single dose of lithium or phenytoin sodium was given to the rats before administering tranylcypromine (a monoamine oxidase inhibitor) plus L-tryptophan. Moreover, if either drug was given in multiple doses over two days there was a pronounced increase in brain synthesis of serotonin. Although they did not examine the combined effects of lithium and phenytoin sodium, they drew attention to their similar action. Possibly the two drugs acted synergistically in our patient, with the resultant toxicity despite normal serum lithium concentrations.

A third factor is that our patient probably had pre-existing minimal brain damage, which would explain his odd personality, abnormal EEGs, and history suggestive of epilepsy. There is the remote possibility that such patients have an abnormally low tolerance to lithium.

All three hypotheses bear further investigation and should be considered if further cases of CNS toxicity occur in patients with therapeutic lithium concentrations. In general, closer observation should be kept for the possible synergistic action of drugs in patients who develop severe side effects.

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Ephedrine-induced cardiopathy

Increased secretion of adrenaline in phaeochromocytoma causes symptoms that mimic cardiomyopathy, such as cardiac enlargement, congestive heart failure, tachycardia, and arrhythmias.[1] We describe a patient who developed a similar syndrome after chronic, excessive ephedrine intake. So far as we know, such a case has never been described.

Case report

In 1974 a 35-year-old insurance agent was referred to our pulmonary unit from another hospital for treatment of bronchial asthma. He had had exercise-induced and hyperventilation asthma since the age of 14. In 1958 he began to take a cough mixture containing ephedrine that relieved his bronchial spasms. He progressively increased his ephedrine intake, until he was drinking more than a bottle a day, each of which contained 400 mg of ephedrine. He was also taking liberal doses of prednisolone intermittently, depending on how he felt. In 1972 and 1973 he was treated in another hospital for cardiac failure but continued to take the cough mixture.

On admission he complained mostly of general fatigue and shortness of breath. He was generally healthy but had a raised jugular venous pressure of 6 cm of water and a positive hepatojugular reflux. Examination of the lungs showed no abnormality. On cardiac examination there was a hyperdynamic left apical pulsation with a sinus tachycardia of 110 beats/min and a gallop sound. The extremities felt warm and there was a fine peripheral tremor. Arterial blood pressure was 100/80 mm Hg. The liver was palpable at the right lateral costal border, and there was no peripheral oedema.

The electrocardiogram showed sinus tachycardia of 110/min and left ventricular hypertrophy with strain pattern. Chest radiographs showed generalised cardiomegaly and normal lung fields. Biochemical investigations, including thyroid function studies and a corticotrophin test, gave normal results. No abnormality of lung function was detected, except for a carbon monoxide diffusing capacity of 23·5 ml/min. An external carotid pulse tracing showed depressed left ventricular function with a corrected left ventricular ejection time (LVET) of 65%.[2] End-diastolic pressures in the right and left ventricles were 10 mm Hg and 15 mm Hg respectively on catheterisation. Before and during catheterisation the patient had repeated short bouts of ventricular tachycardia. The aortic pressure showed a mechanical alternans of 10-15 mm Hg and the cardiac output was 4·37 l/min recumbent and 3·44 l/min sitting. He did not undergo a stress test because of the arrhythmias, and the mechanical alternans indicated poor ventricular function.

Routine treatment for cardiac decompensation was begun, and ephedrine was withheld. Prednisolone was progressively withdrawn, and beclomethasone dipropionate aerosol combined with salbutamol aerosol was substituted. Since complete bed rest was considered essential the patient stayed in hospital for five months, and there were no further signs of decompensation on continuous treatment with digitalis, salt restriction, and diuretics. He had no asthmatic attacks. External carotid tracing showed improved left ventricular function, with a corrected LVET of 85%.

A cardiac catheter was reinserted and the patient underwent a stress test on a bicycle ergometer, which showed end-diastolic pressures of 10 mm Hg in the right ventricle and 13 mm Hg in the left ventricle. The resting cardiac output was 4·3 l/min, increasing to 6·1 l/min after four minutes' 20-W cycling. After exercise the patient was exhausted, and his mixed venous oxygen saturation was decreased from 75% to 30%, indicating important peripheral oxygen extraction. Cardiomegaly was still present radiographically.

