Guest Editorial

Do Asians Patients Require Only Half of the Clozapine Dose Prescribed for Caucasians? A Critical Review

The article by de Leon *et al*.[1] raises several important issues regarding treating Asian patients with clozapine. Historically and traditionally, physicians have prescribed antipsychotic drugs by starting with low doses and slowly increasing the dose based upon the patient's individual response and balancing adverse side effects. The "start low and go slow" approach continues to be used by prescribers independent of the patient's ethnic background. Over the last 30 years, significant medical developments occurred that influence regulatory agencies today, affecting drug labels. These developments include pharmacogenomics, modeling simulations, and analytical and imaging technologies that allow drugs in psychiatry to be more accurately individualized to treat patients. Clozapine represents a unique category among antipsychotic medications as it is approved for treatment-resistant patients with schizophrenia by regulatory agencies.[2]

Clozapine has many challenges with patient management because of its well-known adverse effect profile.[2,3] The evidence of clozapine doses being about only half in Asians compared to Caucasians presented by de Leon *et al*.[1] is reasonable, logical, and based upon published studies. This commentary presents additional information warranting clozapine dosage requirements be lower in Asians.

Clozapine disposition has considerable interpatient variability and is dependent upon many individual factors such as sex, smoking, and pharmacogenomics. Therapeutic monitoring of clozapine plasma or serum concentrations provides clinicians information about dosing, drug interactions, and patient response. The recommended clozapine plasma concentrations are >350 ng/mL,[4] with a possible "ceiling effect" range of 600–838 ng/ml.[5] Upon a closer examination of two studies,[6,7] the relationship between clozapine dose and plasma concentrations reveals this interesting finding in a Caucasian population (N = 148) where the data presented was clozapine dosed at 3 mg/kg and 6 mg/kg. The mean (±S.D.) body weight (kg) for the male and female Caucasian groups were 77.6 ± 15.9 and 69.9 ± 12.6, respectively.[6] Those results would translate to mean clozapine daily doses of 232.8 mg (3 mg/kg) and 465.6 mg (6 mg/kg) for the males and 209.7 mg (3 mg/kg) and 419.4 mg (6 mg/kg) for the females, respectively. The corresponding clozapine plasma concentrations for greater than 90% of the male and female patients were <200 ng/ml and <400 ng/ml, respectively. The clozapine study in Taiwanese patients (N = 162) did not separately analyze the differences between males and females.[7] However, clozapine daily doses of 200–250 mg and 400 mg yielded the corresponding mean ± (S.D.) clozapine plasma concentrations (ng/ml) of 320 ± 163 and 591 ± 325, respectively. Collectively, these two studies and subsequent other studies support that Taiwanese and Chinese patients had a clozapine plasma level/dose factor of 1.50 higher than Caucasians. A recent study comparing Chinese (N = 126, from Beijing) to a previously published Caucasian Italian outpatient sample (N = 152) also reported a clozapine concentration/dose (C/D) ratio of 1.57, higher among the Asian group.[8]

Clozapine metabolism has been elucidated and involves mainly hepatic cytochrome P450 CYP1A2.[9] Although other CYPs are involved in clozapine metabolism, CYP1A2 remains the predominant metabolic pathway. Clozapine disposition significantly correlates (r = 0.84, P < 0.0024) with caffeine demethylation (used as a measure of CYP1A2 activity).[10] Smoking and sex are factors that influence CYP1A2 activity, which can then impact clozapine plasma concentrations.[5,6,11] Medications that are CYP1A2 inhibitors (e.g., fluvoxamine) or inducers (e.g., carbamazepine) can lead to significant clozapine drug–drug interactions, impacting patient care.[12]

