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Absence of clinically relevant effect of caspofungin on cyclosporin pharmacokinetics

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Concomitant use of the echinocandin caspofungin and cyclosporin A (CsA) has been limited to patients for whom the potential benefit outweighs the potential risk. The risk involves transient elevations of liver aminotransferases demonstrated in a phase I study in healthy volunteers [1]. Although caspofungin did not change the plasma levels of CsA, the area-under-the-curve (AUC) of caspofungin was increased by ~35% [1]. Caspofungin is a poor substrate for cytochrome P450 (CYP) enzymes. Yet, it is neither an inhibitor of the CYP system nor an inducer of the CYP3A4 metabolism of other drugs. It is neither a substrate for P-glycoprotein. Available data suggest that CsA inhibits the uptake of caspofungin into hepatocytes [1].

We [2] and others [3–6] have recently reported retrospective data from 84 patients treated concomitantly with CsA and caspofungin, which do not show a significant risk of clinically relevant hepatotoxicity. Yet, no confirmatory clinical data are available on the absence of a pharmacokinetic interaction between the two drugs previously documented in healthy volunteers. In our series [2] a retrospective analysis of the pharmacokinetic interaction between casofungin and CsA was performed for 7 of the 14 patients. Patients needed to have ≥5 determinations of CsA levels throughout the study period (from 30 days before concomitant therapy until 15 days after its completion) and ≥2 determinations during co-administration of caspofungin and CsA. Figure 1 (see page 659) shows the changes in CsA blood levels and corresponding dose adjustments over time. These were consistent with the lack of effect of caspofungin on CsA pharmacokinetics found in healthy subjects [1]. Unfortunately, the effect of CsA on caspofungin concentrations could not be studied due to the unavailability of the patients' caspofungin blood levels.Together, routine therapeutic drug monitoring is still essential to guide the optimal dosing of CsA.

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Figure 1

Changes in CsA blood levels and corresponding dose adjustments over time during concomitant administration with caspofungin. Regression analysis was used ad hoc to assess either declining or increasing linear trends for CsA blood levels. Horizontal dotted lines indicate the upper and lower bounds of the aimed therapeutic range for CsA. Vertical dotted lines indicate onset and end of caspofungin therapy.
CsA-assoc: CsA-associated;
HBP: high blood pressure.