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Propantheline Bromide in Massive Upper Gastrointestinal Haemorrhage

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ABSTRACT

The effectiveness of the anticholinenergic, propantheline bromide, administered parenterally in patients with upper gastro-intestinal bleeding has been investigated in a double-blind study. The basic material consisted of 99 patients. No differences were found between the group receiving propantheline bromide and the group receiving placebo in regard to clinical factors such as duration of intensive care, total hospital stay and surgical frequency. However, 21 patients under 50 years of age showed a significantly lower blood transfusion requirement with the use of propantheline bromide.

INTRODUCTION

The treatment of massive upper gastro-intestinal (G–I) bleeding is a current clinical problem. The borderline between medical and surgical treatment and the surgical method of choice has aroused great interest. An active attitude towards the surgical therapy at a relatively early stage seems to be a trend which can favourably affect the high mortality rate of these patients—especially the old ones (3, 7). In emergency operations, however, the mortality is considerably higher than in elective surgery. Older patients with haemorrhagic gastritis especially have a high mortality in emergency surgery (9).

In some places it has been the practice to give anticholinergics to patients with upper G–I bleeding in order to inhibit the production of acid and hence the irritation of the gastric mucous membrane. However, the clinical effect of anticholinergic treatment in acute upper G–I bleeding has not been documented.

The purpose of this investigation was to evaluate the possible effects of an anticholinergic, propantheline bromide (Ercotina®; ERCO Läkemedel AB, Stockholm, Sweden) in upper G–I bleeding by the prospective double-blind method. Propantheline bromide was selected because it can be given parenterally, and therapeutically results in a reliable inhibition of the acid production, with minor side effects (6).

MATERIAL

This investigation includes 99 patients with major upper G–I bleeding who underwent treatment during the period September 1972 through September 1973. These patients had at least one of the following symptoms of haemorrhage:

1. Severe haematemesis.
2. Shock or preshock together with indications of upper G–I bleeding.
3. Severe melena.

Patients with esophageal varices were omitted, but otherwise no further selection was made. All patients were treated primarily in the intensive care unit. Except for other treatment (see below) they received either propantheline bromide (PB) in doses of 180 mg per 24 hours intravenously, or placebo (P). 84 patients were divided into groups of PB (44 cases) and P (40 cases) in a double-blind manner. Besides these, 15 consecutive patients received PB and this group neither diagnostically nor agewise differed from the others and received the same treatment. They were included in the schedule, the staff not knowing whether or not the ampoules contained propantheline bromide or placebo. The PB group thus consisted of a total of 59 cases (average age 64), 45 males (average age 62) and 16 females (average age 68). The P group comprised 40 cases (average age 61), 30 males and 10 females with the same average age (Fig. 1). The diagnostic division into PB and P groups with the age distribution is shown in Table I. One patient in the P group with the diagnosis of gastric cancer has been omitted.

Complicating illnesses such as heart-lung disease, diabetes, malignancy, and severe invalidism were found in 25 patients (42%) of the PB group and in 21 patients (52%) of the P group. Shock or preshock was found in the case histories of 37 PB patients (63%) and in 17 P patients (43%). On admission the Hb-value was 8.7 g per 100 ml. (S.D.=2.4) in both groups.

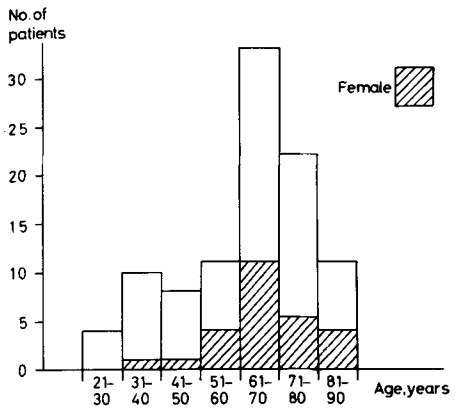

Fig. 1. Age and sex distribution.

