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*Reprints

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Response to Sequential Administration of Clomipramine and Lithium Carbonate in Treatment-Resistant Depression

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Treatment-resistant depression remains a significant clinical problem (Shaw, 1977); none of the currently available treatments for depression claim a 100% response rate. Often, particular treatment regimes for treatment-resistant depression such as a monoamine oxidase inhibitor (MAOI) and a tricyclic antidepressant (TCA) in combination, or stereotactic surgery, involve increased risk of immediate or long-term complications. A number of recent reports have stated that where depression has not responded to TCAs, it has responded if lithium carbonate was added (Heninger *et al*, 1983; de Montigny *et al*, 1983). It has been postulated that the administration of a three-week course of TCAs, followed by these in combination with lithium, is effective in relieving treatment-resistant depression. This is because of the added enhancing effect of lithium carbonate on serotonin-containing neurones, in the setting of the TCA having already sensitised forebrain neurones to serotonin (de Montigny *et al*, 1981). The following case is that of a 73-year-old man with major depression. This persisted for ten months without significant response to three courses of electroconvulsive therapy (ECT), (two unilateral and one bilateral), amitriptyline (AMT) in doses of up to 200 mg, and tranylcypromine in doses of up to 50 mg daily. He subsequently responded, one week after lithium had been added to a three-week course of clomipramine. This case would appear to describe the phenomenon previously reported, but we believe it to be the first report of the use of clomipramine, a drug with predominantly serotonergic effects, in sequential combination with lithium carbonate in the treatment of resistant depression.

Case history

Mr L J is a 73-year-old married, retired post office technician, who was admitted to the intensive care unit of a general hospital, following an overdose of 60 × 20 mg tablets of temazepam. There was a three-month history of increasing depressive symptoms, with diurnal mood variation, early morning wakening, poor appetite, intermittent suicidal ideation, low energy, and a complete loss of pleasure in his usual activities.

Prior to his illness, the patient's personality had been characterised by obsessional traits; he had been a very capable but overly-meticulous man in his working life, although quiet and reserved socially. He had few friends and few outside interests since his retirement, eight years prior to admission. He was the youngest of six children, and was now the only surviving member of his family. He had two children, and was in regular social contact with them. During the three months before admission, he became concerned over his wife's health and his ability to care for her. He was preoccupied with his inability to complete his taxation forms, and this, together with mounting concerns over personal poverty, immediately preceded his overdose.

There was a past history of four severe depressive episodes: initially in his late teens, then when aged 41, at the age of 54, and finally at 61 years; these had lasted about three months each. On these occasions he had been treated with ECT, and for the last 12 years, had been on a maintenance antidepressant (AMT, up to 100 mg). There was a family history of severe depression, a brother having committed suicide in his mid-40s after several severe depressive episodes treated with ECT, but no other family member having been affected.

He was transferred to the psychiatric unit. Mental state examination revealed a weary looking, elderly man, with both psychomotor retardation and marked agitation. His affect was depressed and he was preoccupied with themes of poverty, including ideas of a delusional intensity. On

formal testing, he showed no cognitive deficits, and physical examination was normal. A diagnosis of major depression with melancholia (recurrent) in a man with compulsive personality traits was made. A course of six unilateral ECTs was begun, and he was started on thioridazine, 200 mg a day, and chloral hydrate, 500 mg nocte, to control his agitation and insomnia. On admission, full blood count, erythrocyte sedimentation rate, urea and electrolytes, and thyroid function tests, B12 and folate, syphilis serology, and computer-assisted tomography (CAT scan) were normal. A dexamethasone suppression test (DST) was performed, showing non-suppression. Within two weeks of starting ECT, his mood was lifting, and he appeared less agitated. A week following cessation of his course of ECT, the DST showed suppression. He was feeling somewhat more optimistic, although he still complained of insomnia and was concerned about his recurrent constipation. He was discharged without medication, following his four-week stay in hospital.

Two weeks later a return of symptoms of motor restlessness, poor appetite, and a mild degree of weight loss were noted at out-patient review. He was restarted on AMT, 100 mg nocte, but after two weeks of out-patient therapy, there was further deterioration and he was readmitted.

