

CASE REPORT

Lithium-Neuroleptic Combination Leading to Permanent Neurological Sequelae?

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Abstract

There has been considerable debate regarding the safety of lithium and neuroleptics combination in patients. The resulting neurotoxicity causes persistent sequelae resulting in significant impairment when compared to the effects when lithium or neuroleptics are taken alone. This report describes the case of a 28-year old young man with bipolar disorder who developed residual neurological deficits related to lithium and antipsychotic combination (German J Psychiatry 2007; 10: 18-20).

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Introduction

Lithium is frequently used with neuroleptics. For patients with classic, euphoric acute mania with psychotic features, most experts consider the combination of a high- or medium-potency neuroleptic with lithium to be a first-line treatment (Francis & Docherty 1996). Substantial controversy exists in the literature regarding the safety of such combinations. A number of prospective and retrospective studies (Garfinkel et al., 1980; Goldney & Spence, 1986) support the safety of lithium in conjunction with traditional neuroleptics. There are also case reports suggesting the clinical benefits of combining a neuroleptic and lithium, and synergism between lithium and neuroleptics has been suggested anecdotally (Loew, 1986; Bigelow et al., 1981). In contrast, there is also substantial evidence of adverse reactions to such combinations. These mainly consist of neurotoxicity and the symptoms reported are severe neuromuscular symptoms, hyperthermia and impairment of consciousness. The initial reports were related to lithium and haloperidol combination (Cohen & Cohen, 1974). In one study (Miller et al., 1986), delirium, extrapyramidal signs, and

cerebellar dysfunction were reported in three of five elderly bipolar patients receiving lithium and neuroleptics. In another study (Perenyi et al., 1983), two of 30 patients receiving lithium and a neuroleptic developed severe tremor. Cases in which use of lithium combined with a neuroleptic resulted in severe neurotoxicity, such as delirium, seizures, tardive dyskinesia, encephalopathy, or EEG abnormalities, have been reported. However, Krishna et al. (1978) reported that neurologic symptoms are usually mild and resolve with discontinuation of medication. Given the possibility of long-term treatment, use of lithium in combination with typical and atypical neuroleptics may increase the risk of tardive dyskinesia (Dinan et al. 1984). Lithium-olanzapine neurotoxicity resulting in neuroleptic malignant syndrome (NMS) and encephalopathy have been reported in literature (Swartz, 2001; Goldman, 1996).

This report describes the case of a young man with bipolar disorder who developed residual and persistent neurological deficits. The patient was on a combination of lithium and antipsychotics that contributed to the neurological deficits (Coffey & Ross, 1980). This report highlights the significance of this combination being a possible etiology for developing these sequelae.

Case Report

A 28-year old male with bipolar disorder on maintenance treatment with lithium (800 mg/day) and olanzapine (10 mg/day) was brought to the emergency with 4 day history of fever (38° C), altered sensorium in October 2005. On examination, he was found to have generalized rigidity and renal failure. There was history of having received Intravenous haloperidol (dose not known) in the Intensive Care Unit for controlling agitation in the last 4 days. The psychotropic medications were discontinued. A massively elevated creatine kinase of 293,000 IU/L and leucocytosis was noted. Other investigations including CSF analysis, urine/blood cultures, serology for herpes, rickettsia, Dengue, leptospirosis, *p. falciparum*, hepatitis A, B, C, HIV, TPHA, and Widal were done to eliminate other possible sources of infection and septicemia and were all within normal limits. Electroencephalogram and neuroimaging (MRI) did not reveal any abnormality. In the background of fever, rigidity, elevated creatine kinase levels and neuroleptic use, a provisional diagnosis of neuroleptic malignant syndrome was made and patient was treated with bromocriptine (5–15 mg/day) initially. Patient became afebrile, sensorium improved but he continued to exhibit mutism and rigidity. Psychiatry opinion was then sought by the treating physician and a diagnosis of organic catatonia was made. So patient was treated with lorazepam (8 mg/day) and five modified electroconvulsive therapy over the following 2–3 weeks. Patient gradually improved during his inpatient hospitalization. He would recognize family members and communicate to them by gestures. He was found to have significant dysarthria, hypotonia of limbs and intentional movements of head and neck. The patient remained confined to the bed and had minimal ability to move his limbs. Creatine kinase (CK) levels came down to 400 IU/L and bromocriptine was tapered and stopped. The neurological examination revealed “telegraphic” speech, hypotonia of limbs, titubation, and pendular knee jerk. A repeat MRI revealed mild cerebellar atrophy. The neurologist opined that a possibility of neurological sequelae related to the lithium and antipsychotic combination resulting in NMS be considered. A trial of valproate (1250 mg/day) was given along with intensive physiotherapy and speech therapy. Patient showed significant improvement in the tremors, hypotonia and neck movements during his six week follow up.

