Overexposure to voriconazole associated with inflammation

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Background

Voriconazole, a triazole antifungal, is known for its non-linear pharmacokinetics due to metabolism saturation. Several sources of variability complicate the understanding of this non-linearity, particularly alterations in the activities of cytochromes P450 involved in voriconazole metabolism (2C19, 2C9, 3A4) by phenoconversion (drug interactions or inflammation) and/or genetic variants (PGx). Here, we report a case of voriconazole over-exposure and discuss the implication of inflammation and PGx.

Methods

A 69-year-old woman with acute myeloid leukaemia (del17p) was treated with voriconazole for suspected invasive pulmonary aspergillosis. Voriconazole therapeutic drug monitoring was performed using a validated LC/UV method, eleven samples were collected. Additionally, CYP 2C9, 2C19, and 3A4 genotypes were determined by Next Generation Sequencing (MISeq, Illumina).

Results

Voriconazole trough concentration (C_{min}) was measured at 9.5 mg/L. The elimination phase showed two slopes with calculated elimination half-lives ($t_{1/2}$) of 128 hours (over 72 hours sampling points) and 28 hours (over last 3 sampling points). Both $t_{1/2}$ appeared longer than those reported in the literature (between 53 to 58 hr). PGx analyses were conducted to elucidate such PK variations. The patient was predicted to be a CYP2C19 rapid metabolizer (*1/*17). Furthermore, another heterozygous variant of CYP2C19 was identified (rs144036596), which, although not fully characterized, may reduce protein production by ~30%. Considering these two variations, a near-normal phenotype was assumed. Based on clinical and biological information, no drug interactions, liver impairment or cirrhosis were identified. Therefore, the apparent increase in $t_{1/2}$ could not be explained by the expressed genotype alone. Several studies have reported a correlation between voriconazole C_{min} and C-reactive protein (CRP) concentrations. An increase in CRP results in a decrease in CYP450 enzymatic activity, leading to decrease in the metabolite to parent ratio. In the reported case, the CRP concentration was quantified at 354 mg/L on Day13, which partially explains the overexposure to voriconazole.

Conclusion

These results highlights the complexity of voriconazole dose adjustment and the importance of individualizing voriconazole treatment with consideration to inflammation and PGx. Clinicians must be aware of the impact of inflammation on voriconazole PK to prevent increases in voriconazole concentrations and, consequently, toxic reactions in this context.

Key Words

Voriconazole, therapeutic drug monitoring, pharmacogenetics, phenoconversion, inflammation