Comment

In this study a simple comparison between patients who had and had not received transfusions suggested that transfusion has a significant ($p=0{\cdot}04$) adverse effect on survival time. When adjustments were made for other prognostic factors, notably the tumour pT stage, however, it became obvious that transfusion was not a significant predictor of survival in patients with renal cell carcinoma.

These results do not confirm the results found in patients with colorectal cancer. We suggest that other cancers should be assessed along similar lines.

1 Burrows L, Tartter P. Effects of blood transfusions on colonic malignancy recurrence rate. *Lancet* 1982;ii:662.
2 Blumberg N, Agarwal MM, Chuang C. Relation between recurrence of cancer of the colon and blood transfusion. *Br Med J* 1985;**290**:1037-9.
3 Opelz G, Terasaki PI. Improvement of kidney-graft survival with increased numbers of blood transfusions. *N Engl J Med* 1978;**299**:799-803.
4 Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *Journal of the American Statistical Association* 1958;**53**:457-81.
5 Cox DR. Regression models and life tables. *Journal of the Royal Statistical Society, Series B* 1972;**34**:187-220.

(*Accepted 16 May 1986*)

Department of Urology, Leicester General Hospital, Leicester LE5 4PW
I T MANYONDA, BSC, MB, senior house officer
D E SHAW, BSC, MSC, medical statistician
A FOULKES, MB, FRCS, senior house officer
D E OSBORN, MS, FRCS, consultant urological surgeon

Correspondence to: Mr Osborn.

Industrial exposure to hydrogen cyanide: implications for treatment

We had the opportunity of studying nine patients exposed to hydrogen cyanide in a single incident at an industrial plant and three other patients exposed in separate incidents. We believe that our observations have important implications for treatment of such patients.

Patients and outcome

A suspected leak from a valve allowed hydrogen cyanide to escape. Nine men developed symptoms compatible with cyanide toxicity, of whom three lost consciousness. None of the men had definitely identified the "bitter almonds" smell said to be characteristic of hydrogen cyanide. The symptoms experienced included lightheadedness (eight men), breathlessness (eight), feeling shaky (six), headache (four), and nausea (four). The three unconscious men rapidly recovered consciousness after being moved from the area where they had been working. All nine men were attended by the works medical officer on site and then taken to hospital. All patients either showered or bathed, and oxygen was administered. Arterial blood was sampled and whole blood samples analysed for cyanide[1] (table).

Mean pulse on admission was 104 (SEM 4) beats/min, mean systolic blood pressure 140 (8) mm Hg, and mean diastolic blood pressure 84 (5) mm Hg. These figures, however, include the values found in three patients who showed relative hypotension—that is, systolic blood pressure 20-30 mm Hg below its normal value (nadir values 90, 100, and 110 mm Hg)—for up to three hours after admission. These three men included two of those who had been unconscious. Four patients had headache that persisted for up to eight hours after admission. There was no clearcut relation between blood cyanide concentrations on admission and symptoms, although the three patients who had lost consciousness had the highest concentrations (table).

Biochemical findings in patients exposed to hydrogen cyanide

Case No	pH	Carbon dioxide tension (kPa)	Bicarbonate (mmol/l)	Oxygen tension (kPa)	Cyanide (μmol/l)	
					On admission to hospital	One month after incident
1*†‡	7·40	3·2	19	34·3	115	11
2*	7·44	3·7	23	16·3	130	6
3*†‡	7·34	3·2	24	49·1	104	5
4	7·35	5·1	22	12·3	35	5
5	7·41	4·0	22	11·1	57	5
6	7·42	4·7	24	11·2	96	7
7†	7·40	4·1	22	11·2	50	9
8	7·37	5·1	23	10·4	67	3
9	7·38	4·7	23	9·3	41	3

*Patients initially unconscious.
†Patients with relative hypotension.
‡Patients receiving high flow oxygen when blood was drawn.
Conversion: SI to traditional units—Oxygen and carbon dioxide tensions: 1 kPa≈7·5 mm Hg. Bicarbonate: 1 mmol/l=1 mEq/l. Cyanide: 1 μmol/l≈2·7 μg/100 ml.

Three other men were also treated in separate incidents between 1970 and 1984 after exposure to hydrogen cyanide. Two were unconscious, although both regained consciousness rapidly. Cyanide concentrations in blood taken about 30 minutes after exposure were 284 and 173 μmol/l (768 and 467 μg/100 ml) in the patients who lost consciousness and 59 μmol/l (160 μg/100 ml) in the other patient.

