Clozapine-Induced Electroencephalogram Changes as a Function of Clozapine Serum Levels

Oliver Freudenreich, Richard D. Weiner, and Joseph P. McEvoy

Specific electroencephalogram (EEG) changes during clozapine therapy were prospectively studied in a cohort of 50 chronic state hospital patients with schizophrenia who were randomly assigned to one of three nonoverlapping clozapine serum level ranges (50–150 ng/mL, 200–300 ng/mL, and 350–450 ng/mL). EEGs were obtained before clozapine was instituted, and after 10 weeks of treatment. Fifty-three percent of patients showed EEG changes during the 10-week study period. We observed three seizures (6%), one in a patient on 900 mg (serum level 320 ng/mL) clozapine, and two in patients with lower clozapine serum levels (200–300 ng/mL) who had prior histories of seizures and inadequate valproate coverage. Thirteen percent of patients developed spikes with no relationship to dose or serum level of clozapine. Fifty-three percent of patients developed slowing on EEG. Compared to plasma levels below 300 ng/mL, a clozapine serum level between 350 and 450 ng/mL led to more frequent and more severe slowing. The EEG slowing correlated with observed sleepiness, although this factor was not sufficient to explain the severity of high-dose effects. © *1997 Society of Biological Psychiatry*

Key Words: Clozapine, seizures, electroencephalogram, schizophrenia, serum level

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Introduction

Recent reviews have estimated crude incidence rates for seizures during clozapine treatment of 2.8% (Devinsky et al 1991) and 1.3% (Pacia and Devinsky 1994). For their retrospective review, Pacia and Devinsky utilized the huge database from the Clozaril Patient Management System with 5629 patients, while Devinsky et al analyzed the Sandoz database of 1418 patients prior to U.S. marketing of clozapine. Using life-table analysis, the latter calculated a cumulative 10% risk of seizures after 3.8 years of treatment. Others have reported even higher occurrence rates of seizures in more selected populations such as state hospital patients (Wilson and Claussen 1994) or brain-injured patients (Michals et al 1993). The experience based mainly on case reports and case series suggests that the risk for seizures is dose-related (Haller and Binder 1990; Baker and Conley 1991), although seizures can occur in all dose ranges (Wilson and Claussen 1994) and even at very low doses (Thomas and Goudemand 1992). Some of these seemingly contradictory observations might be explained by clozapine's wide range of plasma level for a given dose (Haring et al 1990).

Clozapine also has an unusually large propensity to induce electroencephalogram (EEG) changes, ranging

From the John Umstead Hospital, Butner, North Carolina (OF, JPM); and Duke University Medical Center and Durham VA Medical Center, Durham, North Carolina (RDW).

Address reprints to Joseph P. McEvoy, MD, John Umstead Hospital. Adult Admission Unit, Butner, NC 27509.

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from 53% (Gunther et al 1993) and 59% (Spatz et al 1978) to 74% (Welch et al 1994). Of these, generalized slowing is the most prominent finding (e.g., Spatz et al 1978; Malow et al 1994; Welch et al 1994), with sharp activity occurring in a smaller proportion (e.g., 16% in Gunther et al 1993). Some but not all studies found EEG changes to be dose-related (e.g., Welch et al 1994; Gunther et al 1993; Braun-Scharm and Martinius 1991).

Only one study was done that related EEG alterations with clozapine plasma levels (Haring et al 1994). The group studied 29 inpatients and found an incidence of 52% for clozapine-induced EEG changes. Using discriminant analysis, they found clozapine plasma levels but not clozapine dose to be a valid indicator of the appearance of pathological EEG changes. The study was naturalistic in the sense that patients were treated with clozapine on a clinically open basis. In addition, only low to moderate ranges of clozapine levels were encountered (group means of 81.6 and 235.7 ng/mL).

No prospective, systematic study with random assignment to specific clozapine serum level ranges has been done in which clozapine serum levels and specific EEG changes were correlated. As part of an ongoing randomized, double-blind, 12-week trial in adults with treatment-resistant schizophrenia comparing three different clozapine serum level ranges (50–150 ng/mL, 200–300 ng/mL, and 350–450 ng/mL), we obtained EEGs before randomization and again after 10 weeks of clozapine therapy. We report the incidence of seizures and prevalence of EEG changes including especially epileptiform activity (spikes/sharp waves) and slowing in our first 50 patients.

