

Analysis of the application of acetaminophen in human health

Zhouzheng Liu*

School of Science, Rensselaer Polytechnic Institute, Troy, USA

* Corresponding Author Email: liuz31@rpi.edu

Abstract. Paracetamol, also commonly recognized as acetaminophen, is a popular medication that can be easily acquired without a prescription, and is extensively utilized for its pain-relieving (analgesic) and fever-reducing (antipyretic) attributes. Despite its pervasive usage and seemingly benign nature, its application in human health carries potential risks, including hepatotoxicity and acute liver failure due to overconsumption. This research examines the clinical efficacy of acetaminophen in pain management and fever reduction, its metabolic pathways, potential risks, and implications of its widespread usage across different age groups. The text elaborates on the function of acetaminophen in dealing with a range of ailments such as the ordinary cold, migraines, joint inflammation, patent ductus arteriosus (PDA) in babies, acute ear infections in youngsters, and migraine headaches and menstrual pain in grown-ups. This research also highlights the importance of understanding individual genetic predispositions to metabolize acetaminophen differently and the need for comprehensive education for healthcare professionals and the general public about its appropriate usage and potential implications.

Keywords: Acetaminophen, Human health, Application.

1. Introduction

IMS Health's data indicates that in 2008, approximately 24.6 billion doses of acetaminophen, were sold globally, lauded for its analgesic and antipyretic properties. Despite its pervasive usage, the comprehensive effects of acetaminophen on human health warrant further scrutiny. Primarily, acetaminophen is recognized for its analgesic and antipyretic properties. It effectively alleviates mild to moderate pain and reduces fever, earning it a role in the management of a multitude of ailments ranging from common colds and headaches to more severe conditions like arthritis. Moreover, due to its relatively safe profile with minimal gastrointestinal side effects, it is frequently considered a first-line treatment option compared to other non-steroidal anti-inflammatory drugs.

Despite its widespread usage and seemingly benign nature, the application of acetaminophen in human health is not without potential risks. Acetaminophen's safety is dose-dependent, and overconsumption can lead to hepatotoxicity, and in severe cases, acute liver failure. These complexities prompt an ongoing need for comprehensive education for both healthcare professionals and the general public about acetaminophen's appropriate usage and potential implications. From the perspective of the age of the applied population, acetaminophen is an all-age drug.

Concerning young teenagers, the incapability to seal the ductus arteriosus (PDA) frequently occurs in infants born prematurely or with insufficient weight, necessitating either medical or surgical intervention to close the PDA. In addition to surgical therapy, acetaminophen can also be used instead of the two prostaglandin inhibitors commonly used, indomethacin and ibuprofen. Worldwide, acute otitis media (AOM) is recognized as a prevalent infectious ailment among children and serves as a significant factor contributing to the global usage of antibiotics in the pediatric population. Middle ear infections can cause pain and pressure behind the tympanic membrane. This is essential to the therapeutic experience. Nonetheless, because antibiotics have a restricted effectiveness, pain relief therapies, including acetaminophen and non-steroidal anti-inflammatory medications, are regarded as the foundational elements in managing acute otitis media in pediatric patients.

In adults, acetaminophen use is more frequent, most commonly for migraine and mild dysmenorrhea in women. The underlying mechanism of primary dysmenorrhea could potentially be tied to an uptick in the production of prostaglandins through the cyclooxygenase pathway. These prostaglandins (PGs) are significant because their increased levels can induce uterine contractions,

which in turn limit blood circulation. This constrained blood flow paves the way for the generation of anaerobic metabolites that trigger pain sensors. This includes about 18% to 26% of the female population and approximately 6% to 9% of the male population [1]. For migraine treatment, the frequently used medications include acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), which are most often utilized for mild to moderate migraines, while triptans are the preferred initial treatment for moderate to severe migraine attacks. Despite their effectiveness, the cost of triptans can be prohibitively high. For other second even third-line drugs usually have some problems in cost, potential adverse effects, the pharmacologic properties, and routes of administration vary widely. Also, the migraine in common are usually not severe, thus the acetaminophen is a drug with high price-ratio in treatment of migraine.

