Quantitative Systems Toxicology Approach Integrates Simcyp PBPK and Core Hepatocyte Metabolism: a Case Study with Valproic Acid

Vipul Gupta¹, Christian Maass¹, Richard MacLennan², Paul Walker², Jo Wilcock², Andrzej Kierzek³, Jeremy Craven¹, Ciarán Fisher¹
¹Certara UK Limited, ²Cyprotex Discovery Limited

Introduction
• Valproic acid (VPA) is a treatment for epilepsy and bipolar disorder
• A known side effect is induction of hepatic steatosis² (lipid accumulation)
• We mechanistically examine and quantify the effect of VPA exposure on lipid metabolism
• We develop a general quantitative systems toxicology (QST) approach integrating Simcyp PBPK with core hepatic metabolism² regulated by PPARα and insulin signalling

Multi-scale QST model

Liver concentration of VPA

- Oral dose: 250 mg (t = 8h)
- Oral dose: 750 mg (t = 24h)

Effect of VPA on lipid metabolism

- Endoplasmic reticulum
- Lipid droplet

VPA causes persistent disturbance in lipid metabolism

Effect of PPARα on lipid metabolism

- PPARα is a key regulator of fatty acid metabolism

Discussion
• We developed a general QST modelling approach to evaluate liver toxicity
• We identify that chronic treatment with VPA results in a persistent disruption in lipid metabolism
• We explore the impact of lipid dysregulation in obese individuals
• We are further evaluating how PPARα regulation affects lipid concentration

Additional Information

Reactions regulated by PPARα

References