Lithium toxicity induced by triamterene-hydrochlorothiazide

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Summary

Two patients on long-term lithium therapy for manic-depressive psychosis developed serious toxicity within days of being prescribed a combination of triamterene (50 mg) and hydrochlorothiazide (25 mg) for mild symptomless hypertension. Reduced clearance of lithium has been reported to follow its concurrent administration with diuretics that deplete both sodium and potassium. A combination of triamterene with thiazide has not been shown previously to precipitate lithium toxicity.

Introduction

Lithium salts are now widely used as therapeutic agents in affective disorders both for treatment and as prophylaxis (Task Force on Lithium Therapy, 1975). During treatment with lithium, serum levels have to be maintained within a narrow range: low levels lack effect and high levels are associated with a risk of side effects or intoxication. Since lithium is excreted exclusively by the kidneys, drugs and procedures which alter its renal clearance are potentially dangerous to patients on lithium. Diuretics that deplete sodium and potassium, e.g. thiazides, frusemide and ethacrynic acid, have been shown to increase proximal tubular reabsorption of lithium and thus can lead to substantial decrease in its clearance (Petersen *et al.*, 1974; Baer, Platman and Fieve, 1972).

Case reports

Case 1.

An obese housewife aged 54 years had been treated with lithium carbonate (1000-1200 mg daily in divided doses) for 5 years. She was admitted in early June 1979 to a psychiatric hospital for control of a manic episode. In addition to lithium (1000 mg daily) she was given mianserine hydrochloride (30 mg) and because her BP was 180/110 mm Hg, dyazide was started (one tablet twice daily). Over the next week, she became progressively more drowsy,

confused and anorexic; her speech was slurred and there were widespread muscular fasciculations. Serum lithium concentrations increased from within therapeutic limits (0.6-1.2 mmol (mEq)/l) to 2.70 mmol (mEq)/l. She was therefore transferred to the renal unit at East Birmingham Hospital: the lithium mianserine and dyazide were stopped, and in view of adequate renal function (urea 7.8 mmol/l and creatinine 120 μ mol/l), forced alkaline diuresis was started (Gains and Serrand, 1970; Forrest, 1975). After 5 days, the serum lithium had fallen to undetectable levels, and the patient's condition considerably improved. However, on the 9th hospital day, she died from a massive pulmonary embolus.

Case 2.

A 63-year-old housewife had been treated with lithium one g daily for at least 3 years. She had recently been found to be hypothyroid, but lithium had not been withdrawn. She was also started on triamterene and hydrochlorothiazide, one tablet twice daily for mild hypertension (BP 180/100 mmHg). She presented to the authors one week later with increasing confusion, lethargy, anorexia and occasional muscular twitching. Serum lithium was 3.5 mmol/l on admission, with blood urea of 7.0 mmol/l and creatinine 160 μ mol/l. Again, lithium and triamterene hydrochlorothiazide were discontinued and forced alkaline diuresis begun. After 7 days serum lithium was undetectable and she made an uneventful recovery.

Discussion

Baer *et al.* (1972) gave chlorothiazide (one g/day) to 2 patients stabilized on lithium but had to stop after 3 days when one of the patients exhibited signs of lithium neurotoxicity and serum lithium was in the toxic range. Himmelhoeh *et al.* (1977) studied 12 patients who underwent mood swings while receiving lithium and a thiazide diuretic. Eight of the 12 patients improved significantly, 2 showed probable improvement; the remaining 2 did not improve.

Seven of the patients, however, developed symptoms of lithium toxicity.

An interesting aspect of diuretic interaction with lithium is that potassium-sparing diuretics, e.g. spironolactone, amiloride and triamterene, either do not affect serum lithium levels or cause a transient rise in its clearance (Baer *et al.*, 1972). Thus, the precipitation of lithium toxicity by a combination of hydrochlorothiazide (50 mg) and amiloride (5 mg) (Macfie, 1975) and by triamterene+hydrochlorothiazide, as reported here, is presumably related to the thiazide component.

As pointed out elsewhere (Ascione, 1977), the clinical evidence for this drug interaction is mostly anecdotal or derives from uncontrolled clinical studies. Nonetheless, sufficient evidence exists to make one wary of prescribing a potassium- and sodium-depleting diuretic to a patient stabilized on lithium. Furthermore, these diuretics should not be given to any pregnant patient because of the increased danger of lithium toxicity in the newborn (Weinstein and Goldfield, 1970).

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