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Prostaglandin E_2: A Study of Intestinal Secretion as a Mechanism of Action for the Gastric Antisecretory Property in the Rat

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PROSTAGLANDIN E_2: A STUDY OF INTESTINAL SECRETION AS A MECHANISM OF ACTION FOR THE GASTRIC ANTISECRETORY PROPERTY IN THE RAT

by

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INTRODUCTION

Prostaglandins (PG) are a family of twenty carbon hydroxylated fatty acids with a cyclopentane ring bearing oxygens on carbons 9 and 11. Prostaglandins were discovered independently by von Euler (1934) in Sweden and Goldblatt (1933) in England. Between 1957 and 1963 Bergstrom and his colleagues in Sweden isolated several prostaglandins from the sheep seminal vesicles and elucidated their chemical structures. Since then, steady progress has been made on the biochemistry and pharmacology of prostaglandins.

Since the present study deals with the action of prostaglandins on gastric and intestinal secretion, it is pertinent to briefly review the literature concerned with these activities.

Several natural prostaglandins of the A and E types were first found to inhibit gastric secretion in dogs stimulated with histamine, food, pentagastrin and 2-deoxy-d-glucose by Robert and coworkers (Robert *et al.*, 1967; Robert, 1968; Nezamis *et al.*, 1971). Volume, acid output, acid concentration, and pepsin output were reduced in a dose dependent manner, whereas pepsin concentration did not change significantly. These findings have been confirmed in dogs (Wilson and Levine, 1969; Jacobson, 1970) and extended to other animal species (Shaw and Ramwell, 1968; Robert *et al.*, 1968; Whittle, 1972) including humans (Classen *et al.*, 1970 and 1971; Wilson, *et al.*, 1971).

PGE_1, perfused directly into the gastric lumen of rats, inhibited gastric secretion induced with pentagastrin (Banerjee *et al.*, 1972; Shaw and Ramwell, 1968; Shaw and Urquhart, 1973; Whittle, 1972) histamine (Shaw and Ramwell, 1968; Shaw and Urquhart, 1972; Whittle, 1972) and vagal stimulation (Shaw and Ramwell, 1968; Shaw and Urquhart, 1972). PGE_2 given intravenously or perfused through the stomach inhibited gastric secretion stimulated by cyclic adenosine monophosphate (cyclic AMP) (Whittle, 1972). In the pylorus-ligated rat, PGE_2 given orally at high doses also inhibited gastric secretion (acid concentration and output but not volume or pepsin output) (Lee *et al.*, 1973; Robert *et al.*, 1976). PGE_2 inhibited gastric secretion (volume acid concentration and output, pepsin output) when given subcutaneously (Robert *et al.*, 1976).

Several prostaglandins, administered either into the superior mesenteric artery (PGA_1, PGE_1, $PGF_2\alpha$ in dogs) (Greenough *et al.*, 1969; Pierce *et al.*, 1971), intravenously ($PGF_2\alpha$ in humans); (Cummings *et al.*, 1973) or directly into the lumen of the small intestine [PGE_1 in humans (Matuchansky and Bernier, 1971, 1973) and dogs (Pierce *et al.*, 1971)], were found to evoke the accumulation of fluid (water and electrolytes) into the lumen. In humans, the accumulation of fluid after PGE_1 was not accompanied by a change in intestinal transit time (Matuchansky *et al.*, 1972). Intrajejunal administration of PGE_2 to healthy volunteers produced net excretion of water, sodium, potassium and chloride. Within two hours after perfusion of 325 µg of PGE_2, all subjects experienced one to three

episodes of watery diarrhea (Hinsdale *et al.*, 1974). Using the distal rabbit ileum incubated *in vitro*, PGE_1 and $PGF_2\alpha$, added to the serosal side, inhibited the absorption of sodium from the mucosal side (Al Awqati and Greenough, 1972). Similarly, PGE_2 inhibited sodium and chloride absorption (fluxes from mucosa to serosa) in rat jejunum *in vitro* (Declusin *et al.*, 1974). Thus, it appears that the net intestinal secretion of fluid produced by prostaglandins is the sum of the fluid transported into the lumen and the portion of the intestinal water and electrolytes whose absorption through the intestine is inhibited. Diarrhea observed in animals and humans receiving large doses of prostaglandins is due for the most part to the accumulation of fluid in the small intestine.

PGE_2 was shown to inhibit gastric secretion several years ago. The mechanism of action for its gastric antisecretory activity is not known. PGE_2 has the opposite effect on the intestine-stimulation of secretion. This study explored the possibility that the accumulation of fluid in the intestine is in part responsible for the reduction of fluid in the stomach.

To investigate this hypothesis, I tested PGE_2 for gastric antisecretory activity in a gutless rat and induced intestinal secretion with hypertonic solutions while monitoring the gastric secretion in the pylorus ligated rat.

MATERIALS AND METHODS

Gastric Secretion Studies

Pylorus Ligated Intact Rat

Female Upjohn rats (derived from the Sprague-Dawley strain) weighing 185-200 gm were used in all experiments. The rats were fasted for 24 hours prior to experimentation. Additionally, water was withheld during 16-17 hours of the fasting period. The rats were placed in cylindrical stainless steel restraining cages to prevent them from eating their hair and feces.

On the morning of the experiments, body fluids lost during fasting were replaced with 10 ml saline, administered subcutaneously. It was observed that rats drank very little when deprived of food and lost 10-15 gms during fasting. Rats receiving hypertonic fluid intraduodenally or isotonic fluid intravenously did not receive (10 ml) saline subcutaneously.

One hour after the saline administration, the pylorus was ligated under ether anesthesia as described by Shay *et al.* (1945). Four or five hours after pylorus ligation, the animals were killed with carbon dioxide, then the stomachs were removed and the accumulated gastric juice was collected in a graduated test tube.

Pylorus Ligated Gutless Rat

The animals were treated the same as the pylorus ligated intact rat except that along with pylorus ligation the intestine was removed. Four ligatures were needed. A ligature was placed around

the rectum and its vessels. The portal vein with coeliac and superior mesenteric vessels were ligated. Next, the bile duct plus the inferior and superior pancreatic-duodenal vessels were ligated. The final ligation was the pylorus.

The rectum was cut and the intestinal mass was lifted toward the stomach. After the gut was freed by severing its ligamentous and venous attachments, the duodenum was cut below the pylorus ligation. The pancreas was separated from the duodenum and left in the abdomen. The spleen was not removed.

Isotonic Fluid (Sodium Chloride or Mannitol) Injection

Following pylorus ligation of the intact or gutless rat, the jugular vein was exposed. Using a 25 gauge needle 5/8 inch long, the vein was punctured by passing the needle through the pectoralis muscle. Seven milliliters of fluid was injected within one minute. The skin was closed using one wound clip. After 1 1/2 hours, the animal was re-anesthetized and an additional 7 ml was injected in the same or the other jugular vein. Control animals underwent the same surgical procedures except no fluid was injected. Rats receiving intravenous fluid and their controls did not receive subcutaneous saline (10 ml) injections.

Hypertonic Fluid (Sodium Chloride or Mannitol) Injection

Immediately after pylorus ligation (under ether anesthesia) using a 25 gauge, 5/8 inch needle, 1 ml or 2 ml of hypertonic NaCl or mannitol was injected into the duodenum. The needle pierced the duodenum 5 mm from the pylorus, fluid was injected in a downward direction.

Intestinal Secretion Studies

At necropsy, the small intestine was cut at the duodenum and at the ileocecal junction, removed from the abdomen and its contents were collected into a graduated centrifuge tube by squeezing the entire length of the small intestine (Robert *et al.*, 1976). The volume was read to the nearest 0.1 ml.