He had fears of bowel cancer, but felt that any medical intervention would be useless. The DST was positive. He was started on a further course of ECT, but when there was no response to nine unilateral ECTs, he was given a further six bilateral seizures, together with the addition of AMT, up to a dosage of 200 mg. After the completion of his second course of ECT, there was only a slight elevation in his mood. As he was developing postural hypotension, and in the light of his poor response to combination therapy, AMT was ceased. After seven days, he was commenced on tranylcypromine (10 mg b.d.), and there was some response to this dosage after 2½ weeks. However, an increase in dosage, up to 50 mg a day, produced severe postural hypotension, without further improvement in his mental state.

Seven months after the onset of his depression, he remained severely agitated; despite intensive treatment, there was increasing hypochondriacal concern, which had a ruminative, obsessional quality. In the following weeks, he developed delusions that his teeth were decaying. His appetite remained poor, and he continued to lose weight despite nursing supervision at mealtimes. Thioridazine (up to 100 mg per day) and bromazepam (9 mg per day) were commenced, together with a reduction in his dose of tranylcypromine, to 20–30 mg per day. However, this combination did not alleviate either his postural hypotension or his symptoms of depression. These drugs were withdrawn over a week, and trifluoperazine (10–15 mg per day) was introduced, but severe extrapyramidal side-effects complicated treatment. His mental state continued to deteriorate, with severe subjective distress. Repeat DSTs continued to show non-suppression. In view of his distress and the deterioration in his mental state, a further course of bilateral ECT was commenced. After six seizures, as there was little change in his mental state, clomipramine (in dosages up to 150 mg per day) was commenced.

A medical review at this juncture revealed a mild anaemia, associated with lowered B12 levels (haemoglobin 11.6 grams d/litre, B12 160 pg per m/litre, serum folate 2.8 ng per m/litre); a Schilling's test was performed. This anaemia was presumed to be nutritional, and he was commenced on replacement therapy of hydroxocobalamin, 1000 mcgm, as his appetite remained extremely poor.

In the ten days following the completion of this course of ECT, there was only minimal change in his mood. In view of the chronicity and severity of his depression, it was decided at a case conference to commence a trial of lithium carbonate in combination with clomipramine. Clomipramine had been commenced three weeks before, but with little appreciable change in his mood. Within a week of attaining therapeutic lithium levels (0.75 mmols/litre), there was a dramatic change in mood and behaviour. His vegetative symptoms abated, he was less preoccupied with morbid themes, and interacted spontaneously with staff for the first time in ten months. He was discharged on a combination of lithium carbonate, 750 mg/day, and clomipramine, 100 mg/day. At repeated fortnightly follow-up, his outlook has remained positive and his symptoms in remission.

Discussion

A 'synergistic' effect between lithium and clomipramine has been reported (O'Flanagan, 1973), but we believe this to be the first report of treatment-resistant depression responding to a combination of clomipramine and lithium carbonate. The hypothesised mode of action for this effect relates to lithium carbonate's serotonin-enhancing properties. Clomipramine, with its potentiating effects of serotonergic function, would seem to be an appropriate TCA to combine with lithium carbonate in tricyclic non-responsive depression. It is noteworthy that our patient was not only tricyclic non-responsive, but also MAOI and ECT non-responsive, prior to the addition of lithium. de Montigny & Aghajanian (1980) have reported that ECT increases the responsiveness of rat forebrain neurones to iontophoretically applied 5HT. It would therefore be interesting to observe the effect of the addition of lithium carbonate to patients not responding to a course of ECT. An alternative explanation for our patient's sudden recovery might be that he responded to the Vitamin B12 replacement, which occurred concurrently with the addition of lithium carbonate. We feel this is unlikely, as Hallstrom (1969) has reported that in patients with Vitamin B12 deficiencies and affective disorders, the affective disorder does not resolve with Vitamin B12

replacement, but rather with appropriate antidepressant treatment.

It could be argued that the patient's improvement was merely a natural remission, not related to the addition of lithium carbonate. There is, of course, no way of determining this, apart from perhaps discontinuing the lithium. This was felt not to be ethically appropriate.

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