hypertension-induced inhibition of gastric emptying. Moreover, carbachol, a muscarinic acetylcholine receptor agonist, significantly reversed the inhibition due to increased ICP. The results of modulation of sympathetic and parasympathetic activity

indicate that alteration in activity of both may play a pathophysiological role in mediating the inhibition of gastric emptying due to increased ICP. Enhancement of cholinergic activity may be particularly useful therapeutically for normalizing this inhibitory effect. The greater protection seen with lower doses of carbachol was, however, a peculiar finding. Probably, greater nicotinic activity at autonomic ganglia with the higher dose level, may partially nullify the gastric prokinetic effect of carbachol.

Increased release of corticotrophin-releasing factor (CRF) has been demonstrated in the CNS in response to various stressful stimuli (Chappell et al., 1986; Haas and George, 1988; Harbuz and Lightman, 1989; Mamlaki et al., 1993). CRF is known to suppress gastric emptying by acting on the dorsal motor nucleus of the vagus (Heymann-Monnikes et al., 1991; Monnikes et al., 1992). Such a vagus-dependent pathway of inhibition of gastric emptying (Tache et al., 1993) may also have been operative in the present study. However, further studies need to be done with CRF receptor antagonists in this experimental model to address this question.

We now described a simple, reproducible and sensitive model for studying changes in gastric emptying due to intracranial hypertension, and to study the effect of various drug interventions. Our findings indicate that gastrokinetic agents and cholinergic agonists may be potentially useful for gastrointestinal complications associated with raised ICP.

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