P369

P369 -Impact of chronic kidney disease on the drugs eliminated predominantly through a non-renal route: A proof of concept study with citalopram

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Background: Chronic kidney disease (CKD) can affect the elimination of drugs excreted not only by the renal route but also through non-renal routes (bile, gut) and through metabolism (liver) by a multitude of mechanisms including alteration in function of hepatic drug metabolising enzymes. Citalopram is an antidepressant drug eliminated predominantly (85%) by the cytochrome p450 enzyme (CYP2C19) mediated hepatic metabolism.

Objectives: To correlate the citalopram concentration in patients with various stages of CKD and to model the impact of CKD on hepatic clearance of citalopram.

Methods: Of the 3115 patients recruited in the Salford Kidney Study between October 2002 until December 2016, 150 citalopram levels were assayed for analysis from the baseline and annual samples of 75 patients who were receiving long term citalopram. Citalopram levels were assayed by Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) technique. The patients were grouped into moderate (CKD stage-2 & 3) and severe CKD (CKD stage-4 & 5) based on their eGFR. Pearson's correlation analysis was used to correlate the citalopram concentrations with eGFR in SPSS. A single compartmental population pharmacokinetic (PK) model was generated using standard citalopram PK parameters and applied to compare the trend in hepatic clearance of the drug across various CKD stages using Monolix software. 43 patients with 2 or more levels were used in this PK trend analysis.

Results: The median age of our cohort was 65 years with predominance of females (56%) and Caucasians (100%). The median dose adjusted citalopram concentration was significantly higher in the severe CKD patient group (6.65 vs 3.78 ng/mL/g, $p<0.001$). In the Pearson's correlation analysis there was a significant negative relationship between eGFR, and dose adjusted citalopram levels, ($r(148) = -29$, $p<0.001$) and this significance extended in the partial correlation analysis after controlling for other important confounding variables. In the Pop-PK model the hepatic clearance was observed to be lower in the severe CKD group compared to the moderate CKD group (figure). A reduction in hepatic clearance was also noted in females, with increasing age and concurrent PPI use as expected.

Conclusion: The study results support the hypothesis that metabolism of drugs eliminated predominantly by the non-renal route (hepatic metabolism) can be reduced with advancing CKD, possibly due to inhibition of the hepatic drug metabolising enzyme activity by uraemic toxins. Further prospective studies are warranted to clearly delineate these differences and aid dosing in advanced CKD.