Hematocrit

Immediately before necropsy, a small part of the tail was cut. Blood was allowed to flow into a capillary tube. The tube was plugged with clay and centrifuged in a clinical centrifuge for 4 minutes.

Gastric Juice Analysis

The volume of gastric juice was measured in a graduated centrifuge tube to the nearest 0.1 ml; acid was titrated with 0.1 N NaOH to pH 7 with the use of a glass electrode (Copenhagen radio-meter) and expressed in mEq/L (concentration) and mEq/4 or 5 hr (output). Pepsin content was determined by the hemoglobin method, as modified by Vatier *et al.* (1968), for an autoanalyzer. Pepsin concentration was expressed as μEq of tyrosine/ml and pepsin output as μEq tyrosine/4 or 5 hours.

Pharmacological Agents

Prostaglandin E_2 (Upjohn) was dissolved in 95% ethanol and administered in 0.5 ml aqueous solution containing 5% ethanol-saline subcutaneously immediately after pylorus ligation at the following doses: 1, 2.5, 5 and 10 mg/kg. Vehicle, 5% ethanol-saline, was given to control animals.

Methscopolamine bromide (Upjohn) was dissolved in 1 ml of saline, administered subcutaneously at a dose of 1 mg/kg immediately after pylorus ligation.

Hypertonic sodium chloride was prepared as a 5% (weight-volume) or 1600 mosmol. in water. Hypertonic mannitol was prepared as a 30% (weight-volume) or 1600 mosmol. solution in warm water. In addition, aqueous isotonic sodium chloride (290 mosmol.) and 5% (w/v) or 290 mosmol. mannitol solutions were prepared.

Statistical Test

The results are expressed as means for all gastric juice, intestinal fluid and hematocrit values. The two-tailed Dunnett T-test was used; significance was expressed as $p < 0.05$ and $p < 0.01$.

RESULTS

Studies on Gastric and Intestinal Secretion of Intact Rats

Gastric Juice

Volume. PGE_2 given subcutaneously inhibited gastric juice volume in a dose dependent manner. A significant reduction ($p < 0.01$) was shown at the 2.5 mg/kg dose of PGE_2 (Figure 1A). This level of inhibition was shown 5 hours after treatment but no reduction was apparent at 1 to 3 hours after treatment (Figure 2). Comparisons were made to control animals receiving vehicle.

Acid. Both acid concentration and output were inhibited by PGE_2 in a dose dependent manner. A significant inhibition ($p < 0.01$) was attained with a dose of 2.5 mg/kg (Figure 1B and 2).

Pepsin. PGE_2 at 10 mg/kg, inhibited pepsin concentration ($p < 0.05$). A lower dose, 2.5 mg/kg, inhibited pepsin output ($p < 0.01$) at 5 hours after treatment.

Intestinal Fluid Secretion

PGE_2 increased intestinal fluid significantly ($p < 0.01$) within 15 minutes after treatment. Volume returned to pre-treatment levels 3 hours after treatment (Figure 2).

Studies on Gastric Secretion of Gutless Rats

Gastric Juice

Volume. No significant change in gastric volume was observed when PGE_2 was administered at any of the doses tested. Unlike the

intact rat, there was no decrease in volume. However, a consistent increase in volume was noted (Figure 3A).

Acid. PGE_2 decreased acid concentration, at the 2.5 mg/kg dose ($p < 0.05$) but not acid output (Figures 3B and 4).

Pepsin. Pepsin concentration was decreased at the 10 mg/kg dose ($p < 0.05$). Pepsin output, however, was not changed.

Effect of Intravenous Isotonic Fluid on Gastric and Intestinal Secretion in PGE_2-Treated Intact Rats

Gastric Juice

Volume. Isotonic mannitol (14 ml) given intravenously to PGE_2 (5 mg/kg) treated intact rats reversed the PGE_2 inhibition of gastric volume 2 and 3 hours after treatment (Figure 5). PGE_2 and intravenous fluid produced more volume in the stomach than did the vehicle treated rats. This reversal was not observed at 4 or 5 hours after treatment, but the PGE_2 inhibition of gastric volume was blocked.

Isotonic NaCl (14 ml) treatment also blocked PGE_2 induced inhibition of gastric secretion.

Administration of intravenous fluids had no effect on basal secretion in the vehicle treated animals. When PGE_2-treated sham operated group was compared to PGE_2 and intravenous isotonic fluid treated group, there is definite stimulation of gastric volume ($p < 0.05$) by isotonic mannitol (Figure 5).

Acid. Isotonic NaCl and mannitol treatment did not alter the inhibitory effect of PGE_2 on acid concentration (Figure 5), nor did it block the effect on acid output.

Pepsin. PGE_2 inhibited pepsin concentration and output ($p < 0.01$) in intact rats. Mannitol did not alter pepsin concentration, but it blocked the inhibitory effect of PGE_2 on pepsin output.

Intestinal Fluid Secretion

The PGE_2 induced stimulation of intestinal secretion was not altered by expansion of extracellular fluid volume (Figure 5).

Effect of Intravenous Isotonic NaCl
on Gastric Secretion in PGE_2-Treated Gutless Rats

Gastric Juice

Volume. PGE_2 (5 mg/kg) increased gastric volume ($p < 0.05$) (Figure 6A). Intravenous saline (14 ml) treatment significantly ($p < 0.01$) increased the gastric volume of the gutless rat receiving PGE_2, 4 hours after treatment (Figure 6A).

Acid. Acid concentration was reduced by PGE_2 ($p < 0.01$), but acid output was not changed from controls. Intravenous saline did not influence the PGE_2-induced inhibition of acid concentration (Figure 6B). PGE_2 did not inhibit acid output in the gutless rat. Intravenous saline plus PGE_2 did not inhibit acid output.

Effect of Intraduodenal Hypertonic NaCl and
Mannitol on Gastric and Intestinal Secretion

Gastric Juice

Volume. Two milliliters of hypertonic NaCl (5%) significantly reduced ($p < 0.01$) gastric volume 3 hours after treatment. This effect was less at 4 hours after treatment. A dose of 1 ml hypertonic NaCl showed significant volume reduction at 2 hours ($p < 0.05$)

(Figure 7).

Hypertonic mannitol (30%) reduced volume ($p < 0.05$) 7 hours after a dose of 1 ml administered intraduodenally (Figure 8).

Acid. It was observed 3 hours after treatment that hypertonic NaCl (2 ml) reduced acid concentration ($p < 0.05$). Acid concentration was the same as in control animals 4 hours after treatment.

Mannitol did not reduce acid concentration during the time period that acid was determined (6 hours after treatment), but acid output was significantly reduced (Figure 8).

Pepsin. Hypertonic NaCl (2 ml) had reduced pepsin output ($p < 0.05$) 4 hours after administration. Pepsin concentration was unchanged. Mannitol inhibited pepsin output ($p < 0.01$) 6 hours after treatment with a 1 ml dose.

Intestinal Fluid Secretion

Hypertonic NaCl and mannitol increased intestinal fluid within 15 minutes after treatment (Figures 7 and 8). A level of stimulation ($p < 0.01$) was maintained for 2 hours (sodium chloride) and 7 hours (mannitol). Intestinal fluid volume stimulated by hypertonic solutions was much greater than PGE_2 induced intestinal secretion; 306% for PGE_2, 652% NaCl and 1113% for mannitol (comparisons were made at 15 minutes after treatment).

Studies on Hematocrit

The hematocrit of control, pylorus-ligated intact and gutless rats did not change significantly during the experimental time

period. PGE_2 did not affect the hematocrit in either preparation (Figures 2 and 4).

Effect of Intraduodenal Hypertonic Mannitol and NaCl on Hematocrit

Hypertonic mannitol showed a significant increase ($p < 0.01$) in hematocrit over control after 15 minutes of treatment whether 1 ml or 2 ml was injected into the duodenum (Figure 8). This increase was evident 1 hour after 2 ml treatment but lasted only 30 minutes following a 1 ml dose. Hypertonic NaCl (2 ml) increased the hematocrit significantly only at 15 minutes after treatment.

