Pharmacokinetik modelling of a high dose acetylcysteine regimen based on the SNAP trial

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Metabolism and Toxicity of Paracetamol

bioactivation $\xrightarrow{P\ 450} N\text{APQI}$

$\text{NCH}_2\text{OCH}_3$

$\text{OH}$

$\text{NCOCH}_3$

$\xrightarrow{\text{detoxification}} \text{GLUCURONIDE SULPHATE}$

overdose $\xrightarrow{\text{Covalent binding}} \Rightarrow \text{Toxicity}$

GSH

SG
ALI by paracetamol concentration at presentation

Cairney et al. 2016
Cmax: 554mg/L (304-875)

Vd: 536 +/- 210 mL/kg

T1/2: 5.7 +/- 2.9 h

The dosage regimen was chosen on an arbitrary basis.

This regimen has not been changed and, although very effective, it is most unlikely to be optimal.

The patients in this study with the lowest Cmax fared just as well as those with the highest
100 mg/kg over 2 hours
200 mg/kg over 10 hours

Monte Carlo simulation

Estimated NAC concentrations with modified 12 hour regimen

NAC concentration (mg/L)

Time/ hours

0 1 2 3 4 5 6 7 8 9 10 11 12

mean 95th centile 5th centile
Anaphylactoid reactions - time to 1st use of rescue medication. Kaplan Meier analysis.

3-compartmental PK model

- 3-compartment PK model

- Simulate NAC concentrations
  - Current NAC regimen: 150mg/kg over 1h, 50mg/kg over 4h, 100mg/kg over 16h
  - 12h SNAP regimen: 100mg/kg over 2h, 200mg/kg over 10h
  - 12h SNAP regimen, 2h break, then further 200mg/kg over 10h
  - 22h SNAP regimen, 100mg/kg over 2h, 400mg/kg over 20h
SNAP regimen: volunteers (n=12) (.) and patient (n=10) (.) samples

Courtesy of: N.Bateman, E.Sandilands, M.Eddleston
PK-PD model following 22g overdose

Kerr 21h

SNAP 12h

SNAP 22h
**High dose IV NAC**

- 140 mg/kg loading followed by 70mg/kg 4hrly for 48 hours
- Total 980 mg/kg
- Well tolerated  28.9% (mainly N&V, flushing), none serious
- ALT>1000
  - 6/91 (6.6%) treated within 10h
  - 24/154 (15.6%) treated within 10-16h
  - 26/64 (40.6%) treated >16h
- 1 death

Smilkstein 1991(n=223); full report Heard 2014(n=309)
Patient need NAC as per current indications

12h SNAP NAC protocol

No more NAC if:
INR 1.3 or less AND ALT less than 100 U/L AND ALT not more than double the admission measurement AND paracetamol concentration less than 20 mg/L

12h bloods

No NAC OR Further 10h 200mg/kg bag

20h bloods

Discharge if:
the INR is less than 1.3 AND the ALT is less than doubled from admission AND the ALT is less than 100 U/L.
Paracetamol poisoning requiring acetylcysteine (as per TOXBASE)

Treat with 12h SNAP protocol

Post SNAP bloods*

≥ 24h after most recent paracetamol intake

24h after most recent paracetamol intake

Timing uncertain

≥24h after paracetamol intake or ambulance call or time of hospital arrival

Repeat post SNAP bloods*

ALT > 2x ULN OR
ALT doubled from admission OR
INR > 1.3 + ALT > ULN OR
Paracetamol > 10

Further acetylcysteine (200 mg/kg over 10 h)

Post SNAP bloods*

INR > 1.3 + ALT > 2x ULN OR
INR > 1.3 AND rising from previous value OR
INR > 3.0

<24h after most recent paracetamol intake

ALT > 2x ULN OR
ALT doubled from admission OR
INR > 1.3 + ALT > ULN OR
Paracetamol > 20

Medically fit for discharge

NO

YES

NO

YES

NO

YES

NO

YES

NO

YES

NO

YES
Conclusions

• PK and PK-PD modelling used to optimise NAC regimen
  – Reduce adverse reactions
  – Provide increased dose of NAC for those at highest risk
    large overdoses leading to persistent paracetamol concentrations 12h post NAC
    early hepatotoxicity
  – Reduce duration of treatment and hospitalisation in those at low risk.

• Strategy needs further evaluation
  – Edinburgh, Newcastle and London
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