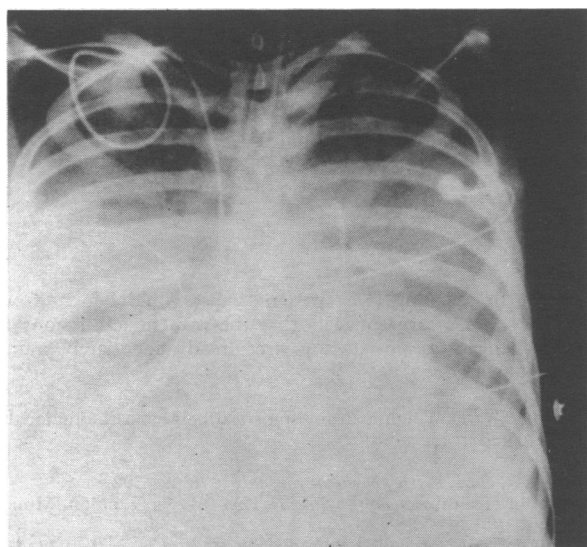


(60 000/mm³); prothrombin index 50%; raised concentration of fibrinogen degradation products (100–400 mg/l); blood urea concentration 30.2 mmol/l (182 mg/100 ml); normal serum electrolyte values; total serum bilirubin concentration 64 µmol/l (3.7 mg/100 ml), direct bilirubin concentration 22 µmol/l (1.3 mg/100 ml); serum albumin concentration 25 g/l; and serum osmolality 290 mmol(mosmol)/kg. While breathing air his arterial pH was 7.17, bicarbonate concentration 5.5 mmol(mEq)/l, PCO₂ 2 kPa (15 mm Hg), and PO₂ 11.6 kPa (87 mm Hg) (normal value for PO₂ in Johannesburg 10 kPa (75 mm Hg)). An electrocardiogram was normal. Chest radiography showed a left upper-lobe infiltrate thought to be due to infection. A peripheral blood smear was heavily infected with *P. falciparum*.

Treatment was instituted with intravenous chloroquine 2.1 g over 72 hours and intravenous dexamethasone 4 mg six-hourly. Sodium bicarbonate was given for the metabolic acidosis, and the anaemia was corrected with packed cells. Intravenous ampicillin was used for the possible chest infection. Recovery of consciousness and elimination of the parasitaemia occurred by 48 hours. Prothrombin index and platelet count returned to normal, and blood urea concentration fell. Average daily fluid intake was 3.5 l and output 3.1 l.

Seventy-two hours after admission the patient suddenly developed tachypnoea and cyanosis with diffuse pulmonary crepitations. There was no evidence of heart failure. Chest radiography showed extensive bilateral confluent opacification (figure). Arterial PO₂ while breathing 80% oxygen



Radiograph showing extensive bilateral confluent opacification.

was 6 kPa (45 mm Hg). A Swan-Ganz catheter was introduced and pressures measured: right atrium 2 mm Hg, pulmonary wedge 5 mm Hg; cardiac output was 7 l/min (cardiac index 4 l/min/m²). The trachea was intubated and continuous positive airway pressure of 15 ml water applied with intermittent mandatory ventilation. Penicillin, cloxacillin, and gentamicin were given intravenously. Arterial PO₂ improved rapidly to 10.7 kPa (80 mm Hg) while breathing 50% oxygen. Pulmonary wedge pressure never exceeded 10 mm Hg. The pulmonary opacification had almost completely resolved after 24 hours. The patient was discharged 10 days later with a normal chest x-ray appearance.

Comment

We have shown that pulmonary oedema may occur in falciparum malaria in the absence of a raised pulmonary wedge pressure. Disseminated intravascular coagulation, uraemia, and intracranial disease may precipitate the oedema by causing microvascular damage.⁴ Small increases in pulmonary capillary hydrostatic pressure lead to pronounced extravasation of fluid into the lungs when microvascular permeability is abnormal.⁵ Hence hypoalbuminaemia and excessive fluid therapy might have been contributory despite the normal pulmonary wedge pressure.

