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Neurotoxic Effects of Lithium with Delayed Rise in Serum Lithium Levels

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Neurotoxicity is a rare but well recognized unwanted effect of lithium therapy (Moore, 1972; von Hartitzsch *et al*, 1972; Tyrer and Shopsin, 1980) which tends to be associated with high serum lithium levels. In clinical practice it is normally assumed that once signs of toxicity are detected and treatment stopped, serum levels will return to normal. We report here a patient who developed toxic symptoms while her serum levels were in the therapeutic range but who developed severe neurotoxic sequelae and high serum levels after treatment was stopped.

Case History

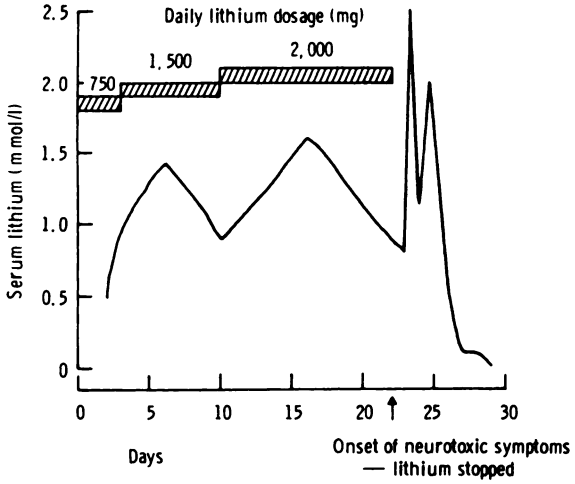
A 43-year-old woman with a history of manic-depressive illness since the age of 21 was treated with lithium carbonate ("Camcolit") 250 mg thrice daily after becoming hypomanic. She was initially treated as a day-patient and it was hoped that lithium alone would bring her hypomania under control without the addition of neuroleptic drugs. Unfortunately her manic behaviour become more pronounced and she was admitted to a psychiatric hospital. She remained overactive with disruptive and aggressive behaviour despite increase in lithium dosage, resulting in normal serum levels (Fig). A single intramuscular dose of 100 mg chlorpromazine was then given and thioridazine 100 mg thrice daily added to her treatment regimen. Two days later she developed nausea and diarrhoea and became confused and disorientated. All medication was stopped but 24 hours later she was semicomatose and was transferred to a general hospital. On the morning of transfer her serum lithium level was 0.8 mmol/l but lithium levels taken at noon and 2200 hours were 2.4 and 2.5 mmol/l respectively. These specimens were later reanalysed and it was confirmed that there was no laboratory error.

After transfer she was in a stuporose state, with her arms held rigidly in flexion and her legs in extension, but she also had a marked tremor of limbs and trunk. She was mildly pyrexial but apart from that general examination was normal, with a blood pressure of 125/85 mm Hg. At this stage her serum urea was 12.3 mmol/l and her serum calcium 2.77 mmol/l. She was treated with forced alkaline diuresis over a 24 hour period and her lithium fell to 1.2, her urea to 3.2 and calcium to 2.11. The clinical state did not alter. Within 18 hours of stopping the diuresis the lithium level had risen to 2.0. By this stage she was unconscious with decerebrate rigidity, opisthotonos and marked generalized tremor. A lumbar puncture was normal. A further period of forced diuresis was performed and her serum lithium fell rapidly. Her clinical state responded more slowly. After 48 hours she responded to command and after a further 48 hours she was talking. The abnormal posture and rigidity improved with the level of consciousness. As she became more co-operative and mobile it was obvious she had a marked cerebellar ataxia of the limbs and trunk, a marked cerebellar dysarthria and nystagmus. The plantars had always remained flexor and the blood pressure was always within the normal range. Two further lumbar punctures were done in the acute phase and they were normal.

After a period of six weeks the clinical state was a marked cerebellar disturbance with ataxia and dysarthria. There were no pyramidal, cranial nerve or sensory signs. A computerized axial tomography (CAT scan) at that stage was normal. Eighteen months later her ataxia and speech have improved but she still has difficulty in walking and although she can cook and do many of her domestic chores, she cannot carry out tasks requiring fine co-ordination. A curious consequence has been that her mood has remained stable without any need for psychotropic drugs since the neurotoxic episode.

