Re: Protocol for Clozapine Rechallenge in a Case of Clozapine-induced Myocarditis

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Shivakumar et al. outlined a successful case of clozapine rechallenge post suspected-myocarditis and suggested a protocol for rechallenges.¹ Their case is very informative, helping to build upon scant literature. While informative, extreme caution needs to be exercised in pursuing clozapine rechallenges post myocarditis, and there are several unique factors present in this case that are important to address which limits the potential generalizability of this case and its proposed protocol. The title of the article refers to this as a case of “Clozapine-induced Myocarditis” when in fact, the case more precisely reflects a case of suspected myocarditis given the absence of indicative findings from cardiac ECHO, brain natriuretic peptide, or biopsy. While it may be prudent to discontinue clozapine under these circumstances, consideration of wider differential is critical. In general, further use of tools like the Naranjo Scale is helpful to delineate whether the adverse reaction is in fact iatrogenic or a result of another factor.² Ultimately, the distinction between confirmed and suspected myocarditis is critical in helping to determine risk in approaching a rechallenge. While serum C-reactive protein and troponins are sensitive markers for myocarditis, their specificity is suboptimal.³

Further distinctive elements in this case, which limit the generalizability of the proposed protocol, include the initial clozapine titration schedule and concomitant agents, adjunctive cardioprotective agents, and absence of clozapine serum levels. The initial trial of clozapine was marked by the presence of valproic acid which has been shown to have a small increased risk of clozapine associated myocarditis.⁴ It would have been helpful to have known the patient’s clozapine level during the initial and subsequent trials. Knowledge of the clozapine level in relation to the dose and other factors may have been helpful to appreciate whether metabolic factors were at play or whether potential toxicity played a role in the initial presentation, especially considering the patients high clozapine dose. The decision to add carvedilol and perindopril is one of the important elements that may offer explanation to the patient’s subsequent tolerance of a clozapine rechallenge. The positive response to the

addition of a beta blocker may have helped to minimize tachycardia, which was present during the initial trial, and as a result may further suggest that the initial reaction to clozapine was less likely true myocarditis.

Additional elements that may help to explain the patient’s response to a slower titration schedule include the fact that patient was nonsmoker and of South Asian descent. Both of these factors are known to yield higher clozapine levels at lower doses, which correspondingly may warrant a more cautious titration schedule.⁵ Further critical information would include knowledge of the patients’ comorbidities in particular cardiovascular risk factors, which may help potentially explain the role of adjunctive ace inhibitor and beta blocker.

While an informative case that helps to build upon the limited existing literature of clozapine associated myocarditis, the variety of distinctive factors at play in this case limit its generalizability and warrant caution with implementing the proposed protocol.

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References

1. Shivakumar G, Thomas N, Sollychin M, et al. Protocol for clozapine rechallenge in a case of clozapine-induced myocarditis. *Can J Psychiatry*. 2019;65(8):176-179. doi: 10.1177/0706743719892709.
2. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30(2):239-245. doi: 10.1038/clpt.1981.154.
3. Winckel K, Siskind D, Hollingworth S, Wheeler A. Clozapine-induced myocarditis: separating the wheat from the chaff. *Aust N Z J Psychiatry*. 2015;49(2):188. doi: 10.1177/0004867414554269.
4. Ronaldson KJ, Fitzgerald PB, Taylor AJ, Topliss DJ, Wolfe R, McNeil JJ. Rapid clozapine dose titration and concomitant sodium valproate increase the risk of myocarditis with clozapine: a case-control study. *Schizophr Res*. 2012;141(2-3):173-178. doi: 10.1016/j.schres.2012.08.018.
5. de Leon J, Rajkumar AP, Kaithi AR, et al. Do Asian patients require only half of the clozapine dose prescribed for Caucasians? A critical overview. *Indian J Psychol Med*. 2020;42(1):4-10. doi: 10.4103/IJPSYM.IJPSYM_379_19.