Failure to confirm evidence for existence of two populations with duodenal ulcer

A previous study on 339 patients attending a gastrointestinal unit suggested that patients with duodenal ulcer could be divided into two types.^{1 2} The distinction was based on maximal acid secretion and apparent differences in the prevalence of several clinical features, particularly family history, bleeding and perforation, and ABO blood grouping. In a further series of two groups of 100 patients referred consecutively to the same unit, however, no such distinction could be made. The results of this further study are presented here.

Methods and results

The two groups of patients, who were investigated between October 1974 and October 1975, were proved radiologically and endoscopically to have duodenal ulcer. In every case the maximal acid output (MAO) was measured in response to 6 µg pentagastrin/kg total body weight (TBW). MAO was expressed as the amount of HCl excreted/kg TBW, thereby reducing the difference between the sexes.³ Mean MAO levels were used and tests of significance based on a comparison of these. Such tests have a better chance of detecting significance than tests based on contingency tables. The results in each of the two groups are given separately.

The mean MAO levels (±SD) in the two groups were 0.48±0.19 and 0.49±0.20 mmol HCl/kg TBW respectively (see table). In the previous study¹ the MAO was lower in patients of blood O, and this was found again in group 1, though the difference was not significant. In group 2 the MAO was higher in patients of blood group O, though again the difference was not significant.

Only sex affected the MAO. In group 1 the mean MAO levels in male and female patients were 0.50±0.19 and 0.41±0.20 mmol HCl/kg TBW respectively. This difference was significant at the 5% level (*t* test). The corresponding levels in group 2, however, were 0.49±0.19 and 0.46±0.22 mmol HCl/kg TBW, which were not significantly different. Furthermore, when the results in the two groups were pooled no significant difference at the 5% level was found between the sexes.

None of the other clinical features examined (see table) could be correlated with MAO. In group 2 the levels were higher in patients with a history of bleeding or perforation, but not significantly so. Moreover, in the previous study¹ the levels were lower in such patients. The distribution of clinical features was similar in the two groups except for a history of dyspepsia of more than 20 years.

Clinical features and sex distribution of patients in the two groups and mean MAO levels (±SD)

	No of patients		MAO (mmol HCl/kg TBW)	
	Group 1	Group 2	Group 1	Group 2
All patients	100	100	0.48 ± 0.19	0.49 ± 0.20
Male patients	77	76	0.50 ± 0.19	0.49 ± 0.19
Female patients	23	24	0.41 ± 0.20	0.46 ± 0.22
Blood group O	54	62	0.46 ± 0.18	0.50 ± 0.20
Blood groups A, B, AB ..	46	38	0.50 ± 0.21	0.46 ± 0.19
Duration of disease:				
≤3 years	22	19	0.44 ± 0.21	0.46 ± 0.18
-10 "	28	27	0.49 ± 0.13	0.48 ± 0.22
-20 "	38	26	0.51 ± 0.23	0.49 ± 0.14
>20 "	12	28	0.46 ± 0.18	0.50 ± 0.23
Positive family history ..	44	44	0.48 ± 0.20	0.48 ± 0.20
History of bleeding	25	23	0.48 ± 0.18	0.53 ± 0.22
History of perforation ..	7	8	0.48 ± 0.10	0.56 ± 0.16
Gastro-oesophageal reflux ..	35	41	0.49 ± 0.18	0.47 ± 0.20

Comment

These results fail to support the existence of two types of patient with duodenal ulcer, for the MAO appears to be unaffected by any variable. Although expressing the absolute MAO in terms of body weight reduces the difference between the sexes, it does not abolish it.³ Likewise, the possibility of certain clinical features being associated with MAO was not confirmed. Though such discrepant observations in the same unit may seem surprising, experience shows that the usually acceptable level of significance of 1 in 20 (*P* < 0.05) is often found in this field when a true association is shown later not to exist. *P* values of <0.01 are also often found and shown later to have been due to chance, almost always because of poor control data.

In practice a probability of less than 1 in 1000 (*P* < 0.001) should be obtained before a difference in ABO blood group frequency from

controls is regarded as significant.⁴ Patients are now referred earlier in the course of the disease and thus the memory of the date of onset is more accurate. Furthermore, during the period covered by this and the previous study (1960-75) there were appreciable social changes in Britain, with an increase in the standards of living and nutrition of the social classes to which most of our patients belonged. Hence, duodenal ulcer altered from being a disease of the well-to-do to that of the "poorer" classes.⁵ Such changes may reflect movement up the social (housing and nutrition) scale of people in occupations that have traditionally been recorded as in classes III-V in the Registrar General's returns.

