Random plasma concentrations of voriconazole decline over time

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Voriconazole (VRC), a widely used, broad-spectrum triazole with efficacy in the treatment of aspergillosis, candidiasis and other mycoses, exhibits non-linear hepatic clearance and marked inter-individual variation in its plasma concentration (PC). This high variability of VRC PC is not correlated with the daily VRC dose and changes in interacting medications or drug compliance. Although correlation of VRC PC with toxicity remains unclear, a PC < 2 µg/ml correlated with progression of aspergillosis in a retrospective single institution study. However, a real-life experience regarding the frequency of, indications for, and use of the VRC PC is lacking, especially in a setting in which this agent is widely used, such as a tertiary care oncology center.

To that end, we identified patients at our institution who underwent measurement of their VRC PC from October 2002 to October 2006 and reviewed their medical records. The data obtained included age, gender, weight, type of malignancy, history of stem cell transplantation, presence of graft versus host disease, VRC daily dose, route of VRC administration, duration of VRC use, reason for request for VRC PC, diagnosis of invasive fungal infection (IFI) (EORTC/MSG criteria), management and outcome of IFI. VRC PC was measured by HPLC (Focus Technologies Inc., Cypress, California). In our institution, VRC PC is a “send out” test with a turnaround time of 5–7 days. We evaluated the relationship of the VRC PC and clinical outcome as well as clinical factors associated with low plasma exposure to VRC. Voriconazole (VRC) is a triazole used for the treatment of fungal infections. It is known for its non-linear hepatic clearance and inter-individual variability in plasma concentrations. The aim of the study was to retrospectively collect data on 29 cancer patients who underwent measurement of their plasma concentration of voriconazole (VRC) from 2002 to 2006. Nine patients (31%) had VRC PC < 1 mg/ml. VRC PC < 1 mg/ml occurred in 7 of 10 patients who were on VRC > 2 months versus only 2 of 19 patients who were on VRC < 2 months (P = 0.001). VRC PCs were infrequently ordered, did not follow clear indications, and the use of the results was variable.

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Three patients had levels drawn less than 7 days after VRC began. The mean VRC PC was 1.8 μg/ml (standard deviation 1.8 μg/ml, range 0.1–7.5 μg/ml). Nine patients (31%) had a VRC PC <1 μg/ml. Seven of 10 patients who received VRC >2 months had a VRC PC <1 μg/ml compared to only 2 of 19 patients who received VRC <2 months (P = 0.001). (Fig. 1). We found no correlation with IFI progression as only 1 patient died of an IFI and 13 of the 23 patients with IFI received VRC in combination with another antifungal therapy (7 along with caspofungin and 6 along with caspofungin and liposomal amphotericin B).

In our retrospective experience with an unselected, yet small group of patients, the measurement of the VRC PC was rare, did not follow clear indications and the utilization of the VRC PC results was both infrequent and variable. Our findings are consistent with the emerging literature that documents significant inter- and intra-individual variability of VRC PC.\(^3\)\(^4\) In addition, we found, for the first time, that the duration of VRC significantly affected its PC. The explanation for this may have been compliance issues, auto-induction of metabolism\(^2\) or improved clearance of VRC in the setting of improvement of liver function in some patients. Our preliminary experience outlines the difficulties in correlating the VRC PC with outcome as use combination antifungal therapy was widespread. Measuring the VRC PC in the context of an organized trial, developing of guidelines are necessary for optimal utilization of and interpretation of VRC serum levels.

Potential conflicts of interest

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