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Timescale analysis of a mathematical model of acetaminophen metabolism and toxicity

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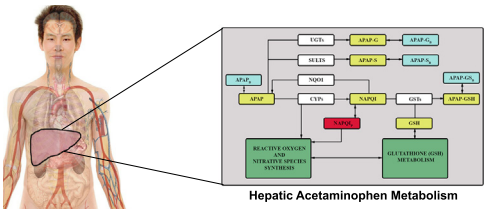
HIGHLIGHTS

- We have created a model, examining acetaminophen metabolism and related hepatotoxicity.
- We modeled multiple pathways associated with APAP metabolism.
- Using numerical, sensitivity and timescale analysis we have identified key parameters.
- Analysis highlights a critical acetaminophen dose in terms of the model parameters..

GRAPHICAL ABSTRACT



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ABSTRACT

Acetaminophen is a widespread and commonly used painkiller all over the world. However, it can cause liver damage when taken in large doses or at repeated chronic doses. Current models of acetaminophen metabolism are complex, and limited to numerical investigation though provide results that represent clinical investigation well. We derive a mathematical model based on mass action laws aimed at capturing the main dynamics of acetaminophen metabolism, in particular the contrast between normal and overdose cases, whilst remaining simple enough for detailed mathematical analysis that can identify key parameters and quantify their role in liver toxicity. We use singular perturbation analysis to separate the different timescales describing the sequence of events in acetaminophen metabolism, systematically identifying which parameters dominate during each of the successive stages. Using this approach we determined, in terms of the model parameters, the critical dose between safe and overdose cases, timescales for exhaustion and regeneration of important cofactors for acetaminophen metabolism and total toxin accumulation as a fraction of initial dose.

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1. Introduction

Acetaminophen (paracetamol; APAP*N-acetyl p-aminophenol*) is a commonly used pain killer and antipyretic. It is an easy to obtain medication that is nowadays widely stocked in pharmacies and corner shops, in packets of up to 32 tablets (16 in Europe); enough to cause serious liver damage if ingested in a single dose. It is estimated that in the U.S. an average of 56,000 people are admitted to the hospital each year due to acetaminophen overdoses and their related effects. Over 450 people a year go on to die from acetaminophen overdose. In the U.S. alone, adverse drug reactions are ranked as being between the 4th and 6th leading cause of death (Lazarou et al., 1998). Worryingly, around a quarter of these deaths are not from an intentional overdose by way of a suicide attempt, but from chronic use of the drug. The number of

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deaths associated with acetaminophen overdose in the U.S. almost doubled over a 4 year period, from 98 deaths in 1997 to 173 deaths in 2001 (Nourjah et al., 2006). In the UK, 90–155 people died per year between 2000 and 2008 with additional deaths due to acetaminophen being taken with other drugs (Hawton et al., 2011). This ease of availability and lack of awareness of its potential hazards means that acetaminophen is responsible for 80% of drug-associated cases of liver injury (Ostapowicz et al., 2002), and drug-induced liver injury has become the most common cause of acute liver failure and subsequently transplantation in Western countries (Lee et al., 2003). Much of our understanding of the metabolism and toxicology of APAP comes from animal models, particularly rat and mouse. Interestingly there is considerable variation in toxicity between species (Davis et al., 1974).

APAP is taken orally and is absorbed into the blood stream. It arrives in the liver via the hepatic portal vein and moves through the liver mass to the central vein (Fig. 1). In this time, APAP is absorbed into the hepatocytes where it is metabolised. In the liver, hepatocyte function is determined by position relative to the portal vein, with functions differing if a hepatocyte is near the blood inlet (periportal) or outlet (centrilobular), an affect known as zonation and is present across all areas of the liver (Allen et al., 2005). APAP is metabolised in the liver primarily by the sulphation and glucuronidation pathways (Riches et al., 2009; Mutlib et al., 2006), while around 5% is metabolised, via oxidation, to form the toxic metabolite *N-acetyl p-benzoquinone imine* (NAPQI) (Duan et al., 2001). A detailed pathway diagram is shown in Fig. 2 and a simplified one used as the basis for the mathematical modelling is shown in Fig. 3. The sulphation pathway involves the conjugation of APAP with the cosubstrate 3'-phosphoadenosine 5'-phosphosulfate or PAPS. This cosubstrate is finite within the liver cell and at toxic doses we see PAPS levels fall (Sweeny and Reinke, 1988) and a saturation of the sulphation pathway, leading to higher metabolism through glucuronidation and oxidation. The cofactors associated with the glucuronidation pathway have a much higher capacity than those of the sulphation pathway (Reith et al., 2009) and we assumed in our modelling that the pathway does not saturate at clinically relevant, high APAP doses. Via the oxidation pathway, APAP is catalysed by select enzymes from a 'superfamily' of enzymes known as Cytochrome P450 (Patten et al., 1993). The main enzymes involved in this reaction in human cells are Cytochromes CYP2E1, CYP3A4 and CYP1A2 (Patten et al., 1993; Chen et al., 1998; Thummel et al., 1993), however, the sub-type and hence nomenclature of the enzymes varies by species when looking at animal models. Metabolism through oxidation produces NAPQI, a chemically reactive and toxic metabolite. NAPQI can be detoxified by GSH, an antioxidant which conjugates to NAPQI preventing binding with essential proteins and thus preventing damage to the liver. At sufficiently high doses, the sulphation cosubstrate, PAPS, can be exhausted, diverting quantitatively more APAP through the oxidation pathway, leading to higher amounts of NAPQI being