Discussion

This patient had bipolar disorder, with fever and marked agitation. He was treated with high doses of oral and injectable haloperidol, together with lithium and olanzapine. It has been suggested that patients with a diagnosis of catatonia or mania, the presence of severe agitation/excitement, treatment with large doses of high potency antipsychotics such as haloperidol or lithium and parenteral drug use, are all potential risk factors for developing neuroleptic malignant syndrome (Keck & Pope, 1989). The patient described in

this report, having several of these risk factors, was therefore at high risk for developing neuroleptic malignant syndrome. The possibility of neurotoxicity related to lithium, olanzapine and haloperidol combination in this patient cannot be ignored (Goldney & Spence, 1986). The combination of lithium and haloperidol causing neurotoxicity is more in the acute phase of manic illness (Spring & Frankel, 1981). Firstly, he presented with pathognomonic clinical features, such as hyperthermia, generalised rigidity, altered sensorium, and evidence of autonomic dysfunction. A raised CK level and leucocytosis were also detected at first presentation. These indices subsequently became normal. The patient's symptoms, developed following exposure to neuroleptics in combination with lithium. Finally, every effort was made to exclude other pathology that could account for the symptoms. In this regard, there was no evidence of any preexisting physical illness to explain his symptoms, or the neurological sequelae which subsequently developed. It became evident gradually that he had sustained brain damage. The prominent neurological symptoms that reflected cerebellar damage are ataxia, hypotonia, dysmetria, titubation, scanning speech, and pendular jerks. The MRI done at this stage confirmed the presence of mild cerebellar atrophy. The case series of lithium-haloperidol incompatibility reported by Cohen & Cohen (1974), the olanzapine-lithium encephalopathy reported by Swartz (2001) and the current case are quite striking. In two of similar case reports, haloperidol used in combination with tetrabenazine or lithium carbonate was implicated as a causative factor (Lee & Merriam, 1989; Jefferson & Greist, 1995). NMS developed subsequent to lithium intoxication in the other instance. The case reported by Lal et al. (1997) concerned a 55-year-old woman with bipolar disorder who developed NMS when haloperidol was added to lithium for treatment of an acute manic episode (Lee & Merriam, 1989). After recovering from NMS, this patient was initially mute, with ocular dysmetria, ataxia, and limb and trunk tremors, all suggestive of pancerebellar involvement. Four months later, his condition was largely unchanged, except that he now had minimal speech output, which was scanning in character. The authors ascribed the initial (transient) muteness to acute bilateral cerebellar injury, and the cerebellar symptoms to NMS-induced hyperthermic injury resulting from lithium-haloperidol combination. There have been reports of organic brain syndromes and NMS in patients treated with combination of high dose haloperidol and lithium (Cohen & Cohen, 1974; Jefferson & Greist, 1995; Loudon & Waring, 1976). Lithium in combination with neuroleptics may also increase the risk of a hypermetabolic crisis, possibly through serotonergic mechanisms (Addonizio & Roth, 1987). Lithium has been known to cause permanent cerebellar damage mostly reported after an episode of acute intoxication (Jefferson & Greist, 1995). Lithium in combination with neuroleptics especially haloperidol and thioridazine have been known to produce toxic malignant syndrome that has enhanced extrapyramidal and diencephalic features (Goldney & Spence, 1986). Goodwin & Jamison (1990) emphasized that (1) the risk of neurotoxicity appears to be higher in patients with preexisting encephalopathy, (2) neuroleptics should be used in lower doses when combined with lithium, and (3) lithium levels should be maintained below 1.0 meq/liter when lithium is used with neuroleptics. The patient was on long term lithium and olanzapine and re-

ceived haloperidol additionally that could have worsened the neurotoxicity in the background of his confusional state.

