O2

THE ROLE OF PROTEIN ADDUCTS IN DETERMINING THE AETIOLOGY OF LIVER FAILURE

L Nelson
Department of Emergency Medicine, New York University, USA

Drug-induced liver injury is common around the globe and acetaminophen poisoning is among the most common causes. The diagnosis of acetaminophen poisoning is generally accomplished through accurate history-taking along with the determination of serum acetaminophen concentrations. In most cases the nature of the exposure is well defined, and is typically due to self-harm or chronic overmedication. However, in approximately 14% of patient who present with signs of hepatic necrosis the aetiology remains mysterious. In such patients, particularly those without a clear history of exposure, serum acetaminophen concentrations can prove misleading. For example, in some patients the acetaminophen concentration may have fallen to undetectable levels prior to testing and in others acetaminophen may be present but represent medication taken therapeutically for the treatment of abdominal pain due to hepatitis. The metabolism of acetaminophen by the hepatic cytochrome system produces the reactive electrophile NAPQI, which binds locally in the liver to proteins, initiating a cascade of inflammation leading to hepatic necrosis. Binding of NAPQI to cysteine residues on some proteins results in the formation of acetaminophen-cysteine adducts (ACA) that are released into the systemic circulation and can be assayed. In both adult and pediatric patients with acetaminophen hepatotoxicity, ACA can be detected for several days after APAP overdose, much longer than for the parent compound. It is currently understood that in patients with known acute acetaminophen-induced hepatotoxicity, the serum concentrations of ACA will be elevated to greater than 1.0 nmol/mL, although the clinical utility of the assay in this setting may be limited. When applied to a group of patients with liver failure of unknown aetiology, 18% had ACA concentrations >1 nmol/L suggesting unrecognised acetaminophen toxicity. This group had demographic, clinical, and laboratory findings consistent with this diagnosis. In healthy, non-alcoholic patients experimentally administered therapeutic doses of acetaminophen, low concentrations of ACA are identified (less than 0.4 mmol/L). Interestingly, those with alcohol consumption had lower ACA concentrations. Patients with hepatic necrosis from other causes, toxicologic and nontoxicologic, without concomitant exposure to acetaminophen had undetectable ACA. Less well-defined are the concentrations of ACA in patients with repeat supratherapeutic acetaminophen dosing. Although availability of this test remains limited, our understanding of clinical utility of ACA in identifying acetaminophen as the underlying cause of acute hepatitis is continuing to expand.