

CASE REPORT

Acute Extrapyrarnidal Reactions Following Lithium and Sulpiride Co-administration: Two Case Reports

TIMOTHY G. DINAN* and VERONICA O'KEANE

Department of Psychiatry, Trinity College Medical School, St James's Hospital, Dublin 8

Two case reports are presented in which lithium and sulpiride were used jointly in patients with affective disorder. In both cases significant extrapyramidal reactions occurred. The reactions were successfully treated by withdrawing the drug combination. It is suggested that the adverse events relate to the mechanism of action of sulpiride which, unlike other neuroleptics, requires sodium to bind to the dopamine receptor. Lithium may substitute for sodium-enhancing sulpiride binding.

KEY WORDS—Lithium, sulpiride, extrapyramidal reactions.

Sulpiride is a neuroleptic of the benzamide variety which has potent anti-schizophrenic activity (Edwards *et al.*, 1980) and is more selective than earlier neuroleptics, preferentially blocking the non-adenyl cyclase linked dopamine (D)-2 receptor (Costall and Naylor, 1976). In general it has been found to cause fewer extrapyramidal side-effects than traditional neuroleptics (Peselow and Stanley, 1982), presumably due to its cleaner pharmacological profile.

Recently Christie *et al.* (1989) reported the efficacy of sulpiride in treating acute manic episodes. If sulpiride were to be used in the treatment of mania then clearly any interactions with lithium would be of relevance. The finding of Jenner *et al.* (1985) that sulpiride, unlike other neuroleptics, increases its binding to D2 receptors in the presence of lithium may have important clinical implications. We report here two cases in which lithium and sulpiride were used jointly, with the development of significant extrapyramidal side-effects.

CASE 1

Case 1 is a 21-year-old admitted to a mother-and-baby unit 3 weeks following the birth of her daughter. The patient was unmarried, unemployed and living at home with her parents. The birth itself was unremarkable and the patient developed symptoms approximately 1 week postpartum. On admission she showed marked lability of mood with

rapidly changing unsystematized paranoid delusions. One year previously she had been treated as an outpatient for a major depressive episode with amitriptyline. She had a strong maternal history of bipolar affective disorder. She was initially commenced on chlorpromazine 100 mg q.i.d. Within 3 days she developed marked postural hypotension and was changed to sulpiride 800 mg b.d. She settled gradually over the next 4 weeks on a maximum dose of sulpiride 2 g/day. Prior to discharge it was decided to commence her on lithium. The sulpiride was decreased to 800 mg b.d. and lithium was started at 800 mg nocte. Following a single dose she developed a severe parkinsonian syndrome with choreiform movements of the upper limbs. Her lithium level at 10 a.m. was 0.5 mEq/l. The lithium was discontinued and the syndrome resolved over the next 24-48 h.

CASE 2

Case 2 is a 48-year-old man with a 20-year history of bipolar affective disorder. He had been largely symptom-free for the past 3 years and now presented with a manic episode of at least 2 weeks duration. Following admission he remained on lithium 1200 mg nocte which gave him a stable serum level of 0.6 mEq/l. He was commenced on sulpiride 800 mg b.d. Within 12 h he developed a marked orofacial dyskinesia, together with significant acute akathisia.

The sulpiride was withdrawn and he was given procyclidine 5 mg b.d. His symptoms subsided

* Author to whom correspondence should be addressed.

slowly over a 3–4-day period. He remained manic and was subsequently successfully treated with haloperidol.

These two cases demonstrate significant extrapyramidal reactions resulting from the co-administration of sulpiride and lithium. Cohen and Cohen (1974) first reported neurotoxicity with a lithium/neuroleptic (haloperidol) combination in four acutely manic patients. Spring (1979) suggested that a combination of thioridazine and lithium increased the risk of neurotoxicity as compared to treatment with lithium alone. The reaction is characterized by fever, delirium, seizures, extrapyramidal symptoms (EPS), and may result in irreversible brain damage. In almost three-quarters of cases with lithium/neuroleptic neurotoxicity EPS are found (Prakesh *et al.*, 1982) and almost one-third of the reversible cases respond well to lithium withdrawal. Most reported cases of toxicity are associated with high neuroleptic doses.

Addonizio and his colleagues, having observed that lithium exacerbated neuroleptic-induced EPS in the absence of a severe toxic reaction, looked at a mixed group of 10 affective disorder and schizophrenic patients when lithium was added to various neuroleptics (Addonizio *et al.*, 1988). They found a steady increase in EPS with no particular sensitivity to either thiothixine, haloperidol or fluphenazine. It has been suggested that the above reactions, ranging from EPS through to full-blown encephalopathy, may represent a continuous spectrum of neurotoxic reactions to either neuroleptics or to lithium/neuroleptic combination (Addonizio *et al.*, 1986). There are no previously published reports of significant reactions to the lithium/sulpiride combination.