¹ Lam, S K, and Sircus, W, *Quarterly Journal of Medicine*, 1975, **44**, 369.
² *British Medical Journal*, 1975, **3**, 557.
³ Sircus, W, *The Physiology of Gastric Secretion*, ed L S Semb and J Myren, p 581. Baltimore, Williams and Wilkens, 1968.
⁴ McConnell, R B, personal communication.
⁵ Litton, A, and Murdoch, W E, *Gut*, 1963, **4**, 360.

Department of Statistics and Medical Computing, University of Edinburgh Medical School, Edinburgh

R J PRESCOTT, BSC, PHD, lecturer

Gastrointestinal Unit of the University of Edinburgh, Western General Hospital, Edinburgh EH4 2XU

W SIRCUS, PHD, FRCP, consultant physician and reader in medicine
C L LAI, MB, MRCP, clinical research fellow (seconded on Commonwealth scholarship from the University of Hong Kong)

Department of Medicine, University of Hong Kong, Queen Mary Hospital, Hong Kong

S K LAM, MD, MRCP, lecturer

Consumption coagulopathy after intra-amniotic urea

Haemorrhage is a well-documented complication of intra-amniotic hypertonic saline and glucose but frank bleeding has not previously been reported after intra-amniotic urea. Several reports have suggested that urea is safer to use than saline and glucose,¹⁻³ though McKenzie⁴ showed subclinical changes in many patients treated with urea. No such changes have been observed with oxytocin alone. We report a case of proved consumption coagulopathy resulting from the use of intrauterine hypertonic urea and intravenous oxytocin to induce a mid-trimester abortion.

Case report

A 24-year-old French primipara was admitted to a private nursing home at 16 weeks' gestation for termination. Amniocentesis was reported as uneventful, a free flow of liquor being obtained. A dose of 80 g urea in 200 ml normal saline was injected slowly. At the same time 50 U oxytocin in 1000 ml 5% dextrose was given intravenously over 12 hours. Although contractions were noted, abortion had not occurred 28 hours later. The cervix was dilated, however, and curettage was performed without further dilatation under general anaesthesia. The fetus and placenta were removed uneventfully. On her return to the ward persistent vaginal bleeding was noted, and a second and later a third examination under anaesthesia was performed and the uterus packed. No residual products of conception or cervical or uterine injury were found. By the third examination the blood was noted to be failing to clot. Fibrinogen titre was 1/4 (control 1/32). She was transfused with 3 U triple-strength plasma, 1 U (about 2.5 g) fibrinogen concentrate, and 2 units whole blood and transferred to hospital.

On admission she was found to be shocked. No fresh bleeding was noted. The uterus was well contracted but enlarged to 18 weeks' gestation. There was a purpuric area around the site of the amniocentesis. Central venous pressure was monitored and 2 U whole blood and 2 U fibrinogen were given. Results of haematological investigations were: haemoglobin 11.7 g/dl; white cell count 14 × 10⁹/l (14 000/mm³); platelets 96 × 10⁹/l (96 000/mm³); prothrombin time 25 s (control 15 s); partial thromboplastin time 57 s (control 29 s); thrombin time 16 s (control 11 s); fibrinogen titre 1/4 (control 1/256); and fibrin degradation products (FDPs) greater than 40 mg/ml. Fragmented red cells were seen in the blood film and, together with the

abnormal coagulation results, confirmed the diagnosis of disseminated intravascular coagulation. The transfusion of freeze-dried plasma (which has little if any coagulant activity), fibrinogen concentrate, and whole blood that she was given before admission would have had no appreciable effect on the coagulation results obtained and would not have caused the appearance of FDPs or fragmented red cells.

Twelve hours later the prothrombin time was 16 s (control 14 s); partial thromboplastin time 45 s (control 35 s); and thrombin time 15 s (control 12 s). FDPs in the serum still exceeded 40 mg/ml and the film showed occasional fragmented red cells.

Comment

It seems likely that all intra-amniotic hypertonic solutions have a similar effect on the placenta and trophoblast, and these changes are probably responsible for the alteration in clotting. The use of hypertonic solutions such as urea has two advantages. Firstly, the mean induction-abortion time is shorter than with oxytocin or prostaglandin used alone, and, secondly, urea in particular almost invariably kills the fetus, which avoids emotional confusion on the part of the patient and nurses at the abortion.

¹ Burnett, L S, *et al*, *American Journal of Obstetrics and Gynecology*, 1975, **121**, 7.