Methods

Eligibility

Subjects were all hospitalized patients with chronic schizophrenia or schizoaffective disorder according to DSM-III-R criteria. All patients were treatment-resistant, as defined by having failed repeated trials of at least two different neuroleptics in the past. No patient had received clozapine before. Two patients with a seizure history who were in need of treatment with an anticonvulsant were switched to valproic acid prior to entry. No other patients had any available history of prior seizure activity.

The protocol was reviewed and approved by the investigational review boards of both Duke University and John Umstead Hospital. All patients gave written informed consent.

Patient Population

Fifty patients (11 women and 39 men) participated in the study; 26 were white, 24 were black. Their mean age was 38 years (range from 21 to 56). They had had between 2 and 44 lifetime admissions (mean 10), were between 2 and 33 years past their first hospitalization (mean 15), and had a Global Assessment of Functioning between 15 and 40 (mean 29) at baseline. Assignment to one of the three clozapine serum range groups was not associated with significant intergroup differences in any of the demographic variables.

Study Design and Treatment Regimen

In an effort to achieve consistency of conventional antipsychotic treatment during baseline assessments, eligible patients were switched over to haloperidol or fluphenazine and treated for 1–2 weeks before baseline assessments were done. Patients were tapered off all other medication except if given to treat a concomitant medical condition. Patients were then randomly assigned to one of three nonoverlapping clozapine serum level ranges (group I: 50–150 ng/mL, group II: 200–300 ng/mL, and group III: 350–450 ng/mL). Patients were slowly (by 25–50-mg increments every day or every other day) titrated up to their assigned serum level range. Blood was drawn weekly throughout the duration of the study, and a physician not involved in the patient assessments made the necessary dose adjustments to keep each patient in his or her assigned serum level range. We decided a priori to give a maximum of 900 mg as a daily dose. No sedative medications (e.g., benzodiazepines, barbituates) were permitted throughout the study. Doses of haloperidol or fluphenazine were given as necessary on rare occasions during the first 2 weeks of clozapine dose titration.

Assessments of Psychopathology

Severity of psychopathology was assessed at three time points by a physician blind to the assigned serum level and the dose: during the haloperidol lead-in period, and again both 6 and 12 weeks after randomization. For this report, we examined response at a criterion level of a 33% decline in total brief psychiatric rating scale (BPRS) score. The treatment outcome data will be reported elsewhere.

In addition, sleepiness was assessed by a research nurse three times during the study with an ordinal scale from 0 to 3 (0, energetic; 1, alert but calm; 2, slightly sleepy; 3, very sleepy).

EEGs

A 21-channel EEG was recorded, using all 19 standard scalp locations of the International 10/20 system of electrode placement and a 21-channel Nihon Kohon EEG machine. The EEG was repeated after 10 weeks and, for 24 subjects, an intermediary recording was made when the

Table 1. Mean Clozapine Doses and Mean Achieved Clozapine Serum Levels from 50 Schizophrenic Patients for Each of Three Designated Clozapine Serum Level Ranges

Group	Assigned clozapine serum level	# patients	Clozapine dose in mg		Serum level in ng/mL [mean (SD)]
			Mean (SD)	Range	
I	50–150 ng/mL	16	157 (75.9)	64–350	94 (13.5)
II	200–300 ng/mL	22	421 (229.2)	150–900	248 (15.0)
III	350–450 ng/mL	12	594 (175.6)	300–900	391 (26.8)

patient first reached the assigned target serum level range. This extra recording, performed between the baseline and 10-week follow-up study, was instituted midway through the protocol because of the appreciable incidence of seizures (see below) in this population. All EEGs were interpreted blind to subject, group assignment, and time in study by a board-certified clinical electroencephalographer (RDW). EEGs were rated on anchored 5-level ordinal scales from 0 to 4 (0, absent; 1, borderline; 2, mild; 3, moderate; 4, severe) for polymorphic slowing, frontal intermittent rhythmic delta slowing (FIRDA), other rhythmic slowing, sharp/spike activity, and overall asymmetry (Weiner et al 1986). For the purpose of this study, four measures were used: 1) overall abnormality; 2) overall asymmetry; 3) spike/sharp activity; and 4) a slowing index (sum of scores for the three slowing ratings).

