Case report

A case report of voriconazole therapy failure in a homozygous ultrarapid *CYP2C19**17/*17 patient comedicated with carbamazepineMirte M. Malingré,¹ Peggy C. R. Godschalk² & Saskia K. Klein³Departments of ¹Pharmacy, ²Medical Microbiology and ³Internal Medicine, Meander Medical Center, Amersfoort, the Netherlands

Recently this journal published an article in which the authors examined by literature search the clinical implication of the ultrarapid *CYP2C19**17 variant allele [1]. The authors concluded that the *CYP2C19**17 increased enzyme activity is unlikely to be clinically significant for voriconazole. However, a comment to this article [2] replied that in the case of voriconazole the variant allele *CYP2C19**17 certainly is clinically relevant and that data have shown that in subjects carrying a single *CYP2C19**17 allele, exposure may be reduced by up to 50% compared with normal metabolizers. The authors of the comment also mention that they are not aware of published studies of homozygous *CYP2C19**17/*17 patients; and they assume that these subjects would display further reduced voriconazole exposure. In this case report we present a case of voriconazole therapy failure in a homozygous *CYP2C19**17/*17 patient comedicated with carbamazepine.

A 62-year-old Caucasian woman with acute myeloid leukemia was admitted to our hospital for myelosuppressive chemotherapy. Shortly after administration of the second cycle of cytostatic drugs she developed neutropenic fever which persisted despite of treatment with broad spectrum antibiotics. A high-resolution CT scan showed multiple lesions in the lungs, liver and spleen, suspect for a disseminated fungal infection. Because a zygomycosis was also considered, treatment with both voriconazole and liposomal amphotericin B was started. Oral voriconazole was started with a standard loading dose of 400 mg twice daily (1 day) and a maintenance dose of 200 mg twice daily. Because of the potential induction interaction with carbamazepine (200 mg twice daily orally, given at least since 2005 for treatment of a bipolar disorder), we performed therapeutic drug monitoring of voriconazole. No other drug–drug interactions for voriconazole were present. At day 5 after the start of voriconazole therapy, the voriconazole trough serum concentration was very low, i.e. <0.3 mg l⁻¹ (therapeutic range 1–2

to 5 mg l⁻¹) [3]. To achieve higher voriconazole concentrations, the administration route of voriconazole was switched to intravenous and the dose was raised substantially to a loading dose of 6 mg kg⁻¹ (510 mg) and a maintenance dose of 5 mg kg⁻¹ (425 mg) twice daily, a dosage regimen recommended for other inducers such as phenytoin and rifabutin [4]. We did not stop carbamazepine therapy since this would not result in a direct stop of the induction and therapy was highly desirable for this patient. Four days after the start of this raised dosage regimen measurement of the voriconazole concentration was repeated. Again the trough concentration was subtherapeutic, i.e. 0.5 mg l⁻¹. Therefore, we stopped voriconazole therapy and switched to caspofungin. Liposomal amphotericin B had been discontinued when cultures confirmed infection with *Candida tropicalis* and not a zygomycete. Because of the extremely low voriconazole concentrations despite the high dosage regimen, we suspected *CYP2C19* ultrarapid metabolism. *CYP2C19* genotyping was performed and revealed a homozygous ultrarapid *CYP2C19**17/17 genotype. The patient improved gradually and was discharged from the hospital. Antifungal therapy was switched from intravenous caspofungin to oral posaconazole.

The prevalence of the homozygous *CYP2C19**17/17 genotype is not known. For Caucasians, the prevalence of the heterozygous *CYP2C19**17 is about 20% [1]. Theoretically, if the prevalence of heterozygous *CYP2C19**17 is 20%, the prevalence of homozygous *CYP2C19**17/*17 can be estimated at 4%. Voriconazole exposure in homozygous *CYP2C19**17/*17 ultrarapid metabolizers has not yet been described. Recently an article has been published in which retrospective analysis of routine therapeutic drug monitoring for voriconazole samples showed that in a subgroup of low voriconazole concentrations of 0.2 mg l⁻¹ or less the frequency of the genotype *CYP2C19* ultrarapid metabolism (heterozygous *CYP2C19**1/*17 or homozygous

*CYP2C19*17/*17*) was significantly higher than in the reference group of healthy volunteers [5]. In a defined subgroup (without potential confounders such as inductive co-medication), 80% of the patients carried the *17 allele (heterozygous *CYP2C19*1/*17* or homozygous *CYP2C19*17/*17*). However, the data of heterozygous *CYP2C19*1/*17* and homozygous *CYP2C19*17/*17* groups are combined and no individual data are presented for homozygous *CYP2C19*17/*17* subject(s).

In our patient voriconazole concentrations were extremely low due to a combination of homozygous ultrarapid *CYP2C19*17/17* metabolism and metabolism induction by carbamazepine. The individual contributions of the genotype and co-medication cannot, however, be distinguished. Although not many patients will have this 'unfortunate' combination, because of the substantial prevalence of altered *CYP2C19* metabolism, ultrarapid but also poor metabolizers, and the multiple potential drug-drug interactions, we recommend routine therapeutic drug monitoring of voriconazole therapy. In our hospital we have recently introduced this policy.

Competing Interests

There are no competing interests to declare.

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