² Weinberg, P C, *et al*, *Obstetrics and Gynecology*, 1973, **41**, 451.

³ King, T M, *et al*, *American Journal of Obstetrics and Gynecology*, 1974, **120**, 704.

⁴ McKenzie, I Z, *et al*, *Lancet*, 1975, **2**, 1066.

Obstetric and Haematology Departments, Middlesex Hospital, London W1N 8AA

M F B GRUNDY, MRCOG, FRCSED, senior obstetric registrar

E R CRAVEN, MB, MRCPATH, consultant (present address: Kettering General Hospital, Kettering, Northants)

Effect of cimetidine on lower oesophageal sphincter

Erosive oesophagitis is a major complication of fulminant hepatic failure (FHF). In a previous study¹ the incidence of bleeding was decreased by the prophylactic administration of the H_2 -receptor antagonists metiamide and cimetidine intravenously. This was attributed to a reduced acidity of gastric contents, which may reflux in recumbency and in the presence of a nasogastric tube. Another possibility, however, is that the treatment increased the lower oesophageal sphincter pressure (LOSP), as occurs in opossums given metiamide.² We have examined whether such an effect does, in fact, occur in man.

Methods and results

Oesophageal manometry was performed on six normal volunteers (four men and two women) with an average age of 28 years after an overnight fast. A single-lumen (internal diameter 1.5 mm, outer diameter 6 mm), continuously perfused (4.4 ml/min) catheter was used with three recording orifices at the same level 120° apart. Pressures were measured with an Aksjeselskapet AE 840 transducer and a Simonsen and Weel BAP 001 pressure amplifier recording through a Servoscribe 1S RE 541 flatbed recorder. LOSP was measured at 15-minute intervals for 90 minutes by a standard rapid-pull-through technique.³ With the volunteer's breath held in mid-inspiration the recording catheter was withdrawn at 0.5-1.0 cm/s from the gastric fundus to the lower body of the oesophagus. The mean of three measurements at each interval was calculated, the intragastric pressure being

used as a baseline of zero. During the first 60 minutes of the 90-minute study cimetidine 150 mg was given as a continuous intravenous infusion. The same measurements taken on another day without the administration of cimetidine served as control values.

When the results for each volunteer were considered individually no significant difference was found at each 15-minute period between the control LOSP and the value obtained during infusion (paired *t* test). When the average values for all six volunteers at each 15-minute period were compared with the starting values (time 0; see figure), however, some differences were apparent. In the first 15 minutes the control value fell significantly below the starting value ($P=0.0125$), whereas the LOSP recorded during infusion fell only slightly in five volunteers and in one it greatly increased, giving an overall slight fall. During the infusion all volunteers showed an increase in LOSP at 30 minutes, and at 60 minutes a value significantly below the starting value ($P=0.0125$).

Mean ($\pm$ SE of mean) LOSP measured over 90 minutes in six volunteers. Dashed line indicates values recorded during (first 60 minutes) and after infusion of cimetidine 150 mg. Solid line indicates values recorded in same volunteers on another day without cimetidine infusion.

Comment

In the opossum study² metiamide increased the LOSP when infused at 2 mg/kg/hour, but at higher infusion rates a decrease in pressure occurred. Only one of our six volunteers showed an increase in LOSP with low blood cimetidine levels and a fall as the blood cimetidine concentration increased. Perhaps there was some positive influence on the LOSP occurring at 15 minutes in the remaining five volunteers, as the early and unexplained drop in pressures measured during the control studies appeared to have been attenuated.

Thus cimetidine may have a bimodal effect on LOSP in man, with stimulation of the sphincter at low blood levels and slight inhibition at high blood levels, accounting for an early pressure rise and a decrease 30 minutes later. The failure of cimetidine to cause a sustained increase in LOSP, however, suggests that it prevents bleeding erosive oesophagitis in FHF by decreasing gastric acidity.

We thank Smith Kline and French Ltd for supplies of cimetidine. R J Bailey was supported by the Canadian Hepatic Foundation.

¹ Bailey, R J, *et al*, *Gut*, 1975, **5**, 389.

² Cohen, S, and Snape, W J, *jun*, *Gastroenterology*, 1975, **69**, 911.

³ Dodds, W J, *et al*, *Gastroenterology*, 1975, **68**, 437.

Liver Unit, King's College Hospital, London SE5 9RS

R J BAILEY, MD, FRCP(C), research fellow

S N SULLIVAN, MD, research fellow

B R D MACDOUGALL, MD, MRCP, research fellow

ROGER WILLIAMS, MD, FRCP, director of unit and consultant physician