During the next two years cardiac function progressively improved and treatment for heart failure was withdrawn when no abnormality was detectable in the electrocardiogram or radiographically. The corrected LVET on the mechanocardiogram was 92% after one year and 98% after two years.

At cardiac catheterisation 14 months after discharge the end-diastolic pressure was 2 mm Hg in the right ventricle and 5 mm Hg in the left ventricle. The resting cardiac output was 6 l/min, increasing to 16·5 l/min on a progressive stress test, with an end-diastolic pressure of 6 mm Hg in the left ventricle. The patient returned to work at the end of 1977.

Comment

Our patient's longstanding abuse of high doses of ephedrine produced symptoms resembling those of cardiomyopathy. Ephedrine stimulates both alpha- and beta-receptors. Part of its peripheral action is due to release of noradrenaline, but it also has direct effects on receptors. Its effects on the cardiovascular system are similar to those of adrenaline.

The clinical, haemodynamic, and electrocardiographic features of heart disease in our patient resembled those seen in phaeochromocytoma.[1 3] Prolonged bed rest, continued after discharge, may have contributed to the favourable outcome, as in other types of toxic cardiopathy.[4] The progressive resolution of symptoms after withdrawal of ephedrine suggests a causal relation between the cardiac disorder and the drug abuse.

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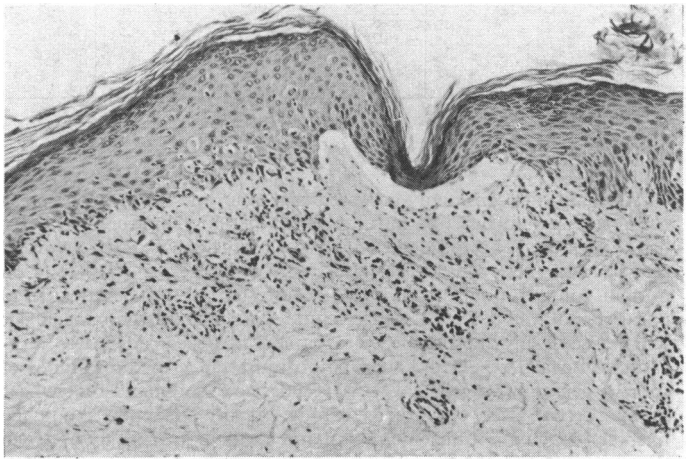
Bullous lichen planus caused by labetalol

The recognition of drug-induced lichen-planus-like eruptions is of great importance. Lichen planus induced by agents such as gold or antimalarials may be severe and permanently disfiguring,[1] while lichenoid eruptions after treatment with certain beta-blockers may be associated with serious damage to other organs.[2 3]

We report a case of atypical lichen planus with blister formation that occurred during treatment with a new beta-blocking agent, resolved after withdrawal, and recurred on challenge with the drug.

Case report

A 67-year-old man took labetalol (Trandate) 400 mg thrice daily and clonidine 0·3 mg daily from June 1977 for hypertension. Methyldopa had been withdrawn because of diarrhoea, and propranolol and clonidine had proved ineffective. Twelve weeks after beginning labetalol he developed an itchy eruption on his penis, which spread to the trunk and limbs. When he attended hospital 10 weeks later the eruption consisted of reddish purple macules and papules, many of which were oval and had a pityriasis-rosea-like distribution on the trunk. On the legs many of the lesions were bullous. Wickham's striae were present on the glans penis, and typical lichen planus lesions were also seen on the limbs. Biopsy of one of the lesions showed an infiltrate of mononuclear cells in the upper dermis associated with liquefactive degeneration of the basal layer and early bulla formation. Some necrotic keratinocytes were present in the epidermis (figure). Labetalol and clonidine were replaced by atenolol and Moduretic. Dilute topical steroids were given for symptomatic relief, but within two days after altering his antihypertensive treatment his symptoms had settled and topical agents were discontinued. One month later severe post-inflammatory pigmentation was visible on the trunk but no inflammatory component was present. Treatment with labetalol 200 mg thrice daily was restarted. After 15 days he noted itching of his penis; five days later examination showed lichen planus lesions on the penis, with reactivation of the lesions on the trunk. Labetalol was discontinued.



Histological appearance of biopsy specimen. (H and E. × 116.)

