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Seizure Incidence in Patients under Clozapine

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Abstract **Original Research Article**

Clozapine can cause potentially fatal side effects, including seizures. In the absence of therapeutic alternatives, well-coded guidelines are required for the management of this adverse effect in order to maintain treatment. Our aim is to determine the incidence of seizures associated with clozapine use in our hospital, to study the factors associated with this side effect, and to establish a clear, unified attitude based on a review of the literature. Among 483 patients treated with clozapine, 11 cases of seizures were reported, with a rate of 2.27% and an incidence of 1.62 cases per 1000 person-years. 80% of these patients presented tonic-clonic seizures, preceded by myoclonus in 2 cases, and the average seizure onset dose was estimated at 560mg/day. The course of action varied from one psychiatrist to another. Clozapine was discontinued in the case of one patient after the first episode, and doses were reduced in 8 patients from 28 to 75% of the therapeutic dose reached before. Six patients received additional antiepileptic agent.

Keywords: Clozapine; Seizure; Incidence; Antiepileptic Drugs.

INTRODUCTION

Since its release on the market, clozapine has generated substantial debate concerning its use and prescription. Its mechanism of action is based primarily on the blockade of dopaminergic D2 and serotonergic 2A receptors, conferring significant antipsychotic and thymoregulatory effects, providing benefits for particularly resistant symptoms, while preventing the worsening of motor impairment and cognitive changes [1].

The decision to initiate clozapine treatment in routine medical practice is frequently dictated to clinicians, in situations where therapeutic alternatives are limited. It may also be necessary in cases of intolerance to other antipsychotics or severe adverse reactions such as neuroleptic malignant syndrome or dyskinesias [2].

Resistant schizophrenia is defined as a lack of response to two antipsychotics of different classes, taken for a sufficient duration (at least 6 weeks) at a therapeutic dose.

Despite clozapine's many indications, it is reserved in our context for cases of mainly resistant schizophrenia.

It is initiated within the hospital following a relatively rapid titration of 25 mg/day, based on titration patterns reported in the literature [2]. All patients started on clozapine at our facility require a pre-therapeutic EEG to rule out any activity disturbance prior to initiation. The doses used vary according to the patient's clinical response, from 350 mg to 950 mg in the least responsive cases.

In addition to the risk of neutropenia, the use of clozapine carries potential risks of fatal side-effects, including myocarditis, paralytic ileus, seizures, dilated cardiomyopathy, hyperosmolar coma and acid-ketotic decompensation. [1]. In the absence of alternative treatments, clear, standardized guidelines are essential to manage each adverse effect and thus maintain treatment.

The frequency of clozapine-induced seizures remains unknown, and the medical approach to this phenomenon is still unclear. As a result, some patients discontinue clozapine while others have their dose reduced. With this in mind, our aim is to assess the incidence of seizures associated with clozapine administration in our hospital setting, identify the factors contributing to this type of side effect, and develop a standardized approach based on a literature review.

METHODS

This is a retrospective, descriptive study of all patients hospitalized and treated with clozapine since its introduction in our hospital in 2009.

Information extracted from the clinical record included:

- Socio-demographic data, the age being that of the patient in the year of the first seizure on clozapine.
- Medical and surgical history, to rule out other factors likely to lead to seizures,
- Use of psychoactive substances (tobacco, alcohol, benzodiazepines, etc.),
- The dose of clozapine used at the time of the seizure,
- Description of the event to determine the type of seizure,
- Therapeutic associations used with clozapine at the time of the seizure,
- The physicians' attitude after the onset of the seizures: addition of an antiepileptic, reduction in dose, discontinuation of clozapine, etc.

Inclusion criteria

All patients meeting the criteria of resistant schizophrenia or lack of tolerance to other molecules who were prescribed clozapine.

Exclusion criteria

Patients with a history of epilepsy were excluded, as it would be difficult to determine if the seizures were drug-induced

RESULTS

Since its introduction, 483 patients have been treated with clozapine at our hospital. 73% were male (n=353) and around 27% female (n=130). 11 cases of seizures were reported. The incidence of seizures was 1.62 cases per 1000 person-years, with a rate of approximately 2.27%. Socio-demographic and seizure-related data are detailed in Tables 1 and 2.

Table 1: Clinical course of patients experiencing seizures

Cases	Gender	Age Y/o	Clozapine dose mg/day	Type	Maintenance vs titration phase	Antipsychotic association	Clozapine concentration	Clinician Attitude after 1st seizure	Antiepileptic medication
Case 1	Male	21	550	A - TC	Titration	No	NR	Discontinued	-
Case 2	Male	23	600	A	Titration	No	NR	75% reduction	-
Case 3	Male	50	550	A	Maintenance	Aripiprazole	NR	45% reduction + AE	lamotrigine
Case 4	Male	20	600	TC	Titration	No	NR	AE	valproate
Case 5	Female	16	300	TC-M	Titration	Chlorpromazine	NR	33 % reduction +AE	lamotrigine
Case 6	Female	23	650	TC-M	Titration	Risperidone Chlorpromazine	NR	31 % reduction +AE	valproate
Case 7	Male	42	600	TC	Titration	No	NR	66.6% reduction	-
Case 8	Male	34	650	TC	Maintenance	Quetiapine	NR	38.4 % reduction +AE	lamotrigine
Case 9	Male	34	700	TC	Titration	No	NR	28.6 % reduction +AE	lamotrigine
Case 10	Female	27	400	TC	Titration	Quetiapine	794 µg/L	50% reduction	-
Case 11	Female	30	NR	NR	NR	NR	NR	NR	