Pulmonary oedema in falciparum malaria has a high mortality rate.^{1,2} Accurate haemodynamic monitoring via a Swan-Ganz catheter may be of value when complications such as renal failure, cerebral abnormality, and disseminated intravascular coagulation occur. Fluids should be administered cautiously in the presence of these complications. Diuretic treatment aimed at lowering pulmonary wedge pressure may be ineffective in the absence of fluid overload. The main object of treatment is to oxygenate the blood adequately with safe concentrations of inspired oxygen until the abnormality of

the pulmonary microcirculation has resolved and reabsorption of the oedema fluid has occurred. This may be achieved by efficient ventilation with the judicious use of continuous positive airway pressure.

We thank D P Myburgh, of No 1 Military Hospital, Voortrekkerhoogte, for permission to report this case; and Anita Wise for help in preparing the manuscript.

Requests for reprints should be addressed to: Professor S Zwi, Department of Medicine, Medical School, Hospital Street, Johannesburg, 2001 South Africa.

¹ Brooks, M H, *et al*, *New England Journal of Medicine*, 1968, **279**, 732.

² Punyagupta, S, *et al*, *American Journal of Tropical Medicine and Hygiene*, 1974, **23**, 551.

³ Fein, I A, Rackow, E C, and Shapiro, L, *American Review of Respiratory Disease*, 1978, **118**, 425.

⁴ Robin, E D, Cross, C E, and Zelis, R, *New England Journal of Medicine*, 1973, **288**, 292.

⁵ Staub, N C, *American Review of Respiratory Disease*, 1974, **109**, 358.

(Accepted 16 May 1979)

Department of Medicine, University of the Witwatersrand, and General Hospital, Johannesburg, South Africa

R W MARTELL, BSC, MB, registrar

J KALLENBACH, MB, MRCP, senior physician

S ZWI, BSC, FRCP, professor of respiratory medicine and principal physician

Fetal death in utero managed with vaginal prostaglandin E₂ gel

Fetal death in utero warrants early induction of abortion or delivery to reduce emotional distress and the risk of intrauterine sepsis or consumption coagulopathy. An expeditious method causing a minimum of trauma is provided by intravenous¹ or extra-amniotic² prostaglandin. In an effort to reduce the side effects of intravenous infusion and simplify extra-amniotic instillation we have evaluated the efficacy of prostaglandin E₂ (PGE₂) in viscous gel instilled vaginally.

Patients, methods, and results

Fifty women aged 18–36 years with confirmed fetal death in utero were treated; 28 were primigravidae and 22 multigravidae (see table). PGE₂ (Prostin E₂) was administered in 10 ml volumes of a 6% aqueous solution of hydroxyethylmethylcellulose (Tylose MH 300). Gel preparation and administration were as described.³ Dosage varied with uterine size (estimated as gestational-age equivalent), 15 mg being used when under 29 weeks and 5 mg when 29 weeks or more. PGE₂ gel was usually instilled between 1500 and 2100. Diamorphine 10 mg or papaveretum 15 mg was given intramuscularly when analgesia was required, vaginal examination having been performed first. Next morning if expulsion had not occurred an intravenous infusion of oxytocin was begun: those with uterine size below 29 weeks received a constant 100 mU/min, while the others began with 4 mU/min increasing as required to 32 mU/min. Patients whose uterine size was 29 weeks or more underwent amniotomy when necessary once the cervix was dilated at least 5 cm. Surgical evacuation was performed only when expulsion of the placenta was incomplete.

Details of patients treated with PGE₂ gel

		Dosage of PGE ₂	
		5 mg (n = 23)	15 mg (n = 27)
Gestational age (weeks)	Range	29–42	15–33
	Mean	36.2	24.7
Uterine size (gestation equivalent)	Range	29–40	11–28
	Mean	34.8	19.7
Calculated time since fetal death (days)	Range	1–28	1–42
	Mean	7.3	13.0
Treatment-delivery/abortion interval (h)	Range	4–0–33.5	3–4–40–0
	Mean	14.7	15.5
Duration of labour (h)	Range	1–4–23.8	—
	Mean	6.2	—
No (%) of mothers needing intravenous oxytocin		9 (39.1)	10 (37.0)
Analgesia { No (%) not needing injections		1 (4.3)	10 (37.0)
{ No (%) needing two or more injections		7 (30.4)	2 (7.4)
No (%) with gastrointestinal side effects		0	4 (14.8)