Comment

All of our patients had absorbed appreciable amounts of cyanide, as shown by their blood cyanide concentrations. One of the problems in interpreting previous reports is that blood concentrations were measured in only a few patients after short term exposure to hydrogen cyanide, experience at Billingham being the exception (D D Bryson, personal communication). It has been suggested that cyanide concentrations above 111 μmol/l (300 μg/100 ml) are potentially lethal,[2] yet four of our patients had values above this. Thus blood cyanide concentrations are not accurate in predicting severity of toxicity and should be used only to confirm that appreciable cyanide absorption has occurred, not to determine treatment.

The most important lesson to be learnt is that patients can recover spontaneously and quickly from apparently severe poisoning with hydrogen cyanide, as shown by the five patients who lost consciousness: their conscious level had largely returned even in the short time before the arrival of the works medical officer (probably less than 10 minutes). This emphasises the importance of making the decision to give antidotes to cyanide on clinical grounds and on the basis of the patient's changing condition, particularly his conscious level.[3] Our experience suggests that if the patient has been removed from the area of exposure and further absorption of hydrogen cyanide prevented then even if he is unconscious an antidote does not have to be administered immediately unless the vital signs are deteriorating. Caution in giving antidotes to cyanide, particularly dicobalt edetate, the most popular antidote in the United Kingdom, is advisable because of their potential toxicity.[3,4] Clearly, appropriate supportive care must be begun immediately: several severely poisoned patients who have ingested potassium cyanide have recovered after being given full supportive measures but no antidote.[2,5] Most probably any patient exposed to hydrogen cyanide who reaches hospital fully conscious will require merely observation and reassurance.

We thank Drs D D Bryson and J E Leeser, Imperial Chemical Industries plc, Agricultural Division, Billingham, for comments and information based on their own experience and Mrs Y McKeeman for secretarial help.

1 Kanai R, Hashimoto K. Determination of acrylonitrile cyanide and thiocyanate in biological materials. *Industrial Health* 1965;**3**:47-51.
2 Graham DL, Laman D, Theodore J, Robin ED. Acute cyanide poisoning complicated by lactic acidosis and pulmonary oedema. *Arch Intern Med* 1977;**137**:1051-5.
3 Bryson DD. Cyanide poisoning. *Lancet* 1978;i:92.
4 Dodds C, McKnight C. Cyanide toxicity after immersion and the hazards of dicobalt edetate. *Br Med J* 1985;**291**:785-6.
5 Edwards AC, Thomas ID. Cyanide poisoning. *Lancet* 1978;i:92-3.

(*Accepted 16 June 1986*)

Medical Unit, Falkirk and District Royal Infirmary, Falkirk FK1 5QE
N R PEDEN, MRCP, consultant physician
A TAHA, MRCPI, medical registrar
P D McSORLEY, MRCP, consultant physician

BP Chemicals Ltd, Grangemouth
G T BRYDEN, MB, CHB, works medical officer
I B MURDOCH, MRCGP, works medical officer
J M ANDERSON, PHD, chief works chemist

Correspondence to: Dr Peden.

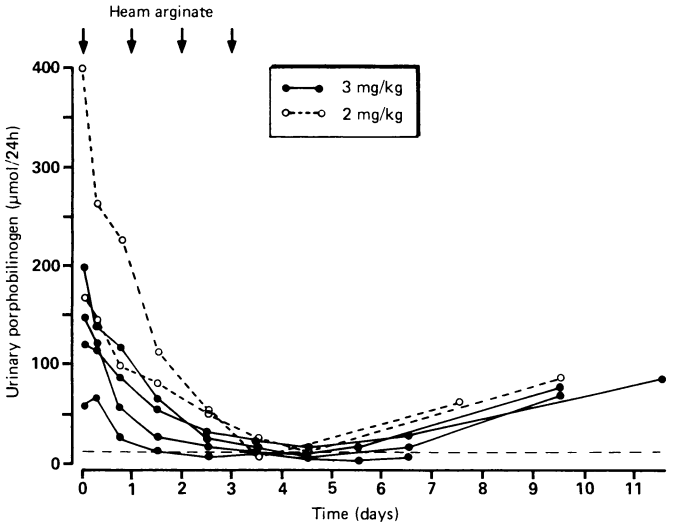
Haem arginate in the treatment of acute hepatic porphyrias

Haematin has been used for 15 years to treat acute porphyric attacks. Its disadvantages are instability in solution, harmful effects on coagulation, and thrombophlebitis.[1-3] For these reasons safer, more stable preparations have been developed. We report the effects of haem arginate, a new haem preparation, in patients with acute intermittent porphyria and variegate porphyria.

