

Effect of Intravenous Infusion of Propantheline Bromide on Gastric Secretion

B. FURBERG, U. KRAUSE and Å. RIMSTEN

From the Departments of Clinical Physiology and Surgery, University Hospital, Uppsala, Sweden

ABSTRACT

The effect of 2 hours' intravenous infusion (7.5 mg/h) of propantheline bromide (Ercotina®, Erco Läkemedel AB) on basal or pentagastrin-stimulated gastric secretion was studied in 7 healthy subjects and in 11 patients with acute duodenal ulcer. A moderate to marked decrease in acid secretion rate and acid output was found both in subjects and patients during the infusion period. The acidity decreased in most of the subjects but did not change much in the patients. Two other dose rates (3.75 and 15 mg/h) were studied in a few subjects and patients. The lowest dose rate gave as good an inhibition of the gastric secretion as the higher ones. No troublesome side effects were noticed. It was concluded that a dose rate of around 5–10 mg/h may be suitable for prolonged i.v. infusion, for example as trial therapy in patients with upper gastro-intestinal bleeding.

INTRODUCTION

Surgical vagotomy has a good effect in some patients with massive upper gastro-intestinal bleeding (2, 9). However, the operation mortality at emergency operation is high, especially in patients with haemorrhagic gastritis (5). This means that medical treatment almost always is primarily preferred. From a theoretical point of view, pharmacological blockade of gastric secretion could be valuable. The effectiveness of treatment of patients with massive upper gastro-intestinal bleeding with anticholinergics is not documented, however.

The effect of orally given anticholinergics on gastric acid secretion is well known. In attempts to predict the effect of surgical vagotomy in patients with duodenal ulcer, intravenous injection of propantheline bromide in a single dose has been used by some authors (1, 3, 6). However, no studies have been published on the effects of continuous intravenous infusions of anticholinergics. We are planning to study the effect of intravenous infusion of propantheline bromide (Ercotina®, Erco

Läkemedel AB, Stockholm) in patients with massive upper gastro-intestinal bleeding. In these patients it is difficult to find an individual optimal dosage. Maximum anticholinergic effects must be obtained without troublesome side effects.

The aim of the present investigation is to study the effect of continuous intravenous infusion of propantheline bromide (PB) on gastric secretion, and to find an optimal dosage for the planned clinical trial.

SUBJECTS AND PATIENTS

In the first of three series, the effect of PB on basal and pentagastrin-stimulated acid secretion was studied in 7 healthy male students, aged 23–28 years (average 25).

In the second series, the same studies were made in 11 patients (6 men, aged 28–61 years, average 47; 5 women, aged 49–63, average 55) with acute duodenal ulcer. None of the patients had undergone ulcer surgery.

In the third series, consisting of 6 patients with acute pancreatitis, the concentration of PB in serum was measured during and after 24–48 hours' infusion of PB at a constant dose rate, performed for therapeutic reasons. The aim was to control that a steady state of drug concentration in blood was attained and that the drug disappeared within 12 hours after the end of the infusion.

METHODS

Medical therapy was omitted for at least 2 days before the investigation. During the test, the patient was semirecumbent and the stomach was emptied intermittently, once or twice during each "collecting period" of 15 minutes, by manual suction via a plastic stomach tube. The volume of gastric secretion was measured for each sample and was expressed as rate of secretion (ml/min) per collecting period. One ml of each sample was titrated against 0.1 NaOH with Töpfer's reagent as indicator. The acidity was expressed in mmol/l and the acid output (secretion rate times acidity) in $\mu\text{mol/min}$.

In the basal secretion study, the secretion was first measured for one hour. Continuous intravenous infusion of PB (3.75, 7.5 or 15 mg/h) was then given during the next 2

Table I. Effects of intravenous PB infusion (7.5 mg/h) on basal and pentagastrin-stimulated gastric secretion in healthy volunteers and in patients with acute duodenal ulcer

