Zaponex Fact Sheet
Seizures

Important Information

The information provided in this fact sheet is intended for healthcare professionals and should not be used as a patient information leaflet.

The information in this document is not intended as a definitive treatment strategy, but as a suggested approach for clinicians. It is based on information from scientific literature and previous successful experience. Each case should, of course, be considered individually.

Background

SmPC statements

The Summary of Product Characteristics (SmPC) of Zaponex[1] states the following on seizures in **section 4.8 'Undesirable effects'**: "Clozapine can cause EEG changes, including the occurrence of spike and wave complexes. It lowers the seizure threshold in a dose-dependent manner and may induce myoclonic jerks or generalised seizures. These symptoms are more likely to occur with rapid dose increases and in patients with pre-existing epilepsy. In such cases the dose should be reduced and, if necessary, anticonvulsant treatment initiated. Carbamazepine should be avoided because of its potential to depress bone marrow function, and with other anticonvulsant drugs the possibility of a pharmacokinetic interaction should be considered."[1]

Section 4.5 'Interaction with other medicinal products and other forms of interaction': "Rare but serious reports of seizures, including onset of seizures in non-epileptic patients, and isolated cases of delirium where clozapine was co-administered with sodium valproate have been reported. These effects are possibly due to a pharmacodynamic interaction, the mechanism of which has not been determined."[1]

Section 4.4 'Special warnings and precautions for use': "Patients with a history of epilepsy should be closely observed during clozapine therapy since dose-related convulsions have been reported. In such cases, the dose should be reduced (see section 4.2) and, if necessary, an anti-convulsant treatment should be initiated."[1]

Furthermore, "uncontrolled epilepsy" is listed as a **contraindication** for clozapine use in **section 4.3**.[1]

Incidence of clozapine-induced seizures

Seizures/convulsions/myoclonic jerks are listed in the Zaponex SmPC[1] as common events, i.e. occurring at a rate between 1/100 and 1/10.

Devinsky *et al*. reported that 2.9% of 1,418 patients in the United States had generalised tonic-clonic seizures during treatment with clozapine.[2] Life-table analysis predicted a likelihood of 10% that a patient will experience a generalised tonic-clonic seizure during the first 3.8 years of treatment.[2] Pacia *et al*. reviewed the incidence, clinical features and management of clozapine-related seizures in 5,629 patients monitored by the Novartis Patient Management System during the first 6 months after marketing. Seventy-one of these patients experienced generalised tonic-clonic seizures, which yielded a frequency of 1.3%. Twenty-four of these 71 patients (34%) had recurrent seizures.[3] The seizure incidence of clozapine appears higher than with most other antipsychotics.[4,5]

In reviews on the association between clozapine and seizures, tonic-clonic seizures were the most frequently described clozapine-induced seizures in literature, followed by myoclonic seizures, partial

seizures, and atonic seizures.[4,6] Myoclonic and atonic seizures together constitute about one-quarter of the reported seizures.[4,6] Myoclonic seizures may occur earlier in treatment, during dose titration, and they may be regarded as warning signs for an increased risk of developing tonic-clonic (grand mal) seizures.[4,6,7] Around 6% of clozapine-induced seizures are considered to be partial seizures.[4] Clozapine-induced absence seizures are limited to a couple of case reports.[8,9] Subtle types of clozapine-induced seizures, such as myoclonic, atonic, partial or absence seizures, may be difficult to recognise.[4,6]

A retrospective observational study investigating electroencephalograms in 71 clozapine-treated patients with refractory schizophrenia or bipolar disorder found electroencephalogram abnormalities in 71.8% (51) of the patients, although none of them reported clinical seizures.[10]

Seizures may occur at any time, although most occur at the start of clozapine therapy: half of seizures reported occurred within the first 34[11] or 42[3] days of clozapine treatment. The risk of seizures is thought to be enhanced by fast dose titration[2,7] and/or large dose increments,[12] but also discontinuation of seizure-protective medication.[5,13–15] However, strong evidence for the correlation between fast dose titration and seizure risk is lacking.[4]

In some cases, prophylactic medication is not effective in preventing seizures. Seizures are considered "uncontrolled" when they are not controlled with adequate trials of two appropriate antiseizure medications. A number of different terms may be used to describe these including: "uncontrolled," "intractable," "refractory," or "drug-resistant." Approximately, one-third of adults and approximately 20-25% of children have epilepsy that fails to come quickly under control with medicines (https://www.epilepsy.com/learn/drug-resistant-epilepsy).