There were no obvious differences between the primigravidae and multigravidae, and no apparent association between success and the duration of pregnancy or estimated time since fetal death. Four out of six patients with a missed abortion whose uterine size was below 14 weeks underwent suction evacuation 24 hours after treatment, abortion having failed to occur. All patients were well controlled with the analgesic used; only one needed three injections, while most of those with uterine size below 29 weeks needed none or one injection immediately before abortion. Four patients vomited, two of whom had diarrhoea, and all were given 15 mg PGE₂. No other side effects were observed. There were no complications. Surgical evacuation was performed on six patients, and one retained placenta was removed manually. Four patients lost over 500 ml blood, and one required transfusion. No patient was feverish, and none developed consumption coagulopathy.

Conclusions

The results with vaginal PGE₂ gel were comparable with those obtained in this unit with extra-amniotic administration,² 31 patients (62%) having aborted or delivered without further uterine stimulation; in the remainder the oxytocin infusion generally rendered expulsion of the conceptus inevitable within a few hours. The vaginal route, however, is simpler than the intrauterine and avoids the risk of sepsis without reducing therapeutic efficacy. Physical and emotional distress were minimal, 11 patients not requiring analgesia and only four suffering any gastrointestinal side effects. Abortion and delivery times compared favourably with those of Southern *et al.*,⁴ who used repeated administration of 20 mg PGE₂ vaginal pessaries, which provoked diarrhoea in 42.7% and vomiting in 56.4%.

The 15 mg dose of PGE₂ used for a uterine size below 29 weeks seems appropriate; a larger dose, although possibly reducing the need for oxytocin, would probably provoke more side effects. Success was reduced when uterine size was 11-13 weeks; however, suction evacuation was then easily performed and seems reasonable treatment when the uterus is this small and the cervix already softened and dilated. In more advanced pregnancies the larger dose to reduce the need for oxytocin might be inappropriate. Violent labour in the presence of a dead fetus incurs the risk of amniotic fluid embolism, and any great increase in dosage might therefore be imprudent.

We thank Sister Anna Fry and Sister Sue Bradley for expert nursing care, and the medical staff of the John Radcliffe Hospital for referring patients.

¹ Pedersen, P H, Larsen, F J, and Sorensen, B, *Prostaglandins*, 1972, **2**, 135.

² Calder, A A, MacKenzie, I Z, and Embrey, M P, *Journal of Reproductive Medicine*, 1976, **16**, 271.

³ MacKenzie, I Z, and Embrey, M P, *British Journal of Obstetrics and Gynaecology*, 1978, **85**, 657.

⁴ Southern, E M, *et al*, *British Journal of Obstetrics and Gynaecology*, 1978, **85**, 937.

(Accepted 2 May 1979)

Nuffield Department of Obstetrics and Gynaecology, John Radcliffe Hospital, Headington, Oxford OX3 9DU

I Z MACKENZIE, MRCOG, clinical lecturer

A J DAVIES, MRCOG, research fellow (present address: Department of Obstetrics and Gynaecology, Jessop Hospital for Women, Sheffield S11 8TE)

M P EMBREY, FRCOG, clinical reader

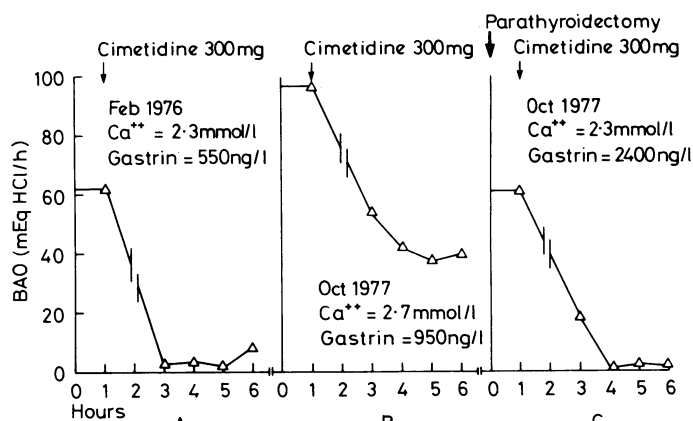
Hyperparathyroidism—a reversible cause of cimetidine-resistant gastric hypersecretion

Cimetidine has been successfully employed in the long-term treatment of gastrinoma.¹⁻⁴ We report the case of a patient in whom changing parathyroid function appeared to effect the course of acid-peptic disease and the response to the drug.