METHODS

Immediately upon admission to the emergency room the patients were treated with dextran 70 (Macrodex®; Pharmacia AB, Uppsala, Sweden). Blood samples were taken for blood typing, Hb, haematocrit, electrolyte balance, coagulation time, and routine liver tests. The patients were then conveyed to the intensive care unit. As soon as blood was available, transfusions in the form of whole blood or erythrocyte concentrate were given in order to control the shock as soon as possible, and to gradually obtain a Hb-value of around 10 g per 100 ml or a haematocrit of about 30%. Haemoglobin, haematocrit, and thrombocyte determinations were done at least daily. A central venous catheter was inserted in 31 patients of the PB group and 17 of the P group. The central venous pressure was measured at least every 30 minutes during the acute phase of the haemorrhage. After catheterization, pulmonary X-ray was performed. The arterial blood gases were determined. A complete ECG was recorded and the patients were kept continuously on ECG monitoring. PB or P were given in an invertose–electrolyte solution. All patients received phytomenadione intravenously (Konakion®; F. Hoffmann LaRoche & Co. AG, Basel, Switzerland) 20 mg×2 and ascorbic acid (ACO Läkemedel AB, Solna, Sweden) 2 g per 24 hours. A nasal gastric tube was inserted. X-rays were taken of the esophagus and stomach during the first 24 hours of care in all patients, when their condition so permitted. Emergency gastroscopy was performed on a smaller number of patients when the X-ray diagnosis was uncertain or negative and there was no need for emergency surgery.

The following indications for surgery were established (8):

I. For patients>50 years of age or with complicating illness

1. Primary shock controlled but repeated preshock or shock.

2. Primary shock controlled but continued bleeding which required more than 1200 ml of blood during the following 24 hours.

3. No shock, but patient required 1600 ml of blood or more in 24 hours.

II. For patients<50 years of age and otherwise essentially well

1. The bleeding had not stopped within 36 hours and the patient had received more than 1600 ml of blood in 24 hours.

2. Patient had required 2000 ml of blood within 24 hours or less and the bleeding had not stopped.

III. Primary shock could not be controlled.

The following indications for surgery were followed (8):

A. For patients over 60 years of age or with a complicating illness

1. Duodenal ulcer: suturing of ulcer+vagotomy+drainage.

2. Gastric ulcer: preferably Billroth I. If poor general condition suturing of the ulcer+vagotomy+drainage.

B. For patients below 60 years of age and otherwise essentially well

1. Duodenal ulcer: suturing+vagotomy+drainage or Billroth II.

2. Gastric ulcer: Billroth I.

A+B. Erosive gastritis: Billroth I or II+vagotomy.

Table I. *Diagnosis in relation to age for PB and P groups and for total material*

Figures indicate numbers of patients. D.u.=duodenal ulcer, E.g.=erosive gastritis, G.u.=gastric ulcer

	P			PB			Both groups					
Age (years)	D.u.	G.u.	E.g.	D.u.	G.u.	E.g.	D.u.	G.u.	E.g.	P	PB	Total
21–30	1	0	1	1	1	0	2	1	1	2	2	4
31–40	6	0	1	1	1	1	7	1	2	7	3	10
41–50	0	1	0	4	1	1	4	2	1	1	6	7
51–60	2	3	1	1	1	4	3	4	5	6	6	12
61–70	5	3	1	11	7	6	16	10	7	9	24	33
71–80	2	3	4	7	4	1	9	7	5	9	12	21
81–90	2	1	2	2	4	0	4	5	2	5	6	11
Average age	56.4	63.5	64.2	63.3	67.2	59.8	60.5	65.8	61.7	60.4	63.8	62.4
Total	18	11	10	27	19	13	45	30	23	39	59	98
	46%	28%	26%	46%	32%	22%	46%	31%	23%			
		100%			100%			100%				

RESULTS

Of the 59 patients in the PB group, 10 (17%) died, and of the 40 in the P group, 4 (10%) died. All patients who did not survive were 65 years of age or older. In the PB group there were 35 within this age range while there were 21 in the P group. Thus the mortality in the former group was 29% and in the latter 19%. Among the dead, 7 of the PB group had severe complicating illness and 4 of the P group. All 10 deceased in the PB group had a history of shock, while this was the case in only 2 of the 4 deaths in the P group. Severe surgical complications occurred in 5 of the dead in the PB group but not in any of those in the P group (Table II).

Emergency surgery was performed on 25 patients 0–9 days after admission to the hospital and all except 3 were operated upon within the first 48 hours. No patient died on the day of surgery. 1–7 days after surgery, 7 patients died and 1 after 18 days. In the PB group 5 deaths occurred out of 16 operated upon (37%) compared with 2 out of 9 in the P group (22%). Among the patients undergoing elective surgery there were no deaths. The average age for emergency surgery was 66 in the PB group and 63 in the P group. Those undergoing elective surgery were somewhat younger, on average 60 years in the PB group and 57 in the P group. Emergency surgery was performed with vagotomy+pyloroplasty in 10 cases in the former group and in 6 cases in the latter, while gastric resection *ad modum* Billroth II was done in 6 PB patients and in 3 P patients. Later elective surgery was performed on 7 patients in the PB group and 8 patients in the P group (Table III).

