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Letter to the Editor

Effect of cytochrome P450 1A2 inhibitors on rhabdomyolysis in patients on clozapine: Analysis using the US Food and Drug Administration's Adverse Event Reporting System

Clozapine is the only atypical antipsychotic approved for treatment-resistant schizophrenia (Kar et al., 2016). This drug has been reported to reduce mortality by about 50 % compared with other antipsychotics, suggesting that clozapine is a key drug for treatment-resistant schizophrenia (Vermeulen et al., 2019). Nonetheless, patients on clozapine can cause life-threatening adverse events such as agranulocytosis, myocarditis, and rhabdomyolysis (Kar et al., 2016; Béchard et al., 2022). Although a previous review has reported risk factors for agranulocytosis and myocarditis (Gurrera et al., 2022), risk factors for rhabdomyolysis remain unclear. Rhabdomyolysis can cause life-threatening complications including acute kidney injury (Béchard et al., 2022), and has a mortality rate as high as 42 % (Ward, 1988). Therefore, identifying risk factors for clozapine-induced rhabdomyolysis may contribute to improved outcomes in patients on clozapine. Given that rhabdomyolysis has been reported in patients with acute clozapine overdose (Jansman et al., 2015), clozapine-induced rhabdomyolysis may be associated with increased serum concentrations of clozapine. In particular, inhibition of cytochrome P450 (CYP) 1A2 has been associated with increased serum concentration of clozapine (Doude van Troostwijk et al., 2003). In fact, the CYP1A2 inhibitor ciprofloxacin has been reported to increase the serum concentration of clozapine (Brouwers et al., 2009). However, it is unclear whether CYP1A2 inhibitors increase the risk of rhabdomyolysis in patients on clozapine. Herein, we evaluated the effect of CYP1A2 inhibitors on rhabdomyolysis in patients on clozapine using the US Food and Drug Administration's Adverse Event Reporting System (FAERS) database.

Reports submitted from July 2014 to June 2022 were extracted from the US Food and Drug Administration's website (https://www.fda.gov/) on September 15, 2022. Data stored in the FAERS database was anonymized by regulatory authorities; thus, institutional review board approval was not required. Patients on clozapine were investigated, and risperidone was defined as a negative comparator because it is metabolized mainly CYP2D6, not CYP1A2. Rhabdomyolysis was defined as a report of the Preferred Term "rhabdomyolysis". Exclusion criteria were patients not taking clozapine or risperidone, and patients taking clozapine and risperidone concomitantly with another antipsychotic (Fig. S1). Antipsychotics were defined as shown in Table S1. Data on CYP1A2 and CYP3A4 inhibitors were collected to evaluate their drug–drug interactions with clozapine because it is mainly metabolized by CYP1A2, and partly metabolized by CYP3A4 (Doude van Troostwijk et al., 2003) (Table S2). Data on hydroxymethylglutaryl-CoA reductase inhibitors (statins) and fibrates were collected as specified in Table S3 because these drugs are known to increase the risk of rhabdomyolysis. First, Fisher's exact test was used to compare the proportion of patients on clozapine or risperidone with rhabdomyolysis between those who were taking CYP1A2 inhibitors and those who were not. Reporting odds ratio (ROR) and 95 % confidence interval (CI) were calculated. Next, multivariable logistic regression analysis was used to identify risk factors for rhabdomyolysis. Use of statin, use of fibrates, use of CYP1A2 inhibitors, and use of CYP3A4 inhibitors were included in the analysis. All analyses were performed using R version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria). A P-value <0.05 was considered statistically significant.

Over the review period, a total of 58,370 adverse events were reported for clozapine and 53,947 for risperidone. Of these, there were 108 (0.19 %) and 286 (0.53 %) reports of rhabdomyolysis for clozapine and risperidone, respectively. A disproportionality for rhabdomyolysis was observed in patients on clozapine who were taking CYP1A2 inhibitors compared with those who were not (ROR 13.1, 95 % CI 4.13–32.1, $P < 0.01$) (Table S4), but not in patients on risperidone. Multivariable logistic regression analysis showed that rhabdomyolysis in patients on clozapine was significantly increased only in the presence of CYP1A2 inhibitors (odds ratio 12.5, 95 % CI 4.98–31.5 $P < 0.01$) (Table 1). Among patients on clozapine and CYP1A2 inhibitors, all 5 who developed rhabdomyolysis were taking ciprofloxacin (Table S4).

This study suggests that the use of CYP1A2 inhibitors, especially ciprofloxacin, may increase the risk of rhabdomyolysis in patients on clozapine. Ciprofloxacin increases the serum concentration of clozapine due to inhibition of clozapine metabolism (Brouwers et al., 2009), and a high serum concentration of clozapine is associated with increased risk of rhabdomyolysis (Jansman et al., 2015). Two possible mechanisms can be considered: inhibition of CYP1A2 by ciprofloxacin and down-regulation of CYP1A2 activity by infection, leading to an increased serum concentration of clozapine associated with prolonged clozapine metabolism (Brouwers et al., 2009; Clark et al., 2018). By contrast, statins and fibrates were not associated with increased risk of rhabdomyolysis in our study, and these findings are consistent with previous research (Nomura et al., 2018).

This study has some limitations. First, reporting bias in the FAERS database may have resulted in some factors associated with increased frequency of rhabdomyolysis being missed. Moreover, due to the limited number of cases, we could not examine covariates associated with rhabdomyolysis such as age, sex, antipsychotic dosage, presence of chronic kidney disease and smoking status. In particular, smoking has a substantial effect on the serum concentration of clozapine (Kar et al., 2016), and this may be one reason for the lower incidence of rhabdomyolysis in patients on clozapine compared with patients on risperidone. Finally, the number of cases is too small to evaluate interactions between clozapine and CYP1A2 inhibitors, and it may be important to perform evaluations in other databases and to assess the validity of our results. Although further studies are needed, avoiding the use of CYP1A2 inhibitors may decrease severe adverse events in patients on clozapine,

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Table 1
Multivariable logistic regression analysis of potential risk factors for rhabdomyolysis in patients on clozapine.

	Rhabdomyolysis / Total, n (%)	Odds ratio (95 % CI)		P-value*
		Crude	Adjusted	
Non-use of CYP1A2 inhibitors	103/58,150 (0.18)	1 [Reference]	1 [Reference]	
Use of CYP1A2 inhibitors	5/220 (2.27)	13.1 (5.29–32.5)	12.5 (4.98–31.5)	<0.01
Non-use of CYP3A4 inhibitors	108/58,290 (0.19)	NA	NA	NA
Use of CYP3A4 inhibitors	0/80 (0)			
Non-use of statins	103/56,840 (0.18)	1 [Reference]	1 [Reference]	
Use of statins	5/1530 (0.33)	1.81 (0.73–4.44)	1.40 (0.55–3.55)	0.48
Non-use of fibrates	107/58,227 (0.18)	1 [Reference]	1 [Reference]	
Use of fibrates	1/143 (0.70)	3.83 (0.53–27.6)	3.57 (0.48–26.5)	0.21

A P-value <0.05 was considered statistically significant.
Modeling was based on complete case analysis.
CI, confidence interval; CYP1A2, cytochrome P450 1A2; CYP3A4, cytochrome P450 3A4; NA, not applicable.
* Multivariable logistic regression analysis.

leading to improved outcomes.

Declaration of competing interest

The authors have no conflicts of interest to disclosure.

Data availability

Data supporting the findings of this study are available from the corresponding author upon reasonable request (kottanketty@gmail.com).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2023.10.042.

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