Changing the Management of Paracetamol Poisoning

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ABSTRACT

Purpose: The management of paracetamol poisoning was revolutionized after use of acetylcysteine in the 1970s. The protocol used, 3 weight-related infusions, requires almost 24 hours in hospital. It is associated with adverse events in treated patients, particularly anaphylactoid reactions and vomiting. Present treatment nomograms were based on a small series of untreated patients: only 5 of 22 (23%) and 6 of 25 (24%) between the 100 to 200 mg/L and 200 to 300 mg/L nomogram lines, respectively, developed liver injury (alanine transaminase >1000 IU/L). Many patients treated today are unlikely to be at actual risk for major hepatotoxicity. This article discusses the background to future prospects in this area.

Methods: The history behind approaches to the use of acetylcysteine is presented briefly. The rationale for, and key findings of, a new 12-hour antidote regimen for paracetamol poisoning are detailed. Newer markers of hepatotoxicity, such as miR-122, HMGB1, and necrosis K18, which predict patients at risk more reliably and earlier than existing tests, are discussed.

Findings: A 2-phase 12-hour acetylcysteine infusion protocol (100 mg/kg over 2 hours: 200 mg/kg over 10 hours) was studied in a formal factorial design against the traditional 3-phase 20.25-hour infusion protocol, with and without pretreatment with ondansetron or placebo. The 12-hour regimen was associated with very significant reductions in anaphylactoid reactions (odds ratio = 0.23; 95% CI, 0.12−0.43; $P < 0.0001$) and vomiting (odds ratio = 0.37; 95% CI, 0.18−0.79; $P = .003$) compared with the 20.25-hour infusion protocol. There were few withdrawals from the clinical trial, indicating the feasibility of conducting such studies in Europe.

Implications: Novel proteomic markers are better than existing standard tests (alanine transaminase and international normalized ratio) early in the course of paracetamol poisoning. Together with these new biomarkers of hepatotoxicity, a 12-hour acetylcysteine protocol offers clinicians and patients the possibility for better targeting of therapy, fewer adverse effects, a simpler dosing regimen, and shorter hospital stay. (*Clin Ther*. 2015;▮:▮▮▮–▮▮▮) © 2015 Elsevier HS Journals, Inc. All rights reserved.

Key words: paracetamol overdose, antidotes, risk assessment.

BACKGROUND

Paracetamol was introduced into medical practice in the United States in 1955 and in the United Kingdom in 1956. Poisoning was first described in humans in Scotland in 1966.[1,2] Subsequently, the mechanism of paracetamol toxicity, production of a reactive benzoquinoneimine metabolite (N-acetyl-para-benzoquinoneimine), was understood after work by Mitchell et al in the United States.[3] This led to the development of antidotes that were designed to replace the naturally occurring antioxidant glutathione consumed by binding and neutralizing N-acetyl-para-benzoquinoneimine. Availability of glutathione is influenced by environmental factors, particularly nutritional status. Production of N-acetyl-para-benzoquinoneimine from paracetamol, primarily by CYP2E1, is potentially inducible, and can also be inhibited by acute ingestion of ethanol. These different factors might be difficult to assess in poisoned patients.[4,5]

The lead candidate antidote in the 1970s soon became acetylcysteine, given intravenously in a 3-step regimen. This is known in the United Kingdom as the "Prescott" regimen, and consists of weight-related dosages of acetylcysteine given in 3 infusions, initially 150 mg/kg over 15 minutes, then 50 mg/kg over 4 hours, and finally 100 mg/kg over 16 hours.[6,7]

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Methods of risk assessment were also derived in Edinburgh based on patients not treated with antidote, and using paracetamol concentrations at presentation to derive nomograms. A nomogram was published by Rumack and Matthew[8] in 1975, although the article has no patient data included. Subsequently, further risk analyses were derived from the Edinburgh patient population by Prescott.[9] The case data extracted from the Prescott publication are shown in the Table, and are based on an alanine transaminase (ALT) of > 1000 IU/L as the marker of hepatotoxicity. This is a relatively poor indicator of prognosis, even though it is a sensitive measure of liver injury, as judged by its noninclusion in the Kings College criteria of prognosis.[4] However, it is clear from the data in the **Table** that only one quarter of patients at concentrations below the 300 mg/L line and above the 100 mg/kg line developed important liver injury. There was no gradation in the proportion developing an ALT >1000 IU/L in those lying between the 100 to 200 mg/L and 200 to 300 mg/L lines, even though liver failure and renal injury were seen in those above the 200 mg/L line only.

In untreated paracetamol poisoning cases in which the liver is damaged, the clearance of paracetamol is reduced and half-life is prolonged in proportion to the degree of liver injury.[10] Without liver damage, paracetamol has a half-life of about 2 hours.[11] Because treatment is not commenced until at least 4 hours after ingestion, it is clear that with a half-life of 2 hours, paracetamol will be undetectable in the blood of patients not at risk many hours before the end of the current 21-hour antidote infusion. This means that many patients are likely to be kept in hospital well after their risk of paracetamol-induced liver injury could be excluded. Based on these data, clearance of paracetamol combined with other tests could be used as an indicator of good prognosis, but is rarely applied in this way.

Table. Patients with untreated paracetamol overdose who developed liver injury (ALT >1000 IU/L), renal failure, or death stratified by paracetamol nomogram lines. Data are given as n (%) unless otherwise noted and are derived from Prescott.[9]

Paracetamol Line (mg/L)	No. of Patients	Liver Injury	Renal Failure	Death
<100	9	0 (0)	0	0
100–200	22	5 (23)	0	0
200–300	25	6 (24)	1 (4)	0
>300	27	25 (93)	5 (20)	3 (12)

Problems with the Paracetamol Nomograms

The nomogram lines derived in the 1970s were drawn by eye rather than by using any statistical derivation. They are lines drawn from a 4-hour post-overdose time point, commencing at 300, 200, 150, or 100 mg/L (1.98, 1.32, 0.99, and 0.66 mmol/L respectively), and all have a half-life of decline of 4 hours, despite the known variability of paracetamol clearance in poisoned patients.[10] In the United Kingdom, the Prescott article[9] supported a 200-mg line, which was adopted in the late 1970s. In the United States, Rumack and Matthew's[8] original suggestion of a 200-mg line was modified by the US Food and Drug Administration to the 150-mg line. The rationale was that 150 mg was half the concentration of 300 mg/L, which at that time was believed to cause death.[12] Subsequent reports have found that deaths can occur in untreated patients at concentrations below the 200 mg/L line and, in very rare patients who are fasting, even below 100 mg/L.[5,13,14] In the 1990s, the United Kingdom changed its policy to include a risk assessment in those patients with paracetamol concentrations between the 100 and 200 mg/L nomograms.[15] The risk factors used to influence a treatment decision included malnutrition, debilitating disease (including AIDS), chronic high ethanol consumption, and enzyme-inducing drugs.[4] This was subsequently changed after a review by the UK regulator (The Medicines and Healthcare Products Regulatory Agency [MHRA]) to a single decision tool in 2012, the 100-mg/L nomogram line, after the death of a young woman with a presentation concentration just over the 100-mg line but who was not treated, as risk factors were reportedly not apparent at presentation.[5] The impact of these changes on clinical practice in the United Kingdom was reported subsequently, with many additional hospital presentations and admissions, at an estimated cost of £17.3 m (95% CI, £13.4 m–£21.5 m) (€21.2 m, $29 m) to prevent one death.[16] Few modern health care systems would find such costs justifiable.