aminoglutethimide and hydrocortisone, but no other medication known to cause marrow failure, and all started with a normal blood count. At the time of agranulocytosis none had metastatic bone marrow disease or other evidence of recurrence of tumour, suggesting a direct toxic effect of the drug. Finally, none of the patients had had any type of drug reaction or allergy in the past.

Case reports

Case 1—A 73 year old woman presented on 12 December 1983 as an acute surgical emergency with abdominal pain 56 days after starting adjuvant treatment with aminoglutethimide. She was shocked, had a temperature of 39.8°C, and was diagnosed as suffering from intestinal perforation with peritonitis. Her white cell count, however, was $0.3 \times 10^9/l$ (no granulocytes) (figure). Haemoglobin concentration and platelet count were normal and the bone marrow aspirate showed absence of myeloid precursor cells. Despite intensive resuscitation she died. Necropsy confirmed septicaemia with no evidence of metastatic breast cancer.

Case 2—On 27 August 1984 a 64 year old woman developed septicaemia with agranulocytosis (white cell count $0.5 \times 10^9/l$) while having postoperative radiotherapy. She had been receiving adjuvant aminoglutethimide for 47 days. Haemoglobin concentration was 11.2 g/dl and the platelet count $439 \times 10^9/l$ (figure). Bone marrow aspirate showed erythroid dysplasia, scanty myeloid

White cell (●— — — ●) and platelet counts (○— — — ○) during aminoglutethimide treatment of three patients with primary breast cancer. Arrows indicate day aminoglutethimide stopped.

cells (myeloid to erythroid ratio 1:1), normal megakaryocytes, and no malignant cells. She was successfully treated with antibiotics and the white cell count recovered to $>3.0 \times 10^9/l$ 12 days after stopping aminoglutethimide with an associated thrombocytosis of $985 \times 10^9/l$. Three weeks after stopping aminoglutethimide bone marrow aspirate and peripheral blood cell count were normal, and four months later she remained well with a normal blood count and no evidence of recurrent carcinoma. Since 1978 this patient has been taking chlorthalidone (50 mg/day) for mild hypertension, which she continued with no adverse reaction.

Case 3—On 29 December 1982 a 67 year old woman developed agranulocytosis (white cell count $0.1 \times 10^9/l$) with a haemoglobin concentration of 9.7 g/dl and a platelet count of $272 \times 10^9/l$ (figure). She had been taking adjuvant aminoglutethimide for 60 days. She was asymptomatic apart from mild monilial stomatitis. Although there was no evidence of septicaemia, she was admitted for observation and prophylaxis with antibiotics. Bone marrow aspirate was hypocellular with absent myeloid precursors, scanty erythroid precursors, and occasional megakaryocytes with no malignant cells. Nine-

teen days after stopping aminoglutethimide her white cell count had recovered to $6.4 \times 10^9/l$ with an associated thrombocytosis ($534 \times 10^9/l$). Eight months later she remained well with a normal blood cell count and no evidence of recurrent carcinoma. She had also taken ferrous sulphate (200 mg/day) and occasional metoclopramide (10 mg) and diazepam (2 mg) in the weeks before developing agranulocytosis.

Comment

These three patients developed agranulocytosis five to eight weeks after starting aminoglutethimide and hydrocortisone. None had evidence of metastases and we therefore presume that the cause of bone marrow failure was drug toxicity by aminoglutethimide. Although serious and potentially fatal, the condition is uncommon (roughly 2% of cases) and reversible on stopping treatment. The reduction in granulocytes and other precursors in the bone marrow may indicate a direct toxic effect of the drug rather than immune peripheral destruction. This is consistent with the relatively rapid recovery associated with a rebound thrombocytosis. Finally, the serial blood counts in case 2 showed a gradual decrease in white cells. Careful monitoring of serial blood counts for the first three months of treatment would minimise the risk of septicaemia. This hazard should be evaluated against the potential benefit of adjuvant aminoglutethimide.

By February 1985 the Committee on the Safety of Medicines had documented four cases of marrow depression and aplasia, seven of agranulocytosis and granulocytopenia, and one of thrombocytopenia, including six deaths associated with aminoglutethimide. The manufacturers (Ciba-Geigy) have informed us of 36 similar cases of marrow failure reported between 1962 and 1984.

- 1 Harris AL, Powles TJ, Smith IE. Aminoglutethimide in the treatment of advanced postmenopausal breast cancer. *Cancer Res* 1982;42 (suppl):3405-8.
- 2 Lawrence B, Santen RJ, Lipton A, Harvey HA, Hamilton R, Mercurio T. Pancytopenia induced by aminoglutethimide in the treatment of breast cancer. *Cancer Treat Rep* 1978;62:1581-3.
- 3 Austerlitz J. Leukopenia associated with aminoglutethimide therapy: a case report. *Cancer Treat Rep* 1982;66:1879.
- 4 Flegel KJ, Dunn PM, Bentley RW, Miller MN. Hematologic adverse effects of aminoglutethimide. *Ann Intern Med* 1984;100:159.

