Effects of aspirin on gastric prostaglandin E (PGE) and acid output in normal subjects¹

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SUMMARY Aspirin administration to normal subjects resulted in a reduction in gastric prostaglandin E (PGE) output. Both PGE concentration and gastric juice volume were decreased. Gastric acid output also decreased, although the difference was not statistically significant. An increased sensitivity of the PGE system to inhibition by aspirin at 11 pm, midnight, and 1 am was observed.

Prostaglandins are a group of long chain fatty acids found to be biologically active in a number of mammalian tissues, including the stomach. Inhibition of basal, pentagastrin, histamine or food stimulated gastric acid secretion has been demonstrated in animals after the administration of PGE₁ (Wilson, 1974). In rats, gastric (Robert *et al.*, 1968) and duodenal (Robert *et al.*, 1971) ulcers have been prevented by PGE₁ and PGE₂ respectively. In humans, Classen *et al.* (1971) found that the intravenous infusion of PGE₁ significantly inhibited gastric acid secretion. However, oral administration was associated with increased gastrointestinal motility without a reduction in gastric acid secretion (Horton *et al.*, 1968). In addition, PGE is present in human gastric juice. In normal subjects a circadian rhythm in gastric PGE output with higher levels during the day than during the night has been reported from our laboratory. This PGE rhythm was in reciprocal phase relationship with the circadian gastric acid secretion in normal subjects. On the other hand, a disruption of PGE and acid rhythms and their phase relationship was found in patients with peptic ulcer (Tonnesen *et al.*, 1974). In an attempt to understand the relationship between PGE and gastric acid secretion, we studied the effects of aspirin, a known prostaglandin inhibitor (Vane, 1971) on gastric PGE and acid secretion in normal subjects. Our findings are reported here.

Methods

Gastric juice was collected hourly for 24 consecutive hours without (control period) and after aspirin administration in eight normal male subjects (age range 22-34 years, mean 25.2 years). Studies were begun at 8 am or 4 pm after a 12 or 16 hour fast, respectively. Subjects were assigned at random to start with either the control or the aspirin period. During the latter, subjects received 3.3 g aspirin (1.1 g every eight hours) on each of five consecutive days before the 24 hour collection of gastric juice. The last oral aspirin dose was given eight hours before the collections of gastric juice were begun. Since oral ingestion of aspirin was not desirable while gastric collections were made, rectal suppositories containing 1.3 g aspirin were given every four hours. A sump nasogastric tube was positioned fluoroscopically in the gastric antrum. Gastric juice was obtained continuously by automatic interrupted suction and pooled at hourly intervals. During both collection periods each subject was studied under the same controlled conditions in a semi-isolated environment, receiving a continuous intravenous infusion of 3 000 ml 0.45% saline over 24 hours. Blood samples for salicylate levels were drawn every four hours.

For each hourly sample, the volume was measured and titratable acidity was determined with a pH meter by neutralization with 0.1 N Na OH. Results were expressed in mEq/l or in mEq/h. The concentration of PGE was determined by radioimmunoassay as developed in our laboratory for plasma (Jubiz *et al.*, 1972) and modified for gastric juice (Tonnesen *et al.*, 1974). Results were expressed in $\mu\text{g/ml}$ or in $\mu\text{g/hour}$. Salicylate levels were measured by a colorimetric technique (Trinder, 1954).

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		Volume (ml/h)	PGE concentration ($\mu\text{g}/\text{ml}$)	PGE output ($\mu\text{g}/\text{h}$)	Acid concentration (mEq/l)	Acid output (mEq/h)
Control (n = 8)	(mean $\pm$ SD)	83.1 $\pm$ 16.5	1.6 $\pm$ 0.6	126.0 $\pm$ 52.3	66.9 $\pm$ 14.9	5.8 $\pm$ 2.3
Aspirin (n = 8)	(mean $\pm$ SD)	69.5 $\pm$ 20.5	1.3 $\pm$ 0.4	80.0 $\pm$ 31.9	61.5 $\pm$ 14.7	4.8 $\pm$ 1.7
P*		< 0.01	< 0.025	< 0.0025	< 0.25	< 0.10

Table Hourly gastric juice volume, PGE concentration and output, acid concentration and output in eight normal subjects before and after aspirin administration

*P values were calculated by *t* test for correlated means based on chi squares (one tailed probability).

Results

Hourly gastric juice volume, concentration, and output for PGE and acid for the eight normal subjects during the 24 hour period are shown in the Table. After aspirin administration, a statistically significant reduction in PGE output, at the expense of PGE concentration and volume, was observed. A fall in acid concentration and output was also noted, although the difference was not statistically significant.

PGE concentration, gastric juice volume, and calculated PGE output before and after aspirin administration for each hour are shown in Fig. 1. Serum salicylate concentration was maintained between 20 and 30 mg/dl throughout the study. At these levels, we observed an obliteration of the circadian rhythm in PGE output primarily as the result of a fall in PGE concentration between 6 pm and 4 am. Nonetheless, the differences were statistically significant ($p < 0.05$) only at 7, 11, 12 pm and 1 am. Gastric juice volume also decreased but statistically significant differences were found only at noon. When the values after aspirin administration were expressed as a percentage of the corresponding control values, similar results were obtained (Fig. 2).

Results of gastric acid concentration and output and of gastric juice volume are presented in Fig. 3. In response to aspirin administration, gastric acid output did not change significantly.

Discussion

We have found an inhibition of the mean hourly gastric PGE output by aspirin in normal subjects resulting from a decrease in both PGE concentration and volume. As a result of this inhibition, the normal circadian rhythm in gastric PGE output was

Fig. 1 Gastric PGE concentration and output and gastric juice volume in eight normal subjects before (○) and after aspirin administration (●). Values represent mean $\pm$ SEM. * $P < 0.05$.

Fig. 2 Gastric PGE concentration and output and gastric juice volume in eight normal subjects after aspirin administration expressed as percent of control value (control mean is considered to be 100% for each hour). * $p < 0.05$.

abolished. Although the changes in PGE concentration and output appeared to have occurred mostly during the evening and early morning hours, a statistically significant difference was found only at four hours. Bennet *et al.* (1974) observed a fall in PGE output after indomethacin administration that was attributed to a decrease in volume rather than concentration. In our study with aspirin, we also observed a decrease in volume but an even greater decrease in PGE concentration. The reduction in prostaglandin output suggests that aspirin inhibits prostaglandin synthesis, presumably by inhibiting the enzyme prostaglandin synthetase that is believed to be present in the stomach fundus (Pace-Asciak, 1972). An increased sensitivity of the PGE system to the inhibitory effects of aspirin, unrelated to the time of administration, was observed around midnight. The significance of this finding is not apparent at the present time.

Fig. 3 Gastric acid concentration and output and gastric juice volume in eight normal subjects after aspirin administration expressed as percent of control value (control mean is considered to be 100% for each hour). * $p < 0.05$.

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