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Review Article

New potential biomarkers of acetaminophen-induced hepatotoxicity

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ABSTRACT

Acetaminophen (APAP) is one of the most common antipyretic and analgesic drugs. Despite various precautions patients use APAP in amounts exceeding acceptable daily doses. APAP overdosing contributes to APAP intoxication, which leads to acute liver injury or necessity of exigent liver transplantation. Biomarkers that can be helpful in early diagnosis of liver injury during APAP overdosing are studied worldwide. This review presents recent reports on new potential biomarkers and their prospective application in clinical practice.

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Contents

1. Introduction

Acetaminophen (N-acetyl-p-aminophenol, APAP, paracetamol) is one of the most commonly used antipyretic and analgesic drugs. Taking it in therapeutic doses, is harmless, however, APAP overdosing may cause hepatotoxicity. Many pharmaceutical products contain APAP and are available without any prescription. Their easy availability results in constantly-increasing rate of APAP poisoning cases. For this reason, the safety of APAP is still widely discussed.

APAP has similar properties (analgesic and antipyretic properties) to nonsteroidal anti-inflammatory drugs (NSAIDs), but it does not possess any anti-inflammatory activity. Applied in recommended doses, APAP does not cause gastrointestinal side effects, which is common for NSAIDs. After ingestion, about 90% of APAP is

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metabolized in the liver, where it is conjugated with glucuronic acid (50–60%) and sulfuric acid (25–35%). A small amount of this drug (3%) binds to cysteine. The products of these conjugations are pharmacologically inactive and are eliminated by the urinary system. About 5% of APAP is eliminated by the kidneys in an unchanged form. Another 5% of APAP undergoes N-hydroxylation by cytochrome P450 enzymes, producing a toxic metabolite i.e. N-acetyl-*p*-benzoquinone imine (NAPQI, *N*-acetylimidoquinone). In therapeutic APAP doses, reactive NAPQI is sufficiently deactivated by conjugation with sulfhydryl groups of glutathione (GSH). The final product of APAP metabolism is mercapturic acid, which is eliminated with urine. The situation changes if APAP is overdosed. Metabolic reactions cause hepatic GSH depletion and NAPQI binds to various hepatocyte macromolecules such as proteins, lipids and DNA. It leads to metabolic disturbances and cell death. N-acetylcysteine (NAC) restores GSH resources, therefore administration of NAC plays an essential role in medical care of patients with APAP overdose. However, NAC is fully hepatoprotective only when distributed within 8 h after APAP ingestion [1].

After APAP overdose, NAPQI reacts with protein sulfhydryl groups forming adducts with them [2]. Protein adducts are formed primarily in mitochondria causing their dysfunction and leading to oxidative stress. It begins from the activation of various MAP kinases [3], which after chain reactions, causes phosphorylation of c-jun-N terminal kinase (P-JNK). P-JNK translocates to the mitochondria which enhances formation of reactive oxygen species, mainly peroxynitrite [4,5]. It leads to the opening of the membrane permeability transition (MPT) pores. Consequently, the membrane potential collapses and the ATP synthesis is inhibited. Another consequence of the MPT opening is mitochondrial matrix swelling and the resulting rupture of the outer membrane. The rupturing of the membrane triggers leakage of various intermembrane proteins (for instance endonuclease G) into cytosol. The proteins are transported to the nucleus where they initiate DNA fragmentation [6]. The end result is a hepatocyte necrosis [7].

The mitochondrial dysfunction that occurs in liver damage can be assessed trough measuring the mitochondrial matrix enzyme glutamate dehydrogenase (GDH) or mitochondrial DNA (mtDNA) in patient's serum [8]. Furthermore, protein adducts can also be observed in serum after APAP overdose [9]. Numerous studies on APAP toxicity have been carried out in recent years. Researchers discovered several novel potential diagnostic biomarkers of liver necrosis. The markers belong to the cell death markers group and were observed both in mouse and in human serum: cytokeratin-18, microRNA-122, high mobility group box 1 protein (HMBG-1), nuclear DNA (nDNA) fragments or argininosuccinate synthetase (ASS) [8,10–12].