Mechanism of clozapine-related seizures

The mechanism of clozapine-related seizures may be due to the combined actions of multiple receptors. Animal studies demonstrated that dopamine reduces the excitability of the primary sensorimotor cortex in adult rats.[16] Clozapine, a dopamine antagonist, may thus increase cortical excitability by reducing dopamine neurotransmission.[16] Besides the dopaminergic pathway, serotonin receptors are expressed in almost all neural networks associated with seizure. Consumption of serotonin in the brain can enhance the excitability of neurons, reducing the seizure threshold and increasing seizure frequency.[17] The antiepileptic effects of selective serotonin reuptake inhibitors have been demonstrated in controlled trials.[18] Another hypothesis states that mesolimbic areas are closely related to seizure initiation regions and clozapine can induce epileptogenic activity by inhibiting D4 receptors in the mesolimbic system and cortex[19,20] (as clozapine displays a 10-fold higher affinity for D4 compared to D2 or D3 receptors[21]). More in-depth molecular and translational research is needed to further elaborate the mechanism involved in clozapine-induced seizures and how to subsequently translate this to the clinic.

Relation of seizures to clozapine dose and plasma levels

The risk of seizures with clozapine therapy appears to be related to dosage.[4,7,22] Among the many severe and dose-dependent side effects of clozapine, tonic-clonic seizures are considered to be the most dangerous.[7,23] An incidence of approximately 1-1.6% was reported at dosages less than 300 mg daily, 0.9–2.7% at 300–600 mg daily, and 1.9-4.4% at high dosages of 600–900 mg daily.[2,3] Patients who have an Indian heritage may be at increased risk for seizures when receiving high doses of clozapine, especially when the daily dose is above 500 mg.[24] However, seizures may also occur with low plasma clozapine levels,[22,25] particularly in patients with a history of epileptic events.[3] A review by Remington *et al*. concludes that although the results of different studies vary, 500-600 mg/day seems to be the threshold for increased risk of seizures.[26]

As dose correlates to plasma levels, it may be postulated that plasma levels also relate to the risk of seizures. In fact, clozapine plasma levels probably are a more reliable indicator since plasma levels vary widely at a given dose.[7] Indeed, high plasma levels seem to predict EEG changes and seizures,[4,7,10,26] although data is lacking to allow a statistical conformation for seizure risk. The estimated seizure threshold was stated in different studies to be 0.236 mg/L,[27] 0.350-0.450 mg/L,[28] above 1 mg/L,[29,30] or above 1.3 mg/L.[31] In addition to this, the incidence of a full clozapine-induced tonic-clonic seizure has been reported to be five-fold increased when serum concentrations exceed 0.75 mg/L.[32] However, note that, although there seems to be a relation between seizure risk and dose/plasma levels in some studies, the relation is not very strong and there is no clear cut-off range. Seizures can occur at any dose/level and at any time.[4]

One of the challenges with clozapine dosing is the relatively narrow target serum concentration range (0.35-0.60 mg/L[33]), which is the basis for therapeutic drug monitoring practice. The information above however also implies that there may be overlap between levels necessary for optimal therapeutic effect and those inducing side effects. An example of this is clozapine-induced seizures potentially occurring at concentrations within the range necessary for optimal clinical response.[34] This issue indicates that in some cases, additional measures such as prophylaxis or augmentation are needed for optimal clinical response whilst also dealing with the significantly increased seizure risk. This also highlights the importance that patients should always be treated with clozapine at the lowest possible therapeutic dose.

Due to the relationship between seizures and plasma levels, factors that can cause clozapine plasma levels to rise, such as smoking cessation,[35] increased caffeine intake, infection,[36] *CYP1A2*1F/*1F* genotype,[37] or drugs affecting clozapine metabolism can lead to increased risk of seizures.[4,7] Asian patients usually display higher clozapine levels at a given clozapine dose and, therefore, may be at higher risk of developing seizures.[13,38] More information about factors affecting clozapine plasma level can be found in the Zaponex fact sheet “Clozapine metabolism and plasma level monitoring” which can be obtained via the ZTAS website.[39]

