Signal

Clozapine – Drug dose titration not performed

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Summary

In screening for medication errors in VigiBase, a case series was identified describing lack of dose titration when re-starting clozapine. It is known that when patient stops clozapine for more than 48 hours, a gradual re-introduction is required until the therapeutic dose is reached, to minimise the risk of sedation, seizure, orthostatic hypotension and cramps.

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Introduction

In a screening for medication errors in the WHO global database for individual case safety reports, VigiBase, we identified a case series describing lack of dose titration when re-starting clozapine.

Clozapine is an atypical antipsychotic drug that was approved in 1956 for the indication of treatment-resistant schizophrenia (TRS) as well as for patients who have problems with extrapyramidal side effects when taking other types of antipsychotic drugs.[1] The drug has also been seen to reduce the mortality rate in patients suffering from persistent suicidal or self-injurious behaviour. Clozapine is the only available evidence-based treatment for TRS.[2] In 1975, almost two decades after its approval, 18 Finnish patients who had been taking clozapine developed severe blood disorders. Sixteen out of 18 patients were diagnosed with agranulocytosis, and eight of them died. This led to the withdrawal of clozapine in Finland and in several other European countries where the drug had been approved. On-going studies were stopped, and upcoming trials were forced to undertake a detailed investigation into how the drug, and potentially other antipsychotic drugs, may affect the blood. Despite withdrawal of clozapine, some psychiatrists, while closely monitoring for agranulocytosis, still had to revert to clozapine for patients who suffered relapses due to the drug's exceptional efficacy. In the late 1980s, the US FDA conducted the pivotal Clozaril study, to evaluate the efficacy and safety profile of clozapine, which found that the efficacy of the drug was higher in patients who had failed to respond to at least three previous antipsychotic drugs, in comparison with chlorpromazine, another drug indicated for schizophrenia. The outcomes from this six-week study were the basis for the US FDA to finally approve clozapine in 1989, with the requirement that the patient should be closely monitored for white blood cells (absolute neutrophil count) before and during treatment, since the risk of developing agranulocytosis is 1% in the first year and 0.1% thereafter.[1]

Schizophrenia

Schizophrenia is a chronic mental illness which affects more than 21 million people globally. Anyone can get the disease, but people in early adolescence and, generally, men appear to have a higher risk of developing it. The reason why some people contract schizophrenia is still not fully understood, but it is thought that an individual's genes, in combination with both psychosocial and environmental factors, can trigger the disease.[3,4] Schizophrenia can manifest in different ways, and the signs are divided into positive and negative symptoms. Hallucinations and delusions, typically experienced during psychosis, are examples of positive symptoms; patients interpret the world differently by seeing things and hearing voices that are not there, often resulting in abnormal behaviour and disorganized speech. Self-neglect, apathy, social withdrawal and loss of motivation are examples of negative symptoms, as they describe behaviours which result in a loss for the individual.[4] Among patients with schizophrenia, around 30% are diagnosed with TRS, defined as a failure to respond to two or more anti-psychotic drugs.[5]

Dose

The recommended dose for clozapine is 300 mg per day but doses up to 900 mg are acceptable if needed. It is important that the patient is started on a low dose which is then slowly titrated, otherwise there is a higher risk of developing cardiac arrest, orthostatic hypotension, bradycardia, seizures, and syncope, all of which are dose dependent. The starting dose is 12.5 mg once or twice the first day, followed by 25 mg once or twice a day during the second day under close monitoring. If the patient tolerates the dose, it may be increased successively until a safe and optimal clinical effect is achieved, which generally takes two to three weeks. When the maximum daily dose has been achieved, it should be divided to prevent side effects. A slow dose titration is important not only at the beginning of treatment, but after an interruption lasting more than 48 hours.[6]

Mechanism of action

Clozapine, whose pharmacological mechanism is not fully established, is recommended as the second-line atypical anti-psychotic treatment (due to its difficult side effect profile) for patients who do not respond to other antipsychotic drugs, because of its action on both positive and negative symptoms. Clozapine has an absorption of between 90 to 95% when given orally, but bioavailability is only 50 to 60% due to its first-pass metabolism. The drug has a rapid

antipsychotic and sedative effect on patients, as its peak concentration is achieved after approximately 2.5 hours. The agent is atypical, meaning that the likelihood of the drug causing extrapyramidal side effects, such as tardive dyskinesis, is less than the typical first-generation antipsychotic drug. Clozapine is mainly metabolized by the hepatic enzymes CYP-3A4 and 1A2 to the metabolites desmethylclozapine and clozapine N-oxide. Desmethylclozapine is the only active metabolite with similar features to clozapine but has a much weaker and shorter effect. The half-life of clozapine is dependent on the dose taken, but clinical studies have shown that the mean half-life is 12 hours.[6]