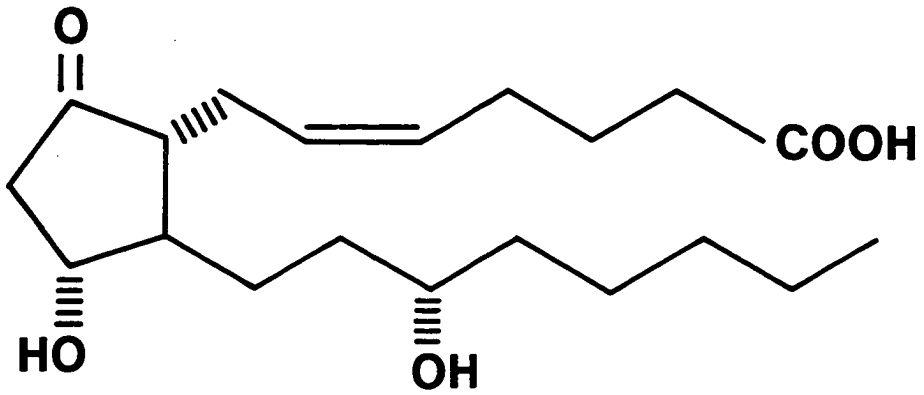
Effect of Intravenous Isotonic NaCl and Mannitol on Hematocrit in PGE_2-Treated Rats

The hematocrit of rats receiving isotonic intravenous NaCl or mannitol and vehicle showed no difference from rats receiving isotonic intravenous solution and PGE_2 (Figure 5).

Effect of an Anticholinergic Drug on Gastric and Intestinal Secretion and Hematocrit in the Intact and Gutless Rats

Methscopolamine bromide (1 mg/kg, subcutaneously) inhibited ($p < 0.01$) gastric volume and acid (concentration and output) in the intact as well as the gutless rat (Figures 9 and 10). Unlike PGE_2, this antisecretory drug had the same effect on both the intact and the gutless rat.

Intestinal secretion was not changed by methscopolamine bromide nor did the hematocrit show any difference from control rats (Figure 9).



Prostaglandin E_2

FIGURES

In all figures, each column represents mean values. The same animals were used for measurement of gastric volume and acid, intestinal fluid and hematocrit. The times indicated in Figures 2, 4, 5, 7, 8, and 9 gives the interval between treatment and necropsy.

A significant comparison between a group and the vehicle-treated group is indicated by * = $P < 0.05$ and ** = $P < 0.01$. A significant comparison between PGE_2 plus another treatment or surgery compared to PGE_2 alone plus sham surgery is indicated by † = $P < 0.05$ and †† = $P < 0.01$.

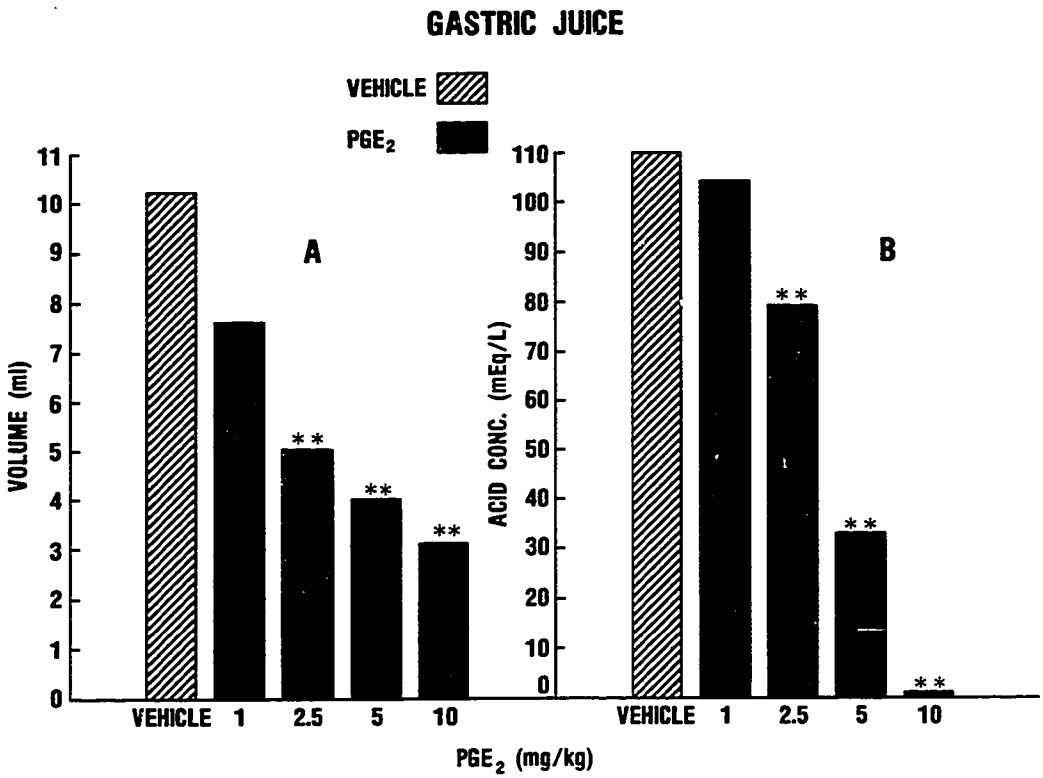


Figure 1. Effect of Various Doses of Prostaglandin E_2 on Volume (A) and Acid Concentration (B) of Gastric Juice, 5 Hours After Pylorus Ligation. Each Column Represents the Mean of 7-11 Rats.