A: atonic seizure, TC: Tonico-clonic seizure, M: myoclonic, NR: not reported, AE: antiepileptic drug

Table 2: socio-demographic data for the sample

Parameters	Our Sample N=11
Mean of age	29 y/o
Gender	
Female	4 (36.3%)
Male	7 (63.7%)
Mean dose of clozapine	560 mg
Type of seizures	
Tonic-clonic	8 (80 %)
Myoclonic	2 (20%)
Atonic	3 (30%)
Antipsychotic association	5 (45.4%)

Data from one patient (case 11) could not be collected due to lack of records. Of the 10 patients who experienced seizures in our hospital, 2 occurred during the maintenance phase of treatment. (Table 1) Five patients were treated with a combination of

antipsychotics at the time of seizure: quetiapine, risperidone, chlorpromazine and aripiprazole.

At the time of seizure onset, the mean dose of clozapine used in our ten patients was 560 mg/day, with a minimum of 300 mg/day and a maximum of 700 mg/day.80% of our patients experienced tonic-clonic generalized seizures. Two patients had myoclonus prior to seizure generalization. Three patients had atonic seizures (30%). All patients benefited from a treatment break on the day of seizure occurrence.

After the first seizure, clozapine was discontinued in one patient and doses were reduced in 8 patients from 28 to 75% of the therapeutic dose reached. Treatment was discontinued in two other patients after recurrence of seizures and removal of treatment consent.

In the case of one patient, no dose reduction was made and only valproate was added at a dose of 1g/day, with no subsequent recurrence. For five other patients, in addition to dose reduction, an antiepileptic was added, mainly lamotrigine for four subjects and valproate for the fifth. A slower, more cautious re-administration followed, with some patients reaching the last dose without any further seizures.

DISCUSSION

Since 2009, clozapine has been part of our therapeutic arsenal as a 3rd-line treatment for resistant schizophrenia or mania. In terms of side-effect monitoring, in our practice metabolic parameters are obtained prior to treatment initiation, then monitored at day 15, day 30 and then quarterly if no change has been established. Blood counts are monitored according to French guidelines, which are less stringent than those in the U.S., weekly for 18 weeks and then once a month. Monitoring of other side effects does not require the same level of attention, and the course of action will depend on the experience of each clinician.

Seizures are sudden, uncontrolled electrical disturbances in the brain, resulting in the transient appearance of signs and/or symptoms due to abnormal, excessive or synchronous neuronal activity.[3- 5]. The presentation and severity of seizures can vary considerably, from mild, barely perceptible episodes to severe convulsions or loss of consciousness. They can be classified into different types according to their clinical presentation and electroencephalographic (EEG) characteristics. The two main categories are focal seizures, which originate in a specific area of the brain, and generalized seizures, which affect both cerebral hemispheres from the outset.[3- 5]

The rate of seizures under clozapine found in our context (2.27%) is close to the rate found by Devinsky & Al 2.8% and Pacia & Al 1.3%.[6, 7]. In some case series, these rates were as high as 22% [8]. The clinical course of clozapine-induced seizures varies little. In the majority of cases, the seizures are generalized, in the form of tonic-clonic seizures, myoclonic seizures or atonic seizures in decreasing order of frequency. Partial seizures are infrequent or rare. Our results support this [2- 10].

Despite the fact that the majority (90%) of our patients who presented seizures were on high doses of clozapine, and that the only patient who developed them on a dose of 300 mg was of young age (16 years), the occurrence of seizures during the first days of titration, with doses lower than even 300 mg per day, is possible and its rate is estimated at 1% versus 4.4% for doses ≥ 600 mg/day. [9]. Several case reports have been published in this regard [11- 15].

In fact, this means that the hypothesis of a direct link between the occurrence of seizures and the use of high doses of clozapine or its rapid titration, which has been put forward before, cannot be supported [16]. In our setting, the incidence of seizures remains low compared with other studies, despite the average daily dose of clozapine varying between 450mg and 550mg (>300mg) and rapid titration (25mg/d). A case report published in 2019 by Skelly & Al describes the case of a patient who developed a seizure 72 hours after abruptly stopping high-dose clozapine (1400mg/d - 628ng/ml) [17].

