Clozapine is strongly associated with the risk of pneumonia and inflammation

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ABSTRACT

Clinicians need to remember that (1) systemic inflammations can increase clozapine level; (2) clozapine, by itself, can cause inflammation, particularly during titration that is too rapid for that patient; (3) clozapine may increase the risk of infection; and (4) more specifically, clozapine may be particularly strongly associated with the risk of pneumonia. Pneumonia appears to be associated with high mortality in clozapine patients around the world. Clinicians who are alert to the risk of pneumonia in clozapine patients may significantly decrease mortality in clozapine patients. There is no data on COVID-19 infections in clozapine patients, but based on what we know about clozapine pharmacology, we can hypothesise that clozapine, possibly by impairing immunological mechanisms, may increase the risk of pneumonia in infected patients. More importantly, once fever and/or pneumonia develops, the clozapine dose should be cut in half to decrease the risk of clozapine intoxication. If there is any doubt that in spite of halving the dose there are still signs of clozapine intoxication, completely stopping clozapine may be indicated. Once the signs of inflammation and fever have disappeared, the clozapine dose can be increased to the prior dosage level.

INTRODUCTION

This forum article reviews the multifaceted relationship of clozapine and inflammation and its impact on the clinical care of patients. After briefly reviewing clozapine metabolism, four major topics are discussed: (1) inflammation can increase clozapine levels; (2) clozapine can cause inflammation, particularly during titration; (3) clozapine may increase the risk of infection; and (4) more specifically, clozapine may be particularly strongly associated with the risk of pneumonia.

This data provides a consistent pattern, but the studies are limited by their observational nature. Obviously for ethical reasons, it is not possible to randomise clozapine patients to infections versus placebo.

There is no data on COVID-19 in clozapine patients, but based on what we know about clozapine pharmacology, we can hypothesise that clozapine, possibly by impairing immunological mechanisms, may increase the risk of pneumonia in infected patients. More importantly, once fever and/or pneumonia develops, the clozapine dose should be cut in half to decrease the risk of clozapine intoxication. If there is any doubt that in spite of halving the dose there are still signs of clozapine intoxication, completely stopping clozapine may be indicated. Once the signs of inflammation and fever have disappeared, the clozapine dose can be increased to the prior dosage level.

CLOZAPINE METABOLISM

In 1989 before pharmacokinetic studies were required, the United States (US) Food and Drug Administration (FDA) approved clozapine with very limited information on clozapine metabolism. In 1994, Bertilsson *et al*[1] described CYP1A2 as its major metabolic pathway. CYP1A2 pharmacology is highly relevant in clozapine dosing. Norclozapine is the main metabolite of clozapine and appears to be mainly eliminated by the kidney, since its conjugated metabolites are present in the urine and the serum free norclozapine is excreted by an unknown renal transporter that can be inhibited by gemfibrozil. With geriatric age, clozapine clearance from the body decreases; this is probably explained by the decrease in renal function and subsequent decrease in renal clearance of norclozapine and other metabolites eliminated in the urine.

Tobacco smoke has polycyclic aromatic hydrocarbons which bind to the aryl hydrocarbon receptor and induce CYP1A2 expression, increasing the levels of CYP1A2, which is mainly expressed in the liver. Therefore, smokers tend to have serum concentration values that are approximately 0.80 that of non-smokers when using the same clozapine dose.[2] Conversely, oestrogens have inhibitory effects on CYP1A2 activity. Male patients, then, tend to have serum concentration values that are approximately 0.86 that of females when using the same clozapine dose.[2] Co-medication with inducers such as carbamazepine, phenytoin or rifampicin increase clozapine metabolism and decrease clozapine levels. The most important inhibitors of clozapine metabolism are ciprofloxacin, oral contraceptives, fluvoxamine and caffeine in high doses. Valproic acid can be an inducer and/or an inhibitor of clozapine metabolism; this varies from patient to patient and over time. During clozapine titration, clinicians should be more concerned about the potential of valproic acid to act as an inhibitor.