The stay in the intensive care unit for the non-surgical cases was the same for both groups—25.6 hours on average for the PB group and 25.9 hours for the P group.

The amount of blood transfused during the first 24 hours was recorded. The total amount was also calculated for the non-surgical cases and for the preoperative period of the surgical cases. The average number of transfusions within the PB and P

Table II. *Mortality in relation to age, severe concurrent disease, surgical procedure, cause of death and to diagnosis*

D.u.=duodenal ulcer, E.g.=erosive gastritis, G.u.=gastric ulcer, GE=gastro-enterostomy, EA=entero-anastomosis, B I=Billroth I, B II=Billroth II

Pat.	Age	Severe concurrent disease	Operation	Cause of death	Diagnosis	P/PB
I	68	+	Vagotomy+GE	Septicemia	D.u.	P
II	81	+	None	Septicemia	E.g.	P
III	73	+	Vagotomy	Septicemia+pulmonary oedema	E.g.	P
IV	68	+	None	Heart infarct.+cardiac shock	G.u.	P
V	68	+	None	Ventricular fibrillation	D.u.	PB
VI	65	+	None	Heart infarction	G.u.	PB
VII	84	+	Vagotomy+GE	Respiratory insufficiency	E.g.+G.u.	PB
VIII	69	+	1. Vagotomy+GE+EA 2. BI	Wound rupture+peritonitis	D.u.	PB
IX	77	–	BII+splenectomy	Colic infarction+gastric bleeding+heart failure	D.u.	PB
X	74	–	1. BII 2. Enteric resection	Enteric gangrene	G.u.	PB
XI	75	+	1. Vagotomy 2. Sec. suture	Wound rupture+gastric bleeding	D.u.+E.g.	PB
XII	68	–	Vagotomy	Mediastinitis+peritonitis	E.g.	PB
XIII	78	+	None	Gastric bleeding+aspiration	G.u.	PB
XIV	90	+	None	Gastric bleeding	G.u.	PB
	65–90	11/14	8/14 operated			4 P 10 PB

Table III. *Number of elective and acute operations in PB and P groups*

	Propantheline bromide			Placebo		
	All	Emergency op.	Elective op.	All	Emergency op.	Elective op.
Duodenal ulcer	27	9	3	18	5	6
Gastric ulcer	19	4	4	11	2	2
Erosive gastritis	13	3	0	10	1	0
Gastric cancer	0	0	0	1	1	0
Total	59	16	7	40	9	8

groups in relation to diagnosis are shown in Table IV and for surgical or non-surgical therapy in Table V. Hb on admission was on an average 8.7 g per 100 ml in both groups. The lowest recorded Hb-values were, on average, 7.6 g per 100 ml in the PB group and 7.3 g per 100 ml in the P group. The highest recorded Hb was the same in both groups, namely 12.2 g per 100 ml. A tendency towards a smaller transfusion requirement was noticed in the PB group compared with the P group. However, statistical significance was not reached. Therefore, the severity of haemorrhage was evaluated, considering both the transfusion requirement and the Hb-values recorded during the same time. Different age groups were analysed in this manner. In order to make adequate comparisons between the PB and P groups the amount of blood that was needed to maintain the same Hb-value during the first 24 hours was calculated. This calculation could be done as both groups were treated identically with regard to blood volume replacement. The patient's blood volume that was needed for the calculation was obtained from Nadler et al. (10). In Table VI 21 patients, 50 years and younger, are presented according to age, Hb-value on admission, lowest Hb-value recorded and Hb-value after the first 24 hours of treatment. The amount of blood given during the first 24 hours is presented and also the calculated blood requirement for maintaining a constant Hb-value during the same time. The PB and P groups were comparable with regard to age, Hb-value on admission and blood given ($P>0.05$). Neither the frequency of patients with a history of shock nor their total hospital stay differed. However, the blood requirement for maintaining the same Hb-value during the first 24 hours was significantly lower among patients in the PB group compared with those in the P group ($P<0.001$).

In Table VII the same variables as in the preceding table are shown for the 12 patients 50–60 years of age. No differences were observed in any of the variables between the PB and P groups.

DISCUSSION

Massive upper G–I haemorrhage was especially observed among elderly persons and, among these, males seemed the most predisposed. The average age of the patients in this material was 63 years, without any great difference between the PB and P groups. In comparison with the extensive material of Boulos et al. (2), Crook et al. (3), and Himal et al. (7), the average age in this investigation was about 10 years higher. However, this result is in agreement with a Swedish study on 200 patients with a similar age distribution (4). The average age was higher among the patients with gastric ulcer than those with duodenal ulcer and this agrees with the above-mentioned Swedish study.