Several Factors Have Been Identified and Studied:

- High plasma concentration with levels > 1000 ng/ml or > 3057 nmol/l has been suggested, but results are contradictory [9]. Thus, depriving the patient of an increase in dose for greater efficacy, for fear of seizures, is not justified [2].
- EEG disturbances after initiation of clozapine (every 4 weeks) may predict the occurrence of seizures. Conversely, the same abnormalities may predict a good clinical response. [11- 18] In the absence of sufficient evidence in this regard, EEG monitoring is unnecessary and will not improve management [2- 10].
- Kinetic interactions can cause a seizure in the sense that withdrawal of an enzyme inducer (phenitoin, carbamazepine, omeprazole, tobacco) or addition of an enzyme inhibitor (fluvoxamine, fluoxetine, paroxetine) will induce a sudden increase in clozapine plasma concentration [2]. It would therefore be useful to look for the presence of sudden smoking cessation or reduction in case of seizures.
- Although there are no studies comparing different antipsychotics in terms of seizures, the highest rates reported in the literature are associated with clozapine, followed by olanzapine, risperidone and then first-generation antipsychotics. Quetiapine and aripiprazole are the lowest-risk molecules. [9-

15]. Thus, the combination of several antipsychotics can increase this risk, even when clozapine is used in low doses. [19, 20].

An analysis of the different courses of action taken by the various psychiatrists at our hospital reveals the absence of a unified approach. This would have led to excessive discontinuation of treatment due to a therapeutic decision, or refusal by the patient or his family to continue treatment due to a lack of psycho-educational support.

The literature agrees on the need for therapeutic discontinuation of the drug for 24 hours.[2-21). Meyer and Stahl in their book "the clozapine handbook" recommend: 1- in the event of a seizure following a dose increase, withdrawal or addition of a substance having a kinetic interaction with the molecule: request a clozapinemia and then reduce doses to the previous tolerated dose or to the dose adapted to the interaction, with subsequent monitoring of concentration. The addition of divalproate is justified only after recurrence of the seizure. 2- In the absence of evidence of a kinetic interaction, hepatic and renal function should be checked, serum clozapine levels obtained, treatment stopped on the day of the seizure and doses reduced by 25%. In the absence of an etiology, divaproate should be added. Lamotrigine can be used in cases where the initiation of divalproate is not desirable [2].

The addition of valproate has also been supported by Stahl [1] in his prescribing guidelines and by Taylor *et al.,* in their prescribing guidelines [22]. However, it may increase the risk of neutropenia, and its prescription for women of childbearing age may be limited.

The use of lamotrigine is controversial. Lamotrigine has a weak interaction with other drugs [23] and acts synergistically with clozapine [24], but may worsen some symptoms or cause Lyell syndrome [22]. The use of carbamazepine is undesirable in view of its kinetic interaction . [1, 2]

Authors' recommendations differ in terms of the percentage of dose reduction and choice of added antiepileptic drug. Some authors support the addition of an antiepileptic drug as prophylaxis when high doses of clozapine are used. These recommendations are summarized in Table 3.

Table 3: Recommendations for the management of clozapine-related seizures

Reference	Seizures	Prophylaxis
Taylor and Al (22)	50% reduction + add antiepileptic drug - If myoclonus: dose reduction +valproate; lamotrigine may worsen symptoms	Addition of topiramate, lamotrigine, gabapentin or valproate if doses >500mg / day or plasma levels ≥500mcg/L
Mayer and Stahl (2)	-25% reduction -Divalproate if recurrence -Lamotrigine as 2nd-line treatment	Not recommended
Wong and Al (10)	1st seizure: dose reduction and elimination of other factors 2nd seizure: add an antiepileptic drug; valproate then lamotrigine or gabapentin	Not recommended
Yadav and AL (21)	50% reduction + addition of an anti-epileptic drug Valproate: if schizoaffective disorder Lamotrigine: if woman of childbearing age, poor response to clozapine or negative symptoms Topiramate: if a loss of weight is desirable	Valproate or lamotrigine if plasma levels >600 µg/L.

Study Limits

- Cases of seizures may have been omitted, as monitoring was mainly carried out during periods of inpatient hospitalization.
- Cases of myoclonus and partial seizures may go unnoticed by families and go unreported.
- Among the limitations of this study is the failure to examine the relationship between seizure occurrence and norclozapine plasma levels in our setting. In fact, the literature indicates a significant link between these two parameters when comparing results with clozapine doses per day. This could not be confirmed in this study [21- 25].

CONCLUSION

While most authors do not consider seizures on clozapine to be a reason to discontinue treatment [2-11], it is essential to establish a clear course of action to avoid excessive treatment discontinuation following the most severe seizures in general. However, in certain situations, families devastated by the onset of a seizure may also refuse to initiate treatment by retracting their consent. Hence the importance of good psycho-education prior to initiating treatment, with clarification of the situations in which treatment should be stopped, with reference to the data in the literature.

After a first episode, we recommend stopping treatment for 24 hours, requesting a plasma concentration test and then reducing doses by 50%. Research into one of the factors increasing clozapine plasma concentration should be carried out and corrected. The addition of an antiepileptic agent may be discussed in the event of a recurrence of the seizure, with valproate being preferred, except in the case of women in childbearing age, who may be put on lamotrigine.

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