

Case Report

Delayed Onset, Protracted Delirium and Aspiration Pneumonitis Associated with a Combination of Clozapine and Electroconvulsive Therapy

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ABSTRACT

Few studies reported the efficacy and safety in combination of clozapine and electroconvulsive therapy (ECT) in schizophrenia; systematic studies are lacking. Side effects like seizure, and confusional state are reported. Authors report two cases of delayed onset/protracted delirium with ECT and clozapine in schizophrenia, one of whom developed aspiration pneumonitis possibly due to clozapine hyper-salivation. Delirium improved with stopping of ECT and clozapine. Clozapine monotherapy restarted to previous dosages in both cases without recurrence of delirium. Authors recommend for careful monitoring for delirium in ECT augmentation on high dose clozapine. Unilateral ECT may be preferred for augmenting clozapine.

Key words: *Aspiration pneumonitis, clozapine, delirium, electroconvulsive therapy*

INTRODUCTION

Clozapine is found to be superior to traditional neuroleptics in the treatment of refractory schizophrenia.^[1] From the available evidences, clozapine is preferred as a second- or third-line agent for schizophrenia.^[2] The need for necessary caution against significant adverse-effects like agranulocytosis, seizures, hypotension, weight gain, sialorrhea and so on have been emphasized. However, the distressful side-effect of hypersalivation has seldom been studied for its secondary complications. The efficacy and safety of electroconvulsive therapy (ECT) augmentation of clozapine has been reported earlier.^[3-14] The immediate post-ECT delirium is self-limiting and

transient, requiring no active intervention. Reports on delayed onset and prolonged delirium after ECT, which might require a different plan of management, are scarce.^[15] The authors here report two cases of delayed onset/prolonged delirium developed with a combination of clozapine and ECT, one of whom further developed aspiration pneumonitis.

CASE REPORT

Case 1

A 39-year-old married male was admitted with treatment-resistant paranoid schizophrenia (ICD-10) for clozapine trial. After pre-clozapine evaluation, the clozapine monotherapy was started at a dose of 12.5 mg/day, and was gradually increased to 400 mg/day with regular blood count monitoring. The target symptoms were delusions, auditory hallucinations and negative symptoms. Bitemporal, thrice-weekly, suprathreshold, modified ECT was started as augmenting strategy. Twenty-four hours after the 12th ECT, the patient developed confusion, clouding of consciousness, disorientation and poor responses to commands and

Access this article online	
Website: www.ijpm.info	Quick Response Code 
DOI: 10.4103/0253-7176.85402	

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was diagnosed as delirium (ICD-10). Both clozapine and ECT stopped immediately. Serum electrolytes and computed tomography (CT) of the brain showed no abnormality. Supportive treatment with regular monitoring of the vital signs was performed. Complete recovery from delirium was observed within 48 h without any further complications. Clozapine was restarted after 2 days of observation, and the dose was gradually increased to 150 mg. The patient discharged with advice for regular follow-up.

Case 2

A 40-year-old married male was admitted with treatment-resistant paranoid schizophrenia (ICD-10) with multiple relapses. After pre-clozapine investigations, clozapine monotherapy was started at a dose of 12.5 mg/day, and gradually titrated up to 300 mg/day with periodic blood count monitoring. The patient developed hypersalivation with clozapine. Target symptoms in this patient were formal thought disorder, delusions, auditory hallucinations and negative symptoms. As response for target symptoms with clozapine was poor, augmentation with bitemporal, thrice-weekly, suprathreshold, modified ECT was started. Thirty-six hours after the 6th ECT, the patient developed disturbed sleep followed by slurring of speech and, hence, the dose of clozapine was reduced to 200 mg. Forty hours after the 6th ECT, the patient became disoriented, with incomprehensible speech and bladder incontinence. The patient was diagnosed as delirium (ICD-10), and both clozapine and ECT were stopped. The patient had stable vital signs. Biochemical parameters, electrocardiography and CT scan of the brain showed no abnormality. Twenty-four hours later, after developing delirium, the patient developed a sudden onset of dyspnea with bilateral diffuse crepitations over the entire lung fields and was transferred to the medical Intensive Care Unit. The patient diagnosed as aspiration pneumonitis and treated with piperacillin and supportive care. After 2 days, the patient was transferred back to the psychiatry ward after regaining complete orientation/consciousness. Clozapine monotherapy was restarted at a dose of 300 mg/day without re-emergence of delirium. The patient was discharged following reduction in the target symptoms.

DISCUSSION

The self-limiting (emergence) delirium during the immediate postictal phases are reported in 10% of the patients, which rarely lasts more than 30 min.^[16] Prolonged delirium after ECT is considered to be associated with some aspect of treatment, such as lithium co-administration or induction of multiple seizures per treatment session.^[16]

In the above cases, the initial ECTs were uneventful in both patients and delirium developed after 12 ECTs in the first case and after six ECTs in the second case while on therapeutic doses of clozapine.

There was no immediate post-ECT confusion in both patients. However, both developed delirium following a considerable duration after the last ECT. The duration of the delirium was also prolonged as compared with emergence delirium. Therefore, the authors speculate that ECT with clozapine may precipitate delayed onset and protracted delirium.

The second patient had hypersalivation, a known side-effect of clozapine, which could have resulted in aspiration during the delirious state, leading to pneumonitis.

Clozapine is known for reducing the seizure threshold, which might precipitate delirium. The bilateral ECT could be another possible factor for delirium, especially after successive ECT^[17] (after the 12th and 6th ECTs in the first and second patient, respectively).

Because the incidence of postictal confusion^[16] with unilateral over bilateral ECT is low and the period of confusion in unilateral, and because the brief pulse ECT is remarkably brief lasting,^[17] the authors propose that in patients who need augmentation with ECT on clozapine, unilateral ECT may be preferred over bilateral ECT to reduce the chances of prolonged delirium.

Even though immediate postictal/emergent delirium is a self-limiting condition and does not require stoppage of ECT/medication, delayed onset/protracted delirium may require stoppage of medication and ECT with supportive management.

The authors postulate that the cause for delirium could be increased serum clozapine to a seizurogenic level due to pharmacokinetic interaction with ECT usage at a higher dose of clozapine, because delirium can occur in acute clozapine intoxication.^[18] Complete recovery from delirium occurred in 2 days after stopping ECT/clozapine. This hypothesis was also supported by the fact that delirium did not reappear on restarting the clozapine monotherapy at the original dosage soon after recovery from delirium. However, the serum clozapine level was not estimated at the time of delirium.

CONCLUSION

High-dose clozapine/ECT combination needs careful monitoring for delayed onset/protracted delirium.

Clozapine-induced hypersalivation is a potential source of aspiration in the delirious state and, therefore, careful monitoring and preventive measures is advised. Unilateral rather than bilateral ECT may be a better augmenting strategy with clozapine.

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How to cite this article: Manjunatha N, Ram Kumar GS, Vidyendran R, Muralidharan K, John JP. Delayed onset, protracted delirium and aspiration pneumonitis associated with a combination of clozapine and electroconvulsive therapy. *Indian J Psychol Med* 2011;33:80-2.

Source of Support: Nil, **Conflict of Interest:** None.