

Model-based optimisation of N-acetylcysteine for the treatment of paracetamol overdose

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Background and Purpose: The recommended dosing regimen for treating paracetamol (APAP) overdose consists of an intravenous dose of N-acetylcysteine (NAC) 150 mg·kg⁻¹ over 60 min, then 50 mg·kg⁻¹ over 4 hr and finally 100 mg·kg⁻¹ over 16 hr. Empirical evidence suggests that this protocol is both effective and safe, but an increased incidence of cases in which patients taking massive overdoses (>30 g APAP) have had poor outcomes seems to highlight the need for a stoichiometric basis to the current regimen. We critically evaluate the current nomogram and explore the correlation between APAP overdose and NAC regimens using modelling and simulation.

Experimental Approach: A population pharmacokinetic model was developed using published literature data to characterise the disposition of APAP and NAC. Model parameters were subsequently used to simulate both moieties and explore the implications of variable exposure to NAC on treatment outcome in a cohort of 28 consecutive patients, who were admitted and treated for paracetamol overdose at a tertiary London hospital.

Key Results: A review of the clinical records showed that eight (28.6%) patients reported opioid co-ingestion, and 11 (39.3%) overdoses were staggered. The reported ingested dose was 12 g (IQR: 8–21 g, maximum 56 g). The median plasma paracetamol concentration at presentation was 50.9 mg·L⁻¹ (18.55–101.025 mg·L⁻¹, maximum 305.2 mg·L⁻¹). All patients received N-acetylcysteine, with a median dose of 22.9 g (IQR: 19.8–30.7 g), with six (21.4%) patients receiving additional NAC infusions beyond 21 hr of treatment. Despite prompt intervention following hospital presentation, 12 patients (42.9%) developed an ALT rise above the upper limit of normal, with six (21.4%) above 1,000 IU·L⁻¹, and five (17.9%) patients had an INR rise to >1.3. Simulated APAP and NAC profiles shed further light on the limitations of the nomogram for APAP toxicity based on the lack of a stoichiometric basis for the current NAC regimen.

Conclusions and Implications: NAC remains an important measure for prevention of severe hepatic damage following APAP overdose. Current NAC therapy recommendations have been effective, but evolving insight from pharmacokinetic modelling and simulation demonstrates that its regimen can be optimised. Most importantly, simulations make clear that a revised nomogram is needed to ensure appropriate clinical management of acute overdose.