PHARMACOLOGICAL STUDY OF PARACETAMOL METABOLISM AND ITS HEPATOTOXIC EFFECTS (LITERATURE REVIEW)

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https://doi.org/10.5281/zenodo.22877381

Abstract. Paracetamol (acetaminophen) is one of the most widely used analgesic and antipyretic drugs worldwide. It is available over the counter and is widely used by people across all age groups. Despite its relatively favorable pharmacological safety profile, paracetamol can become one of the most common causes of acute liver failure when taken in doses exceeding the recommended therapeutic range or when misused chronically. The significant proportion of acute liver failure cases associated with paracetamol intoxication in developed countries further emphasizes the medical and social importance of this issue. Furthermore, the fact that paracetamol is generally safe at standard therapeutic doses but may become hepatotoxic at higher doses or in the presence of certain risk factors, such as chronic alcohol consumption, fasting, and drug–drug interactions, necessitates a detailed investigation of its metabolic pathways. Therefore, analyzing the biotransformation processes of paracetamol in the body and the mechanisms underlying its hepatotoxic effects on hepatocytes from a pharmacological perspective is a relevant issue in clinical toxicology and practical pharmacology.
Keywords: paracetamol, acetaminophen, hepatotoxicity, NAPQI, glutathione, cytochrome P450 2E1, glucuronidation, sulfation, N-acetylcysteine, hepatic necrosis.

PARATSETAMOL METABOLIZMI VA UNING GEPATOTOKSIK TA'SIRINI FARMAKOLOGIK JIHATDAN O'RGANISH (ADABIYOTLAR TAHLILI)

Annotatsiya. Paratsetamol (atsetaminofen) - dunyoda eng ko'p qo'llaniladigan og'riq qoldiruvchi va isitma tushiruvchi dori vositalaridan biri bo'lib, u retseptsiz sotiladigan preparatlar qatoriga kiradi va aholining barcha yosh guruhlari tomonidan keng qo'llaniladi. Uning nisbatan xavfsiz farmakologik profiliga qaramay, tavsiya etilgan dozalardan oshirib qabul qilinganda yoki surunkali holda noto'g'ri ishlatilganda o'tkir jigar yetishmovchiligining eng ko'p uchraydigan sabablaridan biriga aylanadi. Rivojlangan mamlakatlarda o'tkir jigar yetishmovchiligi holatlarining sezilarli qismi aynan paratsetamol intoksikatsiyasi bilan bog'liqligi ushbu muammoning tibbiy-ijtimoiy ahamiyatini yanada oshiradi. Bundan tashqari, paratsetamolning oddiy terapevtik dozalarda xavfsiz, ammo yuqori dozalarda yoki ma'lum xavf omillari (surunkali alkogolizm, ochlik, boshqa dorilar bilan o'zaro ta'sir) mavjud bo'lganda gepatotoksik bo'lib qolishi uning metabolik yo'llarini chuqur o'rganishni talab qiladi. Shu sababli paratsetamolning organizmdagi biotransformatsiya jarayonlarini va jigar hujayralariga zararli ta'sir mexanizmlarini farmakologik nuqtai nazardan tahlil qilish klinik toksikologiya va amaliy farmakologiya uchun dolzarb masala hisoblanadi.
Kalit so'zlar: paratsetamol, atsetaminofen, gepatotoksiklik, NAPQI, glutation, sitoxrom P450 2E1, glyukuronidlanish, sulfatlanish, N-atsetilsistein, jigar nekrozi.

ФАРМАКОЛОГИЧЕСКОЕ ИЗУЧЕНИЕ МЕТАБОЛИЗМА ПАРАЦЕТАМОЛА И ЕГО ГЕПАТОТОКСИЧЕСКОГО ДЕЙСТВИЯ (ОБЗОР ЛИТЕРАТУРЫ)

Аннотация. Парацетамол (ацетаминофен) является одним из наиболее широко применяемых в мире анальгетических и жаропонижающих лекарственных средств. Он относится к препаратам, отпускаемым без рецепта, и широко используется представителями всех возрастных групп населения. Несмотря на относительно благоприятный профиль фармакологической безопасности,

при приёме в дозах, превышающих рекомендуемые, либо при хроническом неправильном применении парацетамол становится одной из наиболее распространённых причин острой печёночной недостаточности. Значительная доля случаев острой печёночной недостаточности в развитых странах связана именно с интоксикацией парацетамолом, что дополнительно подчёркивает медико-социальную значимость данной проблемы. Кроме того, тот факт, что парацетамол является относительно безопасным в стандартных терапевтических дозах, но может проявлять гепатотоксическое действие при применении высоких доз или при наличии определённых факторов риска, таких как хроническое употребление алкоголя, голодание и лекарственные взаимодействия, обусловливает необходимость детального изучения путей его метаболизма. В связи с этим анализ процессов биотрансформации парацетамола в организме и механизмов его повреждающего действия на клетки печени с фармакологической точки зрения является актуальным направлением клинической токсикологии и практической фармакологии.

Ключевые слова: парацетамол, ацетаминофен, гепатотоксичность, NAPQI, глутатион, цитохром P450 2E1, глюкуронирование, сульфатирование, N-ацетилцистеин, некроз печени.