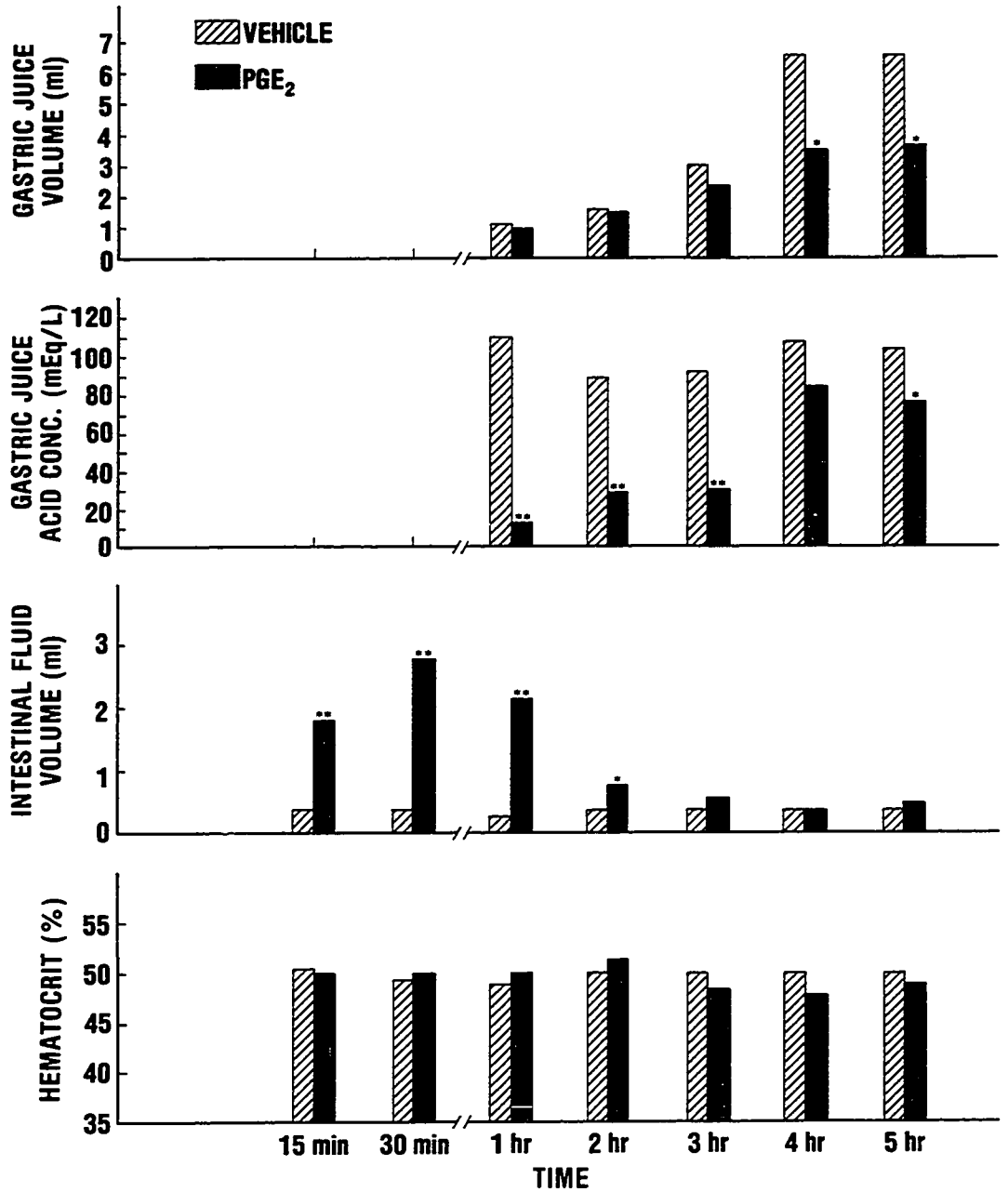


Figure 2. Effect of PGE_2 (2.5 mg/kg) on Gastric Volume and Acid Concentration, Intestinal Fluid Volume and Hematocrit at Various Times After Treatment. Each Column Represents the Mean of 3-8 Rats.

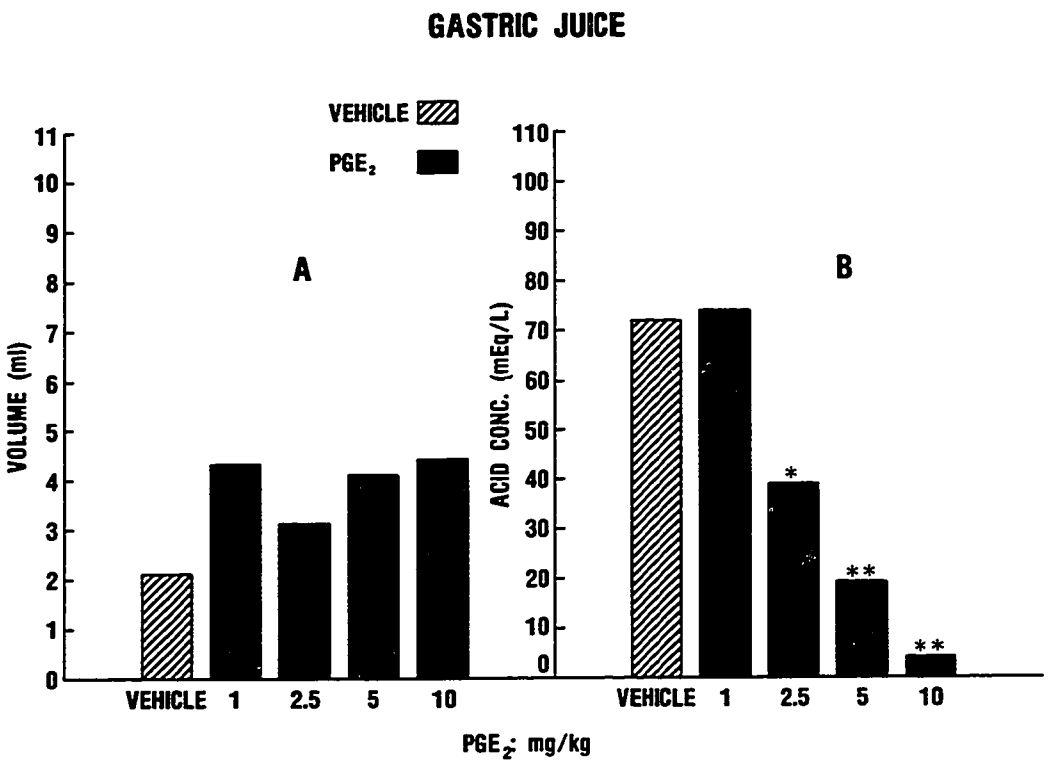


Figure 3. Effect of Various Doses of PGE_2 on Volume (A) and Acid Concentration (B) of Gastric Juice, 5 Hours After Pylorus Ligation in Gutless Rats. Each Column Represents the Mean of 4-6 Rats.

