Toxic irreversible encephalopathy induced by lithium carbonate and haloperidol

A report of 2 cases

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Summary

Toxic irreversible encephalopathic syndromes developed in 2 patients treated with lithium carbonate and haloperidol. Symptoms consisted of lethargy, fever, tremulousness, confusion, and extrapyramidal and cerebellar dysfunction, accompanied by leukocytosis and elevated serum enzyme, blood urea nitrogen, creatinine and fasting blood glucose levels. One patient suffered widespread irreversible brain damage; the other was left with persistent dyskinesias. Although causal factors have not been identified, this report and others in the literature suggest that diffuse irreversible encephalopathy may occasionally develop in individuals with abnormal brain sensitivity to the lithium carbonate/haloperidol combination. Evidence for this is based on the fact that in our patients and others mentioned in the literature the dosage and blood levels of lithium were not high.

Lithium carbonate is probably the most effective therapy available for mania. It can produce euthymia without sedation and can therefore be used in subtoxic dosages. The time required for it to take effect differs from that of other neuroleptic agents; usually at least 5 - 10 days pass before full benefits are achieved. In order to overcome the disadvantage of delayed effect, a combined regimen of lithium carbonate and haloperidol at varying dosages has been advocated. The purpose of high doses of haloperidol is to obtain immediate amelioration of mania while awaiting the later, more specific effect of lithium carbonate, which can then be used for maintenance.

This report concerns 2 patients who were treated with a combined regimen of lithium carbonate and haloperidol. Both patients developed severe encephalopathic syndromes. One patient suffered widespread irreversible brain damage; the other was left with persistent dyskinesias. In both patients blood lithium levels were only slightly above the normal therapeutic range. This suggests that certain individuals may exhibit abnormal brain sensitivity to the lithium carbonate/haloperidol combination.

Case reports

Case 1

A 42-year-old woman was admitted to hospital in an agitated and confused state. Depressive episodes had occurred in the past, and a diagnosis of manic-depressive illness was made. At the time of admission she was taking lithium carbonate 750 mg daily and haloperidol 10 mg daily. On examination she was restless but not aggressive. Tremor at rest, rigidity, expressionless facies and generalized weakness were evident. Her speech was slow and dysarthric and she was unable to stand or walk without support. During examination she had one grand mal seizure which was controlled with intravenous phenytoin. During her stay in hospital her mental and physical condition deteriorated. She exhibited progressive clouding of sensorium and weakness, and had further grand mal seizures which were resistant to phenytoin. General examination on admission revealed a blood pressure of 100/60 mmHg, a pulse rate of 96/min and a temperature of 37.8°C. An ECG showed sinus rhythm of 100/min and diffuse nonspecific T-wave depression. Computed tomography (CT) of the brain was negative. Laboratory analysis revealed a white cell count of 12.7 x 10^9/l with a normal differential count, a haemoglobin value of 12.1 g/dl, and the following biochemical values: urea 16.2 mmol/l, creatinine 328 \( \mu \)mol/l, lactate dehydrogenase 240 mU/ml, creatine kinase 300 mU/ml and alkaline phosphatase 250 mU/ml. Lumbar puncture was negative. The serum lithium level on admission was 1.21 mmol/l (normal therapeutic range 0.6 - 1.2 mmol/l). Lithium carbonate therapy was discontinued, with the result that the patient's acute reaction subsided and she became gradually more lucid, less rigid, and less atactic. When seen 3 months after discharge she was conscious but with mask-like facies, markedly demented, incontinent and mute. She was completely helpless and exhibited occasional gross, wildly unco-ordinated movements of all extremities. Generalized increase in muscle tone was associated with positive frontal lobe release signs. She was transferred to a psychiatric institution.

