Despite these measures she required mechanical ventilation and was subsequently transferred to the Queen Elizabeth Hospital. Artificial ventilation was continued for a total of six days, during which time she received subcutaneous terbutaline 0.25 mg six-hourly and a reducing dose of hydrocortisone, later changed to oral prednisolone (figure). She also required soluble insulin for transient hyperglycaemia and intravenous heparin for an axillary vein thrombosis. The plasma potassium concentration was reduced to 2.0-3.0 mmol(mEq)/l during sympathomimetic treatment but returned promptly to normal when this was stopped.

Steroid dosage and serum creatine kinase concentrations in case of acute hydrocortisone myopathy. Day 1 is day of initial presentation. Timing of electromyography (EMG) and muscle biopsy indicated.

Myopathy first became evident when the patient was slow to resume spontaneous respiration despite resolution of her bronchospasm. She was unable to raise her limbs from the bed, both proximal and distal muscle groups being profoundly weak. There were no sensory or reflex changes and the cranial nerves were intact. Serum creatine kinase concentration 888 U/l (normal female range 0-65 U/l) and aspartate transaminase 168 U/l (normal range 5-30 U/l). Serum bilirubin, creatinine, and thyroxine concentrations were normal. The subsequent slow fall in creatine kinase concentration is shown in the figure. Electromyography showed no specific abnormalities. A biopsy specimen of the left deltoid muscle showed vacuolar changes in all fibre types and regenerating basophil fibres throughout the specimen. There was no evidence of denervation. Results of routine histochemical tests were normal. The major electron microscopic feature was the presence of large numbers of glycogen granules in the intermyofibrillar spaces, both within lysosome-like vesicles and free in the sarcoplasm.

Muscle power slowly improved. Recovery was almost complete after six months despite the continuation of prednisolone 5-10 mg daily to control her asthma. Detailed inquiry elicited no evidence of preceding or familial muscle disorder.

Comment

The clinical features of the only other reported case of myopathy attributable to hydrocortisone¹ were remarkably similar to those described here. Both patients required ventilation for status asthmaticus and were given several grams per day of intravenous hydrocortisone. Both developed an acute myopathy that took several months to resolve, and distal limb muscles were as severely affected as proximal. It may be relevant that both patients were given intravenous beta-stimulants in addition to hydrocortisone, though only one of them became hypokalaemic. We suggest that hydrocortisone myopathy is an entity distinct from other forms of steroid myopathy but closely resembling experimental cortisone myopathy. Massive glycogen accumulation is a characteristic ultrastructural feature in the animal model² and has been occasionally reported in human steroid myopathy due to other agents.^{3,4} It is probably an early change. The pathogenesis of the muscle damage is unknown. Possibly hypoxia or beta-adrenergic stimulants were contributory factors in the two cases described.

Although an accurate dose-response curve would be hard to construct, there is evidence that for an adult of average size the optimal dose of hydrocortisone is not more than 1 g 24 hours by

continuous infusion.⁵ Higher doses are probably unnecessary and potentially hazardous.

We thank Dr GW Pearce for reporting on the muscle biopsy specimen and for his helpful comments on the case.

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Phenobarbitone and serum unconjugated oestriol concentrations in four pregnant women with hypertension

In most cases studied over one year kit method serum unconjugated oestriol estimations (IM 94, Radiochemical Centre, Amersham, UK) proved to be valuable and reliable indicators of fetoplacental function in "at risk" pregnancies. Oestriol concentrations that fall or fail to rise normally have generally been associated with additional clinical evidence of either fetal distress or an unfavourable outcome of the pregnancy at term, or both.

Serial serum unconjugated oestriol concentrations in four hypertensive pregnant patients receiving phenobarbitone.
Conversion: SI to traditional units—Oestriol: 1 nmol/l $\approx$ 28.8 ng/100 ml.

Patients and results

We have observed falling oestriol concentrations in four patients with severe hypertension shortly after they began treatment with phenobarbitone (figure); in only one of these (small-for-dates baby and meconium-stained amniotic fluid) was there evidence of impaired fetoplacental function. Neither we nor previous workers¹ have recorded falls of this kind in patients with hypertension, either untreated or receiving alternative treatment,

thereby permitting the fairly confident exclusion of hypertension as such as the precipitating factor. It was considered possible that phenobarbitone present in the serum might interfere with the laboratory procedure and result in artificially low oestriol values, but this was discounted after evidence showed that the behaviour of the assay was not appreciably affected by the in-vitro addition of phenobarbitone in amounts considerably above those reached during normal treatment.

Comment

Even in the normal dose range (30–120 mg/day) for men and women, phenobarbitone is known to be a powerful inducer of the hepatic microsomal detoxicating enzyme system, an effect greatly potentiated by the presence of polyunsaturated fatty acids in the diet.² In view of the relatively short half life of free oestriol in plasma (about eight minutes),³ it is tempting to speculate that even a minimally enhanced conjugation rate may exert a profound effect on concentrations of unconjugated oestriol.