Clozapine is prone to cause side effects, called adverse drug reactions (ADRs) by pharmacologists. Some of these clozapine ADRs, such as sedation, hypersalivation, constipation and seizures, are dose-related. It is probably more accurate to describe them as serum concentration-related. An expert guideline recommends for efficacy in schizophrenia trough steady-state clozapine concentrations of 350–600 ng/mL.[3] This indicates a narrow therapeutic index. The serum concentration of norclozapine does not contribute to antipsychotic efficacy since norclozapine has no antipsychotic activity. On the other hand, it is possible that serum norclozapine concentration may contribute to most or all clozapine ADRs.

If clinicians have access to clozapine levels, they should use them to maintain each clozapine patient on the

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lowest dose possible that provides stable trough steady-state clozapine levels within the therapeutic range. Assuming that the patient practices good medical adherence and is reliable, we recommend establishing a clozapine dose that provides stable serum concentrations between 350 and 400 ng/mL, to allow some room for normal fluctuations in the clinical environment. To increase compliance and reduce daily ADRs, a single administration at night can be used.

Clozapine dosing is not only influenced by geriatric age, smoking, gender and co-medication but ethnicity (Asian vs non-Asian). In 1997, Asian researchers first described Chinese patients as having serum concentrations similar to those of Caucasians with only half the clozapine dose used in the US.[4 5] A meta-analytic review[2] showed that Chinese and other East Asians have lower clozapine clearance than Caucasians. The lower clozapine clearance, probably explained by lower CYP1A2 activity, appears to be present not only in Chinese patients but is also common to other Asians.[6] The FDA describes Asians as those people whose ancestral origins range geographically from Pakistan to Japan.[6] In Asians, to reach 350 ng/mL, a non-smoking female with average metabolism needs around 150 mg/day and a male smoker 300 mg/day, requiring typical doses in Asians from 150 to 300 mg/day.[6] On the other hand, a non-smoking US Caucasian female with average clozapine metabolism needs around 300 mg/day while a US Caucasian male smoker needs 600 mg/day, requiring typical doses in the US from 300 to 600 mg/day.[6]

To define clozapine poor metabolisers (PMs), it is necessary to stratify Asians versus non-Asians. Within the ethnic group, taking powerful clozapine inhibitors and/or being severely obese can be explained as being a phenotypic PM. In five Asian samples, around 7% of the patients (2%–13%) were phenotypic PMs, with no known cause, but four of the five studies were limited by not ruling out current inflammation, which can make a patient look temporarily like a clozapine PM.[7] Thus, it is possible that around 7% (2%–13%) of Asians may have unknown genetic mutations possibly at the CYP1A2 gene associated with being a clozapine PM.[7]

Until there is a better definition of clozapine PMs, we recommend considering Asian clozapine PMs as those who reach concentrations of 350 ng/mL with clozapine doses <150 mg/day. A more precise definition, including smoking and gender stratification, is provided in a review article.[6] Asian female non-smokers who are PMs need a clozapine dose around 50 mg/day to reach 350 ng/mL, while Asian male smokers who are PMs need a clozapine dose around 125 mg/day.[6] Until a better definition of clozapine PMs in non-Asians is established, we recommend considering non-Asian clozapine PMs as those who reach 350 ng/mL with clozapine doses <300 mg/day.[2]

INFLAMMATION CAN INCREASE CLOZAPINE LEVELS

The US package insert for theophylline, a drug metabolised by CYP1A2, indicates that upper respiratory infections with fever increase serum theophylline concentrations. The release of cytokines during the infection decreases the activity and/or expression of CYP1A2. More relevant for clinicians, experts on theophylline[8] recommended that the theophylline dose should be approximately halved to avoid intoxication during these infections. Therefore, the first author reduced the clozapine dose by half[8] when he first diagnosed a clozapine intoxication during an upper respiratory infection with fever in one of his patients. The later arrival of the clozapine serum concentration level verified his diagnosis of clozapine intoxication.[8] In 2004, based on this case[9] and the available literature, he proposed that during severe inflammations/infections, including pneumonia, the clozapine dose should be halved until clozapine levels are available to better personalise clozapine dosing.[9] Through 2016, there are 40 published cases of clozapine elevation during infections.[10] There are also published clozapine intoxications during severe inflammation without infection.[11]