Table IV. *Mean values of the amount of transfused blood (ml) in relation to diagnosis for PB and P groups*

Numbers of patients in parentheses

	PB-group (59)	P-group (40)
All (99)		
First 24 h	1 596 (59)	1 844 (40)
Total blood	2 577 (59)	2 921 (40)
Erosive gastritis (23)		
First 24 h	1 346 (13)	1 780 (10)
Total blood	2 227 (13)	2 640 (10)
Ventricular ulcer (30)		
First 24 h	1 700 (19)	1 958 (11)
Total blood	3 124 (19)	3 125 (11)
Duodenal ulcer (45)		
First 24 h	1 575 (27)	1 712 (18)
Total blood	2 340 (27)	2 747 (18)

Table V. *Mean values of the amount of transfused blood (ml) in surgically and non-surgically treated patients for PB and P groups*

Number of patients in parentheses

	PB-group (59)	P-group (40)
All (99)		
Preop.	2 509 (16)	3 444 (9)
First 24 h	1 596 (59)	1 844 (40)
Total blood	2 577 (59)	2 921 (40)
Not operated (74)		
First 24 h	1 217 (43)	1 228 (31)
Total blood	1 660 (43)	1 579 (31)
Operated (25)		
Preop.	2 441 (16)	3 445 (9)
First 24 h	2 711 (16)	3 848 (9)
Total blood	5 219 (16)	7 244 (9)

Patients with duodenal ulcer represent 46% in both the PB and P groups. The number of duodenal ulcer patients was smaller in this investigation than in the studies of Boulos et al. (2), Crook et al. (3), and Himal et al. (7). In those materials the percentage of patients with duodenal ulcer was 70%, 55%, and 52% respectively. The reason for the smaller number of patients with duodenal ulcer in this series is probably the greater proportion of older patients.

Of the 14 patients who died in connection with the actual haemorrhage, 10 were PB cases and 4 were P cases. The causes of death in these patients are shown in Table III. The primary cause of death was: septicaemia in 3 cases, cardiopulmonary complications in 5 cases, surgical complications in 5 cases, and the haemorrhage was judged as being the direct cause in 2 cases. In these latter 2 patients, surgery was indicated but they were judged inoperable. Furthermore, it is considered in this study that the PB therapy could be excluded as having no relation to the cause of death in any of the 10 deaths occurring in the PB group.

The essential variables used for evaluation of the effect of PB were the severity of the haemorrhage as indicated by the transfusion requirement and the Hb values. The average value for the amount of blood transfused tends to be lower in the PB group than in the P group, and this tendency is especially noticeable among the patients with gastric and duodenal ulcer (Table IV). However, this trend for the amount of blood transfused was not statistically significant (Student's *t*-test).

Surgical vagotomy is a recognized operative procedure in a bleeding ulcer (5). Analogously, an effect by pharmacological vagotomy might also be expected. This should thus be observed in patients with a high acid production, i.e. in the younger patients (1). Furthermore, bleeding in older patients often occurs because of hardened, arteriosclerotic vessels, and in these cases one probably should not expect any great effect from anticholinergic therapy. As 66% of the patients were over 60 years of age in this investigation, it was decided to examine more particularly the records of those patients under 50 and 60 years of age in regard to the severity of the haemorrhage during the treatment. This was determined as the transfusion requirement during the first 24 hours to maintain a constant Hb (Tables VI and VII). The transfusion requirement in patients under 50 years of age was significantly lower in the PB group than in the P group ($P<0.001$) (Table VI). However, no significant difference was

Table VI. *Age, Hb-values (g/100 ml), amount of transfused blood (ml), blood requirement for constant Hb (see text), number of patients with a history of shock and total hospital stay in patients 50 years and younger for PB and P groups*

	Age		Hb-value on admission		Lowest Hb-value recorded		Hb-value after 24 h		Blood given during 24 h		Blood requirement for constant Hb		Number of pats. with history of shock		Total hospital stay, days	
	P	PB	P	PB	P	PB	P	PB	P	PB	P	PB	P	PB	P	PB
$\bar{x}$	35.9	40.4	9.4	8.1	7.3	7.6	9.0	9.9	1 290	764	1 461	130	6	7	8.4	10.7
S.D.	4.3	8.3	2.2	2.8	1.9	2.5	1.9	1.2	849	726	721	399			4.9	5.0
n	10	11	10	11	10	11	10	11	10	11	10	11	10	11	10	11
	$P>0.05$		$P>0.05$		$P>0.05$		$P>0.05$		$P>0.05$		$P<0.001$		$P>0.05$		$P>0.05$	

Table VII. *The same parameters as in Table VI for patients 51–60 years of age for PB and P groups*