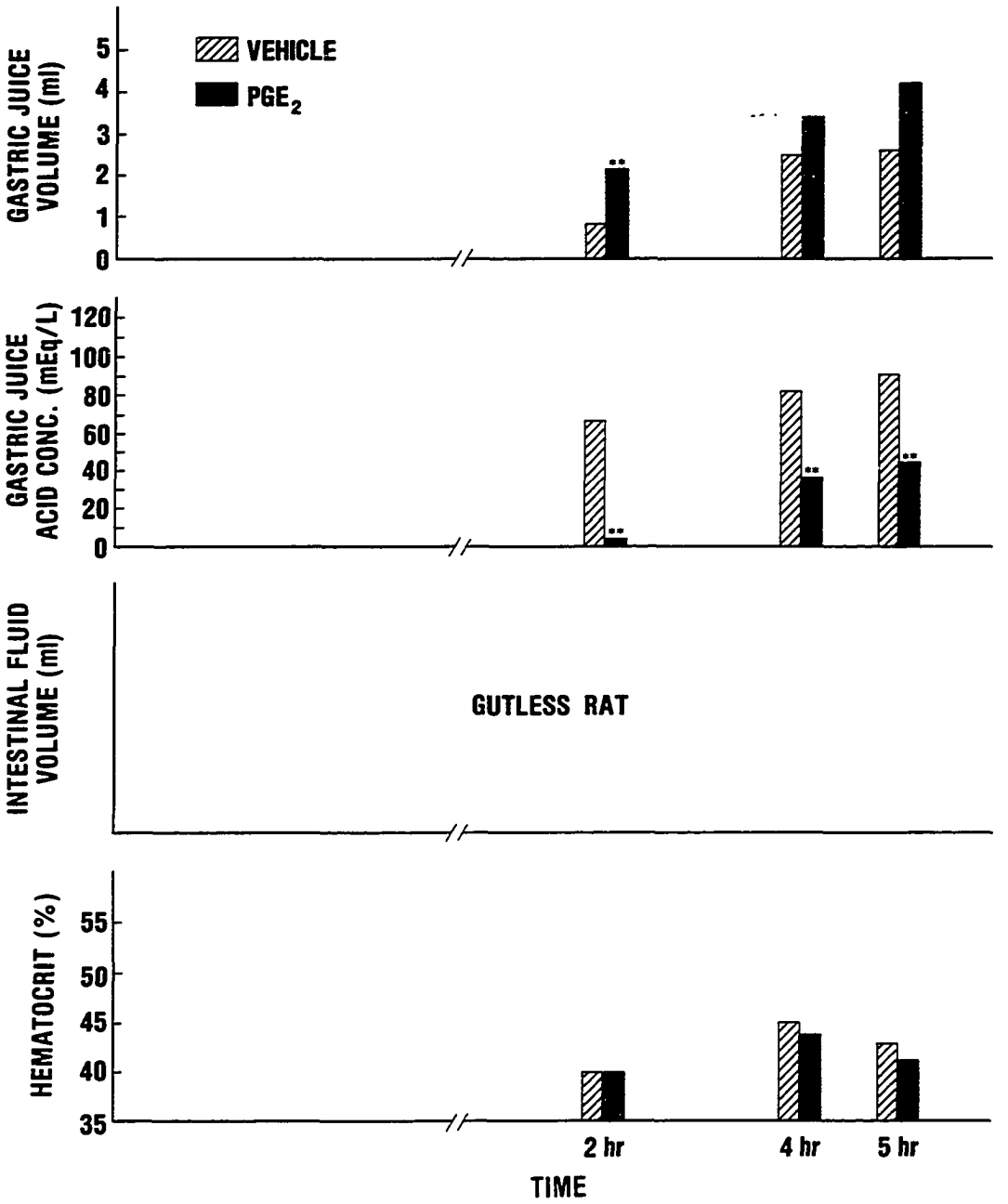


Figure 4. Effect of PGE_2 (2.5 mg/kg) on Gastric Volume and Acid Concentration, and Hematocrit in Pylorus Ligated Gutless Rats at Various Times After Treatment. Each Column Represents the Mean of 5-6 Rats.

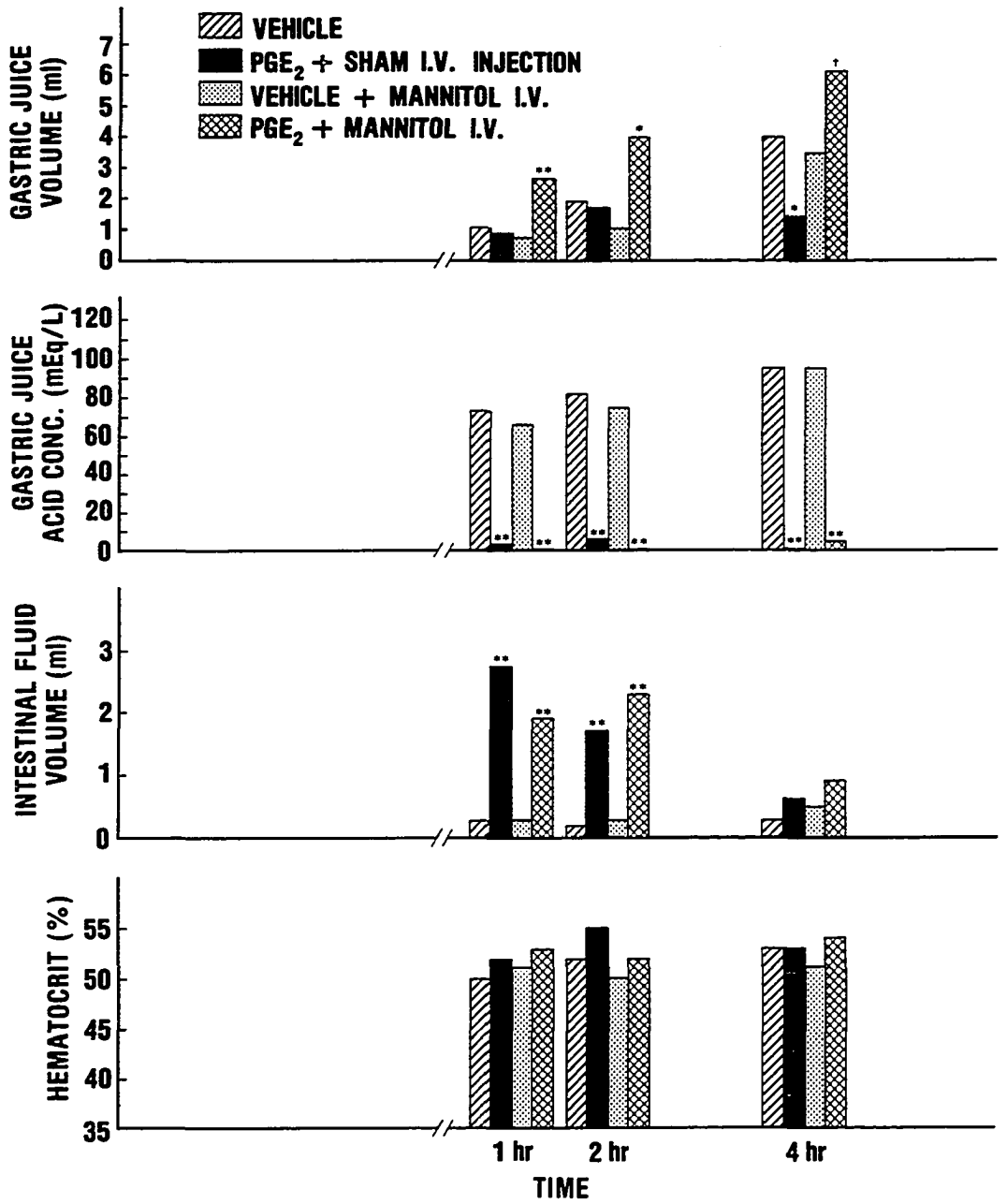


Figure 5. Effect of PGE_2 (5 mg/kg) on Gastric Volume and Acid Concentration, Intestinal Fluid Volume and Hematocrit as Influenced by 14 ml of Isotonic (5%) Mannitol Given Intravenously in Pylorus Ligated Rats at Various Times After Treatment. Each Column Represents the Mean of 3-4 Rats.

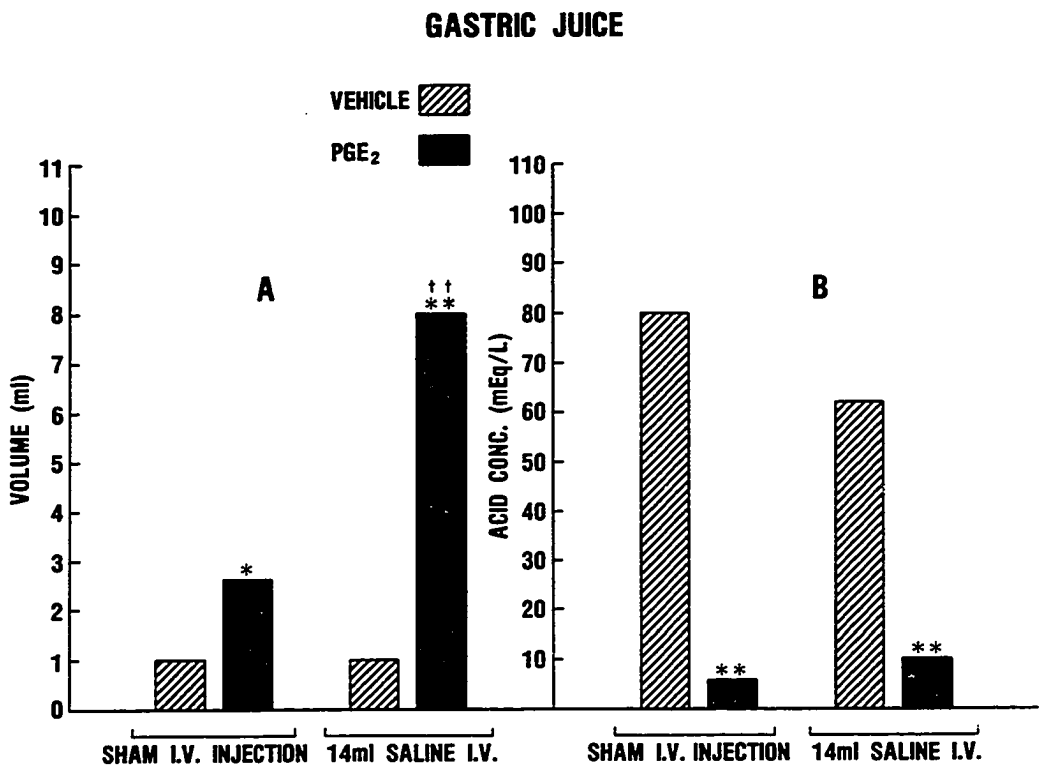


Figure 6. Effect of PGE_2 (5 mg/kg) on Volume (A) and Acid Concentration (B) of Gastric Juice as Influenced by 14 ml of Isotonic NaCl (0.9%) Given Intravenously in Pylorus Ligated Gutless Rats, 4 Hours After Treatment. Each Column represents the Mean of 4-5 Rats.