While acetaminophen (or paracetamol) has solidified its place as a primary player in the over-the-counter medication industry, it's paramount that we understand its intricate workings within the human system. This knowledge enables both healthcare professionals and consumers to utilize the drug optimally and safely. As we move deeper into its pharmacological dynamics, we'll discover how acetaminophen stands out and the myriad of implications it brings to the fore in the arena of human health. This paper aims to provide an analysis of the application of acetaminophen in human health, examining its benefits, side effects, and the implications of its widespread usage. It will delve into the clinical efficacy of acetaminophen in pain management and fever reduction and potential risks associated with prolonged or high-dose usage.

2. Absorption And Distribution

Upon orally consuming acetaminophen, the gastrointestinal tract swiftly and nearly entirely absorbs it. Its bioavailability is commendable, with peak plasma concentrations being reached in a short span of 30 minutes to 4 hours post-ingestion [2]. In the initial 60 minutes subsequent to the ingestion of an acetaminophen solution by healthy individuals, it was observed that the area under the curve (AUC) of plasma concentration versus time demonstrated a direct correlation with the percentage of the solution that had been emptied from the stomach (Fig. 1). Unlike some drugs which are selective in their distribution, acetaminophen freely circulates in most body fluids. With a volume of distribution hovering around 0.9 liters per cent kilogram, it easily permeates various tissues [4].

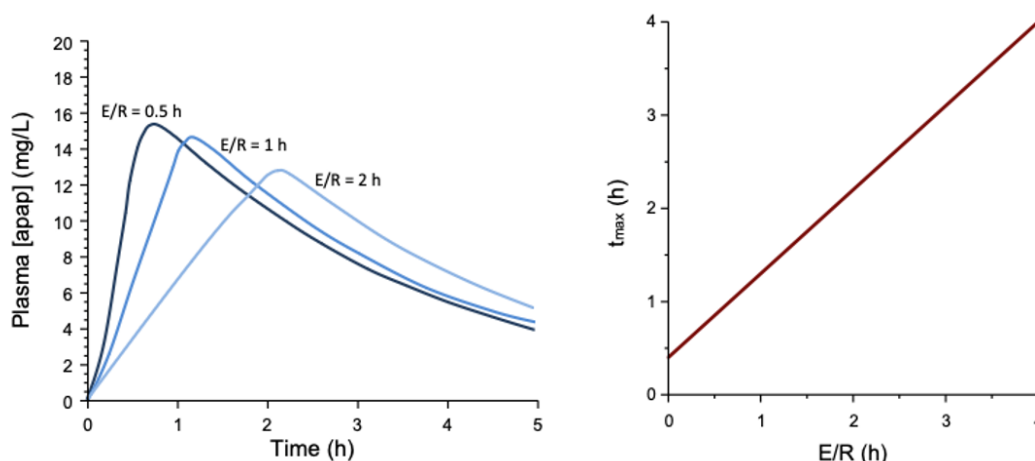


Fig. 1 Plasma acetaminophen (apap) level– time plot [3].

At its core, acetaminophen is a master manipulator of the central nervous system (CNS). Unlike its counterparts, it chooses to act centrally rather than at peripheral injury sites. Acetaminophen inhibits prostaglandin synthesis in the CNS. These prostaglandins, which are essentially chemical messengers, play a pivotal role in mediating fever and pain. The drug's action primarily targets the COX-3 enzyme, a brain-centric variant of the common COX enzyme. By blocking COX-3, acetaminophen effectively douses the production of pain signals and brings down febrile body temperatures.

Notably, the absence of peripheral action is why acetaminophen does not manifest the anti-inflammatory benefits seen in NSAIDs and, more importantly, why it refrains from causing the gastrointestinal troubles frequently associated with NSAIDs.

