N-ACETYLCYSTEINE – 40 YEARS OF GETTING THE DOSE WRONG?

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The 'Prescott' acetylcysteine regime, consisting of 3 separate infusions (150 mg/kg over 15 mins; 50 mg/min over 4 hours; 100 mg/kg over 16 hours, total 300 mg/kg) was shown to be effective almost 40 years ago, especially for those treated soon after overdose, but disadvantages include complexity and the high frequency of dose-related adverse effects, especially gastrointestinal and anaphylactoid reactions. There is therefore interest in evaluating alternative approaches.

The rationale for the Prescott regimen has not been published, although some of the reasoning can be inferred.[2] No dose ranging studies were done, so alternative regimens might be better tolerated and have similar efficacy. A'one size fits all' approach may also not be optimum as dose requirements for those with high paracetamol loads or other risk factors are expected to be greater, while a longer duration of infusion may be needed in those with very high initial paracetamol concentrations or prolonged paracetamol absorption (including use of modified release preparations) or elimination.

The initial infusion rate was apparently designed to give the maximum tolerated dose as early as possible, when therapeutic efficacy was greatest, but is responsible for most of the adverse effects. A longer initial infusion duration (1 hour) has therefore been used in the USA, Australasia and more recently the UK, but there remains no good evidence that this has reduced adverse reactions. [3, 4] Further reduction in initial infusion rate does, however, substantially reduce rates of adverse reactions [5] and various infusion designs, including variable rate/duration regimens could be better tolerated while maintaining efficacy. For patients with very large paracetamol loads, higher total doses and durations of acetylcysteine are appropriate. Currently patients with developing hepatotoxicity are usually given a 4th (16h) acetylcysteine infusion at the end of therapy, but this dose may not be adequate; higher infusion rates are logical, especially for those with persisting detectable plasma paracetamol concentrations.

The Scottish and Newcastle Acetylcysteine for Paracetamol (SNAP) regimen is a simpler 2 infusion regimen with a slower initial infusion rate (100 mg/kg over 2 h then 200 mg/kg over 10 hours). SNAP has a substantially lower rate of adverse reactions and offers the opportunity to continue acetylcysteine infusion at a higher rate (20 mg/kg/h) in those developing hepatotoxicity.[5] The regimen offers substantial advantages in terms of safety, simplicity and flexibility, provided outcomes from a large patient cohort confirm similar efficacy to the original Prescott regimen.