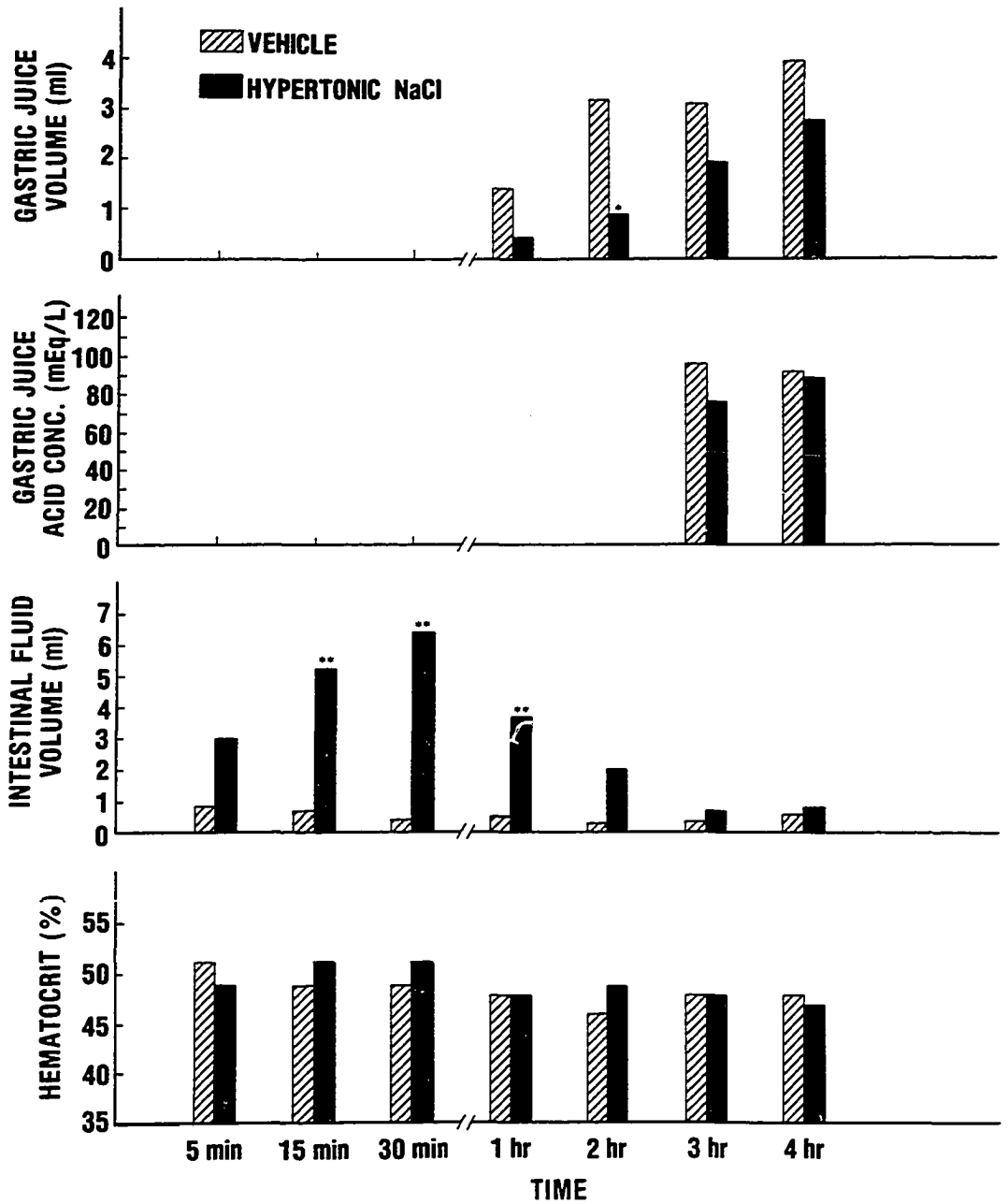


Figure 7. Effect of 1 ml of Hypertonic (5%) NaCl, intraduodenally at the Time of Pylorus Ligation, On Gastric Volume and Acid Concentration, Intestinal Fluid Volume and Hematocrit at Various Times After Treatment. Each Column Represents the Mean of 3-4 Rats.