NSAIDs and APAP provide relief from inflammation, fever, and pain for people dealing with various health issues. They alleviate inflammation by inhibiting the enzymes activity. The COX pathway consists of COX1-2 enzymes and COX-3, which is derived from COX-1. This mechanism transforms arachidonic acid (AA) into PGH₂, which then becomes various PGs such as prostaglandin (PG) E₂ due to specific PG synthases. In addition, the AA is transformed by the lipoxygenase (LOX) and cytochrome P450 (CYP450) pathways, producing leukotrienes and hydroxy eicosatetraenoic acids (HETEs) respectively. The LOX pathway can produce leukotrienes and are involved in allergies and inflammation. Both leukotriene and HETE byproducts influence hormone secretion from the pituitary gland that oversees reproductive organ functions, enhancing the effect of the luteinizing hormone in rat Leydig cells. The CYP450 process involves two enzymes, producing 20-HETE and EETs. These compounds combat inflammation indirectly by reducing the expression of COX-2 and 5-LOX. When NSAIDs inhibit the COX pathway, AA processing is shifted to the LOX route, increasing the production of leukotriene compounds.

Acetaminophen's metabolic intricacies inevitably create a web of potential drug interactions. In the majority of situations, a well-functioning liver has the capability to neutralize NAPQI, a toxic metabolite, through a two-step process involving conjugation with glutathione (GSH), a process that occurs naturally and may also be facilitated by the enzyme, resulting in the formation of harmless mercapturate and cysteine byproducts. On the other hand, NAPQI can also be converted back into its original form, paracetamol, as shown in Fig. 2 [5]. Chronic alcohol consumers should exercise caution: the alcohol-induced cytochrome P450 system may elevate NAPQI production, even at therapeutic acetaminophen doses. This interaction amplifies the risk of liver damage.

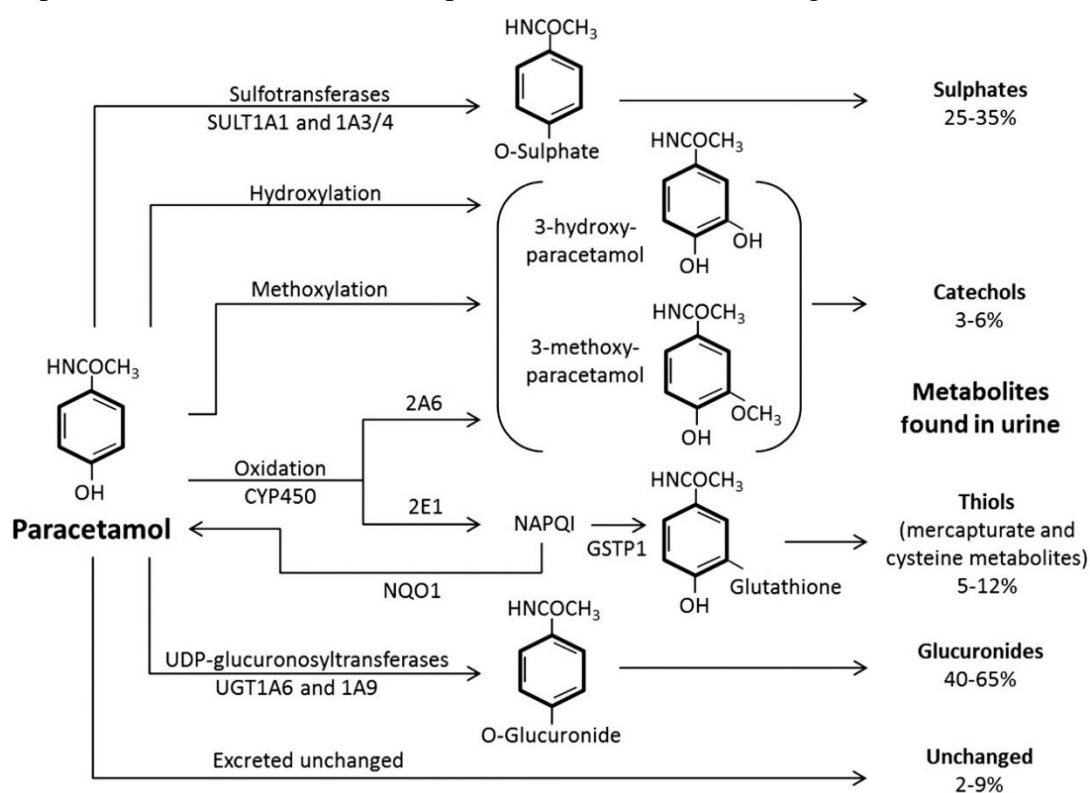


Fig. 2 Pathways of paracetamol metabolism [5].