	Normal subjects				Ulcer patients			
	Basal secretion		Pentagastrin stimulated secretion		Basal secretion		Pentagastrin stimulated secretion	
	Before PB infusion	PB infusion	Before PB infusion	PB infusion	Before PB infusion	PB infusion	Before PB infusion	PB infusion
Secretion rate (ml/min)								
<i>n</i>	6	6	6	6	3	3	8	8
<i>M</i>	0.87	0.11	1.90	0.44	1.18	0.38	3.14	1.03
<i>r</i>	0.21–1.67	0.05–0.24	1.26–2.96	0.00–0.91	0.52–1.68	0.10–0.71	1.23–6.84	0.54–1.37
Acidity (mmol/l)								
<i>n</i>	6	6	6	6	3	3	8	8
<i>M</i>	22.3	5.5	91.1	69.5	37.9	35.2	99.1	99.4
<i>r</i>	9.3–46.5	3.8–10.0	50.3–134.5	0.0–119.3	18.5–62.8	20.0–60.3	86.3–114.5	74.5–118.0
Acid output (μmol/min)								
<i>n</i>	6	6	6	6	3	3	8	8
<i>M</i>	20.0	1.1	178.1	43.3	42.5	17.6	309.5	106.8
<i>r</i>	4.5–41.8	0.1–2.7	58.3–318.0	0.0–108.3	16.5–80.2	2.0–42.5	111.2–685.3	41.2–167.7

hours. In the study of stimulated gastric secretion, a continuous intravenous infusion of pentagastrin (0.05 μg/h per kg body weight) was given until a constant level of acidity was reached. The infusion of pentagastrin was maintained while a continuous intravenous infusion of PB (3.75, 7.5 or 15 mg/h) was given for 2 hours. For the last four collecting periods (i.e. one hour) before infusion, and for the last four periods during PB infusion, the mean values for secretion rate, acidity and acid output were calculated. In 4 of the healthy subjects and in 4 of the ulcer patients, the effect of different PB dose rates was investigated on different occasions.

In the healthy subjects the nearpoint distance for vision and the heart rate were measured at least every 15th minute. Subjective symptoms such as a feeling of dryness in the mouth, accommodation disturbance, tachycardia or micturition disturbance were noted.

The measurements of PB concentration in serum were made with a spectrofluorometric method (8).

RESULTS

Gastric secretion studies

The effect of PB infusion (7.5 mg/h) on the basal acid secretion appears in Table I. In all of the healthy subjects a marked decrease in secretion rate, acidity, and acid output was found. The acid output reduced on an average by 95 % of the value before PB infusion. In the 3 studied ulcer patients a moderate decrease in secretion rate and acid output was found. The acid output decreased, on average, by 57 % of

the value before PB infusion. The acidity remained unchanged. Fig. 1 shows the effect of PB infusion on the basal secretion in one of the patients with duodenal ulcer. The decrease in acid output in general occurred during the first 30 minutes of the PB infusion.

The effect of PB infusion (7.5 mg/h) on pentagastrin-stimulated acid secretion also appears in Table I. In all of the healthy subjects a marked decrease in secretion rate and acid output was found. The acid output decreased by an average of 76 % of the value before the infusion. The acidity decreased in 3, was unchanged in 2, and increased in one of the subjects. The secretion rate decreased in the 8 studied ulcer patients but the acidity did not change appreciably in any of them. The average decrease in acid output was 62 % of the value before PB infusion.

The effect of PB infusion was also studied in 3 of the subjects with a dose of 3.75 mg/h, and in 2 with 15 mg/h. The smaller dose was as effective as 7.5 mg/h, and no further decrease in acid secretion was found with the higher dose. In 4 ulcer patients, who received doses of both 3.75 and 7.5 mg/h, the effect also was just as good with the smaller dose.

Side effects

The heart rate increased during PB infusion in all of the subjects and reached an average peak value of

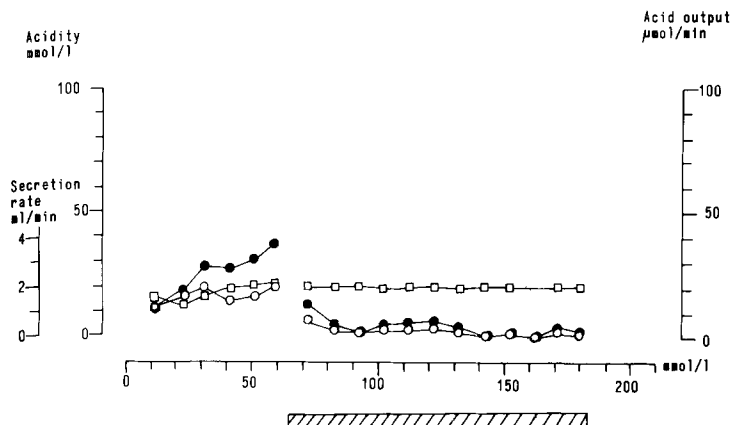


Fig. 1. Basal gastric secretion rate, acidity and acid output before and during infusion of propantheline bromide of 7.5 mg/h in a patient with duodenal ulcer. ○=secretion rate, □=acidity, ●=acid output. Hatched bar along abscissa indicates PB infusion.