Case 2

A 44-year-old man presented with a 2-week history of 'being shaky'. He had been taking lithium carbonate 750 mg daily for the past 12 months, and haloperidol (15 mg daily) had been introduced 3 weeks before presentation. On admission he was confused and atactic. His speech was slow and dysarthric and a coarse resting tremor was noted in both upper limbs. There was no nystagmus, but occasional oculogyric crises occurred. There were no focal neurological deficits and the optic fundi were normal. Laboratory analysis revealed the following: white cell count 22.0 x 10^9/l, haemoglobin value 8.5 g/dl, urea 15.7 mmol/l, creatinine 485 \( \mu \)mol/l, pH 7.32, bicarbonate 8.3 mmol/l, and a base excess of 16.4 mmol/l. An ECG showed a sinus rhythm of 110/min, axis +90° and diffuse T-wave
depression. The blood lithium level on admission was 1.24 mmol/l. The CSF was normal and CT was negative. Therapy consisted of discontinuation of lithium and correction of the acid-base status. Within 5 days the patient's myoclonus disappeared and a neurological examination was negative. When seen a month later he was alert, orientated and co-operative, and had normal speech. However, a prominent buccofacial dyskinesia had developed, as well as gross tremor at rest. He also had a slightly unsteady gait, cogwheel rigidity and mild diffuse muscle weakness.

Discussion

There was clinical evidence that both these patients suffered from a toxic reaction to the combined lithium carbonate/haloperidol regimen. Presenting features in both cases included weakness, lethargy, fever, tremulousness and increasing confusion. The second patient had marked extrapyramidal and cerebellar signs, whereas the first patient exhibited cerebellar extrapyramidal as well as marked epileptogenic activity. Both showed similar physiological and chemical reactions: leucocytosis, impaired renal function, ECG changes and fever. In both the biochemical abnormalities and clinical signs returned to normal several days after cessation of lithium carbonate/haloperidol therapy.

Most of the neurological signs observed, as well as fever, leucocytosis and elevated enzyme levels, have been established as transient effects of lithium carbonate or haloperidol therapy. Patient 1 suffered permanent sequelae that included a striking cerebellar-parkinsonian syndrome with dementia. Patient 2 exhibited troubling dyskinesias and parkinsonian features.

Haloperidol has not been shown to cause permanent neurological deficit, even in high doses. It would seem therefore that lithium carbonate was responsible for the toxic irreversible brain damage. This drug shows two established types of toxicity: (i) severe and fatal intoxication associated with very high dosages or very high serum lithium ion levels or both; and (ii) toxic reactions in patients receiving lower dosages and with lower serum levels, associated with low sodium intake, poor renal function, cardiopulmonary or hepatic dysfunction, and pre-existing brain damage. The most severe neurotoxicity has coincided with high serum lithium ion levels. This did not occur in either of our cases, nor were there any abnormalities in any of the previously demonstrated critical factors. Both patients therefore do not fit easily into either of these categories of lithium carbonate toxicity.

It seems possible that both patients exhibited an abnormal brain sensitivity to the lithium carbonate/haloperidol combination, evidenced by the fact that the blood lithium ion levels were not unusually high or related to the extent of neurological involvement. This puzzling occurrence of apparent neurotoxic reactions in patients without high serum lithium levels may be explained by the fact that the lithium ion can accumulate in nerve cells for long periods and can be pumped out at a slow rate only. Persistence of intracellular lithium ion concentration in the brain will not be reflected by the serum lithium ion level. These findings may explain the following clinical observations: (i) particular predilection for toxic effects on the central nervous system; (ii) prolongation and progression of the neurotoxic syndrome in both reported cases, despite cessation of treatment with lithium; and (iii) persistence of diffuse electro-encephalographic changes for weeks.

In 1970 Shopsin et al. reported eight cases of reversible neurotoxicity in lithium carbonate-treated schizophrenics and patients in non-manic states. They believed that the toxic manifestations indicate an 'intolerance or abnormal sensitivity to lithium' in schizophrenics. In both our patients there was no previous evidence of schizophrenia and both developed irreversible brain damage. These catastrophic effects cannot therefore easily be included in Shopsin et al.'s group. A more tenable explanation would be that the concomitant administration of haloperidol was in some way responsible for the late neurological sequelae in our patients. Lithium carbonate and haloperidol may have interacted synergistically, causing extreme alteration of neuronal metabolic or cell membrane function, resulting in permanent nerve cell destruction of greater or lesser extent. Whatever the precise mechanism, this and other reports suggest that combined therapy with lithium and haloperidol may have grave consequences in certain patients with abnormal sensitivity to this drug combination.

REFERENCES