Whatever the mechanism, there can be no doubt that this patient sustained massive brain damage following neurotoxicity most likely related to lithium-antipsychotic combination.

Conclusion

The case of this young man serves to remind us that, as concomitant lithium and neuroleptic administration is widespread and generally effective, care should be used to minimize the risk of neurotoxicity.

References

- Addonizio G, Susman VL, Roth S. Neuroleptic malignant syndrome: review and analysis of 115 cases. *Biol Psychiatry* 1987; 22: 1004-1020.
- Bigelow LB, Weinberger DR, Wyatt RJ. Synergism of combined lithium-neuroleptic therapy: a double-blind, placebo-controlled case study. *Am J Psychiatry* 1981; 138:81-83
- Cohen WJ, Cohen NFH. Lithium carbonate, haloperidol, and irreversible brain damage. *J Am Med Assoc* 1974; 230: 1283-1287
- Coffey CE, Ross DR. Treatment of lithium/neuroleptic neurotoxicity during lithium maintenance. *Am J Psychiatry* 1980; 137: 736-737
- Dinan T, Kohen D: Tardive dyskinesia in bipolar affective disorder: relationship to lithium therapy. *Br J Psychiatry* 1989; 155:55-57
- Frances A, Docherty JP, Kahn DA. Treatment of bipolar disorder. *J Clin Psychiatry* 1996; 57(suppl 12A):5-58
- Goodwin J, Jamison KR: *Manic Depressive Illness*. New York, Oxford University Press, 1990
- Goldney R, Spence N. Safety of the combination of lithium and neuroleptic drugs. *Am J Psychiatry* 1986; 143: 882-884
- Goldman SA. Lithium and neuroleptic in combination: is there enhancement in neurotoxicity leading to permanent sequelae? *J Clin Psychopharmacol* 1996; 36: 951-962
- Garfinkel PE, Stancer HC, Persad E: A comparison of haloperidol, lithium carbonate, and their combination in the treatment of mania. *J Affect Disord* 1980; 2: 279-288
- Jefferson JW, Griest JH. Lithium. In: Sadock BJ, editors. *Comprehensive Textbook of Psychiatry* .6th ed. Baltimore: Williams & Wilkins; 1995: 2022-2030
- King DJ. Neuroleptics and treatment of schizophrenia. In King DJ, editor. *Seminars in Clinical Psychopharmacology*. London: Gaskell; 1995: 259-327 .
- Keck PE Jr, Pope HG Jr, Cohen BM. Risk factors for neuroleptic malignant syndrome. A case-control study. *Arch Gen Psychiatry* 1989; 46: 914-918
- Krishna NR, Taylor MA, Abrams R: Combined haloperidol and lithium carbonate in treating manic patients. *Compr Psychiatry* 1978; 19:119-120
- Loew MR: Rapid cycling disorders and the role of combined lithium and haloperidol decanoate. *Can J Psychiatry* 1986; 31: 877-878
- Lee S, Merriam A, Kim TS, Liebling M, Dickson DW, Moore GR. Cerebellar degeneration in neuroleptic malignant syndrome: neuropathological findings and review of literature concerning heat related nervous injury. *J Neurol Neurosurg Psychiatry* 1989; 52: 387-391
- Loudon JB, Waring H. Toxic reactions to lithium and haloperidol. *Lancet* 1970 ; 13: 1088.
- Lal V, Sardana V, Thussu A, Sawhney IM, Prabhakar S. Cerebellar degeneration following neuroleptic malignant syndrome. *Postgrad Med J* 1997; 73: 735-736
- Miller F, Menninger J, Whitcup S. Lithium-neuroleptic neurotoxicity in the elderly bipolar patient. *J Clin Psychopharmacol* 1986; 6: 176-178.
- Perenyi A, Szucs R, Frecska E. Tardive dyskinesia in patients receiving lithium maintenance therapy. *Biol Psychiatry* 1984; 19: 1573-1578
- Perenyi A, Rihmer Z, Banki C.: Parkinsonian symptoms with lithium, lithium-neuroleptic, and lithium-antidepressant treatment. *J Affect Disord* 1983; 5: 171-177.
- Spring G, Frankel M. New data on lithium and haloperidol incompatibility. *Am J Psychiatry* 1981 ; 138: 818-821
- Swartz CM. Olanzapine lithium encephalopathy *Psychosomatics* 2001, 42: 370