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Lopinavir is a substrate for SLCO1A2 but 516A>C and 38T>C polymorphisms do not influence lopinavir plasma concentrations

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Purpose of study

The SLCO1A2 influx transporter is located in the liver, intestine, brain and kidneys. A number of functional single nucleotide polymorphisms (SNPs) have been reported in the *SLCO1A2* gene (including 516A>C and 38 T>C). The aim of this study was to determine if LPV is a substrate for SLCO1A2 in vitro and to assess whether these SNPs impact upon LPV plasma concentrations.

Methods

SLCO1A2 was cloned (with Kozak sequence) into pBluescriptII-KSM, flanked by the 5' and 3' X. laevis β-globin UTR and cRNA was generated by in vitro transcription. *SLCO1A2* or water-injected oocytes were incubated with estrone-3-sulphate ([3H]-E3S; 1 μM; 0.33 μCi/ml; positive control) or [3H]-LPV (1 μM, 0.33 μCi/ml). Statistical analyses were performed on log transformed data by a paired t-test (n = 4 experiments with at least six replicates). Archived plasma samples were available from patients (n = 400) who had previously undergone therapeutic drug monitoring (TDM). LPV peak (2–6 hr) and trough (10–14 hr) concentrations were available. The following exclusion criteria were applied; age <18 years, pregnancy, deranged LFTs and the use of rifamycins, anticonvulsants, acid-reducing agents or NNRTIs. *SLCO1A2* 516A>C and 38T>C were genotyped using real-time allelic discrimination and statistical analysis was performed by Mann Whitney.

Summary of results

SLCO1A2-injected oocytes had significantly higher E3S accumulation compared to water-injected oocytes (0.51 ± 0.17 vs. 0.16 ± 0.04 (pmol/oocyte), $p < 0.05$) and significantly higher accumulation of LPV (4.30 ± 0.72 vs. 2.14 ± 0.43, $p < 0.05$). The allele frequencies of 516C and 38C were 2.5% and 5.8%, respectively. The median (range) Ctrough for 516 AA, AC and CC were 5,170 (818–22,432) 4,859 (2,008–14,273) and 5,609 (1,174–8,396) ng/mL, respectively ($p > 0.05$). The median (range) Ctrough for 38 TT, TC and CC were 5,023 (818–22,432), 5,778 (833–21,945) and 3,899 (2,380–6,815) ng/mL, respectively ($p > 0.05$). Also, no association with peak concentrations was observed.

Conclusion

These data indicate that LPV is a substrate for SLCO1A2. However, *SLCO1A2* 516A>C and 38T>C did not influence plasma concentrations of LPV and does not therefore appear to be a major determinant of intersubject variability. These data must be interpreted with caution due to the limitations associated with a TDM cohort (i.e. selection bias and lack of ethnicity data). As with all pharmacogenetic data, the findings warrant confirmation in other cohorts.