Commentary

Prolonged *N*-acetylcysteine therapy in late acetaminophen poisoning associated with acute liver failure – a need to be more cautious?

T Nimmi C Athuraliya and Alison L Jones

Department of Clinical Pharmacology and Clinical Toxicology, School of Medicine and Public Health, Faculty of Health, University of Newcastle, Callaghan Drive, Newcastle, NSW 2308, Australia

Corresponding author: Alison L Jones, alison.jones@newcastle.edu.au

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See related research by Yang *et al*., http://ccforum.com/content/13/2/R55

Abstract

Since the 1970s, *N*-acetylcysteine (NAC) has shown proven efficacy as an antidote for acetaminophen (APAP) poisoning and APAP-induced liver failure for early presenters. The current evidence of benefits of NAC for late presenters is controversial because of the poor understanding of the mechanism of late toxicity. In the previous issue of *Critical Care*, Yang and colleagues use a mouse model to demonstrate that NAC in doses similar to those used therapeutically to treat APAP poisoning in humans impairs liver regenerative capacity and that the effect is more pronounced when administered for a longer duration. Studies based on cell cultures support this evidence. Cytokine and growth factor signalling pathways are recognised to be involved in the process of liver regeneration and apoptosis. This research paper generates several issues related to the future management of APAP-induced liver failure and research into the mechanism of toxicity, especially of late toxicity.

Introduction

The paper entitled '*Prolonged treatment with N-acetylcysteine delays liver recovery from acetaminophen hepatotoxicity*' by Yang and colleagues [1], published in the previous issue of *Critical Care*, demonstrates that prolonged administration of *N*-acetylcysteine (NAC) at 100 mg/kg in acetaminophen (APAP)-induced liver failure in mice potentially limits hepatocellular regeneration. Activation of a transcription factor, nuclear factor-kappa-B (NF-κB), strongly linked to impairment of liver regeneration, is a putative mechanism for this. Furthermore, the paper postulates that high doses of NAC may interfere with normal metabolic processes of the liver, leading to impairment of its regenerative capacity [1].

N-acetylcysteine in acetaminophen poisoning and acetaminophen-induced liver failure

NAC has been used since the 1970s, and it effectively manages APAP poisoning by glutathione repletion if administered within 8 to 10 hours of ingestion of the overdose [2]. In later years, clinical use of NAC was extended to patients who present more than 10 hours after ingestion and to those with APAP-induced acute liver failure (ALF), and patients in such categories are routinely on NAC infusions for many days, even weeks [3,4]. The putative protective mechanisms of NAC in late-APAP poisoning and APAP-induced liver failure remain poorly characterised but include free-radical scavenging, hemodynamic, and cytokine effects [1,5,6]. Concern has been expressed relating to its extended use in late presenters with APAP poisoning and APAP-induced liver failure because of the possibility of changed kinetics of NAC in liver injury, reduced efficacy, and adverse hemodynamic changes (vasodilatation and increased cardiac index) [7]. This new study raises the issue of whether impairment of regeneration is also a clinical concern for extended NAC use.

Cytokines and liver regeneration

A key issue in liver recovery after any acute injury is tissue repair and regeneration. Such liver regeneration involves replication of mature parenchyma and non-parenchyma liver cells, which requires multiple cytokine and growth factor signalling pathways, including tumour necrosis factor-alpha, interleukin-6, hepatocyte growth factor (HGF), and transforming growth factor-alpha [8,9]. Inhibition of the transcription factor NF-κB was shown to be associated with impaired liver regeneration and apoptosis of hepatocytes [10]. NF-κB is also demonstrated to be responsible for regulation of transcription of a cell cycle regulator cyclin D1 [11].

Other evidence of *N*-acetylcysteine effects on liver regeneration

This new study in a mouse model demonstrates that NAC, in doses similar to those used therapeutically to treat APAP poisoning in humans [2], impairs liver regenerative capacity

ALF = acute liver failure; APAP = acetaminophen; HGF = hepatocyte growth factor; NAC = *N*-acetylcysteine; NF-κB = nuclear factor-kappa-B.

and that the effect is more pronounced when administered for a longer duration (that is, 72 versus 24 hours). The histopathological evidence of this effect was supported by the reduced NF-κB DNA binding in liver and decreased expression of cyclin D1 [1]. It is noteworthy that NAC acting on APAP-treated human hepatoma-derived cell HepG2 cell cultures was shown to have a protective effect against APAP-induced oxidative damage but not from apoptosis [12]. This evidence does support the findings of Yang and colleagues [1], despite the species differences that could contribute to APAP and NAC metabolic pathways.

Issues related to clinical practice

The current clinical literature recommends the prolonged administration of NAC in patients with APAP-induced ALF and in those who present late for medical care until evidence of improvement of the international normalised ratio or transplantation takes place [13]. In this backdrop, the evidence by Yang and colleagues raises two issues with respect to prolonged use of NAC: first, whether prolonged NAC use is potentially harmful by reducing liver regeneration in patients presenting late with APAP poisoning, especially in those with APAP-induced ALF, and second, the issue of appropriate dosing and duration of NAC treatment. The concept of tailor-making NAC therapy to the APAP-poisoned patient has been raised recently in the literature [14,15], and differing protocols of NAC infusion are starting to be evaluated [16,17], albeit with study limitations [18].

Future research and patient management

Future research on APAP-induced ALF patients could be in the direction of monitoring for biomarkers (for example, sFas and HGF) [19] for liver regeneration or apoptosis in order to establish whether there is a 'tipping point' of risk/benefit after which NAC infusion might be stopped. Further research is also required to fully evaluate the impact of NAC on cytokine systems controlling hepatocellular recovery. In the management of late presenters with APAP poisoning and APAP-induced liver failure, clinicians may have to consider individual case scenarios in tailor-making duration and dose of NAC therapy.

Competing interests

The authors declare that they have no competing interests.

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