

- <sup>107</sup> Livingston, S, in *Comprehensive Management of Epilepsy in Infancy, Childhood and Adolescence*, p 159. Springfield, Illinois, Charles L Thomas, 1972.
- <sup>108</sup> Melin, J, *Journal of Pediatrics*, 1953, **43**, 652.
- <sup>109</sup> Veeder, B S, *Journal of Pediatrics*, 1953, **43**, 746.
- <sup>110</sup> Illingworth, R S, *British Medical Journal*, 1965, **1**, 1124.
- <sup>111</sup> Stephenson, J B P, *British Medical Journal*, 1977, **3**, 261.
- <sup>112</sup> Krugman, S, *Journal of the American Medical Association*, 1977, **237**, 2228.
- <sup>113</sup> Public Health Service Advisory Committee on Immunisation Practices, *Morbidity and Mortality Weekly Reports*, 1972, **21**, 4.
- <sup>114</sup> American Academy of Pediatrics, *Report of the Committee on Infectious Disease*, 7th edn. Evanston, Illinois, AAC, 1974.
- <sup>115</sup> Cockburn, W C, *Bulletin of the World Health Organisation*, 1958, **19**, 109.
- <sup>116</sup> Burland, W, et al, *Medical Officer*, 1968, **119**, 17.
- <sup>117</sup> Griffith, A H, *Medical Officer*, 1970, **123**, 97.
- <sup>118</sup> Rodgers, J, *Medical Officer*, 1970, **123**, 153.

- <sup>119</sup> Williams, R M, *Medical Officer*, 1969, **122**, 274.
- <sup>120</sup> Dick, G, *Lancet*, 1976, **2**, 1239.
- <sup>121</sup> Tiru, M, *WHO Informal Consultation on Immunisation against Whooping Cough*. Utrecht, December 1974.
- <sup>122</sup> Sauer, L W, and Tucker, W H, *American Journal of Public Health*, 1954, **44**, 784.
- <sup>123</sup> Snell, E S, and Burland, W L, *Medical Officer*, 1970, **123**, 36.
- <sup>124</sup> Fedrick, J, *British Journal of Preventive and Social Medicine*, 1973, **27**, 217.
- <sup>125</sup> Froggatt, P, Lynas, M A, and MacKenzie, G, *British Journal of Preventive and Social Medicine*, 1971, **25**, 119.
- <sup>126</sup> Peterson, D R, *American Journal of Epidemiology*, 1966, **84**, 478.
- <sup>127</sup> Richards, I D G, and McIntosh, H T, *Archives of Disease in Childhood*, 1972, **47**, 697.

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## SIDE EFFECTS OF DRUGS

### Severe lithium toxicity with "normal" serum concentrations

The severity of intoxication from lithium treatment has been thought to vary with the serum concentrations. Thus anorexia, diarrhoea, vomiting, loss of weight, and tremor are common findings when concentrations exceed 1.5 mmol(mEq)/l; and generalised coarse tremor, hypertonia, and hyperactive reflexes, epileptiform seizures, and coma have been described in patients with concentrations exceeding 4 mmol/l.<sup>1</sup> We, however, report a case of severe central nervous system (CNS) toxicity that went unrecognised for many weeks because the serum concentrations of lithium were in the normal therapeutic range.

#### Case report

A 26-year-old gardener had a 10-year history of admissions for manic depressive psychosis. He required considerable supervision in his work and was a shy, dependent, immature man with difficulties in social skills. For four years he had been taking 100 mg phenytoin sodium and 30 mg phenobarbitone three times a day after several episodes of loss of consciousness. He continued with this treatment throughout. Electroencephalography (EEG) showed 4-6 cps theta rhythm with occasional left-sided emphasis, especially in the frontal area.

In September 1973 he was admitted to hospital with hypomania and stabilised with lithium carbonate (Priadel) 1200 mg by mouth daily. Morning serum concentrations were initially in the therapeutic range but then began to fall, though the dosage remained constant (table). Over the next few months stepped increases in dosage to 2400 mg daily produced only a moderate response in serum concentrations.

He was readmitted on 19 June 1974 with a further hypomanic episode. During the previous two months he had developed a coarse regular tremor, mainly in the legs. He looked generally unwell and had been losing weight. His appetite was poor but he did not have diarrhoea, abdominal pain, nausea, or polyuria. On 2 July his serum lithium concentration was 1.2 mmol/l (table), but in view of his clinical state the dosage was reduced to 2000 mg daily. Physical examination showed no other abnormality and all routine blood test results were normal. Within three weeks his hypomanic state had resolved; he was continuing with 2000 mg daily and his serum

concentration was 0.8 mmol/l. By this time the tremor had become very coarse and was affecting his whole body. On 26 July the lithium was stopped but he continued to deteriorate; he became restless, shaking all over and sweating profusely. Muscle tone became hypertonic and reflexes hyperactive. One week after the lithium was stopped he became drowsy and drifted into coma. He was deeply unconscious and unresponsive to painful stimuli for five hours.

During the coma he was given only intravenous fluids. Results of investigations were: plasma sodium 139 mmol(mEq)/l, potassium 3.8 mmol/l, bicarbonate 30 mmol/l, urea 4.6 mmol/l (28 mg/100 ml), and protein 66 g/l; packed cell volume 0.41 (41%); white cell count  $9 \times 10^9/l$  (9000/mm<sup>3</sup>), normal differential; erythrocyte sedimentation rate 1 mm in first hour; midstream specimen of urine, no pathogens; EEG, 4-6 cps theta activity with proximal bursts of 1-2 cps throughout and no focal features; chest radiograph normal.

