

Delirium and Extrapyrarnidal Symptoms Due to a Lithium-Olanzapine Combination Therapy : A Case Report

We report an elderly patient who developed severe delirium and extrapyramidal signs after initiation of lithium-olanzapine combination. On hospital admission, serum levels of lithium were found to be 3.0 mM/L which were far above toxic level. Immediate discontinuation of both drugs resulted in complete resolution of most of the symptoms except for perioral dyskinesia which persisted for three more months. We critically discussed the differential diagnosis of lithium intoxication and assessed confounding factors which induce delirium and extrapyramidal signs related with combination therapy of lithium and olanzapine.

Key Words : Lithium; Drug Toxicity; Antipsychotic Agents; olanzapine; Delirium; Neurologic Manifestations; Neuroleptic

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INTRODUCTION

Lithium has been the major pharmacological treatment for the management of recurrent bipolar illness for many years (1). Both the combination therapy strategies with lithium and lithium's extremely narrow therapeutic window enhance the potential for neurotoxicity (2). In fact, the vast majority (75-90%) of patients receiving maintenance lithium therapy become intoxicated at some point during the course of therapy (3). Lithium may induce multisystemic adverse and toxic effects which might lead to severe and life-threatening complications if it goes unrecognized.

More than 50% of the patients on lithium treatment received at least one concomitant antipsychotic medication during the course of their treatment (4). The first report of neurotoxicity due to interaction between lithium and haloperidol was reported in 1974 (5). Afterwards, several other case reports which revealed delirium and extrapyramidal signs following use of lithium-antipsychotic drugs (e.g. chlorpromazine, trifluoperazine, thioridazine, etc.) combination have also been published (6-8).

In addition to interaction with typical antipsychotics, there are also several recent reports indicating increased adverse effects associated with concomitant administration of atypical antipsychotics with lithium in clinical practice (9-12). In this article, we reported a patient with a diagnosis of bipolar I disorder who developed severe delirium and extrapyramidal signs after initiation of lithium-olanzapine combination

therapy, and discussed confounding factors and the management of lithium intoxication.

CASE REPORT

A 62-yr-old woman with a diagnosis of bipolar disorder, was referred to our emergency service with symptoms of alteration in mental status, psychomotor slowness, difficulty in walking, and tremor in limbs. The patient had started to experience bipolar episodes twenty years ago and has been on lithium therapy continuously during last seven years. At the time of her current admission to our hospital, she was receiving 900 mg/day lithium and 5 mg/day olanzapine. Her physician reported that in last 12 months, the patient had neither positive symptoms of bipolar disorder nor lithium toxicity symptoms. There were no occupational, interpersonal or marital problem during this follow-up period. Previous month, plasma level of lithium was examined within normal range (0.81 mM/L).

Physical examination on current admission revealed an afebrile and lethargic woman. Her blood pressure was 120/70 mmHg with a pulse rate of 86/min and respiration 16/min. In her mental status examination, the patient's response to simple verbal commands was well but disorientation to place and time was prominent. She also had loosened associations and rhyming. The neurological examination showed clear upward gaze palsy without a supranuclear component, severe

bradykinesia, severe rigidity of the forelimbs with positive cogwheel, and rest and postural tremor with mild amplitude and frequency of 4-5 Hz in all limbs, predominantly on the right side.

At admission our emergency ward, all of the drugs she used were discontinued. The initial plasma level of lithium at the time of admission was 3.0 mM/L. Serum laboratory studies revealed a mild increase in number of white blood cells (8,500 cells/ μ L blood), erythrocyte sedimentation rate of 28 mm/hr. Fasting blood glucose level was 114 mg/mL, and acetone and ketone levels in urine were negative. She had a prerenal azotemia with serum creatinine level of 1.5 mg/dL, urea level of 84 mg/dL and a blood urea nitrogen level of 32 mg/dL. Creatinine phosphokinase (CPK) level was 34 U/L. Serum sodium (Na^+), potassium (K^+) and chloride (Cl^-) levels were 135 mM/L, 4.8 mM/L and 117 mM/L respectively.

Afterwards, the patient's volume-electrolyte balances (5,000 mL/day) and diuresis were examined carefully. She was managed with 0.9% saline and a good diuresis was established. Other routine laboratory studies and a urine toxicology screen were negative. The electrocardiogram on admission showed sinusoidal bradycardia and antero-posterior chest radiography was normal. Cranial computed tomography did not reveal any pathology except age-related cortical atrophy.