Until these findings have been confirmed and their cause more fully elucidated, it would be prudent to temper concern with caution in interpreting falling unconjugated oestriol concentrations in patients receiving phenobarbitone.

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Severe diarrhoea due to small intestinal colonisation during cimetidine treatment

Diarrhoea is occasionally encountered during cimetidine treatment but no satisfactory pathophysiological mechanism has been proposed. The case described here suggests that severe diarrhoea and malabsorption may be due to a reversible bacterial colonisation of the small intestine.

Case report

A 77-year-old woman, admitted to hospital with chest pains, gave a history of recent severe diarrhoea and weight loss of about 5 kg. Two months previously she had been prescribed cimetidine 200 mg thrice daily and 400 mg at night for a duodenal ulcer. The ulcer symptoms had rapidly resolved, but about two weeks after starting cimetidine she had developed diarrhoea with progressive weight loss. Salazopyrine was prescribed without benefit, and cimetidine was continued. When admitted for chest pain she was passing 8–12 pale, offensive, frothy, and floating stools a day and was thought to have steatorrhoea. Cimetidine was continued during her recovery from uncomplicated myocardial infarction. The diarrhoea was then investigated. The results of the following examinations and tests were normal: sigmoidoscopy; stool culture and microscopy; jejunal biopsy; Lundh test of pancreatic function; serum iron and folate; barium enema; small bowel enema. Gastroscopy showed scarring on the lesser curve but no duodenal ulcer. Faecal fat was 4.8 g/day; urinary indican excretion was low normal on two successive days. The lactulose-hydrogen breath test was strongly positive, suggesting intestinal bacterial overgrowth. This was confirmed when jejunal aspirate grew per ml 6×10^6 enterococci, 6×10^5 *Streptococcus viridans*, 4×10^4 coliforms, 1×10^5 staphylococci, and 1×10^6 *bacteroides* spp.

After completion of investigations the cimetidine was stopped and the diarrhoea gradually improved. Two months later she had gained 4 kg in weight and her bowels were acting normally with one solid motion a day. Repeat investigations at that time showed that she was not achlorhydric (gastric pH 3.7) and jejunal aspirate produced only an insignificant growth of *Str viridans* (8×10^2 per ml) with no anaerobes. A lactulose-hydrogen

breath test produced no hydrogen. At no time during this period had she received antibiotics. She has remained well, taking no cimetidine, and had no recurrence of diarrhoea or abdominal pain.

Comment

Cimetidine causes bacterial overgrowth in the stomachs of patients with gastric and duodenal ulcers, presumably by reducing acid secretion.¹ A raised gastric pH is associated with an increase in jejunal bacteria,² but a clinical syndrome of diarrhoea and malabsorption due to intestinal bacterial overgrowth has not been convincingly demonstrated in the absence of an anatomical lesion or severe motility disorder. Bacterial overgrowth was postulated as the cause of malnutrition in a group of elderly patients who responded to antibiotics, but intestinal bacteriology was not performed.³ Our clinical impression of steatorrhoea was not confirmed by the results of faecal fat estimation. Steatorrhoea due to bacterial overgrowth is often intermittent. Although our patient's diarrhoea continued during investigation its character varied and no longer suggested steatorrhoea when investigated. Urinary indican excretion is often normal even with established bacterial overgrowth.⁴

In view of the weight loss and severe diarrhoea there seems little doubt that our patient had "malabsorption." Malnutrition and malabsorption have many causes in association with intestinal overgrowth in addition to fat malabsorption, including impaired fluid and electrolyte absorption, intestinal breakdown and malabsorption of dietary protein, protein-losing enteropathy, and calorie consumption by the bacteria themselves.⁵ The "stagnant loop syndrome" has not been satisfactorily documented in a normal small bowel. In our patient it was presumed to be due to the cimetidine treatment. Long-term treatment with potent gastric antiseptics agents may have undesirable nutritional consequences, particularly in elderly hypochlorhydric patients, who may already have a tendency to bacterial overgrowth in the small intestine.

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Hydrallazine-induced lupus erythematosus-like syndrome in a patient of the rapid acetylator phenotype

Human populations show a bimodal distribution for the rate of acetylation of certain drugs.¹ The lupus erythematosus-like syndrome associated with hydrallazine is almost exclusively confined to slow acetylators,² there being only two cases reported of this syndrome occurring in the rapid acetylator phenotype. In the first of these² very large doses were given, and in the second the idiopathic variety of lupus was subsequently considered a more likely diagnosis.³ We describe here a rapid acetylator of sulphadimidine in whom the acetylation of hydrallazine has also been studied.

Case report

A 49-year-old woman began treatment for hypertension in 1961. She was treated for epilepsy between 1969 and 1976. In August 1975 hydrallazine