The CYP1A2 drug-metabolizing enzyme is found in a cluster with CYP1A1 and CYP1B1 located on chromosome 15 and comprises about 13% of all CYP hepatic protein content. The CYP1A2 enzyme structure is well known, with over 100 drug and endogenous substrates.[13] CYP1A2 activity between Swedish (N = 194) and Korean (N = 150) populations

using a caffeine 100 mg test dose for phenotyping and single nucleotide polymorphism (SNP) genotyping was analyzed.[14] Smoking and oral contraceptive (OC) use were the other main factors between the two groups included in the analysis. The overall findings revealed significantly higher CYP1A2 activity in Swedes than Koreans when considering smoking, OC use, and genotype. The difference between Caucasians and Asians could be clinically relevant for medications that CYP1A2 substrates with a narrow therapeutic index.[13] Another study reported that median CYP1A2 activity is lower among South Asians compared to those with European ancestry, where multiple linear regression analysis reported that 41% of the variability could be explained by diet, lifestyle, and genetics.[15]

However, CYP1A2 is not the only cause for CYP enzyme-linked metabolic differences between Asians and Caucasians. The CYP2C subfamily and CYP2D6 are also known to differ between East Asians and Caucasians.[16] Although clozapine is primarily metabolized by CYP1A2, other CYPs such as CYP2C19 and CYP2D6 are also involved, which can contribute towards the extensive interpatient variability.[17] The incidence of poor metabolizers (PMs) for CYP2C19 is highest among Asians (12–23%) compared to Caucasians (2–5%).[18] A recent study reported that CYP2C19 PMs ($N = 8$) did not appear to be associated with the higher clozapine C/D ratio when patients were stratified by sex and smoking status.[8] Yet, the CYP2C family and CYP2D6 status can contribute towards the wide interpatient variability.

A larger question emerges of what the designation of the ethnic term "Asian" really signifies. The FDA guidance for clinical trials included countries from the Far East, Southeast Asia, and the Indian subcontinent.[19] A perspective commentary reported that according to the Asian Diversity Project, over 40 different populations, ethnic minorities, and indigenous subgroups exist in the Asian category.[20] Further analysis by SNPs from the Pan-Asian study showed that modern genetics identify individuals from specific Asian groups (e.g., Chinese versus Mainland Japanese versus Okinawans).[20] The Indian population alone was shown to have its own genetic diversity with geographical regions (e.g., North versus South).[21] Therefore, Asians are a heterogeneous population with many genetic subpopulations.

Based upon the evidence, Asians represent a distinct population from Caucasians, Africans, and other ethnic groups based upon genetic polymorphisms. So, do Asians require only half of the clozapine doses prescribed for Caucasians? The indications are that lower clozapine doses are found in Asians compared to Caucasians with relatively similar plasma concentrations that include the various factors such as smoking that influence these drug levels. Genetic polymorphism for clozapine metabolism can account for the wide interpatient variability where ethnicity can be incorporated. Every patient differs in clozapine disposition. Prescribers have the tools to assist in drug dosing, such as CYP pharmacogenomics testing, patient information (e.g., sex and smoking history), and analytical support to measure clozapine concentrations. Each of these tools should be employed to maximize clozapine's use.

Michael W. Jann

Department of Pharmacotherapy, University of North Texas System College of Pharmacy, Fort Worth, TX, USA

Address for correspondence: Dr. Michael W. Jann University of North Texas Health Science Center. 3500 Camp Bowie, Blvd., Fort Worth, TX 76107, USA.
E-mail: michael.jann@unthsc.edu

Received: 25th November, 2019
Revision: 03rd December, 2019
Accepted: 05th December, 2019
Publication: 06th January, 2020