Moreover, several other medications, particularly antiepileptic drugs like phenytoin, can manipulate the liver enzymes responsible for metabolizing acetaminophen. Such interactions reinforce the necessity of a tailored approach in medicine. It's not merely about administering a drug; it's about understanding the patient's entire pharmaceutical landscape and adjusting accordingly.

3. Metabolic Pathways

Acetaminophen's metabolism predominantly occurs in the liver, where it undergoes a trifold metabolic process. (1) Glucuronic acid conjugation: This pathway is the primary route for adults, converting the majority of acetaminophen into a glucuronide conjugate, which is then excreted in the urine. (2) Sulfation: Especially significant in children and at lower doses in adults, this pathway conjugates acetaminophen with sulfate. The resultant compound is then also expelled from the body through urine. (3) Cytochrome P450 oxidation: This is where things get complex. The P450 enzyme system in the liver oxidizes a small fraction of acetaminophen, producing the metabolite N-acetyl-p-benzoquinone imine (NAPQI). In standard situations, NAPQI is swiftly neutralized by binding to the body's natural antioxidant, glutathione. However, an overdose can deplete glutathione, letting NAPQI accumulate and wreak havoc in the form of hepatotoxicity.

For Future implications and considerations, given our expanding knowledge of genetics and personal medicine, future research might focus on individuals' genetic predispositions to metabolize acetaminophen differently. Some might naturally produce more of the enzymes leading to toxic NAPQI, placing them at higher risk even without overdose. There's a pressing need to delve into these genetic intricacies to ensure even safer usage of this globally renowned drug. In wrapping up, acetaminophen's pharmacological journey in the human system is nothing short of fascinating. It's a dance of chemistry, biology, and genetics, culminating in effects that millions worldwide have come to rely on. However, like any dance, it requires precision, understanding, and occasionally, caution to ensure that the outcome is as intended. Through continued research and understanding, we can harness acetaminophen's full potential while minimizing its risks.

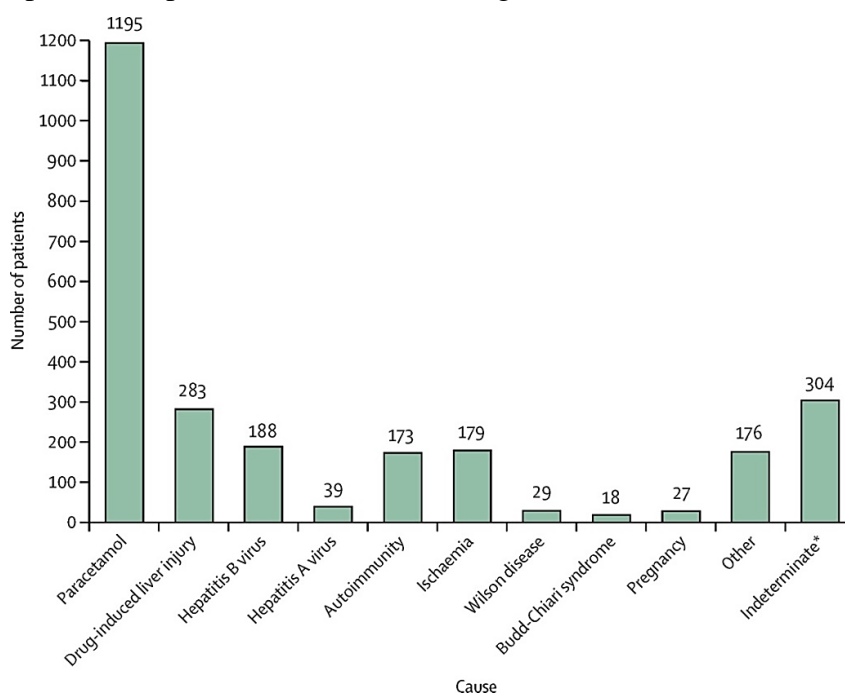


Fig. 3 Cause of acute liver failure [6].