2. Review

2.1. Circulating acylcarnitines

Acylcarnitines are conjugates of carnitine and fatty acids. Long-chain fatty acids cannot pass through the mitochondrial membrane, but conjugation with carnitine facilitates their penetration into the mitochondria. The presence of these fatty acids in mitochondria is necessary for β-oxidation. Accumulation of acylcarnitines (palmitoylcarnitine, myristoylcarnitine, oleoylcarnitine and palmitoleoylcarnitine) was observed in mouse serum after APAP treatment and was linked to β-oxidation impairment [13], although it may be a result of NAPQI binding to carnitine-acylcarnitine translocase (CACT) or carnitine palmitoyltransferase II (CPT II) – enzymes involved in acylcarnitines metabolism [14]. Disturbances to the activity of these enzymes could initiate the accumulation of acylcarnitines in cytosol. It is also possible that the increased levels of acylcarnitines proceed from β-oxidation in mitochondria and after mitochondrial MPT, the acylcarnitines are released to plasma. On the contrary, McGill et al. [15] did not notice a significant difference of acylcarnitines levels in human serum after APAP overdose, compared to the control group. These findings were explained by the effect of NAC treatment that supports mitochondrial function. Another study of human serum after APAP treatment was performed by Bhattacharyya et al. [16]. They examined serum collected from children with APAP exposure (low dose and overdose) and compared to controls. They measured acylcarnitines regardless of alanine transaminase (ALT) levels and checked the influence of time-dependent NAC treatment. Moreover, the study group included more patients compared to the McGill et al. [14] research. Bhattacharyya et al. [16] reported that long-chain circulating acylcarnitines levels, especially palmitoyl- and oleoyl-carnitines, were significantly elevated in children with APAP exposure compared to controls. Whereas there was no significant difference in acylcarnitines levels between both APAP exposure groups. However, in children with APAP overdose receiving delayed NAC treatment (more than 24 h after overdose), acylcarnitines were at a higher level than in early NAC treatment group. These findings confirm that acylcarnitines levels are influenced by the time of NAC treatment after APAP exposure. In summary, the results of the studies discussed above proved that circulating acylcarnitines levels can be evaluated as potential biomarkers of mitochondrial injury and APAP hepatotoxity. Their concentration can be easily measured by applying ultraperformance liquid chromatography quadrupole time-of-flight mass spectrometry (UPLC-QTOFMS).

2.2. Liver-specific blood proteins

Hu et al. [17] identified five liver-specific blood proteins as markers of APAP-induced hepatotoxicity in humans using proteomic technologies (label-free antibody microarrays, quantitative immunoblotting, and targeted iTRAQ mass spectrometry). Betaine–homocysteine *S*-methyltransferase 1 (BHMT), dihydropyrimidinase (DPYS), fumarylacetoacetate hydrolase (FAH) and fructose-1,6-bisphosphatase 1 (FBP1) showed higher concentrations than ALT–which is the gold standard in diagnosing hepatotoxicity. 4-hydroxyphenylpyruvatedioxygenase (HPD) concentration was comparable with ALT. S-adenosyl-L-methionine (SAMe) is a precursor of GSH. Its concentration in the liver decreases dramatically in the case of APAP hepatotoxity. Hu et al. [17] linked the decreasing SAMe with the change in the levels of three enzymes involved in metabolism of SAMe (MAT1A, GNMT and BHMT)–they decreased in the liver but were elevated in the blood. It was suggested that these liver-specific blood proteins might be useful in GSH and SAMe levels' assessment and therefore might have prognostic value in hepatotoxicity. Hu et al. [17] also observed interesting changes in the concentration of membrane-bound catechol-O-methyltransferase (MB-COMT) in mouse plasma and liver tissue after APAP intoxication. Catechol-O-methyltransferase (COMT) is an enzyme that catalyzes the transfer of a methyl group and has two isoforms–soluble and membrane-bound. The western blot assay of liver tissue showed that after APAP overdose, the soluble catechol-O-methyltransferase (S-COMT) level decreased whereas MB-COMT increased. It was suggested that there may be a specific mechanism in the liver that allowed the translation of S-COMT into MB-COMT after overdosing APAP. The mechanism of COMT regulation requires further investigation (Fig. 1).

Another potential new biomarker is the mitochondrial protein, carbomoyl phosphate synthetase 1 (CPS1). This protein level increases faster than aspartate transaminanse (AST) and ALT within the first 3 h after APAP ingestion [18,19]. CYPS1 levels were

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