REFERENCES

1. De Leon J, Rajkumar AP, Kaithi AR, Sschoretsanitis G, Kane JM, Wang CW, *et al*. Do Asians patients require only half of the clozapine dose prescribed for Caucasians? A critical review. Indian J Psychol Med 2020;42:4-10.
2. Kane JM, Agid O, Baldwin ML, Howes O, Lindenmayer JP, Marder S, *et al*. Clinical guidance on the identification and management of treatment-resistant schizophrenia. J Clin Psychiatry 2019;80. pii: 18com12123. doi: 10.4088/JCP. 18com12123.
3. Jann MW, Grimsley SR, Gray EC, Chang WH. Pharmacokinetics and pharmacodynamics of clozapine. Clin Pharmacokinet 1993;24:161-76.
4. Heimke C, Bergmann N, Clement HW, Conca A, Deckert J, Domschke K, *et al*. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: Update 2017. Pharmacopsychiatry 2018;51:e1.
5. Remington G, Agid O, Fousssias G, Ferguson L, McDonald K, Powell V. Clozapine and therapeutic drug monitoring: Is there sufficient evidence for an upper threshold? Psychopharmacol (Berlin) 2013;225:505-18.
6. Haring C, Meise U, Humpel C, Saria A, Fleischhacker WW, Hinterhuber H. Dose-related plasma levels of clozapine: Influence of smoking behavior, sex, and age. Psychopharmacol (Berlin) 1989;99:S38-40.
7. Chang WH, Lin SK, Lane HY, Hu WH, Jann MW, Lin HN. Clozapine doses and plasma drug concentrations. J Formos Med Assoc 1997;96:599-605.
8. Ruan CJ, Zang YN, Wang CY, Cheng YH, Sun C, Spina E, *et al*. Clozapine metabolism in East Asians and Caucasians. J Clin Psychopharmacol 2019;39:135-44.
9. Buur-Rasmussen B, Brosen K. Cytochrome P450 and therapeutic drug monitoring with respect to clozapine. Eur Neuropsychopharmacol 1999;9:453-9.
10. Bertilsson L, Carrillo JA, Dahl ML, Llerena A, Alm C, Bondesson U, *et al*. Clozapine disposition covaries with CYP1A2 activity determined by a caffeine test. Br J Clin

Pharmacol 1994;38:471-3.
11. Dettling M, Sachse C, Brockmöller J, Schley J, Müller-Oerlinghausen B, Pickersgill I, *et al*. Long-term therapeutic drug monitoring of clozapine and metabolites in psychiatric in- and outpatients. Psychopharmacol (Berlin) 2000;152:80-6.
12. Kennedy WK, Jann MW, Kutcher E. Clinically significant drug interactions with atypical antipsychotics. CNS Drugs 2013;27:1021-48.
13. Thorn CF, Aklilu E, Klein TE, Altman RB. PharmGKB summary: Very important pharmacogene information for CYP1A2. Pharnacogent Genomics 2012;22:73-7.
14. Ghotbi R, Christensen M, Roh HK, Ingelman-Sundberg M, Aklillu E, Bertilsson L. Comparisons of CYP1A2 genetic polymorphisms, enzyme activity and the genotype-phenotype relationship in Swedes and Koreans. Eur J Clin Pharmacol 2007;63:537-46.
15. Perera V, Gross AS, McLachlan AJ. Influence of environmental and genetic factors on CYP1A2 activity in individuals of South Asian and European ancestry. Clin Pharmacol Ther 2012;92:511-9.
16. Kim K, Johnson JA, Derendorf H. Differences in drug pharmacokinetics between East Asians and Caucasians and the role of genetic polymorphisms. J Clin Pharmacol 2004;44:1083-105.
17. Linnet K, Olsen OV. Metabolism of clozapine by cDNA expressed human cytochrome P450 enzymes. Drug Metab Dispos 1997;25:1379-82.
18. Goldstein JA, Ishhizaki T, Chiba K, de Morais SM, Bell D, Krahn PM, *et al*. Frequencies of the defective CYP2C19 alleles responsible for the mephenytoin poor metabolizers phenotype in various Oriental, Caucasian, Saudi Arabian, and American black populations. Pharmacogenetics 1997;7:59-64.
19. FDA. Collection of race and ethnicity data in clinical trials. Guidance for industry and FDA Staff. Issued October 26, 2016.
20. Singh R, Teo YY. "Asian" phenotype underestimates the genetic diversity of Asia yet overstates its impact on variability in drug disposition and pharmacodynamics. Clin Pharmacol Ther 2019;105:802-5.
21. Chakrabarti B, Kumar S, Singh R, Dimitrova N. Genetic diversity and admixture patterns in Indian populations. Gene 2012;508:250-5.

Access this article online

Website: www.ijpm.info

DOI: 10.4103/IJPSYM.IJPSYM_495_19

Quick Response Code

How to cite this article: Jann MW. Do asians patients require only half of the clozapine dose prescribed for Caucasians? A critical review. Indian J Psychol Med 2020;42:1-3.