Other risk factors

From a large retrospective and observational case control study with up to 12-year follow-up in the UK, it appears that patients with schizophrenia suffer almost 4 times as often from epilepsy as compared to healthy controls,[40] and strong evidence of clustering of epilepsy and psychosis within families has been reported.[5,41]

In a continuous observational drug surveillance programme, male gender, young age (<30 years), a diagnosis of schizophrenic disorder and psychotropic drug polypharmacy (especially in combination with tricyclic antidepressants, lithium, or triple combinations of antipsychotic drugs) were found to be correlated with a significantly higher seizure rate in antipsychotic-treated patients.[5,42] The most frequently seen risk factors in this population were pre-existing organic brain damage, followed by reduction/cessation of convulsive threshold-raising comedication. A recent retrospective study in a Japanese cohort found that shorter illness duration before clozapine initiation was a risk factor for clozapine-induced CNS abnormalities.[42] Additional risk factors, such as substance abuse, pre-existing EEG abnormalities and high initial or rapidly increasing antipsychotic drug dosages were present in relatively few cases.[5]

Recently, a case report described the event of a potential high-dose clozapine withdrawal seizure. The authors hypothesise that withdrawal syndromes from rapid discontinuation of clozapine are likely secondary to its mixed mechanism of action and pharmacokinetic properties.[43] Serotonin could be involved, as abrupt removal of clozapine, a strong 5-HT_{2A}-serotonin receptor antagonist, may cause overstimulation of these receptor types and cause motor symptoms such as hyperreflexia, catatonia,

agitation and restlessness.[43,44] Also, lack of GABA-ergic activity is known to cause seizures, and clozapine stimulates GABA-ergic signalling.[43] This, together with the fact that abrupt discontinuation is known to cause rebound psychosis, cholinergic rebound, serotonin syndrome and (withdrawal) catatonia, emphasizes the importance of gradual dose reduction when discontinuing clozapine treatment.

Management

Prevention

Prevention of seizures (Table 1) can be aided by slow dose titration, keeping the dose as low as possible, using seizure prophylaxis and avoiding concomitant medication that also lowers the seizure threshold, such as lithium, neuroleptics and tricyclic antidepressants. There is a risk in withdrawal of benzodiazepines during titration, as these may protect against seizures during this high-risk period.[13–15] Benzodiazepines should preferably be stopped prior to clozapine initiation,[1] or alternatively, after obtaining steady state clozapine therapy.[15] It is advised to monitor patients for events that may precede tonic-clonic seizures, such as myoclonic jerks, atonic seizures and stuttering.[7,11]

Table 1. Seizure prevention
Slow clozapine dose titration
Avoid withdrawal of benzodiazepines during titration
Avoid dosages above 500- 600 mg/day or plasma levels above 0.6 mg/L
Avoid concomitant use of substances that increase the clozapine plasma levels, or monitor plasma levels
Avoid concomitant use of other medication that also lowers the seizure threshold
Closely monitor the patient for events that may precede tonic-clonic seizures, such as myoclonic jerks, atonic seizures and stuttering
Extra care is advised in patients who are at increased risk of seizures. EEG monitoring or prophylactic anticonvulsants may be considered
Monitor clozapine plasma levels in patients at increased seizure risk, including those on high clozapine dosages

Patients with a history of seizures/epilepsy, EEG abnormalities or head trauma should be treated with extra care;[33] the dose should be titrated very slowly and high dosages should be avoided. EEG monitoring, including a baseline measurement, may be appropriate. For some patients, co-administration of anticonvulsants may be necessary.[33] Patients, especially those at increased seizure risk, may be advised to avoid activities such as baths, cycling, driving etc. during titration or after dose changes because of the seizure risk.[45] In addition, it is advised to monitor clozapine plasma levels of patients who are at increased risk of seizures, including those who are on high clozapine dosages or have a history of high clozapine plasma levels.

