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CASE REPORT

Response to Clomipramine after Short Course of Lithium in Treatment-resistant Depression: Does Lithium Have a 'Priming' Effect?

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A patient with a treatment-resistant depression of 15 months duration is reported. Initially he showed no response to clomipramine 150 mg daily for 1 month. When lithium carbonate 600 mg daily was added for 4 days he developed signs of lithium intoxication: drowsiness, confusion, and dystonia. After lithium was withdrawn the patient improved dramatically. We hypothesize that lithium may potentiate the antidepressant effect of tricyclic antidepressants (TCA) even if it is administered as a short course of treatment.

KEY WORDS—Lithium, clomipramine, treatment-resistant depression.

INTRODUCTION

There are many pharmacological strategies in the management of 'treatment-resistant' depression, including combination of monoamine oxidase inhibitors and tricyclic antidepressants (TCA) (White and Simpson 1981), intravenous application of antidepressants (Kielholz *et al.* 1981), and addition of thyroid hormones or lithium to TCAs (Goodwin *et al.*, 1982; de Montigny *et al.*, 1983; Price *et al.*, 1986). The mechanism of the last strategy has been suggested to be the enhancing effect of lithium on the serotonergic neurones following sensitization of the forebrain neurones to serotonin by TCAs (de Montigny *et al.*, 1981).

We now report the case of a 64-year-old man with major depressive illness, who was hospitalized for 15 months without any therapeutic response. Nevertheless, he exhibited a remarkable treatment response, when lithium carbonate 600 mg daily was added to clomipramine 150 mg daily for 4 days.

CASE HISTORY

Mr. C.Y. is a 64-year-old unemployed widower, who was admitted suffering from a severe depressive illness, with hypochondriacal features and suicidal ideation. During his first admission imipramine was started, the dose being increased to 200 mg daily. After 4 months there was no response. ECT was suggested but was refused by the patient.

Subsequently, imipramine was tailed off, and amphetamine up to 20 mg daily was administered. One month later the effect of amphetamine was still not impressive and the patient remained continuously depressed and hypochondriacal, although his suicidal ideas had disappeared. Amphetamine was, however, withdrawn in order to avoid dependence and the patient was transferred to the day hospital, where supportive psychotherapy and occupational therapy were given, but no psychoactive drugs. During this period the patient improved slightly, but remained socially withdrawn with practically no interests in anything. His continuous multiple somatic complaints made his children reject him. Prior to his readmission to the in-patient unit he presented with 1 week's history of increasing depression, diurnal mood variation, early morning wakening, poor appetite, almost complete functional inactivity, and strong suicidal ideation.

On readmission, examination revealed a weary-looking, thin man, only 46 kg in weight. He exhibited marked psychomotor retardation and had multiple somatic complaints, being preoccu-

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pied with themes of uselessness, hopelessness, and suicide. No delusions, hallucinations, or cognitive deficits were detected. Physical examination and laboratory investigations were normal. The dexamethasone suppression test showed non-suppression, with a post-dexamethasone cortisol level of 305 mmol/l at 4 pm.

At this stage, ECT was suggested, and was consented to by the patient this time. A total of 14 bilateral ECTs, twice-weekly, were given without any significant effect. Protriptyline was then administered, the dose being increased to 60 mg daily. After 2 months, l-tryptophan 2 g daily and thyroxine 0.1 mg daily were added. The patient complained of dry mouth, constipation, difficulty in passing urine, and postural dizziness; and he remained depressed and hypochondriacal. Three months later these drugs were tailed off and phenelzine was given a week later, the dose being increased to 60 mg daily. The patient developed repeated episodes of urinary retention. Phenelzine was therefore withdrawn and clomipramine treatment was initiated, the dose being increased to 150 mg daily, together with l-tryptophan 2 g daily. He complained of postural dizziness but no urinary retention; however, his depression and hypochondriasis persisted.

