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Commentary

SNAP – A Large Step in the Move towards Personalised Dosing of Acetylcysteine

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In the 1970s, paracetamol poisoning had very high morbidity and mortality from acute liver injury. The initial acetylcysteine regimens proposed were an "intelligent guess"; neither oral nor intravenous regimens had dose ranging studies, or was subject to randomised controlled trials [1,2]. There were some limited comparisons of the oral and intravenous regimens, but largely the intravenous regimen has prevailed due to a shorter duration and ensured delivery. The standard three-bag intravenous weight-based dosage regimen (150 mg/kg body weight over 15–60 min, then 50 mg/kg over 4 h and 100 mg/kg over 16 h (300 mg/kg total)) remained unchanged for 3 decades. The high efficacy was apparent (compared to no treatment), but there were frequent adverse reactions and the complex dosing regimen was error prone [3]. The last decade has brought increasing concern about deficiencies in this "one-size fits all" approach. Patients receive the same weight-based protocol regardless of dose ingested or paracetamol concentration. Those with high paracetamol concentrations (≥300 mg/L at 4 h, double the nomogram line) may receive inadequate doses of acetylcysteine [1,4]. Conversely, with current thresholds for treatment, there are many low risk patients who probably receive treatment for much longer than necessary.

In the last decade various new intravenous acetylcysteine regimens have been proposed: to decrease adverse reactions, administrative errors and shorten treatment duration [3]. Many just slowed the initial loading dose and simplified the protocol to a two-bag regimen (i.e. 200 mg/kg over 4 h), which greatly reduced the rates of adverse reactions [5–8]. A more radical change was examined by the Scottish and Newcastle Anti-emetic Pre-treatment for Paracetamol Poisoning (SNAP) investigators. The SNAP regimen gave a smaller loading dose of 100 mg/kg over 2 h and shortened treatment by 8 h, infusing 200 mg/kg over 10 h (300 mg/kg total over 12 h). This regimen significantly reduced vomiting, and anti-emetic use (36% vs 65%) and severe anaphylaxis (5% vs 31%) [9]. However, the SNAP regimen (and other newly proposed regimens) had not demonstrated equal or better efficacy than the traditional regimen. Given the high efficacy of all acetylcysteine regimens very large numbers of patients are required to demonstrate differences.

In this issue of EClinicalMedicine, Pettie and colleagues report the comparative efficacy of the SNAP regimen in an observational study of over 3000 patients [10]. They show no difference in liver injury between the traditional and SNAP regimens. We believe there is now sufficient evidence to support a change away from the traditional regimen, and indeed this is already occurring around the world. The SNAP regimen is not a "one size fits all" dose, and thus offers additional advantages over the traditional regimen. The "massive" overdoses with prolonged high paracetamol concentrations, will receive increased doses with the SNAP regimen. Further acetylcysteine is given when paracetamol concentration is >20 mg/L or there is evidence of liver toxicity at 12 h. Thus these patients receive 480 mg/kg of acetylcysteine over 21 h compared with 300 mg/kg in the traditional regimen. We recently showed that those with high initial paracetamol concentrations (i.e. greater than 300 mg/L at 4 h) had lower rates of liver injury if later acetylcysteine doses were increased [4]. The SNAP regimen exceeds the typical NAC doses given in this setting (Fig. 1 – bottom panel). The SNAP regimen will also benefit low risk patients. For example, >80% of patients with an initial paracetamol concentration between 150 and 199 mg/L at 4 h only required 12 h treatment; a contrast with other two bag regimens (Fig. 1 – top panel).

However, outside the UK, there are two caveats. Firstly, the regimen requires the rapid availability of further paracetamol concentrations and liver function tests; many people received more than 12 h of acetylcysteine, and the SNAP regimen cannot be assumed to have good efficacy without these tests selecting people for prolonged therapy. Secondly, the UK has much lower treatment thresholds than used by most other countries. In this study, around 40% of the patients had an initial paracetamol concentration between 100–149 mg/L on the 4 h nomogram line (supplementary table 4). These patients would not be treated in most places and are at very low risk of liver injury. The efficacy data presented showing equivalent efficacy that is relevant elsewhere is on 959 patients (alanine aminotransferase (ALT) >1000 U/L

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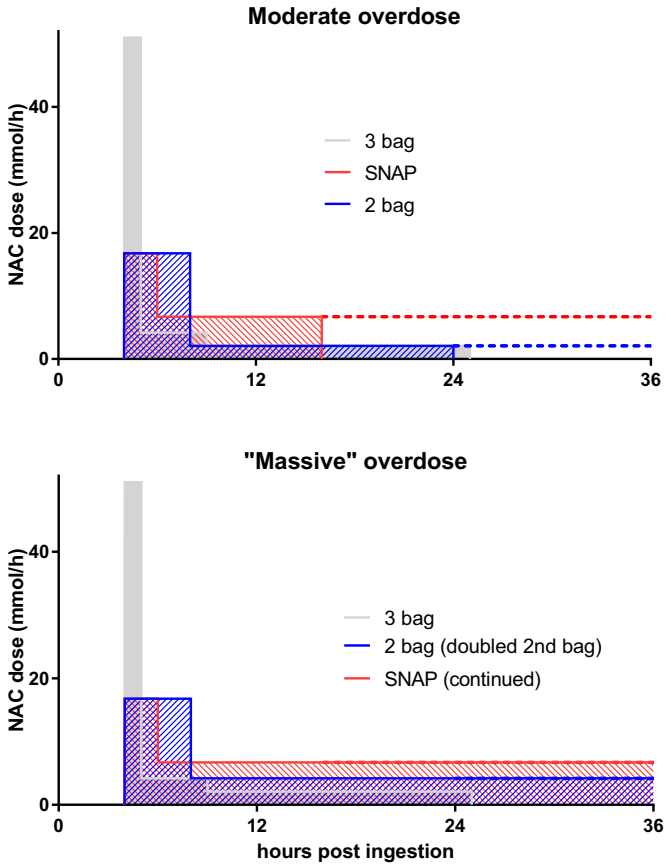

Fig. 1. Acetylcysteine doses over time from traditional, modified 2 bag and SNAP regimen. The top figure shows the likely course for a "moderate" overdose just above the nomogram line, the lower one for a "massive" overdose with prolonged high concentrations, where treatment continues beyond the usual time and doubling of the second bag is generalised advised in two bag regimens.

in those over 150 line: Traditional regimen: 20/485; SNAP: 20/474). Further comparative studies of people with higher concentrations will still be useful, and for the reasons noted above, we suspect may demonstrate superior efficacy of the higher hourly doses in the SNAP regimen.

This and other recent studies show that the time is up for the three-bag traditional "one size fits all" regimen. The SNAP regimen allows low risk patients to receive shorter treatment and higher risk patients to receive increased acetylcysteine doses. There are other regimens to achieve these ends [11,12] but the SNAP investigators are leading in providing the evidence that should now change current UK guidelines, and supports changes occurring elsewhere.

Abbreviations

ALT	alanine aminotransferase
SNAP	Scottish and Newcastle Anti-emetic Pre-treatment for Paracetamol Poisoning

Declaration of Interests

The authors have no conflicts of interest to declare.

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