Using real-world data: Can CYP2C19 genotype predict an individuals' response to voriconazole?

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Background: Up to 40% of patients who receive the antifungal drug voriconazole are exposed to suboptimal drug concentrations and 30% prematurely discontinue therapy due to adverse effects. This variability in pharmacokinetics is, in part, influenced by genetic variation in CYP2C19. Therefore, we aimed to investigate whether CYP2C19 genotype can predict suboptimal exposure or drug-related adverse effects to voriconazole, necessitating a switch to alternative antifungal therapy.

Methods: Data on voriconazole administration (dosing history, plasma drug concentrations), drug-related adverse effects, and alternative antifungal use were obtained from electronic medical records of patients administered voriconazole (1 May 2019 – 31 Dec 2023) at Westmead Hospital, St Vincent's Hospital, and Royal North Shore Hospital, Sydney, Australia. Buccal swabs were collected to determine CYP2C19 genotype (myDNA Pty Ltd). Voriconazole trough concentrations (Cmin) were predicted (InsightRx Nova Inc.) with a target of 1.5-5.5 mg/L. Descriptive statistics and regression analysis were conducted using GraphPad Prism 9.5.1.

Results: Of the 148 patients, most were male (55%), on average (SD) 54 (16) years old and received voriconazole for prophylaxis. Most patients were CYP2C19 intermediate (36%, 53/148) or normal (35%, 52/148) metabolisers followed by rapid (20%, 29/148), ultrarapid (7%, 11/148) and poor metabolisers (2%, 3/148). Despite receiving the same daily dose (400 mg/day), CYP2C19 ultrarapid metabolisers had lower Cmin (0.30 [0.12-0.47] mg/L) compared with normal (1.39 [0.10-4.01] mg/L) and intermediate (1.53 [0.14-5.58] mg/L) metabolisers ($p<0.01$ and $p<0.01$, respectively). Overall, 45% (67/148) were switched from voriconazole to an alternative antifungal, most commonly to itraconazole or posaconazole. The occurrence of drug-related adverse events (55% hepatotoxicity, 30% blurred vision, 22% hallucinations and 9% skin reactions) was associated with a 3-fold (OR 3.21, 95%CI 1.45-7.38) increased odds of switching. Switching to alternative antifungal therapy and the incidence of drug-related adverse effects were not associated with CYP2C19 genotype.

Conclusion: Switching from voriconazole to alternative antifungal therapy due to drug-related adverse effects is common. In this cohort, CYP2C19 genotype was associated with voriconazole exposure but not the incidence of drug-related adverse effects most likely due to very low presence of CYP2C19 poor metabolisers.

Key words: voriconazole, CYP2C19, adverse effects, therapeutic drug monitoring