epidural analgesia.² In abolishing the endocrine-metabolic response epidural analgesia also inhibits the postoperative increase in oxygen consumption,²⁴ thereby reducing the demands on the cardiovascular system.

The increase in plasma glucose and cortisol and the negative nitrogen balance in the control group could not have been caused by halothane, which has a negligible effect on blood glucose²⁵ and cortisol.²⁶ Furthermore, it has an inhibitory effect on plasma catecholamines.²⁷

Blockade of afferent stimuli from the surgical area is the main mechanism by which epidural analgesia inhibits the endocrine-metabolic stress response,^{15 18} but the concomitant blockade of efferent sympathetic pathways to the liver and adrenal medulla possibly plays an important part as well. The nitrogen-sparing effect of epidural analgesia may not operate in more severe forms of stress, such as burns and sepsis, in which mechanisms other than afferent neurogenic impulses may release the stress response.¹⁵

The use of epidural analgesia for neurogenic blockade should enable the physiological importance of the endocrine-metabolic response to stress to be clarified. Although Cannon²⁸ has provided convincing experimental evidence that this stress response is essential for maintaining body homeostasis, this does not necessarily apply to man. No deleterious effect of the abolished stress response to surgery was found in our study, or when the endocrine-metabolic stress response caused by morphine anaesthesia was inhibited.²⁹

Whether other postoperative side effects, such as impaired immunocompetence^{30 31} and phagocytosis,³² could be prevented by inhibiting the stress response is not yet known. If they could, neurogenic blockade might lower surgical morbidity in high-risk patients.

We are indebted to our dieticians, Marianne Haugaard and Lone Onsgaard, for their valuable help. We also thank the nurses from the department of obstetrics and gynaecology for their help and interest.

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(Accepted 23 February 1978)

SIDE EFFECTS OF DRUGS

Irreversible myxoedema after lithium carbonate

The reported incidence of thyroid hypofunction after long-term lithium carbonate treatment varies from 4%¹ to 12%.² Patients receiving such treatment often develop raised serum concentrations of thyroid-stimulating hormone (TSH) and an exaggerated TSH response to TSH-releasing hormone² before symptoms of myxoedema appear. Thyroid function is generally thought to return to normal when lithium carbonate is withdrawn. Few cases of irreversible myxoedema after long-term lithium treatment have been reported. One of these patients had raised concentrations of thyroid autoantibodies indicating underlying thyroid disease,³ and the other apparently recovered one year later.¹

We describe two patients with no signs of underlying thyroid disease or hereditary predisposition to hypothyroidism who developed irreversible myxoedema after prolonged lithium treatment.

Case reports

Case 1—In April 1973 a 56-year-old man began lithium carbonate treatment for endogenous depression. His symptoms were adequately controlled by treatment, but in August 1974 he presented with gross clinical hypothyroidism without goitre. Serum thyroxine (T₄) was 32.2 nmol/l (2.5 µg/100 ml) (normal range 55.3–129 nmol/l (4.3–10 µg/100 ml)), TSH 15.1 mU/l

(normal <1.5), and T₃ resin uptake 0.62 (normal 0.80–1.20). He had no known predisposition to thyroid disease and tests for thyroid autoantibodies gave negative results. Lithium treatment was withdrawn and thyroxine sodium 0.15 mg/day begun. TSH returned to normal and subjective improvement was reported. In March 1975 thyroxine sodium dosage was reduced to 0.05 mg/day, but two months later serum TSH was 36 mU/l, T₄ 47.6 nmol/l (3.7 µg/ml), and T₃ resin uptake 0.76, and thyroxine sodium dosage was raised to 0.15 mg/day. One year later thyroxine sodium dosage was again reduced for six months, and thyroid function values fell to below normal.

Case 2—In February 1973 a 54-year-old woman with no evidence of underlying thyroid disease began lithium carbonate treatment for endogenous depression. Lithium treatment was well tolerated until autumn 1974, when she complained of gain in weight (15 kg in six months), intolerance to cold, and tiredness. Serum T₄ was 32.2 nmol/l (2.5 µg/100 ml), TSH 48.4 mU/l, and T₃ resin uptake 0.90. Goitre was absent. Lithium carbonate was withdrawn and thyroxine sodium 0.15 mg/day instituted. Thyroxine sodium was withdrawn six months later when she was biochemically and clinically euthyroid. After a further six months, however, treatment was reinstituted when she again became clinically hypothyroid. TSH had increased to 50.5 mU/l, T₄ was 51.4 nmol/l (4 µg/100 ml), and T₃ resin uptake 0.93. Treatment with thyroxine sodium 0.15 mg/day was begun, and she remained euthyroid with normal TSH concentrations for two years.

Comment

Irreversible myxoedema after long-term lithium carbonate treatment may not be as uncommon as previous reports suggest. Other complications of such treatment, including focal fibrosis, tubular atrophy, and glomerulosclerosis,⁴ are becoming apparent. A similar

destructive process, leading to irreversible myxoedema, might have occurred in our patients.