Difference scores for each of the four variables were calculated to indicate changes at week 10 compared to baseline EEGs. Since all but 4 patients had normal baseline EEGs, this basically corresponded to the readings at week 10.

Special Lab Studies

Blood was drawn in the morning before breakfast approximately 12 hours after the last clozapine dose. Clozapine was quantified in serum at National Medical Services, Inc., Willow Grove, PA, using capillary gas chromatography (Simpson and Cooper 1978).

We calculated an average clozapine dose and serum level for each patient by taking the means of the doses and actually achieved serum levels for only those times when that patient's blood levels were in his or her assigned target ranges.

Statistical Analyses

Comparability of treatment groups was established using analyses of variance (ANOVAs) for continuous variables and chi-squares for categorical variables. We examined our EEG ratings with ANOVAs, followed up with the Newman–Keuls procedure as our post hoc test. Chi-squares were used if frequencies were to be compared. When indicated, the Bonferroni correction was used. The alpha level was set at $\leq .05$; all tests were two tailed.

Results

During the haloperidol lead-in period, patients received an average of 22 mg haloperidol equivalents daily (ranging from 5 to 60 mg) with no significant difference among treatment groups.

Fifty patients were randomized. Three out of 15 patients assigned to the high clozapine serum level range could not reach it because of either intolerable hypotension (1 patient) or because they had reached the maximum dose of 900 mg (2 patients). They are grouped according to their actual achieved serum level (medium range for all 3 patients). One patient who reached 327 ng/mL on 900 mg was included in the high group. Thus, 16 patients were treated in the low range, 22 in the medium range, and 12 in the high range. It can be seen in Table 1 that mean daily clozapine doses necessary to maintain patients in their assigned clozapine serum level ranges varied widely. Still, clozapine dose and serum level were significantly correlated ($r = .64$; $p < .001$).

Two patients who were both assigned to the medium serum level range began the study on valproate because of seizure histories. Three more patients were started on valproate during the course of the study either after a seizure occurred (1 patient) or because of epileptiform activity seen on EEGs obtained before our week 10 EEG (2 patients).

Overall, 3 out of 50 patients (6%) had seizures. Reports of these seizures were suggestive of the tonic–clonic type; however, none were witnessed by a highly experienced observer who could reliably distinguish myoclonic from tonic–clonic seizures. Both patients who were prophylactically started on valproate had seizures. One seizure occurred during the titration period when valproate was discontinued because of a medication error, and the other one toward the end of the study when valproate levels fell into the subtherapeutic range (38 μg/mL) while the patient was on 650 mg clozapine (level 120 ng/mL). The only other seizure occurred in a patient from the serum level group III while on 900 mg clozapine (320 ng/mL serum

level) at week 8. The seizure incidence in our cohort for all patients without a preexisting seizure disorder requiring valproate was 1 out of 48 (2%).

Five patients who entered the study on valproate or were put on valproate during the study were excluded from the following analyses. Thus, 45 patients were analyzed with no concomitant medication.

Twenty-four out of 45 patients (53%) developed some degree of overall EEG abnormality during the study. Group means (SD) were significantly different for the three groups ($F = 4.0$; df = 2,42; $p = .025$), with post hoc analysis showing that the high serum level group (III) was significantly more affected than either group I or group II. If only overall abnormalities more severe than the borderline rating were examined, 15 out of 45 patients (33%) had new EEG findings with a significant serum level-dependent distribution (group I 20%, group II 21%, and group III 73%; chi-square = 10.2; df = 2; $p = .006$). The highest serum level group had significantly more abnormalities than either group I or II. There was no difference between group I and II.

We then examined spike/sharp activity and slowing separately.