Her detailed history as acquired from her relatives available has shown that she had been hospitalized for four times till the age of 55 yr. Only at this age could she be diagnosed as bipolar disorder and initiated lithium therapy. Severe manic episodes with mood-congruent psychotic symptoms dominated the mood episodes requiring the hospitalizations. There were also milder depressive episodes during which treatment was conducted at outpatient clinics. After the initiation of lithium therapy with a dose of 900 mg/day, the patient remained asymptomatic for seven years. She did not necessitate any other concomitant antipsychotic drug or anxiolytic drug during these period.

Another significant point in her history was the deterioration in her mental status last year after addition of a typical antipsychotic (chlorpromazine 200 mg/day) to her therapy in order to lessen her abrupt insomnia. The patient was brought to emergency ward with signs and symptoms of lethargy, confusion and hyperprexia ten days after initiation of chlorpromazine 200 mg per day. At the examination, she had increased muscle tone of upper limbs and paresia of lower limbs. Laboratory tests including examination of blood, urine, cerebrospinal fluid, protein electrophoresis, electromyography, electroencephalography, enzymes of muscles, kidney functions, and plasma level of lithium (0.69 mmol/L) were within normal range. The cranial magnetic resonance imaging of our patient revealed multiple microlacunar infarcts which were not congruent with the level of the clinical picture. The discontinuation of all drugs resulted in complete remission within 72 hr. Later lithium therapy were re-initiated without recurrence of any mentioned clinical symptoms. She did

not receive any other concomitant drugs till three weeks before admission. A physician prescribed olanzapine 5 mg/day due to her increased suspiciousness towards her neighbors and possible appearance of auditory hallucinations. No other specific information could be obtained concerning the need for adding olanzapine therapy from the patient files.

At current admission, approximately 24 hr later, the patient became more alert but, psychomotor hyperactivity and abnormal extrapyramidal symptoms were keeping on. Two days later, the patient's lithium level had decreased to 1.81 mM/L and her confusion also lessened. At the end of the fourth day, the patient's lithium level was 0.32 mM/L. Her dysarthria had improved dramatically, involuntary movements of limbs and rigidity lessened. At fifth day, the patient became mobile, the neurological symptoms except perioral dyskinesia were almost completely resolved. To prevent the recurrence of bipolar disorder, carbamazepine was started with a slow dose escalation (600 mg/day) at the end of the first month and its plasma level was titrated to 6.5 μ g/L on control. The patient showed a rapid and dramatic recovery. At discharge, she was completely orientated with no further thought disturbances. Examination three months later revealed that her mood was euthymic with appropriate affect. There was no evidence of hallucinations or delusions, but perioral dyskinesia.

DISCUSSION

In lithium intoxication, the patients may present with gastrointestinal and cerebellar manifestations with organic psychopathological symptoms such as confusion, disorientation, and alterations of consciousness. Although extrapyramidal symptoms have also been reported with lithium alone (13, 14), she had well tolerated chronic lithium therapy for approximately seven years and the symptoms above mentioned became apparent only after initiation of lithium-olanzapine combination. Therefore, any side effect of lithium alone does not explain this clinical picture. In several case reports, extrapyramidal system symptoms (e.g. tremor, orofacial or whole body movements and cogwheel rigidity) were observed after lithium-antipsychotic combination therapy (4, 8, 15). Normal motor behavior results from a relative balance between the dopaminergic and cholinergic systems. Extrapyramidal symptoms are induced whenever there is an imbalance between these two neurotransmitter systems. Lithium is known to decrease the amount of dopamine in rat striatum and limbic forebrain (16). The clinical presentation of extrapyramidal system signs is commonly observed after the combined treatment of lithium with an antipsychotic drug. Thus, we thought that concomitant administration of antipsychotics with lithium should be examined more carefully for explaining the delirious clinical symptoms in our case.

After discontinuation of lithium-olanzapine combination, our patient has had perioral dyskinesia for three months. Con-

cerning the distribution of lithium in the brain, animal studies suggest that, after chronic treatment, lithium is preferentially concentrated in the striatum and the hypothalamus as compared to the cerebellum and the cortex. Clinical observations suggest that the combination of lithium and dopaminergic blocking agents (e.g. haloperidol) while having potentiating action, may give rise to persisting neurotoxicity (severe dyskinesias presenting as orofacial or whole body movements) (4). Prakash et al. also report that lithium-antipsychotic neurotoxicity appeared to be persistent in 10.5% of the patients (15). These findings could explain perioral dyskinesia in our patient.