Patients, methods, and results

We studied six patients with acute intermittent porphyria and four with variegate porphyria in remission to investigate the biochemical effects of haem arginate. We also treated nine acute attacks in four patients with acute intermittent porphyria. One of them had paresis, while the others had only abdominal and other gastrointestinal symptoms.

Haem arginate was prepared from out of date human red cells in the laboratories of Medica Pharmaceutical Company Ltd, Helsinki, Finland. In 10 ml ampoules (haem 25 mg/ml) the preparation (Normosang), which is sterile and free of pyrogen, is stable for three years at 6°C. Pharmacokinetic studies of haem arginate have been described elsewhere.[4] Haem arginate (2 mg/kg for two patients without symptoms, 3 mg/kg for the others) was infused in peripheral veins daily for four consecutive days. Urinary porphyrin precursors and faecal porphyrins were analysed by methods given elsewhere.[5] Blood biochemical values were measured by routine hospital methods, and coagulation studies were done by the haemostasis laboratory of the Finnish Red Cross Blood Transfusion Service.



Urinary excretion of porphobilinogen after administration of haem arginate in six patients with acute intermittent porphyria in remission.

Conversion: SI to traditional units—Porphobilinogen: 1 μmol/24 h≈0·22 μg/24 h.

In patients with acute intermittent porphyria without symptoms the mean urinary excretion of porphobilinogen fell during the infusions from 194 (range 60-465) to 17·2 (7·1-30·0) μmol/24 h (from 43·7 (13·5-105·0) to 3·9 (1·6-6·8) μg/24 h) (figure) and that of δ-aminolaevulinic acid fell from 133 (47-281) to 13·8 (8·1-23·4) μmol/24 h (from 17·4 (6·2-36·8) to 1·8 (1·1-3·1) μg/24 h). In the patients with variegate porphyria mean faecal protoporphyrin content fell from 650 (193-1140) to 89 (50-96) nmol/g dry weight (from 365 (126-641) to 50 (28-54) ng/g) and that of coproporphyrin fell from 232 (102-360) to 23 (8·5-40·0) nmol/g dry weight (from 152 (67-236) to 15 (5·6-26·0) ng/g).

In all the patients with acute symptoms abdominal pain and other gastrointestinal symptoms resolved during or immediately after the infusions. The patient with paresis recovered fully in two months. Clinical response was accompanied by an appreciable decrease in the urinary excretion of porphyrin precursors (mean excretion of porphobilinogen before treatment 278 (45-555) μmol/24 h (62·6 (10·0-125·0 μg/24 h); lowest value during treatment 54·0 (7·4-140·0)μmol/24 h (12·2 (1·7-31·5) μg/24 h)).

No appreciable changes were found in liver and kidney function, haemoglobin concentration, or leucocyte and thrombocyte counts. Detailed coagulation studies (Quick time, thrombin time, prothrombin ethanol chelation; and concentrations of factors V, VII, and VIII, plasminogen, antithrombin III, and fibrinogen degradation products) performed in two patients 10 minutes and four hours after an infusion yielded normal results. Moderate thrombophlebitis occurred after only one of the 76 infusions given.

Comment

Biochemical effects of haem arginate were considerable and comparable with those of haematin.[1 2] Clinical effects are more difficult to evaluate because porphyrias have a spontaneous tendency to remit. In all patients with symptoms, however, recovery coincided with the treatment. Haem arginate had no effect on coagulation factors, and thrombophlebitis after infusion was rare. Thus haem arginate probably causes fewer side effects than haematin. Recent observations suggest that effects on coagulation are caused by degradation products of haematin but not by haem itself.[2] The difference between haem arginate and haematin in this respect can be explained by the greater stability and, thus, absence of harmful degradation products in haem arginate.