Spike/sharp waves were seen in 6 subjects (13%). The development of sharp waves and spikes was not confined to higher serum level groups; 1 subject in serum level group I displayed these findings, 3 in group II, and 2 in group III (chi-square = 0.9, df = 2, nonsignificant). One patient from group II had moderate spike/sharp waves that were clearly epileptiform in nature, whereas the other 5 had more equivocal borderline ratings. There was no relationship to dose.

A frequency distribution for the ratings of slowing is given in Figure 1. Twenty-four out of 45 patients (53%) showed some degree of slowing on their EEG ratings; however, this effect was not uniform across all serum levels: 33% of patients in group I showed slowing, 53% from group II, and 82% from group III (chi-square = 6.0; df = 2; $p = .049$). EEG slowing correlated positively with both clozapine dose ($r = .36$; $p = .02$) and clozapine serum level ($r = .44$; $p = .002$). The group means as a measure of severity of EEG slowing [means (SD) for groups I through III, respectively: 0.9 (1.8), 1.0 (1.5), 3.4 (1.9)] were significantly different ($F = 8.7$; df = 2,42; $p < .001$), with more slowing in the highest serum level range compared to the lower serum level groups. We therefore examined EEG slowing by comparing the three serum level groups after categorizing subjects into whether they had more than borderline slowing. Eighty-two percent of the highest serum level group had more than borderline slowing, compared to 26% in group II and 20% in group I (chi-square = 12.2; df = 2; $p = .002$). Post hoc testing showed that there was no difference between group I and II, but a significant difference between I and III and between II and III. Five of the 6 patients with spike/sharp wave activity also showed slowing.

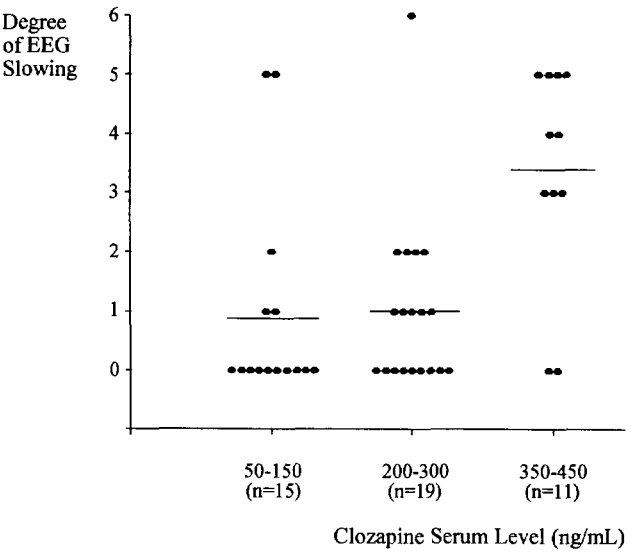

Figure 1. Degree of increased EEG slowing from the predrug baseline condition seen in 45 schizophrenic patients treated in one of three nonoverlapping clozapine serum level ranges. A score of zero indicates no slowing; higher scores indicate more severe slowing. Mean values are denoted by a solid line.

Asymmetrical abnormalities developed in only 1 patient.

When we compared the EEG rating of slowing at week 10 with the clinical rating of sleepiness at week 12 (excluding patients on valproate, which can induce sleepiness), these ratings correlated significantly ($r = .33$; $p = .029$).

Lastly, we examined whether EEG changes were a predictor of therapeutic response. Fourteen of 45 patients (31%) responded according to our response criterion. Of these responders, 6 patients had no EEG changes during treatment, whereas 9 developed abnormal EEGs. In comparison, the group of nonresponders had 15 normal EEGs and 16 abnormal EEGs (chi-square = 0.12; df = 1; $p = .73$).

Discussion

Our data from a prospective clinical trial confirm published frequency figures for clozapine-induced seizures and EEG changes.

Of our 3 patients who had seizures, 1 had a seizure at a high clozapine dose (900 mg) and serum level (320

ng/mL). The initial reports of seizures during clozapine treatment suggested an association with very high clozapine blood levels, exceeding 1000 ng/mL (Simpson and Cooper 1978); however, the other two seizures occurred in patients (treated in the 200–300-ng/mL clozapine range) who had preexisting seizure disorders, stressing the importance of clinical history (vulnerability) and meticulous maintenance of adequate anticonvulsant levels.