The possibility of ingestion of overdose must be ruled out. In our case, there was no sign indicating ingestion of overdose as an accident or as a suicidal attempt. Generally, chronic intoxication are more severe, as tissue levels and therefore end organ toxicity are higher. In acute ingestion, until equilibration between plasma and tissue occurs, serum lithium levels poorly reflect tissue levels and therefore correlate poorly with toxicity. Because of the slow equilibration, patients with acute overdose are usually asymptomatic unless their presentation is significantly delayed (2). Toxic effects could be observed at a serum lithium concentration of about or more than 1.5 mM/L. However, severe clinical toxicity among patients who have therapeutic lithium levels were also reported (4, 17, 18). It is hypothesized that antipsychotics, in particular phenothiazines, increase lithium influx in red cells (4). It appears that the brain lithium level is more closely correlated with RBC concentration than with plasma concentration. Increased levels of lithium in tissues may be related to neurotoxic effects observed during combined therapy. In light of these data, we determined the patient's clinical picture of the confusion and paraparesia at normal lithium level in the previous year as "neurotoxicity or vulnerability to develop the neurotoxicity". In our case, those symptoms became apparent after the initiation of a typical antipsychotic drug, chlorpromazine, with lithium therapy last year. A few studies suggested advanced age, being female, combination with an antipsychotic drug, and presence of acute psychotic symptoms as confounding factors for developing lithium toxicity (18-20). Especially for economic, social and physiological reasons, the elderly are at particular risk. This patient also had most of these factors in developing lithium toxicity in combination therapy.

In current practice, atypical antipsychotics are generally preferred over conventional antipsychotics. One of them, olanzapine is a well tolerated atypical antipsychotic (21). In vitro data indicate that olanzapine is metabolized by cytochrome P450 (CYP) isozymes such as CYP1A2 and CYP2D6. Olanzapine does not appear to inhibit CYP isozymes (22). No clinically significant metabolic interactions were reported between olanzapine and lithium (21). It is apparent that symptoms of lithium neurotoxicity developed when our patient was taking both lithium-olanzapine (current therapy) and lithi-

um-chlorpromazine (previous therapy) combination therapies. Thus, we could speculate that development of neurotoxicity or neurotoxic symptoms as a result of typical antipsychotic drug-lithium combination might aggravate the vulnerability of patients to develop neurotoxicity due to atypical antipsychotic drug-lithium combination. In patients having history of lithium-neuroleptic toxicity, atypical antipsychotic drug-lithium combination might be not a safe treatment choice.

In lithium neurotoxicity, several differential diagnosis have to be taken into consideration. Among those, delirium due to hyperglycemic hyperosmolar nonketotic coma was excluded in our case, because she had no history of diabetes and fasting blood level was within normal range. There are several reports in literature developing diabetic ketoacidosis associated with olanzapine treatment alone (23-25). Our patient's urine acetone and ketone levels were also negative making us completely exclude this possibility. Delirium may present after cerebrovascular diseases. But this condition generally associated with additional neurological findings such as motor and sensory deficits, cranial nerve palsy, etc (26). In our patient, there were no lateralized neurological findings. In differential diagnosis, neuroleptic malignant syndrome (NMS) was also considered. NMS is a life-threatening syndrome characterized by prominent extrapyramidal and autonomic symptoms (27). However, our patient showed neither hyperpyrexia nor abnormal laboratory findings including leukocyte count, CPK and liver enzymes which are pathognomic findings for this diagnosis.

As a conclusion, there is a possibility of a rare but serious interaction between lithium and antipsychotic drugs. Lithium therapy requires close and regular clinical observations, and serum concentration monitoring to avoid any unexpected changes in lithium levels which might sometimes result in intoxication. Because serum lithium levels do not always reflect correctly intracellular concentrations, a normal lithium level does not exclude the possibility of lithium intoxication. It is useful for physicians and patients to keep in mind that those of the confounding and vulnerability factors and especially concomitant administration of antipsychotics might increase the risk of lithium toxicity.

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