As a precaution, EEG monitoring has been suggested, but the evidence of its usefulness is still inconclusive,[6,7] as EEG changes are very common in clozapine treated patients and do not necessarily indicate imminent seizures.[6,10]

Prophylactic use of antiepileptic drugs is advocated by some researchers in patients who are at increased risk of developing seizures,[7,46,47] or even in all patients on clozapine.[4] High-risk patients would include those with a history of seizures, concurrent use of epileptogenic medication, high clozapine plasma levels, stuttering or myoclonic jerks, or EEG abnormalities.[7] However, the prophylactic use of antiepileptic drugs is under debate,[48] for reasons including the risk of drug-drug interactions and the increased risk of side effects (see also "*Pharmacological treatment of clozapine-induced seizures*").[48] Advice from other authors is to use antiepileptic drugs remedially after the occurrence of one seizure[12] or after two seizures.[6,8]

Treatment of seizures
Immediately after the occurrence of a seizure it is recommended to withhold clozapine for 24 hours. Provided that the condition has improved after this time period, clozapine can be restarted at a 50% reduced dose.[33,47,49] The dose may be increased very gradually thereafter in order to regain optimal clinical efficacy. It may be necessary to maintain the patient on a lower dose than prior to the seizure.[3,24] An EEG and a neurological referral should be considered particularly if it is the patient's first seizure.[33,49]

Pharmacological treatment of clozapine-induced seizures
Anticonvulsive therapy may be considered, especially if the patient still requires a high clozapine dose/plasma level.[24,33,47] When a patient experiences a sequential seizure, pharmacological management is strongly advised. The choice of antiepileptic drug should be based on the type of seizure and safety profile in combination with clozapine therapy. The NICE guidance gives a clear overview on pharmacological treatment options by seizure type (https://www.nice.org.uk/guidance/cg137/resources/epilepsies-diagnosis-and-management-pdf-35109515407813).

Sodium valproate
Despite an increased risk of delirium when added to clozapine,[1] sodium valproate is a rational first choice,[3,4,47] as it acts fast, has a broad spectrum of antiepileptic activity and is reported to have mood-stabilising effects.[7] There have been several case reports of successful management of clozapine-induced seizures with sodium valproate.[50–53] Sodium valproate is therefore the most commonly used antiepileptic agent for managing clozapine-induced seizures.[6]

There are, however, some concerns: Firstly, it has been reported that concomitant use of sodium valproate more than doubled the risk of developing clozapine-induced myocarditis.[54] This risk is particularly relevant during the early phase of clozapine therapy, as the risk of myocarditis is largely limited to the first month.[55]
In line with this, the concurrent use of sodium valproate was found to be associated with a substantially increased incidence of neutropenia in a case-control study of 136 cases and 136 controls of clozapine-treated patients. In addition, there was a dose-response effect, with greater associations for higher doses.[56] These results, taken in combination with the results from previous case series,[57–63] suggest that the risk of clozapine associated neutropenia could be reduced by avoiding concurrent valproate treatment.[56] One study analysed 19 patients rechallenged with clozapine following previous neutropenia. Of the 4 unsuccessful rechallenges, 3 (75%) were co-prescribed valproate, compared to 3 of 15 (20%) who were successfully rechallenged. In one of the patients, neutropenia resolved upon withdrawal of valproate.[62]
Although it is difficult to statistically prove the contribution of sodium valproate to other rare clozapine-associated side effects, there are suspicions that sodium valproate prescription may have contributed to at least some published cases of acute interstitial nephritis[64] and pancreatitis.[64,65]

Due to valproate's teratological risk, it must not be used in women of childbearing potential, unless there is a pregnancy prevention programme in place. Valproate is associated with a significant risk of birth defects (around 10%) and developmental disorders (up to 40%) in children born to women who took valproate during pregnancy.[66] A guidance on the use of valproate by women was published by the Medicines and Healthcare products Regulatory Agency (MHRA) in March 2018: https://www.gov.uk/guidance/valproate-use-by-women-and-girls.

Finally, sodium valproate can affect clozapine plasma levels in some individuals. In some reports the clozapine levels were increased,[67] whereas in others decreased levels have been reported after starting sodium valproate.[68–71] The inconsistent results found in the literature may be partially explained by the observation that valproate increases clozapine plasma levels in non-smokers, but decreases clozapine levels in smokers.[72] The mechanism of this interaction is not clear, but the net effect of valproate may be a sum of both inducing and inhibiting actions on clozapine metabolism, influenced by smoking status, valproate levels, and valproate treatment duration.[73] Considering the uncertainties of this possible interaction, clozapine plasma level monitoring is advised before and after starting/stopping sodium valproate.

