

REFRACTORY SCHIZOPHRENIA, CLOZAPINE AND EPILEPSY : MANAGEMENT STRATEGIES

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ABSTRACT

This case of refractory schizophrenia in a 28 year old male showed significant improvement with clozapine. But therapeutic doses of clozapine were associated with generalised tonic clonic seizures (GTCS). Addition of sodium valproate allowed adequate control of schizophrenic symptoms as well as seizures. EEG abnormality correlated surprisingly well with development of GTCS and subsequent improvement with anticonvulsant. Factors that lead to seizure-vulnerability in clozapine treated patients are discussed.

Key Words : Schizophrenia, clozapine, seizures

Clozapine's haematological side effects have received much attention, but seizures constitute another major complication of therapy. Recent studies indicate that the previous incidence of 3-5% may have been an underestimation. One such study reports a cumulative risk of 10% after 3.8 years of treatment (Devinsky & Pacia, 1994). The seizure types reported are generalised tonic clonic convulsions, myoclonic and absence seizures, complex partial seizures, absence status (Freedman et al., 1994), cataplexy like attacks and subtle myoclonic movements. In a report by Welch & colleagues, 5 of their first thirty-five patients developed tonic clonic convulsions, 3 had myoclonic seizures, and 2 suffered from complex partial seizures (Welch et al., 1994).

In our experience in a tertiary referral centre, seizures have been a fairly common complication of clozapine therapy.

CASE REPORT

Mr. S, a 28 year old single male has been suffering from a continuous illness of 10 years characterised by reduced social interaction, hearing voices of unseen men commenting on his thought and behaviour, suspecting family

members of planning to kill him. He believed he was born to become a big filmstar and that some aliens had attached instruments in brain and genitals to control his actions and thoughts. He also complained that his neighbours always talked about him and ridiculed him. His personal upkeep remained poor, and he never took up his studies or any employment. He would suddenly turn violent on minor provocation. His aggressive outbursts were purposive, lasted 1-2 days and there was no history suggestive of automatism during these periods. During one of his numerous episodes of violence, his mother sustained multiple fractures and other injuries.

There was no history suggestive of prominent mood symptoms, substance use or a general medical condition. Family history of a single episode excitatory psychosis was present in a cousin, for which no details were available.

Mental status examination on admission (1991) and serial examination conducted thereafter revealed thought broadcasting, delusion of reference, bizarre delusion, made act, second and third person auditory hallucinations which were mostly imperative, and visual and olfactory hallucinations. Affect and

TABLE
TREATMENT PRIOR TO INTRODUCTION OF CLOZAPINE

Drug	Maxm. dose	Period of administration
Haloperidol (O)	30 mg/day	Oct. '91-Dec.'91
Trifluoperazine (O)	25 mg/day	Dec. '91-Jun. '92, Aug. '92-Jun.'93
Flupenthixol (O)	39 mg/day	June '92-Aug.92
Chlorpromazine (O)	300 mg/day	Jun. '93-Oct. '93
Fluphenazine (I)	50 mg/day	Nov. '91-Mar.'96
Diazepam (O)	185 mg/day	Apr. '92-Mar. '96
*Imipramine (O)	125 mg/day	Jan. '92-Feb. '92
**Clomipramine (O)	75 mg/day	Mar. '95-Mar. '96
ECT	12 such	Feb. '92

O - oral

I - injection

*for negative symptoms

** for compulsive washing. Our patient developed compulsive hand-washing around March 1995, for which clomipramine was added on to his antipsychotic regime. Within a few months of this addition, his compulsive symptoms disappeared completely. Later, clomipramine (and also the antipsychotic he was receiving at that point of time) was discontinued in March 1996 in view of starting clozapine therapy. Thus the compulsive symptoms had disappeared about eight months before clozapine was started and never appeared again.

higher cognitive functions were preserved.

Findings of an initial neurological examination had been unremarkable. However, the neurological examination conducted in September 1996, about 10 years after the onset of illness, showed impaired two point discrimination, clumsier finger-nose test on left side, impaired planning, and stimulus boundedness ; all suggesting a probable fronto-parietal deficit.

In the hospital (since 1991) he received adequate trials of conventional antipsychotics of different classes, augmented with high dose benzodiazepines and ECT (for details, vide table 1), but these did not significantly improve his psychopathology. A higher than usual dose of neuroleptics could not be given for disturbing akathisia and pseudoparkinsonism. He remained deluded, had disturbing auditory and visual hallucinations. There were unpredictable bouts of severe violence secondary to his delusions, command hallucination and experience of somatic passivity. In fact, violence was a major problem in the hospital and to control it

diazepam was added. Violence was effectively controlled with diazepam but his psychopathology remained untouched.

Clozapine (325 mg/day) was started in March 1996 and there was notable improvement. He was even ready to challenge his previous delusional system. But unfortunately, he developed generalised tonic clonic seizures at this stage and continued to have them until the dose was reduced to 250 mg/day.

EEGs were done for this patient in 1992 and 1994. In 1992, the EEG showed a predominantly beta background activity (probably due to benzodiazepines) and doubtful focal abnormal discharge in the form of brief runs of theta waves from bilateral central and occipital areas, more prominent on the right side. In 1994, the only abnormality shown in the EEG was predominantly beta background which could be due to benzodiazepines.

Two months after starting clozapine, however, the EEG showed a poorly organised background alpha activity with generalised

discharges in the form of sharp and slow waves, and spike and slow waves. There were eighteen occasions of seizure discharges, their duration varying from 400 milliseconds to 2 second.

Subsequent EEG done of 16.8.96 revealed seizure discharges on twenty-two occasions, duration varying from 200 millisecond to 2 seconds.

As his dose of clozapine was reduced (250 mg/day), his psychopathology resurfaced. Hence it was decided to increase the dose of clozapine till adequate clinical response was achieved, under cover of an antiepileptic drug (sodium valproate). Since the introduction of sodium valproate, he has had no seizure.

A third EEG (11.9.96), recorded after sodium valproate was added to the existing regime showed only six episodes of epileptic activity, lasting between 600 milliseconds to 1 second.

Meanwhile, as the dose of clozapine was increased, there was significant improvement in psychopathology. Currently his aggressive outbursts are completely under control (last outburst in March '96).

DISCUSSION

Reported risk factors for development of seizures during clozapine therapy include- a) high dose-but recent studies do not confirm this dose-dependant effect (Devinsky & Pacia, 1994), and some have reported the highest risk between doses of 75-400 mg/day (Gunther et al., 1993), b) rapid upward titration of dose, c) polypharmacy, d) discontinuation of diazepam treatment (Gunther et al., 1993), e) preexisting structural brain damage.

Our patient was on 325 to 375 mg/day of clozapine when he developed seizures; initiation of therapy was preceded by a gradual

reduction (10 mg/week) of high dose of diazepam (185 mg/day). Neurological signs implicating his frontal and parietal lobes were present and EEGs prior to clozapine had shown bilateral episodic slowing from occipital-central areas, though no epileptiform activity was seen. All these factors could have contributed to his seizure susceptibility. Treatment with antiepileptic cover successfully controlled his seizures.

There have been reports of priapism following combined sodium valproate and clozapine therapy. Our patient did not develop any such side effect.

We would also like to point out that EEG abnormality alone has been reported in 74% patients on clozapine treatment (Welch et al., 1994). But an abnormal EEG does not always translate into a clinical seizure and hence, does not warrant antiepileptic treatment.

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