EBioMedicine 46 (2019) 9–10

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

EBioMedicine
Published by THE LANCET

Commentary

Emerging novel therapies against paracetamol (acetaminophen) hepatotoxicity

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Paracetamol (acetaminophen) is a popular analgesic and antipyretic drug used worldwide. It is generally considered safe at therapeutic doses. However, due to its widespread availability in different drug preparations, intentional and un-intentional overdosing occurs, which can cause severe liver injury and even acute liver failure [1]. Early mechanistic studies of paracetamol-induced cell death using a mouse model in the 1970s provided evidence for P450-dependent reactive metabolite generation, hepatic glutathione depletion and protein adduct formation [2]. Based on this mechanistic insight, the use of *N*-acetylcysteine (NAC) as an effective antidote against paracetamol overdose was quickly established for patients [3]. Even today, NAC is still the only clinically approved antidote against paracetamol poisoning [3].

Over the years, paracetamol overdose in mice became a popular model to study in-depth mechanisms of drug-induced liver injury. Mitochondrial dysfunction and oxidant stress emerged as key events in the toxicity [4]. Leakage of electrons from the mitochondrial electron transport chain initially due to protein adducts formation and later amplified due to the mitochondrial translocation of phospho-JNK generates superoxide within the mitochondrial matrix. The superoxide radicals can react with nitric oxide radicals to form the very potent oxidant and nitrating species peroxynitrite [5]. In fact, nitrated proteins can be found almost exclusively within the mitochondria, which underscores the central role of mitochondria as the source of the oxidant stress. It also was established that peroxynitrite is the actual toxic mediator of paracetamol-induced cell death [6]. Although GSH is an effective scavenger of peroxynitrite, the depletion of GSH by the reactive metabolite of paracetamol impairs this line of defense [6]. Another mechanism to minimize peroxynitrite formation is to accelerate the dismutation of superoxide to hydrogen peroxide and oxygen. The endogenous mitochondria-specific superoxide dismutase 2 (MnSOD) accomplishes this but MnSOD was also shown to be inactivated by protein nitration during paracetamol hepatotoxicity [7]. Thus, mitochondria-targeted SOD mimetics such as mito-TEMPO have been shown to strongly protect against paracetamol-induced liver injury in the mouse even when given after the metabolism phase [8]. Based on this mechanistic insight in the mouse model and the similarities between the pathophysiology in mice and humans [1], there seems to be a clear rationale for using SOD mimetics in paracetamol hepatotoxicity.

In the current study published in *EBioMedicine*, James Dear and coworkers treated paracetamol overdose patients with a 12 h regimen of NAC alone and in combination with 3 different doses of the SOD-mimetic calmangafodipir [9]. The trial with limited number of patients demonstrated that calmangafodipir was well tolerated and no adverse effects were noted. The authors also measured standard biomarkers of liver injury (ALT, INR) but did not find significant increases in any group during a 20 h time period between first presentation and the end of NAC treatment. This was likely due to the fact that most patients presented early after the overdose (<8 h) and were quickly treated with NAC minimizing the risk of any significant liver injury [9]. In addition to ALT, the authors also measured newer, exploratory biomarkers of liver injury including full-length cytokeratin-18, caspase-cleaved cytokeratin-18 and miR-122, which are considered more sensitive markers of cell death than ALT [10]. Both forms of cytokeratin showed an increase of 60–100% over baseline in the NAC-treated group alone; this increase was prevented in all NAC + calmangafodipir groups [9]. This observation may indicate that calmangafodipir co-treatment further reduced the risk of liver injury in these patients. However, the limitations of this study need to be considered when interpreting the effect of calmangafodipir on any parameters of liver injury. The patient number was very limited ($n = 6$ per group) and none of the patients had severe liver injury. In addition, the on average longer time interval between paracetamol ingestion and hospital presentation and start of NAC infusion slightly increased the risk of liver injury in the NAC only treatment group; this makes the interpretation of a potential drug effect more tenuous. Thus, any reliable conclusion regarding an additional benefit of calmangafodipir administration over the standard of care NAC requires a much larger patient cohort with later presenting patients who have a high risk of developing liver injury and acute liver failure. Nevertheless, the current study showing no adverse effects of calmangafodipir in paracetamol overdose patients is an important step forward that justifies testing the therapeutic efficacy of the drug. If successful, calmangafodipir would be the first new drug against paracetamol poisoning in 40 years.

Disclosure

I have nothing to disclose.

DOI of original article: https://doi.org/10.1016/j.ebiom.2019.07.013.

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https://doi.org/10.1016/j.ebiom.2019.07.054
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