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# Optimal Control Strategies for Reducing Toxic Formation in Acetaminophen Metabolism

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**Abstract** Acetaminophen (N-acetyl-para-aminophenol) is the most widely used painkiller in the world. Consuming acetaminophen involves a complex metabolic system, since it is converted into non-toxic and toxic metabolites called N-acetyl-p-benzoquinone imine (NAPQI). Acetaminophen is metabolized through a series of complex metabolic processes in the liver that involve enzymes as catalysts. This study presents a metabolic analysis of acetaminophen metabolism and its optimal regulation to reduce toxin formation. The metabolic study uses kinetic modeling combined with metabolic control analysis to identify key enzymes that can be modified to reduce hepatotoxicity due to excessive drug consumption. The sensitivity result shows that cytochrome (CYP) and uridine 5'-diphosphate-glucuronosyltransferase (UGT) are the two key enzymes that can be considered as internal control parameters. By inhibiting the reaction rate of CYP and UGT, the formation of N-acetyl-p-benzoquinone imine (NAPQI) can be reduced up to 69.9%, and the formation of Acetaminophen-Glucuronide (APAP-G) can be increased by approximately 0.49% such that Acetaminophen in the liver (APAP-L) can be excreted directly into the urine. Increasing the concentration of antioxidant GSH can also prevent hepatotoxicity by forming the complex NAPQI-GSH so that hepatotoxicity due to overconsumption of acetaminophen can be reduced.

**Keywords** Acetaminophen, hepatotoxicity, kinetic model, metabolic control analysis, optimal control theory

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## 1. Introduction

Acetaminophen, N-acetyl-para-aminophenol (APAP), often called paracetamol, is commonly used to relieve pain and fever [1]. Fever is very uncomfortable, as it usually comes with chills, nausea, headache, abdominal pain, and stomach discomfort [2]. APAP is a class of non-steroidal analgesic drugs that are safe when taken in recommended doses [3]. However, an overdose of acetaminophen can cause severe liver damage, and the extent of hepatocyte damage in patients with APAP overdose depends on the trade-off between induction and inhibition of CYP enzymes [4]. In 2015, the Australian Poison Control Center (PCC) reported receiving 13,322 calls explicitly related to acetaminophen incidents [5]. In the UK, 82,000 to 90,000 are admitted to the hospital due to an overdose of acetaminophen each year, and approximately 150-250 patients die [6].

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Acetaminophen involves a series of metabolic processes in the liver by interacting with enzymes. The metabolism process consists of various metabolic pathways that transform one compound into another in several stages. A specific enzyme guides each stage within this pathway. The metabolic system is essential to determine which compounds are nutrients and which are toxic to the body. Furthermore, acetaminophen metabolism occurs primarily in the liver through three main pathways: glucuronidation, sulfation, and oxidation. The glucuronidation and sulfation pathways are responsible for most acetaminophen detoxification, converting acetaminophen into water-soluble forms for excretion via urine. However, the oxidation pathway, mediated by the cytochrome P450 enzyme, produces a metabolite known as NAPQI (N-acetyl-p-benzoquinone imine). Although NAPQI is normally neutralized by conjugation with glutathione (GSH), excessive production can lead to glutathione depletion, resulting in cell damage and toxicity.

Modeling of acetaminophen metabolism has become an attraction in recent years. Reed et al. [7] studied the association of Michaelis-Menten's kinetics with acetaminophen metabolism through glucuronidation and sulfurization pathways. They used 20 blood and urine samples from patients who took acetaminophen at a dose of 60 mg/kg and 90 mg/kg. Reith et al. [8] also investigated Michaelis-Menten acetaminophen kinetics with the glucuronidation and sulfate pathways. The constructed model is a system of differential equations with fourteen variables related to the patient data. Other researchers have also built a model of the acetaminophen metabolism in the liver. In 2012, based on experimental data, Ben-Shachar et al. [9] formed an acetaminophen metabolism model with intestines, plasma, liver, tissue, and urine compartments. Predictions of death or recovery of patients were obtained depending on the extent of APAP overdose and the length of treatment. The model showed the effects of various acetaminophen doses on liver metabolism. Ramien et al. [10] also constructed a model of acetaminophen metabolism by studying acute liver damage caused by acetaminophen, then tested it on 53 patients at the University of Utah. Their research presented a method that could estimate the number of overdoses, the time since the start of overdose, and the probability of a patient's survival. The construction of the model involves the hepatocyte, APAP, glutathione, International Normalized Ratio (INR), aminotransferase (AST), and dynamics aspartate aminotransferase (ALT). Furthermore, Reddyhoff et al. [11] constructed a simpler mathematical model of acetaminophen metabolism by studying the time scale of the model. Their research was presented in a cell-based model. Their acetaminophen metabolism models in the liver compartment include cytochrome, sulfate, glucuronidation, glutathione, toxic metabolite production, and liver damage. With excessive doses of acetaminophen, the amount of glutathione S-transferase (GST) within liver cells became depleted, leading to N-acetyl-p-benzoquinone imine (NAPQI), which can not be bound by the antioxidant GSH. Their results showed that a high concentration of NAPQI binds with the living cells in the liver, ultimately causing liver damage [11,12]. Therefore, hepatotoxicity is minimal or absent as long as hepatic glutathione (GSH) is adequate for conjugation. However, over time, the depletion of hepatic GSH exceeds its regeneration rate, leading to the accumulation of reactive and toxic metabolites [13]. Hepatotoxicity is observed with the increased production of NAPQI when glutathione is depleted by approximately 70% [14]. Among these studies, a complete modeling of the enzymes involved in the acetaminophen pathway has not yet been considered. Due to the crucial role of enzymes in controlling the metabolic process, in this