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LETTER TO THE EDITOR

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Japanese patients need slower, personalized clozapine titrations: A comment on the case described by Kikuchi et al.

To the Editor,

Kikuchi et al. published an extremely illustrative clozapine case.[1] A 43-year-old nonsmoking male Japanese patient was started on 12.5 mg/day of clozapine and up-titrated to 150 mg/day on day 15. A fever on day 17 led to suspicion of pneumonia and antibiotic treatment. On day 22, clinicians wisely diagnosed clozapine-induced acute eosinophilic pneumonia. After clozapine discontinuation, they waited until there were no signs of inflammation, including a normal C-reactive protein (CRP) level, and used a much slower titration than the titration recommended by the Japanese package insert.

Moreover, Kikuchi et al.[1] kindly reference our adult inpatient clozapine titration guideline,[2] which has now been translated into Japanese (http://www.jscnp.org/clozapine/index.html). The guideline describes (1) six different titration schedules proposed for stratified clozapine dosing and (2) CRP monitoring at baseline and weekly for 4 weeks simultaneous with the white blood cell count.

To achieve the minimum therapeutic concentration of 350 ng/ml, the clozapine dosage needs to be adjusted based on ancestry: from Asians (lowest) to Europeans and to sub-Saharan Africans (highest). Thus, Asians need the slowest titration and the lowest maintenance dose for average patients, ranging from 175 to 300 mg/day (175 mg/day for female nonsmokers and 300 mg/day for male smokers). Clozapine poor metabolizers (PMs) need slower titration and maintenance doses ranging from 75 to 150 mg/day in Asians (Table 1). Nongenetic clozapine PMs include those with (1) obesity, which decreases clozapine metabolism, (2) co-prescription of inhibitors, such as oral contraceptives, or (3) the presence of inflammation that, by releasing cytokines, inhibits the main clozapine metabolic enzyme, the cytochrome P450 1A2 (CYP1A2). Genetic PMs may account for <10% of Japanese patients, as in other Asian countries.[5]

Baseline CRP offers protection from unawareness that a systemic inflammation is impairing clozapine metabolism. Weekly CRP may help to identify unknown clozapine genetic PMs who may develop increased CRP during non-PM-level titrations.[6] The international clozapine titration guideline is a document in progress, already modified[3] to recommend PM titrations for patients on olanzapine or quetiapine (Table 1), who are at greater myocarditis risk.[4]

The patient described by Kikuchi et al. developed a "clozapine-induced inflammation"[6] due to his lack of tolerance of the standard Japanese titration. Lack of tolerance of clozapine titration can manifest through CRP elevations, eosinophilic myocarditis, and other localized inflammations. All of these manifestations are part of a hypersensitivity reaction that has three phases. In the first phase, the titration is too fast for a specific patient; either the psychiatrist was too aggressive in titrating and/or the patient cannot tolerate it due to PM status. This situation leads to a release of cytokines. In the second phase, a positive feedback loop develops; the cytokines inhibit CYP1A2, which further increases plasma clozapine concentrations. In the third phase, if the titration continues, the inflammation becomes complicated by the development of an auto-immune phenomenon, leading to localized inflammation.[6] This hypersensitivity reaction can manifest with eosinophilia too,[7] including a clozapine-related drug reaction with eosinophilia and systemic symptoms syndrome.

The Japanese clozapine titration and dosing schedule is much slower than the US protocol but it may be too fast for Japanese PMs. A presumably Chinese genetic PM only needed 90 mg/day to reach the minimum therapeutic concentration of 350 ng/ml (Supporting Information Figure S1 of the clozapine international guideline[2]). The international titration recommends very slow titration for Asian PMs, but the titrations are designed to provide approximately the same serum clozapine concentration as for non-PMs. Unfortunately, Japanese prescribers have never been warned that the official Japanese titration schedule is associated with an extremely high incidence of clozapine-induced inflammation. Due to lack of space, only three proofs are provided. First, the first published Japanese clozapine study had a 29% (11/38) incidence of clozapine-induced fever,[8] which is not considered normal in other countries. Second, myocarditis[9] in Japan is frequent and explained 73% (30/41) of Asian reports of clozapine-induced myocarditis included in the global pharmacovigilance database. Asian countries had the highest risk of serious (odds ratio = 2.39, P = 0.02) and fatal (odds ratio = 4.35, P = 0.02) outcomes during clozapine-induced myocarditis.[4] Third, a Japanese hospital,[10] following the official Japanese titration schedule, was not aware that other countries do not have and do not

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TABLE 1 Summary of international clozapine titration guideline for adult inpatients focused on Japanese patients who should follow Asian titrations

Obesity[a] (≥30 kg/m^2)	Use PM titration	
	Consider PM titration if severely overweight	
Comedications		
Oral contraceptives[b]	Use PM titration and PM maintenance dose	
Valproate[c]	Use PM titration and PM maintenance dose	
Olanzapine[d]	Use PM titration. After discontinuation ↑ to non-PM dose	
Quetiapine[e]	Use PM titration. After discontinuation ↑ to non-PM dose	
Inflammation[f]	Wait until CRP is normal	
	PMs[g]	Non-PMs
Target maintenance dose	75–150 mg/day	175–300 mg/day
Week 1		
First day	6.25 mg	12.5 mg/day
↑ dose by	6.25 mg	12.5 mg/day
Day 7	25 mg/day	50 mg/day
Alert concentration[h]	>118 ng/ml	>105 ng/ml
Week 2		
↑ dose by	12.5 mg	12.5 mg/day
Day 14	50 mg/day	100 mg/day
Alert concentration[h]	>235 ng/ml	>210 ng/ml
Week 3		
↑ dose by	12.5 mg	25 mg/day
Day 21	75 mg/day	150 mg/day
Alert concentration[h]	>353 ng/ml	>315 ng/ml
Ideally,[i] use clozapine concentration[j] to determine final clozapine dose and then stop any AP[d,e]		
Week 4		
Female nonsmoker	75 mg/day	175 mg/day
	Concentration 1 week later	Concentration 1 week later
Other	75–150 mg/day	175–300 mg/day
↑ dose by	25 mg	25/50 mg/day
	Concentration 1 week later	Concentration 1 week later