Introduction. Paracetamol (acetaminophen) is a centrally acting analgesic and antipyretic agent. Its primary mechanism of action is considered to be related to the inhibition of cyclooxygenase (COX) enzymes within the central nervous system, whereas its peripheral anti-inflammatory activity is relatively weak. When administered orally, the drug is rapidly and almost completely absorbed, with a bioavailability of approximately 70–90%. Its therapeutic safety largely depends on hepatic metabolic pathways; when the balance between these pathways is disrupted, toxic metabolites may accumulate and cause hepatocellular injury. Major Metabolic Pathways of Paracetamol: Paracetamol undergoes metabolism in the liver through three major pathways:

1. Glucuronidation — the Major Pathway

Approximately 50–60% of the administered dose undergoes conjugation with glucuronic acid through the action of UDP-glucuronosyltransferase (UGT) enzymes, forming a pharmacologically inactive and water-soluble glucuronide conjugate. This metabolite is readily excreted in the urine and does not possess hepatotoxic properties.

2. Sulfation: Approximately 25–30% of the administered dose undergoes sulfation through the action of sulfotransferase (SULT) enzymes, forming sulfate conjugates. This pathway is also considered a safe metabolic route. However, because sulfate donors, such as 3′-phosphoadenosine-5′-phosphosulfate (PAPS), are available in limited quantities, the capacity of this pathway can become saturated relatively quickly.

3. Oxidative Pathway — Cytochrome P450-Mediated Metabolism: A relatively small proportion of paracetamol (approximately 5–10%) undergoes oxidation in hepatic microsomes by members of the cytochrome P450 enzyme family, predominantly CYP2E1, with additional contributions from CYP1A2 and CYP3A4. This process generates the highly reactive and toxic intermediate metabolite N-acetyl-p-benzoquinone imine (NAPQI). This metabolite plays a critical role in the development of paracetamol-induced hepatotoxicity. Detoxification of NAPQI and the Role of the Glutathione System: Under normal physiological conditions, the small amount of NAPQI generated is rapidly detoxified by conjugation with reduced glutathione (GSH), the major intracellular antioxidant. This reaction produces pharmacologically inactive cysteine and mercapturic acid conjugates, which are subsequently excreted in the urine. The process is facilitated by glutathione S-transferase enzymes. However, following ingestion of paracetamol at excessive doses, a sequence of pathological events occurs:

1. The glucuronidation and sulfation pathways become saturated and reach their metabolic capacity.
2. A greater proportion of paracetamol metabolism is diverted toward the CYP2E1-mediated oxidative pathway, resulting in a marked increase in NAPQI formation.
3. Hepatic glutathione stores are rapidly depleted, and when GSH levels fall below approximately 30% of normal capacity, the liver's ability to detoxify NAPQI becomes substantially impaired.
4. Excess NAPQI covalently binds to cysteine residues of intracellular proteins, a process known as protein arylation. This results in damage to mitochondrial proteins, membrane components, and other essential cellular structures.

Biochemical Mechanisms of Hepatotoxicity: Covalent binding of NAPQI to cellular proteins initiates a cascade of pathological events.

Mitochondrial Dysfunction: NAPQI damages mitochondrial proteins and disrupts oxidative phosphorylation, resulting in a marked reduction in ATP synthesis and increased generation of reactive oxygen species (ROS). Oxidative Stress: Increased ROS production causes oxidative damage to intracellular lipids, proteins, and DNA. Activation of the JNK (c-Jun N-terminal Kinase) Pathway: Oxidative stress activates the JNK signaling pathway. Activated JNK subsequently translocates to mitochondria, where it promotes opening of the mitochondrial permeability transition pore (MPTP). Disruption of Mitochondrial Membrane Permeability: This process leads to the collapse of mitochondrial function, cessation of effective ATP production, and ultimately hepatocellular necrosis. Nuclear DNA Fragmentation and Hepatocellular Necrosis**:** Ultimately, necrosis develops predominantly in centrilobular (zone 3) hepatocytes, where CYP2E1 activity is particularly high. Several conditions may increase the risk of paracetamol-induced hepatotoxicity:

- Chronic alcohol consumption, primarily through induction of CYP2E1 and depletion of hepatic glutathione stores;
- Fasting or prolonged dietary restriction, due to reduced availability of substrates required for glutathione synthesis and glucuronidation;
- Concomitant administration of drugs that induce CYP2E1 or CYP3A4, such as rifampicin, isoniazid, and certain anticonvulsants;
- Pre-existing chronic liver disease;
- Individual differences in hepatic enzyme activity in pediatric and elderly patients.

The primary antidote for paracetamol poisoning is **N-acetylcysteine (NAC)**. Its hepatoprotective effects are based on several mechanisms:

1. NAC serves as a source of cysteine for intracellular glutathione synthesis, thereby replenishing hepatic GSH stores;
2. It can contribute to the detoxification of NAPQI through direct and indirect mechanisms;
3. It has antioxidant and anti-inflammatory properties and may improve hepatic microcirculation.

The earlier NAC is administered—ideally within the first 8–10 hours following toxic ingestion—the greater its effectiveness in preventing hepatotoxicity. During this period, hepatic glutathione stores may not yet be completely depleted, and the toxic effects of NAPQI can be more effectively prevented or limited.

Conclusion. Paracetamol-induced hepatotoxicity is directly associated with disruption of the balance among its hepatic metabolic pathways. At therapeutic doses, safe elimination is primarily achieved through glucuronidsation and sulfation. Following excessive dosing, however, increased metabolism through CYP2E1 leads to excessive production of the toxic metabolite NAPQI, which depletes hepatic glutathione stores and subsequently induces oxidative stress, mitochondrial dysfunction, and hepatocellular necrosis. A thorough understanding of these mechanisms is essential not only for the timely diagnosis and treatment of paracetamol poisoning but also for developing recommendations aimed at ensuring the safe and rational use of this widely administered medication.

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