Clozapine, a multireceptorial drug, is a partial 5-HT1A agonist that acts by binding to and inhibiting dopamine D1 to D5 and serotonin receptors. It binds more strongly to dopamine D4 than to the other dopamine receptors, which explains its effect on the negative symptoms. Clozapine also binds to the muscarine receptors M1, M2, M3 and M5, adrenergic (α1 and α2), and histaminergic receptors (H1 to H4). The binding to several types of receptor may account for some of the side effects clozapine can cause.[6,7]

Adverse drug profile

Clozapine causes several serious adverse drug reactions, limiting its use. The necessity of carefully monitoring white blood cell counts is another reason for reluctance to prescribe. Beyond agranulocytosis, possible adverse reactions include myocarditis and metabolic side effects. Additional adverse effects which may increase the risk of poor treatment compliance are increased salivation, sedation, somnolence, agitation, vertigo, and weight gain. Patients treated with clozapine have also been found to have a higher risk of developing diabetes, due to the drug's inhibitory effect on the M3 receptor. Treatment resistant schizophrenia is a serious illness, and it is of utmost importance that patients take their drug according to an established treatment schedule.[6,7]

Reports in VigiBase

In VigiBase, as of October 2019 there were 45 case reports on the preferred term *drug dose titration not performed* in relation to clozapine. The reports have been submitted since 2015 by Australia, the United States, the United Kingdom, and Ireland, and a slight increase in the number of reports being submitted has been seen every year. The reports, from both health care professionals and patients/consumers, describe how the drug, for one reason or another, was stopped after it had been taken for several years. When the patient then started the drug again, which in all cases was more than two days after it was stopped, they resumed with the last intake dose.

Three of the 45 case reports are quoted below, showing examples of how the narratives exemplify the reported term.

> *"A 27-year old male had not taken his antipsychotic drug for one week because he had been on vacation. When he came back, he took his usual dose of 300 mg. Following the overdose, the patient became drowsy and altered behaviour and was admitted to hospital."*

> *"36-year old patient that has been taking the drug for more than 15 years forgot to pick up the prescription and therefore didn't take the drug for three days. When he then took the drug again, he continued his normal dose and experienced sedation due to this overdose"*

> *"A male patient stopped taking clozapine for eight days due to a bug he was suffering from. When he then re-started the treatment, he started with 100 mg which lead to mild tachycardia."*

It is known that if a patient stops taking clozapine for more than 48 hours, a gradual re-introduction is required until the therapeutic dose is reached, to minimise the risk of patients experiencing sedation, seizure, orthostatic hypotension and cramps. A slow dose titration is also important since otherwise an overdose reaction may be triggered in the patient.[6]

Additional added terms

VigiBase contains reports with clozapine and the preferred term "drug dose titration not performed" since 2015, the year the term was included in the MedDRA terminology. To capture reports that may have been entered in the database before 2015 for the same problem in relation to clozapine, an expansion of the search to nearby preferred terms including "product dose omission", "product

If you forget to take Clozaril

If you forget to take a dose, take it as soon as you remember. If it is almost time for your next dose, leave out the forgotten tablets and take the next dose at the right time. Do not take a double dose to make up for a forgotten dose. Contact your doctor as soon as possible if you have not taken any Clozaril for more than 48 hours.

Figure 1: Quote from Clozapine (Clozarils®) Product Information Leaflet.

dispensing error", "therapy cessation" and "treatment noncompliance" was made. Reports that included the medical terms orthostatic hypotension, bradycardia, and syncope, terms that the patient had a higher likelihood to get with a rapid dose increase, were included. The search resulted in 154 cases in total, of which three described how the patient had stopped the drug and then re-started without dose titration, which led to confusion, disorientation and feeling unwell. Several of the cases did mention that the patient was re-initiated/re-titrated, but the strengths were not given. The cases demonstrated the importance of involving the patient themselves (which might be challenging in this patient group) or someone close to the patient who knows and understands why the drug should be dose titrated under close monitoring when there has been a treatment break of more than 48 hours.

Labelling

The summary of product characteristics for clozapine states that if the patient has stopped taking the drug for more than two days, "treatment should be re-initiated with 12.5 mg given once or twice on the first day". A faster dose titration up to the optimal therapeutic level is acceptable if the dose is well-tolerated by the patient.[6] In the patient information leaflet however (Figure 1), the first sentence states that if a patient has forgotten to take his dose, he should take it as soon as he remembers. However, further down the same section, it is mentioned that the patient should contact his doctor if they haven't taken the drug for over 48 hours. By setting it out in this way, there is a risk that the patient may not read further and resume his normal dose as soon as possible.[8]

Conclusion

An update in the patient information leaflet for clozapine explaining the importance of re-titration if it has been more than 48 hours since the last dose may increase the treatment compliance within this vulnerable patient group.

References

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8. European Medicines Agency: Product information leaflet for clozapine. Accessed 2019-11-05.