Two days later he was up and about. Tremor was still pronounced, however, though less coarse. He made steady progress and was followed up regularly as an outpatient. Phenytoin sodium 100 mg and phenobarbitone 30 mg three times daily were continued but he was not given lithium. The fine tremor took about six months to disappear, and two years after the episode he was well and had needed no further admissions.

#### Discussion

This patient had a history suggestive of chronic brain damage or epilepsy or both and was taking phenytoin sodium. The case raises several questions.

(1) Why was there a gradual fall in the serum lithium concentrations despite steady dosage after treatment was first begun? Eventually the patient's requirements for lithium doubled, though his serum concentration remained in the therapeutic range (see table).

(2) Why did his serum lithium concentration not correlate with the degree of clinical toxicity?

(3) Is there any interaction between lithium carbonate and phenytoin sodium that could account for the severe CNS toxic reaction despite a normal blood concentration?

The patient's parents were confident that he had been taking the lithium tablets while being treated as an outpatient; during the last month, when he was an inpatient, this was supervised. Lithium was estimated with a standard flame photometer to within 0.1 mmol/l. There is no reason to believe that this was inaccurate.

Lithium is usually measured in serum with the assumption that dynamic equilibrium is established between tissues and blood stream. Red blood cells (RBC), however, concentrate lithium and there may be important interindividual differences in RBC:plasma ratios. These differences are partly genetic<sup>2</sup> but may be related to depression<sup>3</sup> and manic depressive psychosis.<sup>4</sup> The RBC:plasma ratio in any one individual appears to be stable over time.<sup>5</sup> An important factor in lithium toxicity in some patients may be the RBC lithium concentration or the ratio of this to the plasma lithium concentration. It would be well if these determinations could be made in patients with toxic symptoms in the absence of high serum lithium concentrations.

Another explanation is suggested by the work of Graham-Smith and Green,<sup>6,7</sup> who investigated CNS hydroxytryptamine function in rats. They found that lithium and phenytoin sodium have several similar pharmacological properties. In a series of controlled investigations they observed that hyperactivity was significantly enhanced when a

Dosage and serum concentrations of lithium from time of first admission with hypomania

Date (1973)	Dose (mg/day)	Serum lithium concentrations mmol(mEq)/l	Date (1974)	Dose (mg/day)	Serum lithium concentrations mmol(mEq)/l
24 Sept	1200	1.2	4 Jan	2000	0.9
8 Oct	"	0.9	7 Feb	"	1.0
12 "	"	0.4	16 May	2400	1.1
18 "	1600	0.4	13 June	"	1.3
24 "	"	0.4	19 "	"	"
8 Nov	2000	0.8	2 July	2400	1.2
15 "	"	1.1	25 "	2000	0.8
28 "	"	1.3	26 "	Lithium withdrawn	"
13 Dec	"	1.0	15 Aug	Nil	Nil

Conversion: SI to traditional units—Lithium: 1 mmol = 1 mEq.

single dose of lithium or phenytoin sodium was given to the rats before administering tranlycypromine (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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<sup>1</sup> Verbov, J L, Phillips, J D, and Fife, D G, *Postgraduate Medical Journal*, 1965, **40**, 190.

<sup>2</sup> Dorus, E, *et al*, *Archives of General Psychiatry*, 1974, **31**, 463.

<sup>3</sup> Mendels, J, and Secunda, S K, editors, in *Lithium*. New York, Gordon and Breach, 1972.

<sup>4</sup> Lyttkens, L, Soderberg, U, and Wetterberg, L, *Lancet*, 1973, **1**, 40.

<sup>5</sup> Mendels, J, and Frazer, A, *Journal of Psychiatric Research*, 1973, **10**, 9.

<sup>6</sup> Graham-Smith, D G, and Green, A R, *British Journal of Pharmacology*, 1974, **52**, 19.

<sup>7</sup> Green, A R, and Graham-Smith, D G, *Neuropharmacology*, 1975, **14**, 107.

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## Ephedrine-induced cardiopathy

Increased secretion of adrenaline in pheochromocytoma causes symptoms that mimic cardiomyopathy, such as cardiac enlargement, congestive heart failure, tachycardia, and arrhythmias.<sup>1</sup> 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%.<sup>2</sup> 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 pheochromocytoma.<sup>1-3</sup> Prolonged bed rest, continued after discharge, may have contributed to the favourable outcome, as in other types of toxic cardiopathy.<sup>4</sup> The progressive resolution of symptoms after withdrawal of ephedrine suggests a causal relation between the cardiac disorder and the drug abuse.

<sup>1</sup> Garcia, R, and Jennings, J M, *American Journal of Cardiology*, 1972, **27**, 568.

<sup>2</sup> Willems, J, and Kesteloot, H, *Acta Cardiologica*, 1967, **12**, 401.

<sup>3</sup> Baker, G, *et al*, *American Heart Journal*, 1972, **83**, 688.

<sup>4</sup> Regan, T J, *Circulation*, 1971, **44**, 957.

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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,<sup>1</sup> while lichenoid eruptions after treatment with certain beta-blockers may be associated with serious damage to other organs.<sup>2-3</sup>

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.