



Epileptic Seizures and Clozapine Titration

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Abstract

Patients with resistant schizophrenia are commonly treated with Clozapine. They can develop epileptic seizure. In a sample of 62 resistant schizophrenia patients, five of them (8%) had developed Tonic-clonic and myoclonic seizures with EEG abnormalities.

There were no difference in sociodemographic and clinical factors and daily intake Clozapine dose between patients with epileptic seizure and those without.

Plasma Clozapine concentrations were higher in patients with epileptic seizures (1040 ng/ml vs. 640 ng/ml) ($p < 10^{-3}$). No differences were established for Plasma Norclozapine concentration between the two groups.

Norclozapine/Clozapine Ratio were lower in patients with epileptic seizures at first day and after 15 days ($p = 0.006$ and 0.024).

Background

Clozapine has some undesirable side effects, including severe Electroencephalographic (EEG) disturbances [1,2]. The basic mechanism underlying the association between the administration of Clozapine and the EEG abnormalities is unclear [3].

The present study was carried out to elucidate the relation between Clozapine dose and its metabolites (Clozapine and Norclozapine) and epileptic seizures in patients with diagnosis of refractory schizophrenia.

Methods

It was a longitudinal study held in psychiatric department in general hospital of Sousse in Tunisia. Sixty two patients (41 females and 21 males) were recruited and fulfilled criteria for refractory schizophrenia according to the NICE criteria (the National Institute of Clinical Excellence).

Exclusion criteria were: a diagnosis other than schizophrenia in axis I of the DSM-IV (particularly schizoaffective conditions); low white blood cell counts (less than $3.5 \times 10^9/l$); history of alcohol or drug abuse in the last 2 years; serious medical illness; mental retardation and concomitant medication until the end of the study period.

To evaluate the clinical improvement with Clozapine, we used Brief Psychiatric Rating Scale score (BPRS) at first time and after one month of starting treatment with Clozapine. This assessment was made by the same psychiatrist.

Plasma concentrations were evaluated through a Reversed-phase high-performance Liquid Chromatography method (RPLC). Plasma Clozapine, Norclozapine and (Norclozapine/Clozapine) Ratio were determined for each patient at first time and after 15 days.

Results

For the 62 patients, the mean age was 35.5 ± 11.3 years. Age of onset of schizophrenia was 24.4 ± 8.2 years. The average number of psychiatric hospitalization was 3.4 ± 2.9 . Most of them had undifferentiated schizophrenia (69.4%).

The duration average of Clozapine treatment was 16.6 months.

Daily intake Clozapine dose was $493 \text{ mg/day} \pm 175 \text{ mg/day}$. Daily dose of Clozapine related to the weight of each patient was $6.6 \text{ mg/kg/day} \pm 2.6 \text{ mg/kg/day}$. 75% had clinical improvement (defined as a decrease in BPRS $> 20\%$) after one month of Clozapine treatment.

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Table 1: Clozapine and Norclozapine plasma concentration between 2 groups.

| | Epilepsy | No epilepsy | p |
|---------------------------------------|-------------|-------------|-------------------|
| Daily intake Clozapine | 5.05 ± 1.2 | 6.1 ± 2.2 | NS |
| Plasma Clozapine concentration | 1040 ± 311 | 620 ± 316 | <10 ⁻³ |
| Norclozapine plasma concentration | 168 ± 45 | 168 ± 120 | NS |
| Norclozapine/Clozapine Ratio (day 1) | 0.3 ± 0.01 | 0.48 ± 0.16 | 0.006 |
| Norclozapine/Clozapine Ratio (Day 15) | 0.36 ± 0.04 | 0.55 ± 0.18 | 0.024 |

Twenty five refractory schizophrenic patients had developed side effects due to Clozapine.

Four patients had developed both tonic-clonic epileptic seizure and one myoclonic seizure. All this patients had EEG abnormalities.

There were no difference in sociodemographic and clinical factors and daily intake Clozapine dose between patients with epileptic seizure and those without.

Plasma Clozapine concentrations were higher in patients with epileptic seizures (1040 ng/ml vs. 640 ng/ml) ($p < 10^{-3}$). No differences were established for Plasma Norclozapine concentration between the two groups.

Norclozapine/Clozapine Ratio were lower in patients with epileptic seizures at first day and after 15 days ($p = 0.006$ and 0.024) (Table 1).

Discussion

In our sample, 8% of patients treated with Clozapine developed seizures. In literature, prevalence were between 2 and 10% [4,5].

Kikuchi et al., had found that six patients (30%) experienced seizures; one with both tonic-clonic and myoclonic, one with tonic-clonic and four with myoclonic seizures [3].

In this study, the mean baseline PANSS scores were not significantly different between the EEG normal and EEG abnormal groups.

Sajatovic et al., did not found differences in Clozapine dosage between groups with seizures and those without [4].

Freudenreich et al., established significant correlation between Clozapine serum level higher than 350 ng/ml and severity of EEG slowing [2].

Conclusion

In our study, plasma Clozapine concentrations were higher in patients who had developed epilepsy. No differences were obtained for Norclozapine. These results need to be verified in other multicenter studies recruiting a larger number of patients treated with Clozapine. In the same way, EEG monitoring is necessary to detect as soon as possible the occurrence of epilepsy.

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