Finally, after 1 month on clomipramine and l-tryptophan, lithium carbonate 600 mg was added. Over the next 2 days the patient became progressively drowsy, his blood pressure dropped from his usual 120/70 mmHg to 90/60 mmHg, but his pulse rate and body temperature remained around 80/min and 36 °C, respectively. A complete blood picture, liver and renal function tests, blood sugar and thyroxine levels were normal. Serum lithium level was already 0.7 mmol/l on the third day of lithium therapy. On the fourth day the patient became confused and semi-comatose, and refused to eat. He developed dystonia with uprolling of the eyeballs, sustained flexion of upper limbs, and protrusion of the tongue. Lithium was withdrawn but treatment with clomipramine and l-tryptophan was continued. After sleeping for 1 day he became alert again, and the extrapyramidal symptoms disappeared. Surprisingly, during the following days his depression and hypochondriasis also subsided gradually. Eleven days after discontinuation of lithium he requested to be discharged, even though he had been an in-patient for 15 months. He was discharged on clomipramine 150 mg daily and l-tryptophan 2 g daily.

Follow-up for 4 months up to now has not shown any recurrence of the depressive or hypochondriacal symptoms.

DISCUSSION

A synergistic effect between lithium and clomipramine has been known for more than 10 years (O'Flanagan, 1973). Recently, Schrader and Levien (1985) reported a case of treatment-resistant depression responding to sequential administration of clomipramine and lithium. In our patient the appearance of toxic signs in the absence of any other identifiable causes forced us to withdraw lithium therapy. Occurrence of toxic effects at such a low serum lithium level suggests mutual potentiation of lithium and clomipramine. Disappearance of the toxic effects after discontinuation of lithium is further proof that the effects were caused by their mutual potentiation. The subsequent positive response to clomipramine, despite no response before lithium treatment, is interesting. It seems possible that lithium 'primed' the response to clomipramine – as if triggering a clomipramine response 'switch'. The exact mechanism of this 'priming' action is naturally not known, but the following explanation is offered:

Ouabain is a cardiac glycoside that inhibits the enzyme Na^+/K^+-ATPase, i.e. the 'sodium pump'. Lithium is known to decrease the rate of ouabain-binding to this enzyme, thus producing a significant increase in the sodium pump activity (Naylor *et al.*, 1974; Krishnan and Albers, 1980). Naylor *et al.* (1976) have reported that the therapeutic response to lithium is better in manic-depressive patients with low erythrocyte Na^+/K^+-ATPase activity than in patients with high enzyme activity. Recently, Lichtstein *et al.* (1985) discovered an ouabain-like compound (OLC) in mammalian brain and human cerebrospinal fluid. Lithium may increase the Na^+/K^+-ATPase activity by inhibiting central OLC, thus correcting an intrinsic neuronal cell membrane deficiency suggested in affective illness (Sen *et al.*, 1976). The possibly genetically determined impairment of the ouabain-sensitive sodium pump system may at least partially account for the non-response to TCAs in depressed patients. Increased Na^+/K^+-ATPase activity reverses the raised residual sodium in depression reported by Coppen (1965). Decrease in residual sodium may affect the excitability of brain cells,

rendering them more responsive to subsequent clomipramine.

It could be argued that the suggested 'priming' effect of lithium in our patients is unlikely, since lithium was administered for 4 days only. In experimental animal and human studies, however, it has been shown that relatively small and non-toxic doses of lithium are sufficient to induce major biochemical changes in the brain (Berndt, 1975; Ebstein *et al.*, 1976). In treatment-resistant depression with the suggested deficiency of the sodium pump, the inward transport and the uptake of the lithium ion may be augmented, thus rendering the brain more susceptible to lithium intoxication, even at lower plasma level. Furthermore, de Montigny *et al.* (1981) observed a marked alleviation of depressive symptoms within 24 hours of the addition of 900 mg of lithium carbonate to the daily dose of TCA in eight patients who had failed to respond to TCA after 3 weeks of treatment. A similar rapid effect of lithium has also been observed by Oulès and Boscredon (1977) in patients with refractory manic-depressive psychosis treated simultaneously by clomipramine or imipramine. Furthermore, in another series of nine TCA-resistant patients, de Montigny *et al.* (1983) noted a marked improvement 48 hours after lithium addition, and only five of these patients had a relapse 5 days after lithium discontinuation. Consequently, a short treatment course of lithium might prove sufficiently effective to initiate a more favourable outcome in treatment-resistant depressive episodes.

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