Evaluation of the immunosuppressive drugs metabolism, CYP450 and UGT activity by the liver graft using an ex-vivo porcine livers model

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Background

After liver transplantation, the capacity of the graft to metabolize drugs during the early phase following revascularization can impact patients and grafts outcomes. The aim of our study was to evaluate the pharmacokinetics of CYP450 and UGTs using specific probes as well as metabolism of the main immunosuppressants (IS) using a validated normothermic perfused porcine livers graft (PPLG).

Methods

Nine porcine liver grafts were harvested and perfused using autologous whole blood on a normotermic machine perfusion (Liver Assist®) thus simulating the graft revascularization. Six probe drugs of CYP450 and UGT enzymes as well as the 2 main IS (i.e. tacrolimus and mycophenolate acid (MPA) were added (bolus infusion) directly to the circulating blood at T0 at human therapeutic concentrations. Blood samples were collected from 0 to 240 min to study PK of drugs and metabolites in plasma (by liquid chromatography tandem mass spectrometry). In a second time, fluconazole was added with tacrolimus in order to evaluate its impact on tacrolimus's pharmacokinetics.

Results

Median values of elimination half-life of the probes and Tmax apparition of metabolites were respectively: 99 and 120 min for caffeine and paraxanthine (CYP1A2), 14 and 30 min for flurbiprofen and OH flurbiprofen (CYP2C9), 22 and 15 min for omeprazole and OH-omeprazole (CYP2C19), <1 and 7.5 min for dextromethorphan and dextrorphan (CYP2D6), 10 min for midazolam (CYP3A4) (OH-midazolam not detected). Half-lifes were 23 min, 20 min and 36 min for raltegravir (UGT1A1/3), MPA (UGT2B7/1A9) and tacrolimus (CYP3A4/5) respectively. Elimination constant rate of tacrolimus was significantly decreased after administration of fluconazole ($p = 0.025$).

Conclusions

The PPLG model allows evaluation of IS drug metabolism, CYP450 and UGT activity. The observed pharmacokinetics of probe drugs are fast especially for CYP3A4 and CYP2D6. This model may represent an efficient and accelerated model simulating human liver activity for studying liver-mediated drug clearance, drug-drug interactions or the impact of liver alteration on drug pharmacokinetics.