A spectrum of seizure types has been associated with clozapine treatment (Karper et al 1992; Berman et al 1992; Gouzoulis et al 1993; Antelo et al 1994; Welch et al 1994; Geaney 1995).

Given that clozapine-induced seizures have a relatively low probability of occurrence, and that tonic–clonic seizures are the most common type, it is not surprising that we probably saw only the tonic–clonic type. We must acknowledge the possibility, however, that a myoclonic seizure was mistaken as tonic–clonic by an unskilled observer.

The overall frequency of any EEG abnormality was high (53%), consistent with other reports in the literature. On more detailed examination, it appears that the relationship between clozapine dose/serum levels and EEG spikes or sharp waves is different from the relationship between clozapine dose/serum level and EEG slowing. Liukkonen et al (1992) noted spikes across a clozapine dose range of 300–700 mg daily. We saw paroxysmal spike/sharp activity at doses as low as 150 mg (plasma level 100 ng/mL), and found no clear relationship to clozapine dose or serum level; however, Malow et al (1994) reported that decreasing dose and/or addition of anticonvulsant medication appeared to be associated with at least partial resolution in epileptiform activity.

The picture is different for EEG slowing. In their retrospective review, Gunther et al (1993) found a dose-dependent relationship between clozapine dose and EEG slowing, a result that we replicate and extend to clozapine serum levels. In addition, our results confirm findings from the only other study that tried to relate clozapine blood levels and EEG changes prospectively (Haring et al 1994). Haring's group found EEG changes to be associated with clozapine serum levels. Fifty-two percent of their patients showed pathological EEG changes at a mean clozapine serum level of 236 ng/mL. This compares very well with patients from our medium serum level group who had a mean clozapine serum level of 248 ng/mL. In this subgroup, 53% developed an abnormal EEG. Our high serum level group (III), with a mean level of 381 ng/mL, had an even greater incidence of abnormalities (82%). Further, the higher serum level group also demonstrated a higher severity of EEG slowing changes than the low and medium level groups (I and II). Severity of changes cannot be easily compared with the study by Haring and colleagues, since they used a scale to code severity of EEG changes that did not separate slowing and spike waves.

Even though clinically observed sleepiness and EEG slowing correlated, the percentage of patients observed to be sleepy (31%) was lower than the percentage of patients with EEG slowing (53%). Moreover, only EEG slowing was significantly related to serum clozapine levels; clinical observation alone was not adequately sensitive.

EEG slowing is a nonspecific finding, and future studies may, therefore, wish to consider the use of activation tasks to minimize drowsiness. We cannot say with absolute certainty whether the slowing we found reflects encephalopathy or merely sleepiness. Still, neither is desirable and the severity of slowing observed in our high serum level group (III) is clearly more substantial than would be expected with drowsiness alone. Other studies have shown a clear association between slowing and encephalopathic states, such as those encountered with electroconvulsive therapy (Weiner et al 1986) or dementia (Hughes et al 1989). In these cases, slowing indicates central nervous system toxicity. The EEG can be regarded a very sensitive indicator of clozapine toxicity.

An EEG may be particularly indicated during clozapine treatment of patients who have known preexisting compromised brain function, and, in combination with serum clozapine levels, may identify patents who could benefit from a reduction in clozapine dose/serum levels.

In summary, in our cohort of 50 chronic state hospital patients, EEG changes during newly instituted clozapine therapy were common. Only about half the patients showed no EEG changes during the 10-week study period. We had three (6%) seizures, one in a patient on 900 mg (serum level 320 ng/mL) clozapine, and two in more susceptible patients with insufficient valproate coverage. Thirteen percent of patients developed spikes with no relationship to dose or serum levels of clozapine, whereas in the 53% of patients who developed slowing on EEG there was a dose and serum level effect, especially for the severity of slowing. Compared to plasma levels below 300 ng/mL, a clozapine serum level between 350 and 450 ng/mL led to slowing on the EEG significantly more often, and the slowing was more severe. The slowing seen on EEG correlated with reported sleepiness.

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