Comment

The rapid clearance of a lichen-planus-like rash after withdrawal of labetalol with recurrence on challenge with the drug is good evidence for a causal link; furthermore, histological examination showed changes similar to those seen in reactions to other beta-blockers.[2] Labetalol is a new drug that has both alpha- and beta-blocking actions. There are no previous reports of lichenoid eruptions occurring after its use, and it is chemically unrelated to other beta-blocking agents. As propranolol,[4] oxprenolol,[5] and practolol have caused lichenoid reactions,[5] beta-blocking activity itself may be important in the pathogenesis.

We believe that the early recognition of lichenoid reactions to new beta-blocking agents is of great importance and may allow us to prevent the serious damage that has occurred in other organs from this group of drugs.

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SHORT REPORTS

Hypothalamic hypopituitarism from "normal pressure" hydrocephalus

Chronic intracranial hypertension has long been assumed to be a cause of hypopituitarism.[1] We report here a case in which the intermittently raised cerebrospinal (CSF) pressure in "normal pressure" hydrocephalus[2] seems to have produced hypothalamohypophyseal failure.

Case report

A 41-year-old salesman presented with a seven-year history of progressive dementia, a four-year history of gait disturbance, and a six-month history of urinary incontinence. His previous medical history had been healthy apart from a reduced beard growth for one year.

Examination showed drowsiness, confusion, disorientation, dyspraxic arms, paralysed legs, extensor plantar responses, and scanty axillary hair. Investigation showed bilateral delta wave activity, mainly in the anterior EEG leads, with dilated ventricles and normal cortical sulci on computerised axial tomography. At ventriculography air could not be manipulated over the hemispheres. Mild, non-specific neuronal atrophy was found in parietal lobe tissue. Overnight CSF pressure, obtained by direct ventricular manometry, ranged from 0 to over 40 cm H_2O during quiet sleep. Other CSF tests gave normal results.

Endocrinological investigations, which were conducted more than three weeks after completing short-term dexamethasone treatment, showed normal thyroid function but low total androgens on two separate occasions (2·4 and 1·1 nmol/l (0·69 and 0·32 ng/ml)). Abnormal growth hormone and cortisol secretion was shown after insulin-induced hypoglycaemia and after glucagon (see table). The luteinising hormone (LH) response to hypothalamic releasing hormone was abnormal and the high basal prolactin concentration suggested hypothalamic damage. Adrenal responsiveness to tetracosactrin was normal (cortisol 104-379 nmol/l (3·8-13·6 μg/100 ml)).

Results of pituitary function tests

Time (min)	Blood* sugar (nmol/l)	Cortisol* (nmol/l)	Growth* hormone (mU/l)	Thyrotrophin† (mU/l)	LH‡ (U/l)	FSH‡ (U/l)	Prolactin (mU/l)
0	4·2	220 (142)	<1 (1)	6	1	1	444
30	1·9		2 (1)	17	3		827
60	3·1	396 (254)	3 (5)	21	4		668
90	3·3	315 (227)	2 (3)				630
120	3·4	266 (227)	1 (<1)				537
150		(230)	(3)				

*Figures in parentheses are results after glucagon (1 mg intramuscularly); other figures are results after insulin-induced hypoglycaemia.
†Results after thyrotrophin releasing hormone (100 μg).
‡Results after luteinising hormone-releasing hormone (200 μg).
Conversion: SI to traditional units—Glucose: 1 mmol/l ≈ 18 mg/100 ml. Cortisol: 1 nmol ≈ 0·036 μg/100 ml.

Treatment with gonadotrophin-releasing hormone (500 μg subcutaneously every eight hours for two weeks) restored normal pituitary responsiveness (LH levels 2, 23, and 20 U/l at 0, 30, and 60 minutes, basal follicle stimulating hormone 8 U/l, and androgen 8·0 nmol/l), which was lost two months later, when hormone levels after testing were undetectable. Assays were performed subject to national quality control criteria. Routine haematological and biochemical screening, posterior pituitary function, and pituitary fossa tomography gave normal results.

Insertion of a Spitz-Holter shunt improved his drowsiness, orientation, and restored his ability to walk.

Discussion

Hypopituitarism from sustained intracranial hypertension is well documented.[3 4] Wolman[3] suggested that pituitary infarction might be