More recently, in a Beijing hospital, three cases of clozapine intoxication we identified included ones with pneumonia,[12] influenza[11] and dermatitis in the absence of infection.[11] In these three Chinese patients severe infections were associated with roughly double the serum concentrations,[11 12] while the effects in relation to dermatitis depended more on its severity. A doubling of the concentration was only observed when there was an elevation of the serum C-reactive protein (CRP) and widespread effect on the skin all over the body.[11] In a recent retrospective review of 131 clozapine inpatients at Beijing Anding Hospital, we found 18 episodes of infections/inflammations in 16 patients. At the total sample level, these episodes: (1) extended for 2% (482/24 789) of clozapine days and (2) contaminated 3% (46/1384) of trough steady-state serum concentrations of clozapine. At the individual level, we found: (1) no clinically relevant effects on the serum clozapine concentrations in the 11% of infection episodes which presented with no leukocytosis or CRP elevations; (2) halving the clozapine dose would be advisable in 61% of the infection episodes; and (3) reducing the clozapine dose to one-third would be advisable in 28% of infection episodes.[13]

Therefore, based on the US[8 14] and Chinese experiences[11–13] as well as on the literature,[10] we proposed that clinicians need to be very alert regarding clozapine patients' risk of clozapine intoxications during any kind of systemic inflammation associated with fever and/or CRP elevations. Until better data is available, based on our experience in the US and China, we have developed three sets of recommendations regarding infection, based on timeframe: (1) prevention; (2) during the infection; and (3) after the infection.[13]

For prevention, we recommend that psychiatrists using clozapine should educate their outpatients and families to be attentive to signs or symptoms of infection/inflammation

or fever and to contact them immediately to prevent clozapine intoxications. Moreover, a careful clinician, after reaching a stable maintenance clozapine dose, should go ahead and measure two or three trough and steady-state serum clozapine concentrations. By calculating the mean concentration and correcting by the clozapine dose,[2] the clinician can establish a baseline for clozapine metabolism in that patient and the lowest clozapine dose providing a therapeutic serum concentration. In the unfortunate event that the patient develops a systemic infection or inflammation, this baseline clozapine metabolism can be compared with the decreased metabolism during the inflammation.

Once an infection has developed, the psychiatrist should order a CRP level. When fever and/or CRP elevations develop, the psychiatrist should consider immediately halving the clozapine dose and monitor for signs of clozapine intoxication. If the clinician has access to clozapine Therapeutic drug monotoring (TDM) when the lab returns the clozapine TDM, it will be possible to better adjust the dosage. If signs of clozapine intoxication are already present it may be safer to stop clozapine for 2–3 days or until the serum clozapine concentration report arrives.

After the infection/inflammation has resolved and the CRP has normalised, we recommend going back to the prior clozapine dose without uptitration, since half of the dose during infection will provide roughly the same concentration as the dose without infection. If the clinician did not measure clozapine concentrations before the infection, it may be wise to measure them after the infection to establish the lowest clozapine dose providing therapeutic serum concentrations and efficacy for maintenance treatment.

Other antipsychotics may be associated with elevations in serum concentrations during infections or inflammations, particularly those metabolised by CYP1A2 and CYP3A4. Olanzapine is mainly metabolised by CYP1A2 and was associated with increases in serum concentrations during an upper respiratory infection in a case report[8] but it has a wider therapeutic index than clozapine. Some case reports and observational studies previously reviewed in another article[11] suggest that infections can increase the serum concentrations of antipsychotics metabolised by CYP3A4. Three second-generation antipsychotics are mainly metabolised by CYP3A4: cariprazine, quetiapine and lurasidone. Four second-generation antipsychotics are metabolised by CYP2D6 and CYP3A4: aripiprazole, brexpiprazole, iloperidone and risperidone. Until better studies are available, we recommend that clinicians remain aware of this potential for increases in serum concentration levels during infections/inflammations and the wisdom of measuring the serum concentrations of these seven antipsychotics metabolised by CYP3A4 when possible.