SIGNAL

WHO defines a signal as:

"Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously". An additional note states: "Usually more than one report is required to generate a signal, depending on the seriousness of the event and the quality of the information".*

A signal is therefore a hypothesis together with supporting data and arguments. A signal is not only uncertain but also preliminary in nature: the situation may change substantially over time one way or another as more information is gathered. A signal may also provide further documentation of a known association of a drug with an ADR, for example: information on the range of severity of the reaction; the outcome; postulating a mechanism; indicating an "at risk" group; a dose range which might be more suspect; or suggesting a pharmaceutical group effect or a lack of such an effect by a particular drug.

Signals communicated by UMC are derived from VigiBase, the WHO global database of individual case safety reports. This database contains summaries of individual case safety reports of suspected adverse drug reactions, submitted by national pharmacovigilance centres (NCs) that are members of the WHO Programme for International Drug Monitoring. More information regarding the status of this data, its limitations and proper use, is provided in the Caveat on the last page of this document.

VigiBase is periodically screened to identify drug-ADR combinations that are unknown or incompletely documented. Combinations of such interest that they should be further reviewed clinically are sent to members of the Signal Review Panel for in-depth assessment. The Signal Review Panel consists of experienced international scientists and clinicians, usually affiliated with a governmental or an academic institution. The expert investigates the clinical evidence for the reaction being related to the suspected drug.

The topics discussed in the signals represent varying levels of suspicion. Signals contains hypotheses, primarily intended as information for the national regulatory authorities. They may consider the need for possible action, such as further evaluation of source data, or conducting a study for testing a hypothesis.

The distribution of signals is currently restricted to NCs, regulatory authority staff and their advisers, participating in the WHO Programme. Signals are sent to the pharmaceutical companies when they can be identified as uniquely responsible for the drug concerned. UMC does not take responsibility for contacting all market authorisation holders. As a step towards increased transparency, since 2012 UMC signals are subsequently published in the WHO Pharmaceuticals Newsletter.

National regulatory authorities and NCs are responsible for deciding on action in their countries, including communicating the information to health professionals, and the responsible market authorisation holders, within their jurisdiction.

In order to further debate, we encourage all readers of signals to comment on individual topics.

* Edwards I.R, Biriell C. Harmonisation in pharmacovigilance. Drug Safety 1994;10:93-102.

Responses from industry

Signals on products under patent are submitted to patent holders for comments. Responses from industry are unedited. The calculations, analysis and conclusions are theirs, and should be given serious but critical consideration in the same way as any scientific document. The WHO and UMC are not responsible for their findings, but may occasionally comment on them.

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Caveat Document

Statement of reservations, limitations and conditions relating to data released from VigiBase, the WHO global database of individual case safety reports (ICSRs). Understanding and accepting the content of this document are formal conditions for the use of VigiBase data.

Uppsala Monitoring Centre (UMC) in its role as the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring receives reports of suspected adverse reactions to medicinal products from National Centres in countries participating in the WHO Programme for International Drug Monitoring. The information is stored in VigiBase, the WHO global database of individual case safety reports (ICSRs). It is important to understand the limitations and qualifications that apply to this information and its use.

Tentative and variable nature of the data

Uncertainty: The reports submitted to UMC generally describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. In most instances it cannot be proven that a specific medicinal product is the cause of an event, rather than, for example, underlying illness or other concomitant medication.

Variability of source: Reports submitted to national centres come from both regulated and voluntary sources. Practice varies: some national centres accept reports only from medical practitioners; others from a broader range of reporters, including patients, some include reports from pharmaceutical companies.

Contingent influences: The volume of reports for a particular medicinal product may be influenced by the extent of use of the product, publicity, the nature of the adverse effects and other factors.

No prevalence data: No information is provided on the number of patients exposed to the product, and only a small part of the reactions occurring are reported.

Time to VigiBase: Some national centres make an assessment of the likelihood that a medicinal product caused the suspected reaction, while others do not. Time from receipt of an ICSR by a national centre until submission to UMC varies from country to country. Information obtained from UMC may therefore differ from that obtained directly from national centres.

For these reasons, interpretations of adverse effect data, and particularly those based on comparisons between medicinal products, may be misleading. The data comes from a variety of sources and the likelihood of a causal relationship varies across reports. Any use of VigiBase data must take these significant variables into account.

Prohibited use of VigiBase Data includes, but is not limited to:

- patient identification or patient targeting
- identification, profiling or targeting of general practitioners or practice

Any publication, in whole or in part, of information obtained from VigiBase must include a statement:

(i) recording 'VigiBase, the WHO global database of individual case safety reports (ICSRs)' as the source of the information

(ii) explaining that the information comes from a variety of sources, and the probability that the suspected adverse effect is drug-related is not the same in all cases

(iii) affirming that the information does not represent the opinion of the UMC or the World Health Organization.

Omission of this statement may exclude the responsible person or organization from receiving further information from VigiBase.

UMC may, in its sole discretion, provide further instructions to the user, responsible person and/or organization in addition to those specified in this statement and the user, responsible person and/or organization undertakes to comply with all such instructions.

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