Being a stable product and available in ampoules, haem arginate is easy to use in clinical practice. We now give haem immediately when patients present with acute porphyric symptoms and do not try giving carbohydrate first, as is currently recommended.[3] This guarantees that the most effective form of treatment is given early in the course of the acute attack, when a favourable clinical response is most likely.[1]

We thank Dr Vesa Rasi and the haemostasis laboratory of the Finnish Red Cross Blood Transfusion Service for performing the coagulation studies. These findings were presented in part at the international conference on porphyrins and porphyrias, Paris, June 1985, and at the eighth meeting of the International Society of Haematology European and African Division, Warsaw, September 1985.

1 Watson CJ, Pierach CA, Bossenmaier I, Cardinal R. Use of hematin in acute attack of the "inducible" hepatic porphyrias. *Adv Intern Med* 1978;**23**:265-86.
2 Pierach CA. The treatment of the porphyric attack with hematin. In: Nordmann Y, ed. *Porphyrins and porphyrias. Proceedings of the second international congress on porphyrins and porphyrias, Paris, 19-22 June 1985*. London: John Libbey, 1986:217-24.
3 McColl KEL, Moore MR, Thompson GG, Coldberg A. Treatment with haematin in acute hepatic porphyria. *Q J Med* 1981;**198**:161-74.
4 Tokola O, Tenhunen R, Volin L, Mustajoki P. Pharmacokinetics of intravenously administered haem arginate. *Br J Clin Pharmacol* (in press).
5 Mustajoki P, Koskelo P. Hereditary hepatic porphyrias in Finland. *Acta Med Scand* 1976;**200**:171-8.
(*Accepted 16 June 1986*)

University of Helsinki, Helsinki, Finland
PERTTI MUSTAJOKI, MD, senior lecturer in medicine, third department of medicine
RAIMO TENHUNEN, MD, chief of the laboratories, department of clinical chemistry

Research Laboratories of Huhtamäki Oy Pharmaceuticals, Leiras-Medica, Helsinki, Finland
OLAVI TOKOLA, MD, assistant director, clinical research
GUIDO GOTHONI, MD, research leader

Correspondence to: Dr P Mustajoki, Third Department of Medicine, University Central Hospital, SF-00290 Helsinki, Finland.

Adrenaline, bronchoconstriction, and asthma

Adrenaline is a potent bronchodilator, but the role of endogenous adrenaline in regulating airway calibre in asthma is not clear. We report observations made on a patient who developed asthma many years after bilateral adrenalectomy.

Case report

A 37 year old woman had presented in 1965 aged 17 with postpartum amenorrhoea. Cushing's syndrome secondary to bilateral adrenal hyperplasia was diagnosed and bilateral adrenalectomy was performed. Steriod replacement treatment consisted of hydrocortisone 20 mg and fludrocortisone 0·1 mg a day. She developed Nelson's syndrome with increased pigmentation of the skin and a raised adrenocorticotrophic hormone concentration (6000 U/l; upper limit of normal 100 U/l). This was successfully controlled initially with sodium valproate (200-400 mg thrice daily) and from 1983 with the addition of prazosin 0·5 mg thrice daily.

Shortly after the introduction of prazosin she complained of episodes of breathlessness, although pulmonary function was normal (forced expiratory volume in one second 2·5 litres, forced vital capacity 3·1 litres, peak flow rate 420 l/min). During a subsequent admission she again complained of breathlessness and a peak flow chart showed appreciable diurnal variation with morning dipping of 30-40% (figure). Asthma was confirmed by the finding of bronchial hyperreactivity,[1] the concentration of histamine causing a 20% fall in forced expiratory volume in one second (PC_{20}) being 1·4 mmol/l (0·15 mg/ml). Withdrawal of prazosin was associated with clinical improvement and a decrease in bronchial reactivity (histamine PC_{20} of 7·2 mmol/l (0·8 mg/ml)); subsequent rechallenge with the drug, however, did not alter bronchial reactivity or cause a deterioration in symptoms.

Skin testing with a range of common allergens yielded uniformly negative results. Exercise in a room at controlled temperature (18°C) on a bicycle for six minutes produced 90% of the predicted maximum heart rate response but failed to cause bronchoconstriction. Resting plasma noradrenaline concentration was 3·4 nmol/l (0·58 ng/ml) with a normal increase on exercise to 9·1 nmol/l (1·54 ng/ml), while plasma adrenaline concentration was very low on exercise and at rest