CLOZAPINE CAN CAUSE INFLAMMATION

Clozapine can also cause inflammation, although the mechanisms are not completely understood. Most cases of clozapine-induced inflammation occur during titration and the most typical manifestations are CRP elevations, fever and/or myocarditis.[15] Other rarer forms have been described and include serositis, pneumonitis/alveolitis, hepatitis, pancreatitis, nephritis, colitis and dermatological disorders.[15]

Australia appears to have almost 10–100 times more clozapine-induced myocarditis than European countries. Drug agencies from various countries send their data to a WHO database called VigiBase.[16] In July 2019, there were 3048 reports of myocarditis associated with clozapine, which resulted in 6% lethality (170 fatal outcomes). Australia provided >1500 of those reports. Most individual countries from continental Europe provided <30 reports. In the view of Australian experts,[17] a 3% incidence rate of clozapine-induced myocarditis in Australia is explained solely by their intensive cardiac monitoring during titration, which is not practiced in other countries. Psychiatrists in continental Europe, on the other hand, titrate their patients slowly and rarely diagnose clozapine-induced myocarditis. In a real-world study with 3262 clozapine patients from the Danish registry, Rohde *et al*[18] found a 0.03% incidence of myocarditis within the first 2 months of treatment. Based on a 3% incidence of myocarditis according to Australian data and a 6% death rate due to lack of cardiac monitoring, six deaths (3% multiplied by 6% is 0.18% and 0.18% of 3262 is six deaths) were expected in that Danish study, but no myocarditis deaths were identified within the first 2 months of clozapine treatment.[18]

To understand the paradox of clozapine myocarditis, one needs to remember that inflammation decreases clozapine metabolism and then realise that clozapine can also cause inflammation. The history of lamotrigine-induced Stevens-Johnson syndrome provides further understanding.[19] Lamotrigine-induced Stevens-Johnson syndrome was associated with rapid dose escalation and/or normal titration in patients taking an inhibitor, such as valproic acid. The first sign that the titration is too fast for that patient is usually a skin rash. If the escalation continues, auto-antibodies develop, leading to full-blown Stevens-Johnson syndrome. Therefore, after the first approval, the pharmaceutical company had to reformulate the lamotrigine titration by halving the dose during co-prescription of valproic acid. Similarly, we propose that, first, a clozapine titration that is too fast leads to CRP elevations and/or fever; second, cytokine release decreases clozapine metabolism and this causes a positive feedback mechanism; Third, if the clozapine titration continues, the inflammation evolves into myocarditis, probably with the development of auto-antibodies.

This model was supported by five published cases of clozapine-induced myocarditis in New York.[20] After their data was provided to the first author, four cases were found to have rapid titration and the other case could

not tolerate a low clozapine dose of 25 mg/day, which is compatible with being a US clozapine PM. In two of the five patients clozapine levels were available and they were compatible with a decrease in clozapine clearance.[20]

Following this model, clozapine-induced myocarditis can be prevented by using slow, personalised titration: (1) with further slowing for Asians treated by Western psychiatrists, including Australians, who were trained to use Caucasian-level titration in all their patients; (2) considering reversible cases of clozapine PM status by stopping the co-prescription of inhibitors, such as valproic acid and oral contraceptives, and requiring normal CRP before starting clozapine; and (3) considering extremely slow titration for cases of clozapine PMs in which the cause cannot be removed: extreme obesity or an absolutely needed co-prescribed inhibitor. When clozapine dose escalation is associated with an abnormal CRP, cytokines are being released and the titration is too fast for that individual patient. Clozapine dose escalation needs to be held until CRP is normal.

To avoid the risk of myocarditis in Asians, we recommend starting with 12.5 mg as the first dose, followed by targets of 50 mg/day on day 7, 100 mg/day on day 14 and 150 mg/day on day 21. Moreover, Asian companies producing clozapine should consider developing tables of 5 or 10 mg to facilitate slower titrations for Asian clozapine PMs.[6] In the absence of formulation with clozapine doses lower than 12.5 mg, for Asians with severe obesity or with co-prescription of a medication with potential to be a clinically-relevant inhibitor of clozapine metabolism (eg, valproic acid or an oral contraceptive), we recommend starting with 12.5 mg as the first dose, followed by targets of 25 mg/day on day 7, 50 mg/day on day 14 and 75 mg/day on day 21.

In summary, data from (1) the lamotrigine literature; (2) the clinical experience of the authors; (3) the review of TDM studies from the US, Europe and Asia; and (4) VigiBase has been used to reframe the myocarditis debate. Myocarditis is extremely rare in non-Australian countries and can be avoided by slow, personalised titration. The high incidence of clozapine-induced myocarditis in Australia is probably explained by titration that may be fast for Caucasians and is risky for Asian patients or for Caucasians taking an inhibitor, such as valproic acid.