Comment

Lithium alone is a recognized initial treatment for early hypomania (Shaw, 1979) and is often preferred because of alleged neurotoxic damage when neuroleptic drugs, particularly haloperidol, are combined with lithium (Cohen and Cohen, 1974; Loudon and Waring, 1976). Neurotoxicity has also been reported when lithium carbonate is used in combination with



FIG—Delayed rise in serum lithium levels after stopping lithium therapy.

thioridazine even when the serum lithium levels were within the therapeutic range (Spring, 1979) and in our case even the short duration of therapy (48 hours) with thioridazine may have contributed to the development of lithium toxicity. Neurotoxicity has also been reported with normal serum lithium levels when a patient became comatose one week after stopping lithium therapy (Speirs and Hirsch, 1978). In our patient the serum levels rose for 48 hours after lithium was withdrawn, and rose again after forced alkaline diuresis was stopped, findings which are difficult to explain from the known pharmacokinetics of lithium (Tyrer, 1978). It seems most likely that redistribution of lithium from other body compartments (particularly bone, where lithium tends to accumulate, (Birch, 1974) was the cause of the delayed rise in serum levels.

It is unlikely that the neurological symptoms shown could have an independent organic basis. The presence of a lowered level of consciousness, abnormal posturing and marked tremor were entirely compatible with a diffuse metabolic encephalopathy. There were no signs of a focal brain stem infarction and the lumbar puncture ruled out such diagnoses as encephalitis and meningitis. The persisting signs are restricted to the cerebellum and suggest a cellular dysfunction. The CAT scan rules out an infarction of the cerebellum and there were no clinical signs to support any brain stem involvement. The clinical inference must be that lithium toxicity has caused a permanent diffuse cerebellar defect.

These findings and those of other authors (Speirs and Hirsch, 1978; Newman and Saunders, 1979) throw doubt on the value of measuring serum (and plasma) lithium levels as an index of toxicity, and suggest that clinical evidence of unwanted effects is a better guide. It has been proposed that measurement of red blood cell lithium levels may be a better indication of toxicity than serum estimations (Hewick and Murray, 1976) but in one recent report of neurotoxicity red cell and plasma lithium levels correlated well (Pringuey *et al*, 1981). Although the treatment of mania with lithium alone is of proven efficacy, its potential dangers need emphasising and the recording of normal serum lithium levels during treatment may be an exercise in false security.

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References

AGULNIK, P. L., DIMASCIO, A. & MOORE, P. (1972) Acute brain syndrome associated with lithium therapy. *American Journal of Psychiatry*, **129**, 621–3.

BIRCH, N. J. (1974) Lithium accumulation in bone after oral administration in rat and in man. *Clinical Science and Molecular Medicine*, **46**, 409–13.

COHEN, W. J. & COHEN, N. H. (1974) Lithium carbonate, haloperidol and irreversible brain damage. *Journal of the American Medical Association*, **230**, 1283–7.

HEWICK, D. S. & MURRAY, N. (1976) Red blood cell levels and lithium toxicity. *Lancet*, *ii*, 473.

LOUDON, J. B. & WARING, H. (1976) Toxic reactions to lithium and haloperidol. *Lancet*, *ii*, 1088.

NEWMAN, P. K. & SAUNDERS, M. (1979) Lithium neurotoxicity. *Postgraduate Medical Journal*, **55**, 701–3.

PRINGUEY, D., YZOMBARD, G., CHARBIT, J. J., PORTUGAL, H., SAINGRA, A., FRAYSSINET, R., MILECH, T. & DUFOUR, H. (1981) Lithium kinetics during haemodialysis in a patient with lithium poisoning. *American Journal of Psychiatry*, **138**, 249–51.

SHAW, D. M. (1979) Lithium and antimanic drugs: clinical usage and efficacy. In *Psychopharmacology of Affective Disorders* (eds. E. S. Paykel and A. Coppen). Pp 179–192. Oxford: Oxford University Press.

SPEIRS, J. & HIRSCH, S. R. (1978) Severe lithium toxicity with 'normal' serum concentrations. *British Medical Journal*, *i*, 815–6.

SPRING, G. K. (1979) Neurotoxicity with combined use of lithium and thioridazine. *Journal of Clinical Psychiatry*, **40**, 135–8.

TYRER, S. & SHOPSIN, B. (1980) Neural and neuromuscular side effects of lithium. In *Handbook of Lithium Therapy*. (ed. F. N. Johnson). Pp 289–309. Lancaster: MTP Press.

—— (1978) Lithium toxicity. *British Medical Journal, i*, 1281–2.

VON HARTITZSCH, B., HOENICH, N. A., LEIGH, R. J., WILKINSON, R., FROST, T. H., WEDDEL, A. & POSEN, G. A. (1972) Permanent neurological sequelae despite haemodialysis for lithium intoxication. *British Medical Journal, iv*, 757–9.

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