Lamotrigine

Lamotrigine has also been successfully used in the prophylaxis and treatment of clozapine-induced generalised tonic-clonic seizures.[60] The SmPC for lamotrigine[74] mentions that haematological abnormalities including neutropenia, leukopenia, anaemia, thrombocytopenia, pancytopenia, aplastic anaemia and agranulocytosis are very rarely reported (<1/10,000). However, literature provides quite a number of reports on neutropenia or agranulocytosis with the associated use of lamotrigine.[75–83] There is one case report of rapid-onset agranulocytosis in a 60-year-old clozapine-resistant patient, in whom lamotrigine was introduced as augmentation to clozapine. Yet this patient was also still within the high-risk period of clozapine-induced agranulocytosis,[84] so it is unsure what the contribution of lamotrigine was. In general, lamotrigine's side effect profile[74] has relatively little overlap with clozapine's[1] and therefore, few pharmacodynamic interactions are expected in patients who are stable on clozapine.[7]

The use of lamotrigine may provide an extra benefit, since literature indicates that lamotrigine augmentation may be effective for patients who show a suboptimal response to clozapine,[85–88] especially if they have affective symptoms.[89] The downside is that lamotrigine requires up to 6 weeks of titration, so for immediate add-on therapy, it is not useful.

Lamotrigine did not alter clozapine concentrations in a study with 11 patients on stable clozapine therapy.[90] However, two case reports describe raised clozapine plasma concentrations after lamotrigine was started.[91,92] There appears to be no obvious pharmacokinetic mechanism for this interaction, but in one of the case reports, it was suggested that the inflammation associated with a rash caused by lamotrigine could have inhibited clozapine metabolism.[92] Since interactions may affect levels in some patients, it may be worth considering monitoring clozapine plasma levels before and after lamotrigine is started, especially in patients who are known to have high plasma levels.

Topiramate

There have been a couple of cases reporting on successful use of topiramate to treat clozapine-associated seizures.[93,94] Topiramate may be considered particularly if weight loss is required as well.[7,47] However, there have been some reports on reduced response to antipsychotic therapy after topiramate initiation.[95,96] Topiramate also requires several weeks of titration.

Two studies conducted on a total of 22 patients on stable clozapine therapy did not indicate any fluctuations in clozapine plasma levels after topiramate was added.[97–99] Thus, there is no clear indication for plasma monitoring or dose adjustments after topiramate has been initiated.

Other anti-epileptics
There has been 1 case report of successful management of clozapine-induced seizures with 1200 mg gabapentin.[100] In another case report, 600 mg gabapentin was not sufficient to prevent a seizure in a patient on clozapine.[101] The incidence of leukopenia associated with gabapentin as provided by the manufacturer is between 1 and 10% (common),[102] which may lead to increased risk of clozapine discontinuation.

Pregabalin has shown some promise as an add-on strategy in patients on clozapine with anxiety symptoms, but it may also increase the clozapine plasma levels,[14,103,104] possibly even increasing the risk of seizures.[14]

The use of carbamazepine is contraindicated due to the high risk of bone marrow depression.[1]In addition, it is a known inducer of several CYP450 isozymes involved in clozapine's metabolism.[1,105]

Oxcarbazepine has been developed from structural rearrangements of carbamazepine in order to minimise the involvement of these CYP450 isozymes in its metabolism, although at higher doses it may still have some inducing properties. It is indicated in the treatment of partial seizures with or without secondary generalised tonic-clonic seizures.[106] In one case report, a 46-year-old female patient with bipolar disorder and psychomotor agitation was kept stable on a daily combination of 150 mg clozapine, 1,200 mg oxcarbazepine and 4.25 mg rivastigmine. The combination was well tolerated, and no significant side effects were documented.[107]

Levetiracetam has the same therapeutic indication, but may also be used as adjunctive treatment for other seizure types. However, levetiracetam treatment was correlated with significantly more psychiatric/behavioural side effects (16% incidence and 8% discontinuations out of 521 patients) than average in a retrospective chart review by Weintraub *et al.* [108]

Advice for daily practice:

- The risk of seizures increases with rising dose and plasma levels
- Seizures may be prevented by slow dose titration, low dosage/plasma level, seizure prophylaxis and avoiding other medication that lowers the seizure threshold
- Extra attention is recommended in patients with a history of seizures or epilepsy
- Immediately after the occurrence of a seizure it is recommended to withhold clozapine for 24 hours
- Discontinuation of clozapine is not necessary after a seizure, but a dose reduction is recommended
- An antiepileptic such as sodium valproate, lamotrigine or topiramate may be needed to prevent sequential seizures

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