CLOZAPINE MAY BE ASSOCIATED WITH INCREASED RISK OF INFECTION

Clinicians all over the world know that on rare occasions clozapine can cause agranulocytosis since this information is included in the clozapine package inserts and most drug agencies require white cell counts to start clozapine. The mechanism is not well understood but it is believed that, in these patients, antibodies are developed against the neutrophils. The peak incidence occurs at 1 month of exposure and declines to negligible levels after 1 year of treatment.[21] A recent meta-analysis provided a prevalence of agranulocytosis of 0.4% (95% CI: 0.3% to 0.6%); deaths caused by agranulocytosis were 0.05% (CI: 0.03% to 0.09%).[22] This widespread awareness by clinicians is reflected in the almost 35 000 reports of neutropenia in VigiBase with the number of fatal outcomes only in the 500s (2% relative lethality).[16]

More importantly, clinicians may not be aware that even in the absence of neutropenia, clozapine has been associated with a possible increased infection risk. Landry *et al*,[23] based on case reports, proposed that clozapine may increase the risk of tuberculosis and, based on a chart review in a Canadian hospital, may be associated with increased use of antibiotics. Large studies in clozapine patients using the registries of Taiwan[24] and Denmark[25] verified an increased risk of tuberculosis with an adjusted risk ratio of 1.63 (95% CI: 1.10 to 2.40; p=0.014)[24] and increased antibiotic use with a relative risk of 1.43 (95% CI: 1.26 to 1.61, p<0.001).[25] In a British case-control study, a higher proportion of the clozapine-treated group reported taking more than five courses of antibiotics in the preceding year, 5.3% (5/123) vs 1% (1/111) in controls taking other antipsychotics, and this was associated with an increased percentage of patients with low values for all immunoglobulins.[26] In an vitro study, clozapine increased the production of the interleukin-1 receptor antagonist.[27]

Regarding possible increased infection risk in the absence of agranulocytosis, we only recommend that clinicians tell clozapine patients to avoid close contact with contagious people.

CLOZAPINE MAY BE MORE STRONGLY ASSOCIATED WITH PNEUMONIA THAN WITH OTHER INFECTIONS

The second section suggests that infection may be associated with clozapine intoxication and the fourth and prior section that clozapine may increase infection risk possibly by interfering with immunological defenses. As pneumonia is one of the most frequent infections, it is not surprising to find in the literature that pneumonia may be associated with clozapine intoxication and that clozapine, by interfering with immunological mechanisms, may increase the risk of pneumonia. Moreover, attentive reading of the literature suggests that clozapine and pneumonia have strong bidirectional associations beyond what has been described in prior sections.

In 2005, after studying post-marketing surveillance data, the FDA proposed that, by interfering with swallowing, antipsychotics were associated with increases in pneumonia in the elderly and this contributed to mortality in this population.[27] Although clozapine is rarely used in the elderly, its US package insert, as with other second-generation antipsychotics, was modified to include this warning. Then Kuo *et al*,[28] using the Taiwanese registry, demonstrated that clozapine may be the antipsychotic most closely associated with pneumonia. As a matter of fact, compared with other antipsychotics, clozapine

may be associated with a greater number of pneumonia cases and greater mortality.[16] More importantly, clinicians need to be aware that pneumonia may be among the greatest causes of mortality in clozapine patients. VigiBase had >6000 reports of broadly-defined pneumonia in clozapine patients with >2000 lethal outcomes. To get an accurate perspective, clinicians need to be aware that the broad definitions of agranulocytosis or myocarditis were associated with lethal outcomes in the 500s.[16]

Before describing which known mechanism can explain the strong association between clozapine and pneumonia, we have to acknowledge that in countries other than China clozapine is mainly used for treatment-resistant schizophrenia. Thus, in countries other than China, the association between clozapine and pneumonia may be partly explained by the greater severity of illness in clozapine patients, who are frequently the most treatment-refractory patients with relatively high rates of smoking. Therefore, the contributing effects of the severity level of mental illness on pneumonia needs to be further explored by future studies in clozapine patients. On the other hand, clozapine has specific effects independent of the greater severity of illness in the clozapine patients, since using mirror-image design in the Danish registry,Rhode *et al*.[29]

Rhode *et al*[29] found that clozapine gave the largest absolute increase in pneumonia risk although it did not reach significance, probably due to the relatively small sample size. In the year before clozapine, there were 1.22% (23/1872) patients with pneumonia and in the first year 1.87% (35/1872). This is an increase of 0.64% (12/1872) (p=0.10).

