Effect of SNPs in human ABCB1 on daptomycin pharmacokinetics in Caucasian patients

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Sir,

Daptomycin is a cyclic lipopeptide antibiotic, active against Gram-positive bacteria. It is excreted unchanged primarily by the kidneys (78%) and dosage adjustment is required in patients with renal impairment.1

Daptomycin has been shown to be a substrate of P-glycoprotein (P-gp; MDR1) in vitro.2 P-gp is an efflux transporter constitutively expressed in many human tissues with high levels in the kidney and adrenal glands, where it has a major influence on drug disposition.3 P-gp is encoded in humans by the highly polymorphic ABCB1 gene.4 For example, an effect of SNPs in ABCB1 on the pharmacokinetic profile of digoxin, fexofenadine, nelfinavir, tacrolimus, azithromycin, cloxacillin and rifampicin has been reported.5,6 We aimed at evaluating the influence of SNPs in ABCB1 on the pharmacokinetics of daptomycin.

Adult patients presenting to Amedeo di Savoia Hospital (Turin, Italy), receiving therapy with intravenous daptomycin according to the official indications, were enrolled. The main exclusion criteria were age, 18 years, estimated CL CR, 30 mL/min, septic shock and concomitant therapy with drugs that may inhibit (indinavir, nelfinavir, ritonavir, saquinavir, erythromycin, clarithromycin, itraconazole) or induce (rifampicin, midazolam) P-gp function. The study was approved by an Ethics Committee (ASL TO-2, number 44824/13). Sampling was performed after written informed consent was obtained. Blood samples for pharmacokinetic analysis were collected at steady-state (after 3 days of treatment) before dose and after 0.5, 1.5, 5, 9 and 24 h of drug administration.

Genomic DNA was extracted from blood using the QIAamp DNA Mini Kit (Qiagen, Venlo, The Netherlands). SNPs (3435 C>T, rs1045642; 1236 C>T, rs1128503; 2677 G>T, rs2032582) were analysed using the TaqMan assays (Applied Biosystems, Foster City, CA, USA) by real-time PCR (Bio-Rad, Hercules, CA, USA).

Daptomycin plasma levels were assayed using two validated HPLC-MS and UPLC-PDA (photodiode array) methods.7,8 The lower limits of quantification were 1.56 and 0.781 mg/L for the HPLC-MS and the UPLC-PDA methods, respectively. Intra- and inter-day accuracy (CV, %) and precision (relative standard deviation, %) were <15% for both methods.

The values of AUC0–24, Vss, CLss and t1/2 were estimated using Kinetica 5.0 software (Thermo Scientific, Waltham, MA, USA).

A total of 23 Caucasians patients were included in the study: 16 patients (69.6%) were male. Median (IQR) age, weight and BMI were 61 (46–71) years, 74 (60–86) kg and 26 (21–29) kg/m2, respectively. Median daptomycin daily dosage was 6 (5–7) mg/kg.

Figure 1. Influence of ABCB1 3435 C>T genotype on daptomycin dose-normalized AUC0–24 (a) and daptomycin CLss (b). The allele frequencies for 3435T, 1236T and 2677T were 26.1%, 21.7% and 1.0% respectively.

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17.4%, respectively. The Mann–Whitney test indicated that values of median dose-normalized AUC$_{0–24}$ were higher in patients with the 3435 TT genotype, compared with the CC or CT genotype [2.61 (1.96–3.14) versus 1.77 (1.51–1.98); $P$=0.021]. Similarly, CL$_{ss}$ was lower in patients with the TT genotype compared with CC or CT genotype patients [0.38 (0.32–0.51) versus 0.57 (0.51–0.66); $P$=0.021] (Figure 1). Multiple regression analysis showed that 3435 TT was the only individual factor predictive of dose-normalized AUC$_{0–24}$ ($P$=0.01) and CL$_{ss}$ ($P$=0.012).

The 3435 C>T SNP is the only silent polymorphism that might influence P-gp expression in humans, probably by altering protein folding and function and changing the substrate specificity. In this study we found for the first time an influence of the ABCB1 3435 C>T polymorphism on daptomycin dose-normalized AUC$_{0–24}$ and CL$_{ss}$. The following limitations should be noted: there was a small number of patients, and patients were being treated with different daptomycin dosages. These preliminary findings may explain the high inter-subject pharmacokinetic variability in daptomycin disposition and could represent a starting point for individualization of therapy, especially in patients with renal impairment.

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Efficacy and safety of high-dose gentamicin re-dosing in ICU patients receiving haemodialysis

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Sir,
Aminoglycosides are commonly used to treat severe infections in ICU patients. A ratio of $C_{max}/MIC > 8$ has been associated with increased clinical cure, whereas aminoglycoside-related toxicities have been associated with AUC and trough plasma concentrations. Aminoglycoside pharmacokinetics in ICU patients may be altered during sepsis. Increased V results in insufficient plasma drug concentrations and the need for a high loading dose, while altered CL increases the risk of toxicity. Commonly, septic critical-care patients have altered renal function requiring renal replacement therapy, which also interferes with aminoglycoside concentrations. Results of the studies conducted with patients with chronic kidney disease suggest a better pharmacokinetic management if aminoglycosides are administered pre-dialysis. Very few data regarding aminoglycoside use in ICU patients requiring intermittent haemodialysis (IHD) are available aside from our previous study reporting an original schedule for gentamicin administration in ICU haemodialysed patients. It consists of an intravenous injection of 6 mg/kg gentamicin 1 h before dialysis. These recent data involved only a single administration of