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Haem arginate was prepared from out of date human red cells in the laboratories of Medica Pharmaceutical Company Ltd, Helsinki, Finland.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.¹ 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.² 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.² 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

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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 adrenal hyperplasia was diagnosed and bilateral adrenalectomy 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 (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 hyper-reactivity,¹ the concentration of histamine causing a 20% fall in forced expiratory volume in one second (PC₂₀) being 1.4 mmol/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 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

(0.06 nmol/l (0.01 ng/ml)) (normal ranges 0.8-5.9 nmol/l (0.14-1.00 ng/ml) for noradrenaline and 0.1-1.0 nmol/l (0.02-0.20 ng/ml) for adrenaline with intra-assay and interassay coefficients of variation of 2.9% and 4.8% respectively). Lymphocyte β adrenoreceptor numbers, as measured by iodocyanopindolol displacement, were normal at $3.4 \text{ fmol}/10^6$ cells. She showed an appreciable response to intravenous infusion of adrenaline, the peak expiratory flow rate increasing by 20% and 24% at plasma concentrations of 1.5 and 2.2 nmol/l (0.3 and 0.4 ng/ml) (infusion rates of 0.025 and 0.05 $\mu\text{g}/\text{kg}/\text{min}$).

Four hourly recordings of peak expiratory flow in patient with asthma after adrenalectomy (measurements made at 0600, 1000, 1400, 1800, and 2200).

A double blind, placebo controlled infusion of propranolol (10 mg in 20 minutes) did not induce bronchoconstriction despite causing an eightfold diminution in the heart rate response to incremental infusions of isoprenaline. Subsequent infusion of phentolamine 5 mg did not induce bronchoconstriction, confirming that α receptor blockade was not the cause of the original deterioration.

Comment

The cause of the diurnal variation in bronchoconstriction in asthma is not clear. Circadian variation in plasma adrenaline concentration has been proposed as the mechanism of nocturnal asthma.² Our patient had undergone bilateral adrenalectomy and had low circulating adrenaline concentrations, yet she showed morning dipping. Although the influence of adrenaline at low plasma concentrations cannot be excluded, nocturnal asthma is more likely to be due to changes in vagal parasympathetic tone influencing airway calibre.³

β receptor function was normal in our patient. Propranolol did not produce bronchoconstriction, but exacerbation of asthma by β blockade is not invariable. Wheezing was not induced by exercise, suggesting that lack of circulating adrenaline is unlikely to be important in the genesis of exercise induced asthma. The finding that the circulating plasma adrenaline concentration is normal in mild asthma and does not rise during acute attacks leaves little place for circulating adrenaline as a hormone in asthma.⁴

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Subacute hepatic necrosis induced by piroxicam

Hepatotoxicity is a recognised side effect of most non-steroidal anti-inflammatory drugs¹ 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 oxamic class, appears to be the least hepatotoxic non-steroidal anti-inflammatory drug.¹ 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 $325 \mu\text{mol}/\text{l}$ (19.0 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 $407 \mu\text{mol}/\text{l}$ (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 piroxicam² and we have found one report of probable piroxicam induced cholestatic jaundice.³ 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 benoxaprofen.⁴ The reason is

Liver biopsy appearances. Left: two weeks after onset of jaundice. Right: immediately after death.