Case report

A 55-year-old woman developed hyperparathyroidism in 1953. She did well after parathyroidectomy (3 1/2 glands). In 1974 she developed Zollinger-

Ellison syndrome and a non- β islet cell tumour was excised from her pancreas (tail) without return of the serum gastrin concentration or gastric hypersecretion to normal. During 1975 her serum calcium concentration rose to 3.5-4.3 mmol/l (14-17 mg/100 ml) and parathyroid tissue was excised from her mediastinum. Multiple pieces of parathyroid tissue were implanted into the left forearm in November 1975. In February 1976 dyspepsia and diarrhoea led to her admission to hospital. She had multiple peptic ulcers and watery diarrhoea (3 l/day). Her fasting serum gastrin concentration was 550 ng/l (normal <150 ng/l) and basal acid output (BAO) was 50-60 mEq/h. Her serum calcium concentration was normal (2.3 mmol/l (9 mg/100 ml). Cimetidine (300 mg) by mouth reduced BAO to less than 10 mEq/h from the second to the fifth hour after the dose³ (fig A). She was discharged taking cimetidine 300 mg six-hourly. Six months later diarrhoea recurred. The serum calcium concentration was 2.5 mmol/l (10.2 mg/100 ml). From October 1976 to February 1977 her serum calcium concentration fluctuated between 2.2 and 2.9 mmol/l (8.8 and 11.6 mg/100 ml). In June 1977 measurements of parathyroid hormone (PTH) concentrations in the



Effect of single oral dose of cimetidine on basal acid output. A: Three months after excision of mediastinal parathyroid tissue and forearm implantation, and 14 months after excision of islet cell tumour of tail of pancreas. B: Immediately before excision of functionally active parathyroid tissue from left forearm, 18 months after A. C: On fourth postoperative day after B. Serum gastrin concentrations on day of each test are shown in relevant panels.

Conversion: SI to traditional units—Calcium: 1 mmol/l \approx 4 mg/100 ml.

antecubital veins showed on the left 86 μ g/l and on the right 0.41 μ g/l (normal <0.22 μ g/l), a highly significant difference. These figures established the diagnosis of systemic hyperparathyroidism and the presence of functioning tissue in the left arm. By July 1977, because of dyspepsia and diarrhoea, the dose of cimetidine was increased from 1.2 to 1.8 g/day. In October 1977 her BAO was reassessed 48 h after stopping cimetidine.⁴ The effect of the drug on BAO was then recorded (fig B). Compared with February 1976 the BAO had increased by about 50%. Cimetidine (300 mg) by mouth continued to cause an absolute reduction in BAO, quantitatively similar to that achieved previously, but in the postdrug period acid secretion greatly exceeded that measured 18 months earlier. Serum gastrin concentration at this time was 800-950 ng/l, and during the test the serum calcium concentration was 2.7 mmol/l (11 mg/100 ml). The identifiable parathyroid tissue was then excised from her left forearm and the serum calcium concentration fell. On the fourth postoperative day the response to cimetidine (300 mg) was again measured (fig C). At this time the serum calcium concentration was 2.3 mmol/l and the serum gastrin concentration had risen to 2400 ng/l. In spite of the hypergastrinaemia the BAO and drug responses had returned to those of February 1976. Cimetidine 300 mg four times a day abolished diarrhoea and dyspepsia.

Comment

This patient seemed to be "escaping from control" with cimetidine. Development of hyperparathyroidism and hypercalcaemia was accompanied by a sharp rise in BAO. Surgery, which corrected the hypercalcaemia, rapidly reduced BAO to the initial level and abolished symptoms. The absolute response to cimetidine did not change much over the 18-month period, but the BAO rose by 50% when the serum calcium and PTH concentrations rose. Since BAO is the result of a number of stimuli, such as acetylcholine, histamine, and gastrin, the increase in BAO, not blocked by cimetidine, may have been mediated by a stimulus other than histamine.⁵ Altered response to cimetidine may be important in hyperparathyroidism. Conversely, patients with ulcer who deteriorate on cimetidine merit investigation of their parathyroid state.