287. Mathematical modelling of the effect of a high dose acetylcysteine regimen based on the SNAP trial on hepatic glutathione regeneration and hepatocyte death

Harry K. R. Thanacoody[a], Frederik H. Nijhout[b], Michael C. Reed[c] and Simon H. L. Thomas[a]

[a]Medical Toxicology Centre, Newcastle University, Newcastle-upon-Tyne, UK; [b]Department of Biology, Duke University, Durham, NC, USA; [c]Department of Mathematics, Duke University, Durham, NC, USA

Objective: A novel acetylcysteine ("SNAP") regimen (100 mg/kg over 2 h then 200 mg/kg over 10 h) causes fewer adverse reactions.[1] Although likely to be effective in most patients, more prolonged therapy will be needed in those with substantial paracetamol overdose.[2] This could be achieved by administration of a further 200 mg/kg infusion over 10 hours (total 500 mg/kg over 22 hours). We aimed to compare the effect on hepatic glutathione regeneration and hepatocyte death of this extended 22 hour SNAP regimen with the standard 12 hour SNAP regimen and the current UK acetylcysteine regimen (150 mg/kg over 1 hour, 50 mg/kg over 4 hours then 100 mg/kg over 16 hours, total 300 mg/kg over 21 hours). **Methods**: A published mathematical model integrating a model of paracetamol transport and metabolism with a model of glutathione metabolism [3] was used to simulate the effects of acetylcysteine on glutathione regeneration and functional hepatocyte numbers. These were compared between the three regimens evaluated. **Results**: Hepatic glutathione regeneration was predicted to occur earlier and the nadir of functional hepatocytes was predicted to be higher with the 22 hour extended SNAP regimens compared to the currently used and 12 hour SNAP regimens. Hepatic glutathione generation occurred latest and the nadir of functional hepatocytes was lowest with the 12 hour SNAP trial regimen. However, the nadir of functional hepatocytes exceeded 40% with all three regimens suggesting that they were all effective in preventing hepatic failure which is generally associated with 20–30% hepatocyte function. **Conclusion**: Although most patients at lower risk will be treated effectively by the 12 hour SNAP regimen, those with more substantial overdose will require higher dose and more prolonged therapy. This can be achieved by repeating the 10 hour (200 mg/kg) infusion in those at risk, e.g. those with persisting plasma paracetamol concentrations or evolving liver function abnormalities after the initial 12 hour regimen. Further studies are required to evaluate the clinical efficacy of this approach.

References

[1] Bateman DN, Dear JW, Thanacoody HKR, et al. Reduction of adverse effects from intravenous acetylcysteine treatment for paracetamol poisoning: a randomized controlled trial. Lancet. 2014;383:697–704.

[2] Bateman DN, Dear JW, Thanacoody HKR, et al. Treatment of paracetamol overdose - authors' reply. Lancet. 2014;383:1383.

[3] Ben-Shachar R, Chen Y, Luo S, et al. The biochemistry of acetaminophen hepatotoxicity and rescue: a mathematical model. Theor Biol Med Model. 2012;9:55.