	Age		Hb-value on admission		Lowest Hb-value recorded		Hb-value after 24 h		Blood given during 24 h		Blood requirement for constant Hb		Number of pats. with history of shock		Total hospital stay, days	
	P	PB	P	PB	P	PB	P	PB	P	PB	P	PB	P	PB	P	PB
$\bar{x}$	54.0	55.8	8.9	9.6	7.9	7.5	9.6	9.8	1 322	1 278	1 077	1 260	3	4	9.0	14.5
S.D.	3.1	2.6	1.9	2.1	1.3	2.1	0.6	0.4	1 561	1 183	1 705	1 350	–	–	6.5	11.6
n	6	6	6	6	6	6	6	6	6	5	6	5	6	6	6	6
	$P>0.05$		$P>0.05$		$P>0.05$		$P>0.05$		$P>0.05$		$P>0.05$		$P>0.05$		$P>0.05$	

observed between the 12 patients in the age group 51 to 60 (Table VII).

Although this material is small, it seems that PB gives a transfusion-saving effect in the younger patients with upper G–I bleeding. The study indicates that the upper age limit for a therapeutic effect is about 50 years. The asymmetry which was earlier suggested as unfavourable in regard to frequency of shock, complicating illness, and mortality in both groups has lost its significance in the younger patients. There now appears an equal numerical division between the PB and P groups. The smaller transfusion requirement for the patients less than 50 years of age has not resulted in any differences in the necessary duration of intensive care, the frequency of emergency or elective surgery or in the total hospital stay.

The known side effects of anticholinergics are urine retention, tachycardia, accommodation difficulties. Among patients over 60 years practically all received a urinary indwelling catheter primarily as a routine in the intensive care unit. Among the patients below 50 years of age, 3 out of 11 in the PB group and 2 out of 10 in the P group needed a urinary indwelling catheter and any differences in the urinary indwelling catheter frequency between the two groups thus did not exist. Many of the patients noticed accommodation difficulties and dryness of the mouth but these symptoms have not been specifically noted. Discomfort due to the gastric drainage caused considerably more complaints than the mentioned anticholinergic reactions. All patients had tachycardia during a shorter or longer time. No definite differences in pulse rate were observed between the PB and P cases. Hence it is thought that the side effects of propantheline bromide can therefore be more or less neglected in these severely ill patients.

In the patients over 50 there was no evidence that PB has any significant effect. The blood-saving effect which PB seemed to give in the patients below 50 years of age would probably in a larger study show itself in a decreased need for surgery. In those who did not require surgery the lower transfusion need is in itself a positive sign. Therefore, it is thought that propantheline bromide therapy may be indicated in patients below 50 years of age with severe upper G–I haemorrhage.

REFERENCES

1. Blackman, A. H., Lambert, D. L., Thayer, W. R. & Martin, H. F.: Computed normal values for peak acid output based on age, sex and body weight. Am J Dig Dis *15:* 783, 1970.
2. Boulos, P. B., Harris, J., Wyllie, J. H. & Clark, C. G.: Conservative surgery in 100 patients with bleeding peptic ulcer. Br J Surg *58:* 817, 1971.
3. Crook, J. N., Gray, L. W. Jr, Nance, F. C. & Cohn, I. J. Jr: Upper gastrointestinal bleeding. Ann Surg *175:* 771, 1972.
4. von Feilitzen, H. R. & Wedlund, J. E.: Blödningar från magtarmkanalen – ett patientmaterial från Södersjukhuset 1968. Opusc Med *18:* 87, 1973.
5. Foster, J. H., Hickok, D. F. & Dunphy, J. E.: Changing concepts in the surgical treatment of massive gastroduodenal hemorrhage. Ann Surg *161:* 968, 1965.
6. Furberg, B., Krause, U. & Rimsten, Å.: Effect of intravenous propantheline bromide on gastric secretion. In press. 1975.
7. Himal, H. S., Watson, W. W., Jones, C. W., Miller, L. & MacLean, L. D.: The management of upper gastrointestinal hemorrhage: A multiparametric computer analysis. Ann Surg *179:* 489, 1974.
8. Krause, U.: Kirurgiskt handläggande av massiv övre gastro-intestinal blödning. Läkartidningen *69:* 4960, 1972.
9. Lulu, D. J. & Dragstedt, L. R. II: Massive bleeding due to acute hemorrhagic gastritis. Arch Surg *101:* 550, 1970.

10. Nadler, S. B., Hidalgo, J. U. & Bloch, T.: Prediction of blood volume in normal and human adults. Surgery *51*: 224, 1962.

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