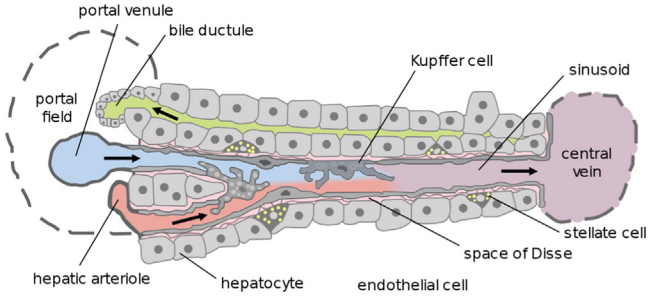

Fig. 1. Structure of the liver (Frevert et al., 2005). Blood flows from the portal field (left) to the central vein. APAP in the blood diffuses into the hepatocytes and is metabolised.

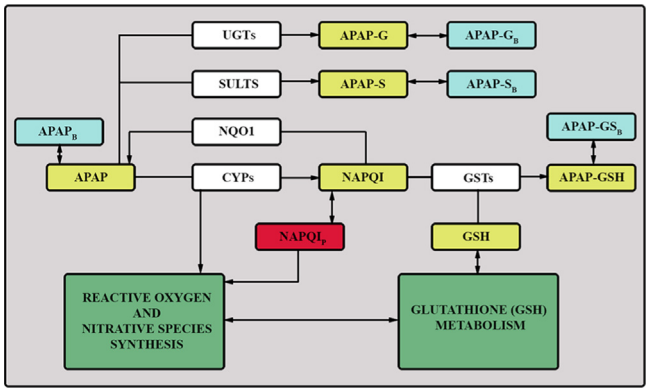

Fig. 2. A diagram of the cell scale metabolic network for APAP metabolism. The abbreviations are: APAP, acetaminophen; UGTs, UDP-glucuronosyltransferases; SULTs, sulfotransferase; NQO1, NADPH-quinoreductase; CYPs, cytochrome P450; APAP-G, acetaminophen glucuronide; APAP-S, acetaminophen sulphate; NAPQI, N-acetyl-p-benzoquinone imine; GSTs, glutathione S-transferase; GSH, glutathione; APAP-GSH, acetaminophen glutathione conjugate. Subscript 'B' denotes non-specific binding to a protein or lipid. Subscript 'P' denotes binding to non-specific protein (Diaz Ochoa et al., 2012). Blue boxes are non specifically bound products, yellow boxes are molecules, white boxes are isozymes, red boxes are protein bound molecules and green boxes are further metabolic systems not described in this diagram. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this paper.)

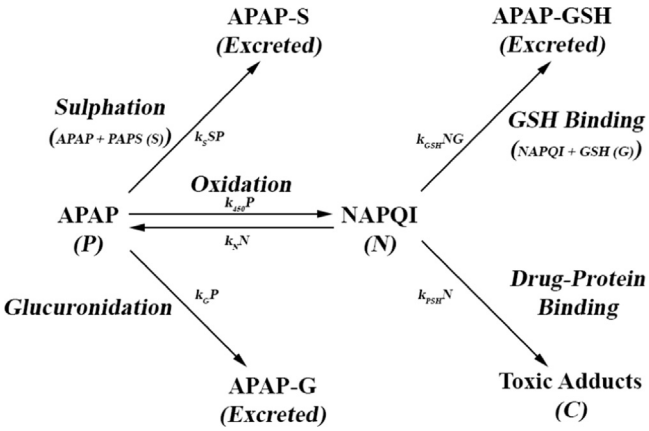

Fig. 3. Pathway Diagram for APAP Metabolism. APAP is metabolised through 3 main pathways, sulphation, glucuronidation and oxidation. CYP oxidation creates NAPQI, a harmful metabolite which can bind with essential cellular proteins within the hepatocytes if no GSH is present. Modelled species are APAP (P), NAPQI (N), PAPS (S), GSH (G) and Drug–Protein Adducts (C).

produced. There are marked species differences in the sensitivity to APAP, e.g. rats are resistant to equivalent doses of APAP compared with humans, and this is due to a much greater capacity for sulphation and a lowered propensity for oxidation (Vaidyanathan and Walle, 2002). Oxidation has the effect of depleting GSH levels in the liver, through binding with NAPQI and hence greater levels of protein adducts are produced. GSH can also be depleted by individual factors such as alcoholism (Guerri and Grisolia, 1980) and anorexia (Kalsi etal., 2011) though this inter-patient variability is beyond the scope of the mathematical model to be presented in this paper.

It is broadly recognised that mathematical modelling now plays a significant part in the drug development process. A successful model provides a cost effective way of understanding and predicting drug efficacy and toxicology, thus offering a systematic means of guiding more focused, less exploratory, use of animal models. Despite acetaminophen being the subject of laboratory studies for many years, it is only recently that theoretical studies on the toxicology of paracetamol have been undertaken. One of

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