(Accepted 28 March 1985)

Royal Marsden Hospital, Sutton, Surrey SM2 5PT

M D VINCENT, MB, MRCP, medical registrar
H M CLINK, MRCPATH, consultant haematologist
R C COOMBES, MD, MRCP, honorary consultant physician
I E SMITH, MD, FRCPD, consultant medical oncologist
R KANDLER, MB, MRCP, senior house officer
T J POWLES, PHD, FRCP, consultant medical oncologist

Correspondence to: Dr T J Powles.

Treatment of air embolism with hyperbaric oxygen

Serious air embolism is a potential complication of central venous catheter lines.¹ We report the first case in the United Kingdom of accidental air embolism treated with hyperbaric oxygen.

Case report

A 20 year old girl was admitted with an exacerbation of Crohn's disease. Owing to the severity of her condition she was treated with intravenous steroids and antibiotics, and a parenteral feeding regimen was begun through a right subclavian line. She steadily improved clinically and was beginning to tolerate oral feeding. After two weeks the subclavian line was due to be removed, but unexpectedly the nurses found her unconscious on the floor of her single room. She had obviously fallen from a bedside commode. She had probably removed the subclavian line (she was unable to recall the event, but disliked the line). The plastic introducer was still in situ through the skin, with blood leaking from it. She had probably been in that position for less than five minutes.

She had signs of severe cerebral irritation, with fixed dilated pupils, extensor limb response to pain, and extreme restlessness. Her reflexes were brisk, but the plantars were downgoing. Her pulse rate was 110/minute and blood pressure 85 mm Hg systolic. Her respiratory rate was raised. Funduscopy yielded normal results, and the only other abnormal finding was a churning noise in the chest on auscultation. Air embolism was diagnosed. She was initially treated with high dose oxygen, dexamethasone, mannitol, and diazepam and was transferred to the intensive care unit.

As there was only marginal improvement she was transferred for hyperbaric oxygen treatment to the nearby naval recompression unit at Portsmouth. Treatment began within two hours after her initial collapse. She underwent 285 minutes of alternating oxygen and air treatment beginning at a pressure of 2.8 bar (atmosphere absolute).² After 90 minutes she suddenly became conscious and responded to simple instructions. Neurological examination yielded normal results. She made a full recovery with no neurological sequelae but with a retrograde amnesia of about two hours.

Comment

This case confirms the reported effect of hyperbaric oxygen therapy in air embolism.³ Treatment should be started immediately, but a successful outcome is possible several hours after the onset of symptoms.⁴ Compression to 2.8 bar reduces bubble size according to Boyle's law (volume is proportional to 1/pressure), and the high partial pressure of oxygen relieves tissue ischaemia and enhances resolution of bubbles by increasing the nitrogen diffusion gradient. Initially 100% oxygen should be given with the patient in a left lateral head down position; this position prevents a large air bubble from blocking the pulmonary outflow tract and reduces the volume of air reaching the carotid arteries. In our patient the embolus was venous and the collapse was probably due to air bubbles ascending the internal jugular veins into the cerebral sinuses. An alternative explanation is that small bubbles coalesced after passing through the pulmonary circulation, or that air passed through a septal defect or an intrapulmonary atrioventricular shunt. The churning sound heard was probably the well described millwheel murmur.⁵

Air embolism is a recognised complication particularly of neurosurgical procedures performed with the patient sitting⁵ and of cardiac bypass surgery but is also common in accidents to central venous lines. This case aptly shows the deficiencies of a central line that requires a plastic introducer to be left in situ. We recommend that this type of catheter be discontinued, or that the introducer be pulled back and taped to the outside of the skin.

We thank Dr P L. Golding for his permission to report this case. Advice on the availability of Royal Navy recompression facilities may be obtained from the duty lieutenant commander, HMS *Vernon*, Portsmouth (telephone 0705 822351).

- 1 Ross SM, Freedman PS, Farman JV. Air embolism after accidental removal of intravenous catheter. *Br Med J* 1979;i:987.
- 2 Pearson RR, Leitch DR. Treatment of air or oxygen/nitrogen mixture decompression illness in the Royal Navy. *J R Nav Med Serv* 1979;65:53-62.
- 3 Hart GB. Treatment of decompression illness and air embolism with hyperbaric oxygen. *Aerospace Medicine* 1974;45:1190-3.
- 4 Bove AA, Clark JM, Simon AJ, Lambertsen CJ. Successful therapy of cerebral air embolism with hyperbaric oxygen at 2.8 ATA. *Undersea Biomed Res* 1982;9:75-80.
- 5 Marshall BM. Air embolus in neurosurgical anaesthesia, its diagnosis and treatment. *Can Anaesth Soc J* 1965;12:255-61.