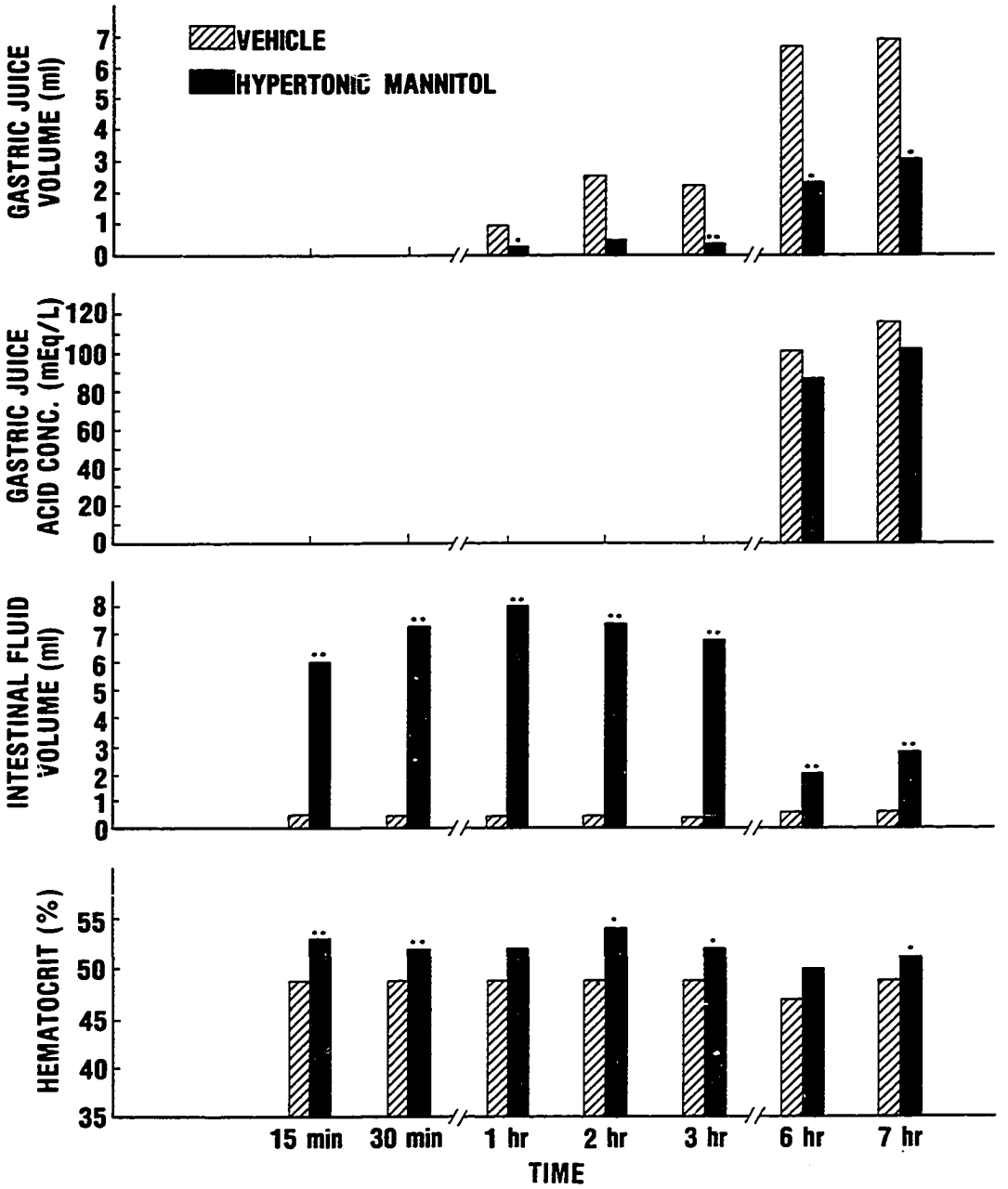


Figure 8. Effect of 1 ml of Hypertonic (30%) Mannitol, Intraduodenally at the Time of Pylorus Ligation, On Gastric Volume and Acid Concentration, Intestinal Fluid Volume and Hematocrit at Various Times After Treatment. Each Column Represents the Mean of 3-4 Rats.

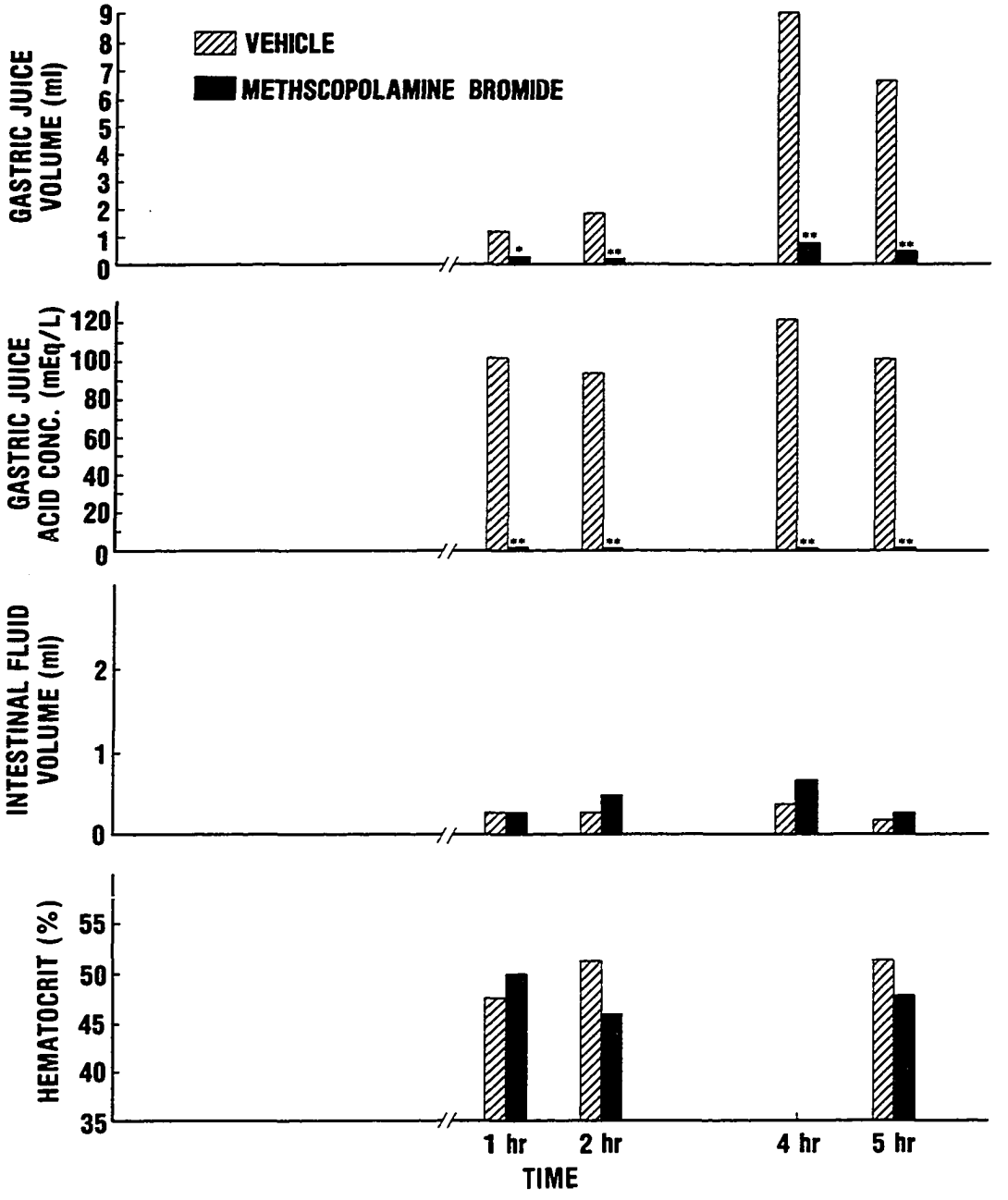


Figure 9. Effect of Subcutaneous Methoscopolamine Bromide on Gastric Volume and Acid Concentration, Intestinal Fluid Volume and Hematocrit in Pylorus Ligated Rats at Various Times After Treatment. Each Column Represents the Mean of 3-4 Rats.

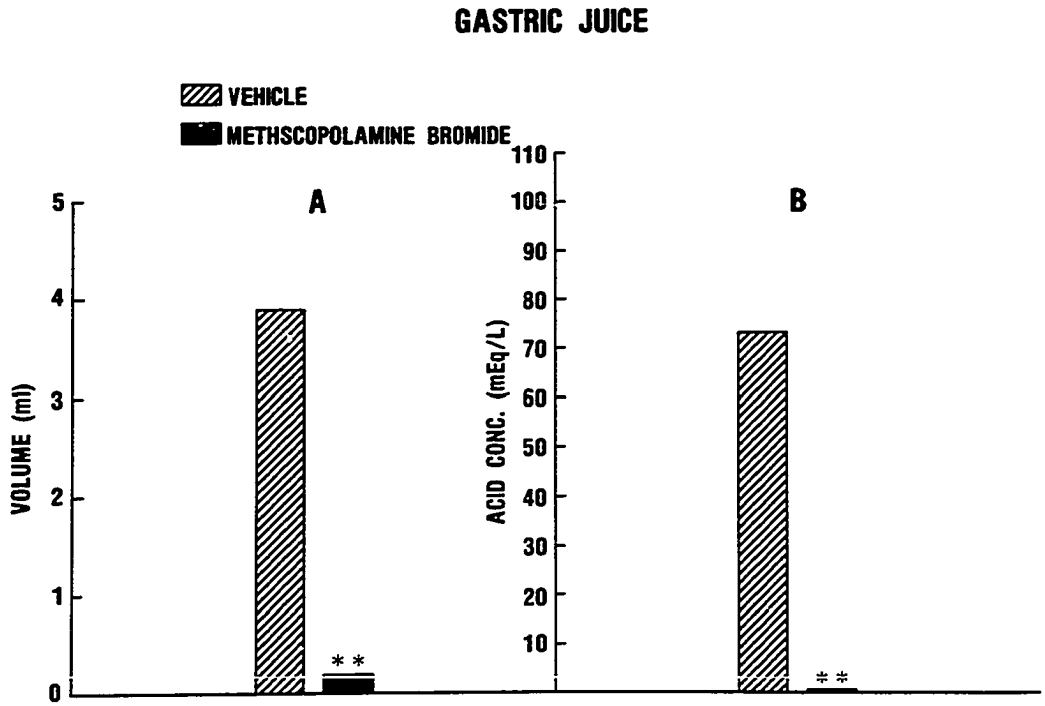


Figure 10. Effect of Subcutaneous Methscopolamine Bromide on Gastric Volume (A) and Acid Concentration (B) in Pylorus Ligated Gutless Rats, 4 Hours After Treatment. Each Column Represents the Mean of 6-10 Rats.