West and Meltzer (1979) hypothesize that a state of acute mania marked by psychotic symptomatology and anxiety predisposes to the development of lithium neurotoxicity at relatively low lithium levels. Both our patients fit the above clinical description, and it may be that this clinical state predisposes to the rapid occurrence of toxic reactions to both lithium and lithium/neuroleptic combination.

Another explanation is that neuroleptics may increase the side-effects of lithium by increasing its uptake into red blood cells (RBC). Pandey and colleagues (1979) found that phenothiazines, but not butyrophenones, increased the lithium rates (RBC level/plasma level). Elizar and associates (1972) have reported increased lithium ratios when patients develop lithium neurotoxicity which

normalize after recovery. However, a recent study of 67 bipolar patients (Ghadirian *et al.*, 1989) found that lower RBC lithium concentrations and lower lithium ratios were associated with lithium/neuroleptic combination than those treated with lithium alone.

There is no consistent evidence that lithium increases neuroleptic levels either peripherally or centrally. It is more probable that toxicity seen in patients on combined therapy is related to some as yet unknown interaction between the neuroleptic and lithium. In the case of sulpiride, an agent noted for its low incidence of EPS, the toxicity may result from the specific binding mechanisms of sulpiride in the brain. Jenner and co-workers (1985) showed that sulpiride only binds to D2 receptors in brain slices in the presence of sodium ions. Lithium can, however, substitute for sodium and restore sulpiride binding to brain slices in the absence of sodium (Jenner *et al.*, 1985). If this occurs in the clinical setting it is possible that lithium may enhance binding of sulpiride to dopamine receptors, thereby producing extrapyramidal reactions.

Until further experience has been gained using lithium and sulpiride together we advise caution with this combination.

REFERENCES

- Addonizio, G., Susman, U. L. and Roth, S. D. (1986). Symptoms of neuroleptic malignant syndrome in 82 consecutive patients. *American Journal of Psychiatry*, **143**, 1587–1590.
- Addonizio, S., Roth, S., Stokes, P. and Stoll, P. (1988). Increased extrapyramidal symptoms with addition of lithium to neuroleptics. *Journal of Nervous and Mental Diseases*, **176**, 682–685.
- Christie, J. E., Whalley, L. J., Hunter, R., Bernie, J. and Fink, E. (1989). Sulpiride treatment of acute mania with a comparison of the effects on plasma hormone concentrations of lithium and sulpiride treatment. *Journal of Affective Disorders*, **16**, 115–120.
- Cohen, W. J. and Cohen, N. H. (1974). Lithium carbonate, haloperidol and irreversible brain damage. *Journal of the American Medical Association*, **230**, 1283–1287.
- Costall, B. and Naylor, R. (1976). A comparison of the abilities of typical neuroleptic agents and thioridazine, clozapine, sulpiride and metoclopramide to antagonize the hyperactivity induced by dopamine applied intracerebrally to areas of the extrapyramidal and mesolimbic systems. *European Journal of Pharmacology*, **40**, 9–19.
- Edwards, J. G., Alexander, J. R., Alexander, M. S.,

- Gordon, A. and Zutshi, T. (1980). Controlled trial of sulpiride in chronic schizophrenic patients. *British Journal of Psychiatry*, **137**, 522–529.
- Elizer, A., Shopsin, B., Gerston, S. and Ehlenberger, A. (1972). Intra/extracellular lithium ratios and clinical counts in affective states. *Clinical Pharmacology and Therapeutics*, **13**, 947–952.
- Ghadirian, A. M., Nair, W. P. V. and Schwartz, G. (1989). Effect of lithium and neuroleptic combination on lithium transport, blood pressure and weight in bipolar patients. *Biological Psychiatry*, **26**, 139–144.
- Jenner, P., David, A., Kilpatrick, G., Kupniak, N. M. J., Chivers, J. K. and Marsden, C. D. (1985). Selective interaction of sulpiride with brain dopamine receptors. In: *Schizophrenia: New Pharmacology and Clinical Developments*, Schiff, A. A., Roth, M. and Freeman, H. L. (eds). RSM, London.
- Pandey, G. N., Goel, I. and Davis, J. M. (1979). Effect of neuroleptic drugs on lithium uptake in the human erythrocyte. *Clinical Pharmacology and Therapeutics*, **26**, 96–102.
- Peselow, E. D. and Stanley, M. (1982). Clinical trials of benzamides in psychiatry. In: *The Benzamides: Pharmacology, Neurobiology and Clinical Aspects*, Rotrosen, J. and Stanley, M. (eds). Raven Press, New York.
- Prakash, R., Kelwala, S. and Ban, T. A. (1982). Neurotoxicity with combined administration of lithium and a neuroleptic. *Comprehensive Psychiatry*, **23**, 567–571.
- Spring, G. K. (1979). Neurotoxicity with combined use of lithium and thioridazine. *Journal of Clinical Psychiatry*, **40**, 135–138.
- West, A. P. and Meltzer, H. Y. (1979). Paradoxical lithium neurotoxicity: a report about five cases and a hypothesis about risk for neurotoxicity. *American Journal of Psychiatry*, **136**, 963–966.