# Utilising prior literature population models to inform clinical practice
## A dosing regimen for immediate N-acetylcysteine treatment of paracetamol overdose


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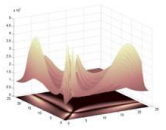
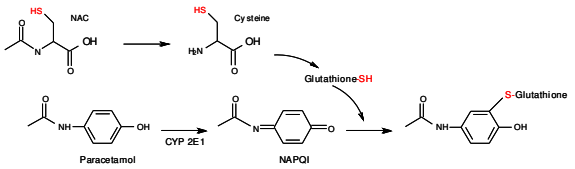


## Background

- Current treatment of paracetamol (acetaminophen) poisoning involves initiating a 3-phase N-acetylcysteine (NAC) IV infusion after comparing a plasma concentration, taken ≥4 hours post-overdose, to a nomogram.[1]
  - 3-phase infusion: 150 mg/kg over 15-60 mins
    50 mg/kg over 4 hours
    100 mg/kg over 16 hours
- This regimen is associated with dosing errors, a delay in treatment, and significant adverse effects.
- *Paracetamol toxicology*[1]
  - Hepatocellular injury results form the formation of the highly reactive toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI) by cyctochrome P450 2E1.
  - NAPQI is normally irreversibly detoxified by glutathione conjugation, but glutathione becomes depleted when large amounts of NAPQI are formed.
  - NAC is hydrolysed in the body to cysteine which replenishes glutathione, additionally NAC supplies thiol groups which can directly react with NAPQI in hepatocytes.
  - NAC is most effective if given within 8 hours of overdose.




## Objectives

- *Clinical*
  - To investigate a novel dosing regimen for the immediate administration of an IV NAC infusion, on admission of a patient post-overdose, using a lower infusion rate.
- *Population analysis*
  - To show the utility of a model from a prior population analysis to assess clinical rationale for a chosen dosing regimen.

## Methods

- *Clinical trial simulation*
  - This was used to explore the concentration-time profiles of different NAC dosing regimens including the conventional regimen.
  - Using a published 3-compartment pharmacokinetic model of NAC[2] we simulated 1000 virtual patients in MATLAB to find a new dosing regimen that is started without delay where:

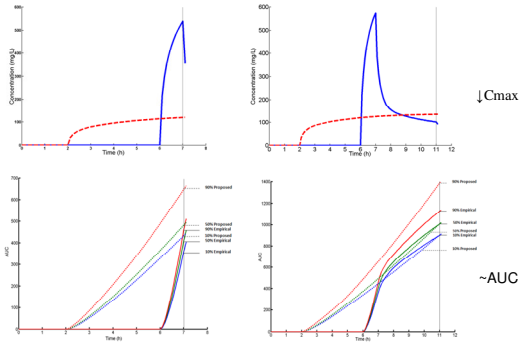
$$\Pr(\text{AUC}|\text{new} \geq \text{AUC}|\text{current}) = 0.9$$

  - We assumed that the:
    - AUC of the concentration-time profile of NAC equates to the effectiveness (based on irreversible binding).[1]
    - Cmax drives the risk of adverse effects (clinical evidence shows adverse effects mostly occur during the first high dose rate infusion and these can be ameliorated by reducing the infusion rate).[3,4]
  - *Hypothetical scenario*
    - The patient arrives 2 hours post-overdose.
    - At 4 hours post-overdose the blood sample is collected.
    - At 6 hours post-overdose the plasma paracetamol concentration is available and the conventional regimen is initiated.

## Results

- *Novel regimen for the hypothetical scenario*
  - An initial infusion rate of 110 mg/kg for 5 hours (22.0 mg/kg/h) gave an AUC the same or higher than the AUC of the conventional regimen at the end of the first infusion on 90% of occasions.
  - The initial infusion rate was 203 mg/kg for 9 hours (22.6 mg/kg/h) when matched to the end of the second infusion.
  - From this a NAC infusion of 23 mg/kg/h can be instigated immediately on presentation of a patient post-overdose, this can be continued for up to 9 hours and then the patient is transferred to the 6.25 mg/kg/h infusion (the third phase of the conventional regimen).
    - For a 70 kg adult this equates to 14 g over 9 hours followed by 7 g over 16 hours.
    - If the plasma paracetamol concentration, when available, is below the critical treatment value on the nomogram treatment is stopped.

| | | End of first infusion | | | End of second infusion | | |
|---|---|---|---|---|---|---|---|
| | | Phase 1 | Phase 2 | Phase3 | Phase 1 | Phase 2 | Phase3 |
| Conventional Regimen | | 150 mg/kg (over 1h) 150 mg/kg/h | 50 mg/kg (over 4h) 12.5 mg/kg/h | 100 mg/kg (over 16h) 6.25 mg/kg/h | 150 mg/kg (over 1h) 150 mg/kg/h | 50 mg/kg (over 4h) 12.5 mg/kg/h | 100 mg/kg (over 16h) 6.25 mg/kg/h |
| Proposed Regimen | /kg | 110 mg/kg (over 5h) 22 mg/kg/h | 50 mg/kg (over 4h) 12.5 mg/kg/h | 100 mg/kg (over 16h) 6.25 mg/kg/h | 203 mg/kg (over 9h) 22.6 mg/kg/h | | 100 mg/kg (over 16h) 6.25 mg/kg/h |
| | 70 kg | 7680 mg (over 5h) | | | 14 210 mg (over 9h) | | |




Concentration versus time graphs (upper) with the conventional regimen (blue) and the novel regimen (red), and AUC versus time graphs (lower) with the conventional regimen (solid lines) and the novel regimen (dashed lines); where the AUC is matched to the end of the first infusion (left) or the end of the second infusion (right).

## Discussion

- The novel regimen:
  - Does not have a delay before treatment is initiated.
  - Should be as effective as the conventional regimen (↔AUC).[1]
  - Should have less adverse side effects (↓Cmax).[3,4]
    - Less rash, urticaria, angioedema, bronchospasm, tachycardia, or anaphylaxis.
  - Has the potential to be less prone to dosing errors.

## Conclusions

- Based on simulations, a dosing regimen of 200 mg/kg over 9 hours (23 mg/kg/h) followed by the third phase of the conventional regimen, 100mg/kg over 16 hours (6.25 mg/kg/h), could be used.
- This methodology identified a novel dosing regimen that should be as effective but simpler and potentially safer than the conventional regimen.

## References


1. Heard K. New England Journal of Medicine 2008; 359(3): 285.
2. Brown M, *et al.* European Journal of Clinical Pharmacology 2004; 60(10): 717-723.
3. Sandilands EA, Bateman DN. Clinical Toxicology 2009; 47(2): 81-88.
4. Bailey B, McGuigan MA. Annals of Emergency Medicine 1998; 31(6): 710-715.