DISCUSSION

PGE_2 inhibited gastric volume, acid and pepsin and increased intestinal secretion in the pylorus-ligated intact rat (Figures 1 and 2). However, the gastric volume was not inhibited in the gutless rat (Figure 3A). PGE_2 may reduce gastric volume through increased intestinal secretion. There are other instances when increased intestinal secretion is associated with reduced gastric secretion. Cholera toxin induced intestinal secretion is abundant in patients with the disease. Similarly, gastric acid output is reduced in cholera patients (Sack *et al.*, 1970). The inhibition of basal gastric secretion by intraduodenal hypertonic solutions is another example of this phenomenon (Figures 7 and 8).

The data obtained from the surgical manipulation of the small intestine indicated that the absorption of certain substances secreted by the duodenum is important in maintaining gastric secretion of the pylorus-ligated rat (Okabe *et al.*, 1975). If this is the case, then abundant intestinal secretion would be expected to inhibit gastric secretion because net intestinal secretion is the result of inadequate absorption.

When the gut was removed, PGE_2 did not inhibit gastric volume at any dose tested (Figures 3A and 4). This is a strong indication that PGE_2 inhibits gastric volume by a mechanism involving the gut.

Intravenous fluids blocked gastric volume inhibition by PGE_2 in the intact pylorus-ligated rat and potentiated gastric volume

increase in the gutless rat, strongly suggesting that blood volume plays a role (Figures 5 and 6). If this is true, then the volume of intestinal secretion in PGE_2-treated rats must be such that blood volume is decreased. The increase in gastric volume produced by intravenous isotonic fluid in the PGE_2-treated gutless rat may indicate that PGE_2 stimulates non-parietal cell secretion of the stomach (Figure 6A). This is supported by the fact that an analogue of PGE_2 (16,16-dimethyl PGE_2) stimulated non-acid secretion from the unstimulated canine gastric mucosa (Bolton *et al.*, 1978).

Hemoconcentration may not be directly involved in the inhibition of gastric secretion produced by PGE_2. Significant hemoconcentration was not shown at doses producing large increases in intestinal secretion (Figure 2). Hypertonic NaCl produced abundant intestinal fluid at a time period which corresponded to the significant decrease in gastric volume but the hematocrit was not affected (Figure 7). An abnormal increase in intestinal secretion, in itself, may stimulate gut substances that regulate gastric secretion. Therefore, it may be concluded that any rapid movement of body fluids from blood to intestinal lumen will cause a decrease in the volume of gastric secretion.

PGE_2 has direct effects on gastric mucosa function. In the isolated canine stomach perfused with blood, the addition of PGE_2 to the blood inhibited acid secretion induced by either histamine, pentagastrin or vagal stimulation (Shaw *et al.*, 1972). The present study does not dispute this finding. I am presenting evidence that

PGE_2 inhibits gastric acid and volume by separate mechanisms.

In the gutless rat, PGE_2 promoted fluid secretion by the stomach similar to its effects on the intestine. Only the H^+ concentration was determined in the gastric juice of this preparation. Whether PGE_2 affects other ions of gastric juice in a manner similar to its effects on intestinal ion secretion is not known.

Reports show that PGE_2 and an analogue, produce ion fluxes in the rat intestinal mucosa and both canine and frog gastric mucosa. Ruwart *et al.* (1979) reported that PGE_2 (1.0 mg/kg) decreased calcium and phosphorus, but increased sodium and chloride concentration in intestinal fluid. Bolton *et al.* (1978) showed that the 16,16-dimethyl PGE_2 induced non-parietal cell secretion, from the canine gastric mucosa *in vivo*. This secretion contains a high HCO_3-content. Other reports support this finding. Garner *et al.* (1979) showed that 16,16-dimethyl PGE_2 stimulated HCO_3-secretion by the frog gastric mucosa. If this is the case, then acid neutralization by the bicarbonate could explain the decrease in acid concentration produced by PGE_2.

Hypertonic NaCl and mannitol administered into the duodenum inhibited gastric secretion, increased hemoconcentration and stimulated intestinal secretion. The mechanism of hypertonic fluid induced inhibition of gastric secretion is not known. Assouline *et al.* (1978) found that hypertonic NaCl (2 ml of a 10% solution) inhibited gastric acid output in the pylorus ligated rat. PGE_2 in the stomach contents increased also. It was concluded thus,

since prostaglandins possess antisecretory activity and hypertonic NaCl stimulated prostaglandin production, then hypertonic solutions inhibit gastric secretion through stimulating endogenous prostaglandin production. Adair (1976) found that 2 millimoles of NaCl (given in a 2 ml volume) administered orally 2 hours before pylorus ligation inhibited gastric secretion (acid concentration and output). He concluded that hypertonic NaCl inhibited gastric secretion by increasing gastric mucosal permeability to ions. This cannot be the case for intraduodenally administered hypertonic NaCl since this route shows parental activity. Adair did not show antisecretory effects of hypertonic NaCl after subcutaneous administration. Therefore, intraduodenally administered hypertonic NaCl may inhibit gastric secretion through mechanisms involving the gut with increased intestinal secretion playing a role.

The first demonstration of antisecretory activity afforded by hypertonic solutions (glucose) was made by Leconte (1900) and later by Clemm (1901). Shay *et al.* (1942) proposed a local osmoreceptor mechanism to explain this gastric inhibitory action of hypertonic solutions in the duodenum. Sircus (1953) concluded that the mechanism of osmotically induced inhibition of gastric secretion is hormonal in nature after he demonstrated that hypertonic solutions inhibit gastric secretion in dogs with innervated, denervated or transplanted fundic pouches. Konturek and Grossman (1965) found that a 20% glucose solution instilled into the duodenum inhibited the Heidenhain pouch response to exogenous gastrin.

From data presented here, it may be hypothesized that intestinal secretion is the mechanism of action of osmotically induced inhibition of gastric secretion. Hypertonic solutions stimulate intestinal secretion which in turn inhibits gastric secretion. Thus, it is likely that intestinal secretion (abnormal levels) may contribute to the gastric volume inhibition by prostaglandins.

Increased intestinal secretion coincides with decreased gastric secretion. This is true when intestinal secretion is induced by cholera toxin, hypertonic solutions or PGE_2. Abundant intestinal secretion may induce gut hormones or initiate osmoreceptor mechanisms which may be involved in the regulation of gastric secretion.

CONCLUSIONS

1. Prostaglandin E_2 does not inhibit gastric volume in the gutless rat. This property is unlike an anticholenergic antisecretory compound, methscopolamine bromide, which inhibits volume with equal potency in both intact and gutless pylorus ligated rats. Both PGE_2 and methscopolamine bromide inhibited acid concentration in the gutless rat.

2. PGE_2 inhibits gastric volume and acid by separate mechanisms. Gastric volume inhibition by PGE_2 involves the gut perhaps through substances produced by the gut.

3. Expansion of extracellular fluid volume by intravenous isotonic fluids blocked PGE_2 induced inhibition of gastric volume in the pylorus ligated intact rat. PGE_2 plus intravenous fluid stimulated gastric volume in both intact and gutless pylorus ligated rat.

4. Hypertonic solutions (NaCl and mannitol) administered intraduodenally, inhibited gastric secretion, stimulated intestinal secretion and increased hemoconcentration. The fluid loss through intestinal secretion may be the reason for the lack of fluid in the stomach.

5. An abnormal increase in intestinal secretion, in itself, may stimulate gut substances that regulate gastric secretion.

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