Notes: These recommendations are provisional and may need modifications in the future as we receive suggestions from clozapine prescribers. Never start a patient on clozapine when he/she has an undiagnosed inflammation. Never start a patient on clozapine when taking fluvoxamine, ciprofloxacin, or amiodarone (powerful inhibitors). It is not a good idea to start clozapine in a patient taking phenytoin, phenobarbital, or rifampicin (powerful inducers).

Abbreviations: CYP1A2, cytochrome P450 1A2; CRP, C-reactive protein; PM, poor metabolizer.

[a]Clozapine binds to fat tissue and that leads to decreased clozapine metabolism.[2]

[b]Estrogen is a moderate inhibitor of CYP1A2.[2]

[c]Valproate can increase clozapine concentrations during titration. During maintenance the inductive effects of valproate on glucuronidation may become obvious and mild decreases in norclozapine concentrations can happen.[2]

[d]We recommend adding clozapine to prior antipsychotics and only stopping them when a clozapine therapeutic dose has been reached by obvious clinical response and/or reaching serum concentration of 350 ng/ml.[3] We recommend using the PM titration schedule for patients on olanzapine, but once olanzapine is discontinued, slowly increase the clozapine dose to the maintenance dose of non-PMs. Adding clozapine to olanzapine appears to increase the seriousness of clozapine-induced myocarditis.[4] During the development of clozapine-induced myocarditis, there is the possibility of saturation of clozapine metabolism; olanzapine competes with clozapine for CYP1A2, which may further saturate the clozapine metabolism. As far as we know, olanzapine by itself produces little or no risk of causing myocarditis.

[e]We recommend adding clozapine to prior antipsychotics and only stopping them when a clozapine therapeutic dose has been reached by obvious clinical response and/or reaching serum concentration of 350 ng/ml.[3] We recommend using the PM titration schedule for patients on quetiapine, but once quetiapine is discontinued, slowly increase the clozapine dose to the maintenance dose of non-PMs. Adding clozapine to quetiapine appears to increase the seriousness and lethality of clozapine-induced myocarditis.[4] Quetiapine by itself may have some small risk of causing myocarditis and may have additive pharmacodynamic effects to the effects of clozapine during clozapine-induced inflammation.

[f]An abnormal baseline CRP value should lead to the investigation of any undiagnosed infection or systemic inflammation; these should be resolved before starting clozapine. Prescribing clozapine during a chronic inflammatory process, such as rheumatoid arthritis or Crohn's disease, is a complex decision. There is need to carefully balance co-medications (some associated with neutropenia), low clozapine doses and repeated clozapine concentration monitoring to avoid inflammatory exacerbations leading to clozapine intoxications.[2]

[g]The candidates likely to be associated with clozapine genetic PM status are alleles (CYP1A2*8, CYP1A2*11, CYP1A2*15, and CYP1A2*16) which appear to be rare (each allele <1% in Japanese population); they have not yet been studied in clozapine-treated patients but combining all these alleles would possibly mean that genetic PM status may describe up to 10% of Japanese patients.[2]

[h]Serum concentrations before week 4 are not at steady state. Measuring them under steady-state conditions will delay titration. These concentrations are alert signs that the titration may be too fast for that patient. These concentrations were estimated in each group using clozapine concentration-to-dose ratios.

[i]When concentrations are not available consider using (1) in non-PM patients 150 mg/day for female nonsmokers and 300 mg/day for male smokers, and (2) in PMs 75 mg/day for female nonsmokers and 150 mg/day for male smokers. Female smokers and male nonsmokers need intermediate doses. Tobacco smoking is a mild inducer of CYP1A2.

[j]Serum clozapine concentrations should be measured at trough and steady-state conditions. Trough means the lowest level during the day, usually occurring in the early morning before medications are administered. Steady state refers to the equilibrium point between absorption and elimination. Most articles suggest five half-lives to reach steady state and typically assume a clozapine half-life of 24 h and recommend waiting at least 5 days after any clozapine dose is changed. Half-life is higher in clozapine PMs. Some clozapine PMs may need 2 weeks to reach steady state.[2] To simplify and make easier to remember, we recommend drawing blood for clozapine concentrations 1 week after any dosing change for the average Japanese patient and waiting 2 weeks when PM status is suspected.

consider normal their high incidences of fever (38%, 57/152), pleuritis (13%, 20/152), myocarditis (5%, 7/152), and interstitial nephritis (1%, 2/152).

We hope this letter contributes to the dissemination of our guideline (Table 1) and its Japanese translation. Using slower and personalized titrations in Japan may resolve the high rates of fever, eosinophilia, myocarditis, and all types of clozapine-induced inflammation during titrations.

AUTHOR CONTRIBUTIONS

Norio Yasui-Furukori helped with the dissemination of the Japanese translation of the international clozapine titration guideline. Yuji Otsuka is a co-author in the international clozapine titration guideline described in this article and completed the Japanese translation which is available at the web page of the Japanese Society of Clinical Neuropsychopharmacology (http://www.jscnp.org/clozapine/index.html). Jose de Leon wrote the first draft of this article. All authors reviewed, provided comments and approved the final version.

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