4. Poison

The most common toxicity associated with acetaminophen is liver damage, such as acute liver failure. Acute liver failure refers to a rare and sporadically seen condition of intense damage to liver cells, resulting in changed coagulation and mental state, without any existing chronic liver disease. It is sudden and develops quickly, impacting individuals who were healthy before, and often leads to a deadly conclusion. Although there are various reasons behind it (Fig. 3), acute liver failure consistently presents with notably alike clinical characteristics. Agents causing damage to hepatocytes either trigger direct toxic necrosis, or apoptosis and immune damage, the latter being a

more gradual process. The various categories of acute liver failure can be characterized: there is the hyperacute liver failure, which is characterized by an extremely rapid, almost immediate onset of damage occurring within a matter of hours; and on the other hand, there is the damage that occurs at a more gradual pace, which is immune-mediated, and this is classified as either acute or subacute liver failure.

In developed nations, the toxicity of paracetamol can lead to acute liver failure [7]. Conversely, the rate of paracetamol overdose is significantly lesser or even non-existent in the majority of Asia and Africa [8]. In addition, studies in recent years have shown the effects of acetaminophen on reproductive development.

Epidemiological research indicated that taking acetaminophen, either by itself or with NSAIDs, in the early and middle stages of pregnancy, is linked with a higher rate of cryptorchidism. Acetaminophen intake for over four weeks during these stages, but not with ibuprofen or aspirin, correlated with a higher cryptorchidism rate in a group of 47,400 male newborns [9]. Similarly, mild analgesic use in the middle pregnancy stage correlated with congenital cryptorchidism, in a dose-related manner, in a group of 491 mothers [10]. Additionally, in a group of 3,184 women, acetaminophen intake in the middle pregnancy stage, but not during the periconception period and early pregnancy stage, elevated the congenital cryptorchidism risk, but not the hypospadias risk [11]. Conversely, hypospadias incidence obviously rose in 29,078 exposed newborns [12].

In the mode of action for liver toxicity by dose, around 60% of acetaminophen is transformed by UDP-glucuronosyltransferases, specifically UGT1A6 and UGT1A9, while roughly 30% is modified by sulfotransferases, namely SULT1A1 and SULT1A3 [13]. These processes result in the formation of harmless glucuronide and sulfate byproducts. NAPQI, this compound can be neutralized by GSH (glutathione) and excreted. At therapeutic doses, the amount of NAPQI formed is minimal, leading to negligible amounts bound to GSH and cellular proteins. Only trace amounts of acetaminophen-cysteine protein adduct are detectable, and these are not deemed harmful. However, when consumed in larger than recommended doses, acetaminophen metabolism can overwhelm the body's detoxification pathways. As the GSH reserves get depleted, more NAPQI binds to liver macromolecules, leading to cellular damage. Excessive NAPQI also forms protein adducts in mitochondria, the cell's energy factories, which can result in cell death. Moreover, overdose induces oxidative and nitrosative stress within the mitochondria, primarily due to the oxidant peroxynitrite, which causes liver injury. Such mitochondrial damage is supported by increased GSH disulfide concentrations inside the mitochondria and elevated peroxynitrite formation, especially following high doses of acetaminophen. The body's defenses, including Manganese Superoxide Dismutase (MnSOD), work to mitigate these harmful effects, but their efficacy might be compromised at high doses. In essence, while acetaminophen is safe at therapeutic levels, overdosing can severely compromise liver health due to metabolic reactions and resultant cellular and mitochondrial damage.

Additionally, NSAIDs and APAP, similar to numerous environmental chemicals, may suppress the production of fetal testosterone, thereby functioning as endocrine disruptors. These disruptors can disrupt the endocrine system, including phthalates, pesticides, and phyto/xenoestrogens.

5. Conclusion

Acetaminophen plays a pivotal role in managing a myriad of health conditions, making it a cornerstone of over-the-counter medications. Despite its widespread use and generally safe profile, potential risks such as hepatotoxicity necessitate caution and comprehensive education on its proper usage. Furthermore, its interaction with other medications and the genetic predispositions of individuals underlines the need for a tailored approach in medicine. Future research should delve into the genetic intricacies that might influence an individual's metabolism of acetaminophen, aiming to ensure even safer usage of this globally renowned drug. Ultimately, with continued research and understanding, it can harness the full potential of acetaminophen while minimizing its risks, optimizing its role in the betterment of human health.

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