¹ Kjellmann, B F, Karlberg, B E, and Kågedal, B, *Nordisk Psykiatrisk Tidsskrift*, 1976, **30**, 528.

² McLarty, D G, *et al*, *British Medical Journal*, 1975, **3**, 623.

³ Brownlie, B E W, *et al*, *Australian and New Zealand Journal of Medicine*, 1976, **6**, 223.

⁴ Hestbeck, J, *et al*, *Kidney International*, 1977, **3**, 205.

(Accepted 21 February 1978)

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Complete heart block due to chronic chloroquine toxicity managed with permanent pacemaker

Chloroquine compounds are widely used as antimalarial and anti-inflammatory agents. The recommended dose for malaria prophylaxis is 300 mg of chloroquine phosphate a week.¹ Although up to 900 mg daily has been used to treat rheumatoid arthritis and systemic lupus erythematosus, the recommended maintenance dose is 250 mg daily.² Numerous toxic effects are associated with prolonged high dosage,¹ including cerebral (mainly headache), dermatological, myopathic, neuropathic, and psychiatric disorders and, most commonly, corneal deposition and retinal degeneration.³ All these, including keratopathy and "premaculopathy," are reversible when the drug is stopped. Severe macular degeneration is rarely reversible, however, and may develop after the end of treatment.³ The development of maculopathy depends on the dosage and duration of treatment. It usually occurs with doses above 300 mg daily and rarely before one year, although occasional idiosyncratic complications occur.

Reports of acute cardiotoxic effects are frequent and usually secondary to intentional overdosage.⁴ Acute idiosyncratic cardiotoxicity occurs even less commonly with chloroquine than with the related compound quinidine and is rarely ascribed to chronic chloroquine intoxication.

Case report

A 30-year-old Liberian businessman presented after four Stokes-Adams attacks in 12 hours. On admission to a local hospital he was in complete heart block with a ventricular rate of 15/min (fig 1). During the insertion of a temporary transvenous pacemaker he became asystolic with a period of ventricular tachycardia, but sinus rhythm returned after a DC shock. Electrocardiography showed right bundle-branch block and left axis deviation (fig 1). The conduction disturbance remained on transfer to this hospital two days later. There was no cardiomegaly, cardiac murmur, heart failure, or neurological, dermatological, or muscular abnormality. There was no history of angina, dyspnoea, or syncope. He was one of 18 siblings, and there was no family history of heart disease.

Malaria is endemic in Liberia, and the patient had taken six to eight chloroquine phosphate tablets (Avlocor, 155 mg chloroquine base) a week for about three years. Whenever he developed a headache he would take extra tablets, believing it to be a sign of cerebral malaria. He took no other drugs and smoked and drank only occasionally. Over the past five months he had experienced progressive loss of vision but continued to take chloroquine. He had severe bilateral scotomata with loss of central vision, so that he could vaguely recognise objects only at the peripheries of his fields. Ocular findings were diagnostic of chloroquine toxicity, with bilateral subepithelial corneal deposits and maculopathy (fig 2). Liver and spleen were not palpable. Haemoglobin, blood film, haemoglobin electrophoresis, and a sickle-cell test were normal. No malaria parasites were found, and liver function and cardiac enzymes were normal. An echocardiogram was normal and showed no evidence of cardiomyopathy.

Three days after transfer the conduction defect remained and the patient was intermittently dependent on the pacemaker. His bundle electrocardiography disclosed normal PA and AH conduction intervals but an HV interval of 65 ms (normal less than 55 ms) and an atrioventricular Wenckebach point of 140/min. A permanent lithium ventricular inhibited demand

FIG 1—Electrocardiograms (a) on admission, showing complete heart block; and (b) after insertion of temporary pacemaker, showing sinus rhythm, right bundle-branch block, and left axis deviation.

FIG 2—Ophthalmoscopic evidence of chloroquine retinopathy. Picture shows hyperpigmentation of macula and accumulation of chloroquine in melanin-containing cells (macular "bull's-eye"), paler central fovea, and surrounding retinal degeneration and oedema.

pacemaker (Teletronics 120B) was inserted with a transvenous right ventricular unipolar endocardial electrode. The threshold of stimulation was 0.3 V. The patient returned to Liberia and was advised not to take chloroquine or related compounds again.

Comment

The therapeutic benefit of chloroquine depends on its interaction with DNA, especially in the mitochondria. In common with other class 1 antiarrhythmic compounds it has quinidine-like effects, being negatively inotropic and chronotropic, and thus causes decreased conduction in excitable cardiac tissues. It is also a prostaglandin antagonist and has been used experimentally for closing a patent ductus arteriosus.⁵ In acute cardiotoxicity⁶ death is secondary to the negative inotropism and chronotropism, with prolongation of His-Purkinje conduction and suppression of sinus node function leading to idioventricular rhythm, ventricular tachycardia, or fibrillation.