Clozapine, as with any other antipsychotic, can interfere with swallowing, increasing the potential for aspiration.[27] The potential for aspiration and aspiration pneumonia during antipsychotic treatment may be further increased by sedation and hypersalivation.[27] As clozapine is more prone to cause sedation and hypersalivation than other antipsychotics,[27] it is not surprising that clozapine may be more strongly associated with aspiration pneumonia. Assuming that clozapine is associated with immunological abnormalities, this may also explain an increased risk for other types of pneumonia not associated with aspiration. Rarely, other severe clozapine ADRs, such as severe constipation complicated with ileus, or myocarditis, can be complicated by pneumonia. Once pneumonia develops, clozapine co-prescription may be particularly lethal and worse than other antipsychotics. Severe inflammation during pneumonia releases cytokines that inhibit CYP1A2 expression and/or activity and increase serum clozapine concentrations, further increasing the risk of concentration-related ADRs including hypersalivation, sedation, aspiration or even arrhythmia, creating very dangerous positive feedback.[16]

Our three sets of recommendations for infections in clozapine patients apply to the most important infection, pneumonia. The general preventive measures related to infection apply, including patient/family education and use of the lowest possible dosage providing efficacious response. Specific preventive measures for aspiration pneumonia are close monitoring of sedation and hypersalivation. Clozapine administration should be moved around to the most convenient times in order to increase adherence and decrease these ADRs; treat hypersalivation, preferably with local antimuscarinic treatments which may have less risk of increasing the risk of constipation than oral anticholinergic drugs, such as benztropine, or biperiden. Discontinuation of other co-medications associated with sedation and/or pneumonia risk should be considered. As benzodiazepines are associated with sedation, swallowing disturbances and pneumonia, clinicians may need to consider decreasing or discontinuing them to decrease the aspiration pneumonia risk. Although there is no data, it may not be unreasonable to give pneumonia vaccines to clozapine patients to decrease risk of pneumonia not associated with aspiration, but it cannot be ruled out that vaccines may not be as effective in clozapine patients due to clozapine effects on immunological mechanisms.

Based on our experience with pneumonia,[12–14] we recommend that clinicians measure trough serum clozapine concentrations to personalise dosing during pneumonia. As the clozapine levels may not be immediately available and due to high lethality, we are convinced that the clozapine dose should be cut in half in all patients with pneumonia. Regarding antibiotic treatment, those such as ciprofloxacin and norfloxacin, which are strong CYP1A2 inhibitors, should not be used.

After the pneumonia has resolved, we make the same recommendation as after infections: return to the prior dose after the CRP has normalised and consider the lowest clozapine dose possible with the fewest ADRs in order to avoid the recurrence of pneumonia in the future.

Clozapine appears to be associated with significantly fewer deaths in patients continuously treated with clozapine compared with other antipsychotics. In a meta-analysis of 24 studies, long-term, crude mortality rate ratios were not significantly lower in patients ever treated with clozapine during follow-up, but significantly lower in patients continuously treated with clozapine compared with patients using other antipsychotics (mortality rate ratio=0.56, 95% CI: 0.36 to 0.85, p =0.007).[30] By being alert to the multifaceted association of clozapine with inflammation, clinicians may further decrease the mortality in clozapine patients.

In summary, clinicians need to remember that: (1) systemic inflammations can increase clozapine level; (2) clozapine, by itself, can cause inflammation, particularly during titration that is too rapid for that patient; (3) clozapine may increase the risk of infection; and (4) more specifically, clozapine may be particularly strongly associated with the risk of pneumonia. Pneumonia appears to be associated with high mortality in clozapine patients around the world.

Clinicians who are alert to the risk of pneumonia in clozapine patients may significantly decrease mortality in clozapine patients.

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