Scottish and Newcastle Anti-emetic Pre-treatment for Paracetamol Poisoning Study (SNAP)

A randomised trial to assess the effectiveness of pre-treatment with ondansetron at reducing nausea and vomiting in patients treated with either the conventional regimen or a modified regimen of acetylcysteine for paracetamol poisoning

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Funder	Chief Scientist Office
Co-sponsors	University of Edinburgh and NHS Lothian
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REC	10/MRE00/20
Background	Paracetamol is the commonest poison seen in the United Kingdom and is present in approximately 40% of patients admitted with self harm. Current treatment involves use of the antidote acetylcysteine in patients deemed at risk of potential liver damage, given by intravenous infusion over a period of 20.25 hours. This regimen was designed in the 1970s and is empirical, in that a large loading dose of the antidote is administered followed by 2 decreasing concentrations. It is cumbersome to calculate and dilute within the ward and therefore subject to error in preparation. The initial infusion is associated with a significant rate of adverse reactions, in particular nausea and vomiting and anaphylactoid reactions. The latter are particularly troublesome and occur in up to 15% of patients treated. Therapy is discontinued and there is often confusion as to whether it can be restarted in a timely manner. Studying antidotes in the management of poisoning is challenging not least because of the patient population and of the limited time available to make decisions and gain consent. This will be the first major clinical trial of antidote therapy in this poisoning in the UK in 30 years.
Design	2x2 factorial design to investigate pre-treatment with anti-emetic (ondansetron) compared to placebo versus conventional 20.25h compared to modified 12h acetylcysteine regimen
Participants	200 patients presenting with paracetamol overdose and requiring treatment with acetylcysteine.
Consent	Where patients are assessed to have capacity to give informed consent, written informed consent or witnessed verbal informed consent will be obtained. Where patients lack capacity, considered to be of a temporary nature, consent will be sought from a legal representative. Retrospective consent will then be sought from the patient when capacity is recovered.
Sites	UK National Poisons Information Service (NPIS) clinical toxicology units and allied Emergency Departments and Acute Medical Assessment Units (Edinburgh and Newcastle upon-Tyne)
Primary objective	Determine whether pre-treatment with intravenous ondansetron 4 mg will reduce the occurrence of vomiting and retching in paracetamol poisoned patients receiving intravenous acetylcysteine.
Secondary objectives	• Determine whether pre-treatment with intravenous ondansetron 4 mg will reduce the occurrence of nausea in paracetamol poisoned patients receiving intravenous acetylcysteine. • Compare the incidence of nausea or vomiting in the modified and conventional acetylcysteine regimens in paracetamol poisoned patients.

Primary endpoint	The proportion of patients who do not vomit or retch within 2 hours of initiation of acetylcysteine treatment and no use of rescue medication. Retching will be defined as a vomit not producing any liquid.
Secondary endpoint	Nausea or vomiting/retching within 12h of initiation of acetylcysteine treatment. Nausea severity will be assessed using an 11–point, whole-number, categorical Likert scale, with 0 representing "no nausea" and 10 representing nausea "as bad as it can possibly be." (White et al 200630; Diemunsch et al 200731) A score of 0-4 will represent good control of nausea. (Diemunsch et al 200731). Vomiting/retching will be recorded objectively by nursing staff as present or absent.

	Pre dose (admission)	**0**	**15min**	**2h**	**4h**	**12h**	**End of infusion (~20.25h)**	**Discharge**
Assess eligibility criteria	X							
Consent (1)	X							
Randomisation	X							
Questionnaire (2)		X		X		X		
Bloods								
Paracetamol concentration levels	X					X	X	
INR	X					X	X	
ALT	X					X	X	
Bilirubin	X					X	X	
ALP	X					X	X	
GGT	X					X	X	
Urea	X					X	X	
Creatinine	X					X	X	
Hb	X					X	X	
MCV	X					X	X	
WBC	X					X	X	
Inflammatory markers (3)		X		X		X	X	
Acetylcysteine levels (4)							X	
Substudy acetylcysteine levels (5)		X		X				
Treatment								
Treatment 1/2 (6)		X						
Conventional modified acetylcysteine (7)		X	X	X	X	X	X	
BP and P		X	X	X	X	X	X	
AE reporting		X	X	X	X	X	X	X

Notes

1. See consent process for further details
2. 11-point Likert scale assessing following symptoms: feeling sick, feeling flushed, itchy skin, skin rash, chest pain, headache, feeling breathless, feeling wheezy, tongue/lip swelling – assessor to measure vomiting/retching after direct questioning.
3. RNA sample and protein sample, taken in **all** patients where practical at 0h, 12h and 20.25 and also 2 h (if applicable) in sub study patients
4. To be taken in convenience sample
5. To be conducted on **sub study only**: convenience sample of 40 patients (20 in conventional arm and 20 in modified arm)
6. Ondansetron or placebo
7. Conventional dose acetylcysteine: 150 mg/kg over 15 mins
   50 mg/kg over 4 hours
   100 mg/kg over 16 hours

   Modified acetylcysteine: 100 mg/kg over 2 hours
   200 mg/kg over 10 hours
   5% glucose (dextrose) over 8 hours