115 beats per minute. The increase occurred during the first 30 minutes of the infusion, after which the heart rate was fairly constant. None of the subjects complained about the tachycardia.

The nearpoint distance remained unchanged or increased insignificantly during PB infusion of both 3.75 and 7.5 mg/h. One of the subjects who received 15 mg/h had some difficulty in reading for the first few hours after the investigation but the others did not notice any accommodation disturbance.

All of the subjects felt dry in the mouth even at 3.75 mg/h. The symptom appeared within 20 minutes from the beginning of the infusion and lasted up to 2–3 hours after the infusion had ended.

None of the subjects noticed any micturition disturbances or other side effects of the PB infusion.

Plasma (serum) concentration

The measurements of the plasma (serum) concentration of PB indicated that a constant level is reached within one hour and that this level remains relatively constant during 24–48 hours of continued infusion. In no case could PB be found in serum 12 hours after the infusion had ended.

DISCUSSION

Many investigations have been made on the effect of orally given anticholinergics on human acid secretion. The result varies with differing dosage and with varying absorption from the gastrointestinal tract. Most of the investigations have shown that the acid output decreases mainly by a decrease in secretion rate. The effect on acidity is a matter of contro-

versy. Some authors (4, 7) have reported that anticholinergic drugs decrease the acidity, while the possibility that anticholinergic drugs increase the acidity also has been discussed (7). We found that intravenous infusion of PB decreased the acidity in most of the healthy subjects, possibly due to a correlation between the secretion rate and acidity. Some of our ulcer patients differed from this rule and an acidity of 80–90 mmol/l was found in spite of secretion rates as low as 0.3–0.5 ml/min.

In subjects or patients who on different occasions were investigated with an infusion rate of 3.75 or 7.5 mg PB/h, no further decrease in acid secretion was found with the higher dose, nor did it produce more side effects. The side effects of 2 hours of PB infusion in healthy subjects were insignificant, neither were any side effects noticed in the patients with duodenal ulcer at this dose rate. However, when infusion of PB is given to older people, signs of urine retention or glaucoma must be looked for. Because of considerable interindividual differences in sensitivity to anticholinergic drugs it seems advisable to give the highest dose which does not cause troublesome side effects. It was therefore concluded that a dose rate of around 5–10 mg/h PB may be suitable for a clinical therapeutic trial in patients with bleeding from the upper gastro-intestinal tract.

REFERENCES

1. Checketts, R. G., Gillespie, I. E. & Kay, A. W.: Propanthelene as an agent for medical vagotomy. *Gut* 7: 200, 1966.
2. Hegarthy, M. M., Grime, R. T. & Schoefield, P. F.: The management of upper gastro-intestinal tract hemorrhage. *Brit J Surg* 60: 275, 1973.

3. Johnstone, D., Goligher, J. C. & Duthie, H. L.: Medical vagotomy: An assessment. *Brit Med J* *II*: 1481, 1966.
4. Kirsner, J. B., Ford, H. & Kassiel, R. S.: Anticholinergic drugs in peptic ulcer. *Med Clin N Amer* *41*: 495, 1957.
5. Lulu, D. J. & Dragstedt, L. R.: Massive bleeding due to acute hemorrhagic gastritis. *Arch Surg* *101*: 550, 1970.
6. Meerooff, J. C., Ferreira, J. A. & Meerooff, M.: Medical vagotomy: New evidence of its potential usefulness as a preoperative test. *Am J Dig Dis* *19*: 617, 1974.
7. Piper, D. W. Antacid and anticholinergic drug therapy of peptic ulcer. *Gastroenterology* *52*: 1009, 1967.
8. Searle, G. D. & Co.: Chicago: Personal communication 1972.
9. Watson, W. C.: Management of acute upper alimentary bleeding. *Canadian J Surg* *14*: 373, 1971.

Received October 14, 1974

Address for reprints:

Dr Bengt Furberg
Department of Clinical Physiology
Centrallasarettet
S-80007 Gävle
Sweden