(Accepted 19 April 1985)

Queen Alexandra Hospital, Cosham, Portsmouth, Hants PO6 3LY

A IRELAND, MB, MRCP, medical registrar
D POUNDER, MB, FFARCS, consultant anaesthetist
D G COLIN-JONES, MD, FRCP, consultant physician

Admiralty Marine Technology Establishment (Physiological Laboratory), Alverstoke, Hants PO12 2DU

J R HARRISON, MB, MSC, senior naval medical officer

Correspondence to: Dr A Ireland, Gastroenterology Unit, Radcliffe Infirmary, Oxford OX2 6HE.

Incidence of hyperkalaemia induced by indomethacin in a hospital population

Non-steroidal anti-inflammatory drugs are among the most widely prescribed drugs. In addition to gastrointestinal toxicity several renal complications are associated with their use, including acute renal failure, the nephrotic syndrome, interstitial nephritis, and abnormalities of water and electrolyte homeostasis.¹ Hyperkalaemia, usually associated with indomethacin, has only recently been recognised as a complication.²⁻⁴ The objective of the present study was to determine prospectively the incidence and severity of hyperkalaemia in a population of outpatients receiving indomethacin.

Patients, methods, and results

We studied all 50 patients admitted to the department of medicine at this medical centre between October 1983 and July 1984 in whom treatment with indomethacin was started. The increase in serum potassium and blood urea nitrogen concentrations after treatment was defined as the difference between the highest measurement before and after indomethacin was started.

The increase in serum potassium concentration was less than 0.5 mmol (mEq)/l in 20 patients (group 1). An increase of 0.5-0.9 mmol/l was observed in 17 patients (group 2) and ≥ 1.0 mmol/l in 13 patients (group 3). Absolute serum potassium concentrations exceeded 5.0 mmol/l in two (10%) patients in group 1 compared with eight (47%) patients in group 2 and all 13 patients in group 3. The mean (SD) daily dose of indomethacin was 168 (37) mg in group 1, 176 (22) mg in group 2, and 173 (35) mg in group 3.

The figure shows the variations in serum potassium concentrations in six patients in group 3 in whom peak values exceeded 6.0 mmol/l. In all patients potassium concentrations steadily increased until treatment with indomethacin was stopped. Peak values were observed on days 3-7 of treatment. Blood urea nitrogen concentration did not change or increased by less than 3.6 mmol/l (10 mg/100 ml) in 37 of the 50 patients. An increase of ≥ 3.6 mmol/l was found in four (20%) patients in group 1, two (12%) patients in group 2, and seven (54%) patients in group 3. These seven patients in group 3 had all had blood urea nitrogen concentrations before treatment exceeding 7.9 mmol/l (22 mg/100 ml).

The indications for treatment with indomethacin were musculoskeletal pain in 33 patients, pericarditis in 12, and fever associated with malignancy in three and autoimmune disease in two. The proportions of patients in these categories were the same for patients with and without a hyperkalaemic response to indomethacin. In contrast, the mean age of patients in group 1 (56.1 (18.8) years) was 10-12 years lower than that of patients in group 2 (66.9 (6.7)) and patients in group 3 (68.3 (11.9)) ($p < 0.025$). An impressive difference was the threefold (61%) increase in the prevalence of mild to moderate (3.7-7.2 mmol/l (22-43 mg/100 ml)) pre-existent azotaemia in group 3 compared with groups 1 (25%) and 2 (18%) ($p = 0.01$).

Effect of treatment with indomethacin on serum potassium concentration. Broken lines indicate measurements made after drug was stopped.

Conversion: SI to traditional units—Serum potassium: 1 mmol/l = 1 mEq/l.

Comment

We think that this study represents the first attempt to determine prospectively the incidence of hyperkalaemia in an inpatient population receiving indomethacin. Our findings indicate that hyperkalaemia is a common and potentially dangerous complication of treatment with indomethacin and that pre-existent mild to moderate azotaemia and old age are associated with an increased risk of the condition. Our findings together with previous reports lead us to make several recommendations for patients treated with indomethacin. Firstly, serum potassium concentrations should be measured in all patients before and repeatedly during the first week of treatment with indomethacin. Particular care should be exercised in patients with pre-existing renal disease, elderly subjects, and patients receiving potassium sparing diuretics, potassium supplements, angiotensin converting enzyme inhibitors, and β adrenergic blocking agents or digoxin. Finally, pre-existent uraemia and hyperkalaemia should be regarded as contraindications to treatment with indomethacin.

In view of these considerations and reports indicating that some non-steroidal anti-inflammatory drugs such as sulindac do not interfere with renal synthesis of prostacyclin⁵ a prospective controlled trial comparing the incidence of hyperkalaemia, uraemia, and other renal complications in patients receiving therapeutic doses of indomethacin