PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELLING OF DIGOXIN FOR THE TREATMENT OF DIGOXIN TOXICITY

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Objective: To create a physiologically based pharmacokinetic (PBPK) model of digoxin so that toxicity scenarios may be simulated to determine the correct dosage of digoxin-Fab required to neutralise digoxin toxicity. Based upon the findings of this model we will propose a dosing regimen of digoxin-Fab so that digoxin poisoning is treated in a safer, precise, and also more cost-effective manner.

Methods: A PBPK model of digoxin was created using Berkeley Madonna™ (version 8.3.18; University of California, Berkeley, CA, USA). The model consists of nine singular compartments each supplied by the central blood compartment. Physiological parameters including tissue volumes, blood distribution, and clearance rates were made proportional to individual physiology so that specific patients could be simulated. Physiological and pharmacokinetic parameter values required for the model were sourced and consolidated from previous studies of digoxin found within the literature. The model was validated by comparison with independent digoxin pharmacokinetic studies and observed digoxin toxicity data collected from participants of the Digoxin Overdose and Response to Antibody (DORA) project. Simulations of toxicity scenarios were then run within the model to investigate the effect of digoxin-Fab on digoxin plasma concentration.

Results: The PBPK model of digoxin simulated the pharmacokinetics of digoxin within the body for various dosages, including overdoses (Figure 1). The model was also used for digoxin toxicity response simulations where digoxin-Fab was administered. These simulations of clinical scenarios allowed for informed predictions of digoxin plasma concentration response to different dosages of digoxin-Fab.

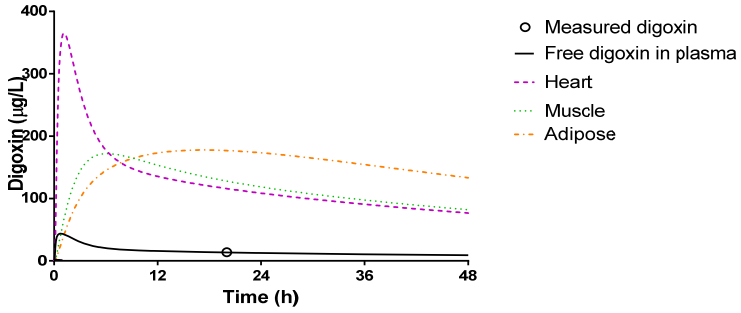

Figure 1. Concentration-time profiles within four separate compartments generated by simulation of an acute overdose of 13.5mg by a patient recruited for the DORA study.

Conclusion: PBPK modelling is a useful tool for creating accurate simulations of digoxin toxicity. These simulations will provide clinicians with a more informed insight into the pharmacokinetics of digoxin and provide a framework for which effective digoxin-Fab dosage can be quantified and standardised.