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Haem arginate was prepared from out of date human red cells in the laboratories of Medicina Pharmaceutical Company Ltd, Helsinki, Finland.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. 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. 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.

**Comment**

Biochemical effects of haem arginate were considerable and comparable with those of haematin. 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 thrombophilia 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. 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. 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.

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.


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**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 Huitlmatki Oy Pharmaceuticals, Leiras-Media, Helsinki, Finland**

OLAVI TOKOLA, MD, assistant director, clinical research

GUIDO GOTHONI, MD, research leader

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

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**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 adrenalc hyperplasia was diagnosed and bilateral adrenalectomies was performed. Steroid 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 (600 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: the concentration of histamine causing a 20% fall in forced expiratory volume in one second (PC20) being 1.4 nmol/l (0.15 mg/ml). Withdrawal of prazosin was associated with clinical improvement and a decrease in bronchial reactivity (histamine PC20 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 bronchocstriction. Resting plasma noradrenaline concentration was 3-4 nmol/l (0.38 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.
Subacute hepatic necrosis induced by piroxicam

Hepatotoxicity is a recognised side effect of most non-steroidal anti-inflammatory drugs and may be hepatocellular, cholestatic, or a combination of both. In most cases the prognosis of those patients who survive the acute phase is good, though recognition and withdrawal of the offending drug is important. Piroxicam, a relatively new agent belonging to the oxicam class, appears to be the least hepatotoxic non-steroidal anti-inflammatory drug.

We, however, describe a patient who presented with features of acute hepatocellular injury that progressed to fatal subacute hepatic necrosis despite withdrawal of the drug.

Case report

A 66 year old woman of previously good health developed jaundice with dark urine and pale stools three days after starting piroxicam for plantar fasciitis (40 mg/day; total dose 120 mg). The drug was immediately stopped. There was no history of blood transfusion, recent injection, contact with jaundice, or ingestion of other drugs or alcohol. Results of investigations were: plasma bilirubin concentration 525 μmol/l (9-0 mg/100 ml), aspartate transaminase activity 430 IU/l, alkaline phosphatase activity 190 IU/l (24 KA units), total protein concentration 74 g/l (albumin 38 g/l), and prothrombin time 16/12 seconds. Tests for hepatitis A and B viruses and antinuclear, smooth muscle, and mitochondrial antibodies gave negative results. Liver biopsy two weeks after the onset of jaundice showed an acute hepatitis with spotty necrosis (figure).

Despite some initial clinical and biochemical improvement she remained severely jaundiced and 12 weeks later developed progressive abdominal and leg swelling with the onset over 24 hours of drowsiness and confusion. She was transferred to the liver failure unit at this hospital. On examination she was in grade II hepatic coma and had gross ascites. Results of investigations were: bilirubin concentration 407 μmol/l (23-8 mg/100 ml), aspartate transaminase activity 730 IU/l, alanine transaminase, activity 258 IU/l, total protein 70 g/l (albumin 21 g/l), and prothrombin time 39/13 seconds. Serum autoantibody screen was positive for antinuclear antibodies (titre 1/160). She began treatment with corticosteroids but shortly afterwards suffered gastrointestinal bleeding. She died 105 days after the onset of jaundice. Liver biopsy immediately after death showed severe confluent centrilobular necrosis with extensive bridging collapse and prominent mixed inflammatory cell infiltrate (subacute hepatic necrosis (figure).

Comment

Mild and transient rises in serum transaminase activities have been described during clinical trials of piroxicam and we have found one report of probable piroxicam induced cholestatic jaundice. In our patient the temporal sequence together with exclusion of viral hepatitis A and B and the initially normal autoantibody screen all point to a drug induced hepatitis.

Despite withdrawing the drug the illness progressed to fatal subacute hepatic failure. It has been thought that adverse drug reactions including hepatotoxicity due to non-steroidal anti-inflammatory drugs may be more common in patients over 65, and this was shown with ibuprofen. The reason is unknown.


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Department of Clinical Pharmacology, St Mary's Hospital, London W2

ALYN MORICE, MA, MRCP, research fellow

PETER SEVER, PHD, MRCP, professor

Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London W12

PHILLIP IND, MA, MRCP, honorary senior lecturer

Correspondence to: Dr A Morice, Clinical Pharmacology Unit, F and G Block, Addenbrooke's Hospital, Cambridge CB2 0QQ.