New guidelines to improve outcomes in paracetamol poisoning-Have we got the NAC yet?

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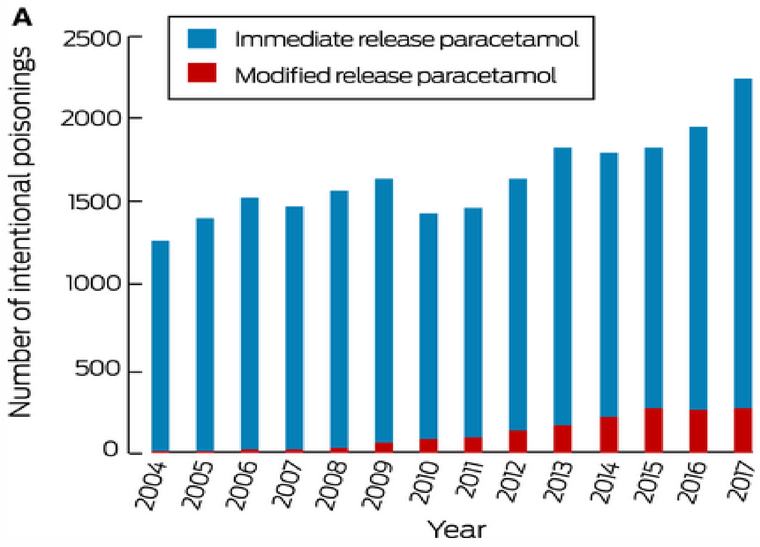
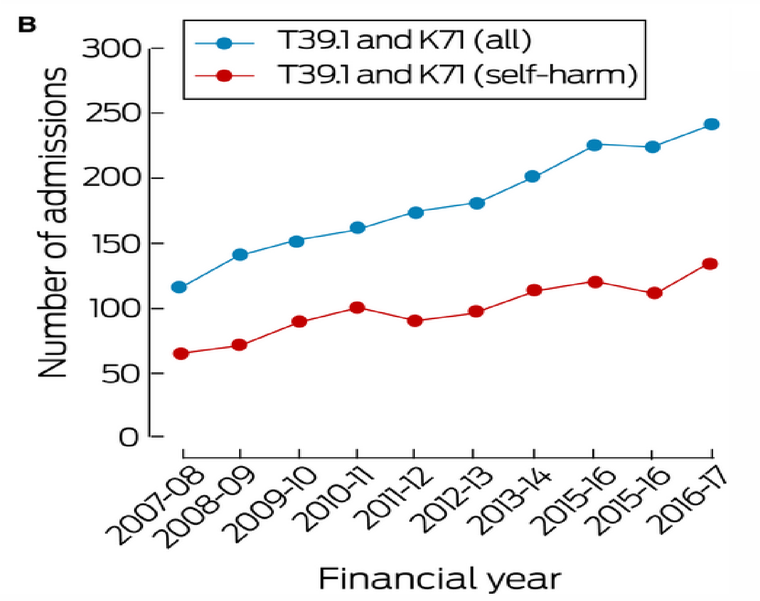
Background

- Paracetamol overdose, hospital admissions and liver injury have increased in Australia since 2004[1]
- Modified release (MR) paracetamol overdoses have erratic and unpredictable absorption. Using the standard paracetamol nomogram for MR paracetamol poisoning does not predict risk and current treatment strategies do not always prevent hepatotoxicity.
- Paracetamol poisoning is treated with IV N-acetylcysteine (NAC). The complex three-bag infusion is associated with frequent adverse reactions, dosing errors and interruption to treatment.
- The NAC regimen has remained essentially unchanged since the 1970's. Increasing evidence of treatment failures with this traditional regimen, particularly for MR paracetamol and "massive" (>35g) overdoses, drove the need for an update of current guidelines to improve management[3,4].
- The biggest early challenge faced by NSW Poisons information Centre (NSW PIC) is to disseminate change and convert users to these new recommendations.

A. Intentional overdose exposures with single ingredient paracetamol products, 2004–2017



B. Hospital admissions of patients with paracetamol poisoning and toxic liver disease, 2007–08 to 2016–17



Source: Paracetamol poisoning-related hospital admissions and deaths in Australia, 2004–2017[1]

Description

Traditional 3-bag NAC[6]

150mg/kg over 15-60 min (200mL) → 50mg/kg over 4 h (500mL) → 100mg/kg over 16 h (1L)

- Associated with GIT reactions (nausea & vomiting) and non- allergic anaphylactic reactions (NAARs) in 14% to 75% of patients[2]

Updated 2-bag NAC (currently used by hospitals affiliated with toxicology units)

200mg/kg over 4 h (500mL) → 100mg/kg over 16 h (1L)

- Lower rates of total NAARs (4.3% vs. 10%) and significantly less severe NAARs (0.5% vs.1.8%) with the two-bag NAC infusion compared to the three-bag infusion, but similar rate of GIT reactions [2]

The cohort study "ATOM-2"[3] examined paracetamol overdoses over 40g (median ingestion 50g); 14% of the 200 patients developed hepato-toxicity despite treatment with NAC. This was still 11% for those treated within 16 hours, if they were given standard NAC and no charcoal. Only 5% of such patients given activated charcoal (AC) and/or receiving doubled dose instead of a 100mg/kg/16hr NAC bag had hepatotoxicity.

The cohort study "ATOM-3"[4] examined MR paracetamol overdoses with a median ingestion of 30g; 18% of the 116 patients developed hepatotoxicity despite treatment with AC and NAC (including 5% treated within 8 hours and 58% treated with prolonged NAC)

Action

- NSW Poisons information Centre has been involved in recruiting for Australian Toxicology Monitoring (ATOM) studies for paracetamol.
- These studies have supported the convening of an expert group to discuss changes to current guidelines published in 2015[5]. The updated paracetamol guidelines is expected to be published in MJA November 2019 and Therapeutic Guidelines in 2020 to include new recommendations and NSW PIC will be referring users to these.
- NSW PIC will be recommending the use of two-bag NAC and support users to convert over from the current three-bag NAC. NSW PIC will continue to provide advice to ensure changes to indications, the dose and duration of treatment are implemented.
- Data on paracetamol related hospital admissions and deaths in Australia[1] has been published and NSW PIC has recommended the Therapeutic Goods Administration limit OTC access and reduce large pack sizes of immediate release and MR paracetamol.

Major changes in Management of Paracetamol overdose

- Initial paracetamol level should include checking LFTs
- 2-bag NAC infusion regimen recommended
- "Massive" overdoses resulting in paracetamol level above double the nomogram line to receive increased doses of NAC
- All toxic MR paracetamol ingestions (≥ 10g or 200mg/kg whichever is less) should receive a full course of NAC, and ingestions ≥30g or 500mg/kg should receive increased doses of NAC

Evaluation Plan

- The updated guidelines have adopted a conservative strategy, and now recommend activated charcoal and NAC for all patients with a MR paracetamol overdose
- Implementation and evaluation of these new guidelines to support the evidence-base is required. ATOM-6 is currently evaluating effectiveness of new treatment recommendations for MR paracetamol.
- NSW PIC will be reviewing which NAC regimen hospitals are using once the new MJA guidelines are published as well as evaluating uptake of changes to guidelines in an attempt to convert non users to two-bag NAC and to assess the best dissemination plan for future changes.

Implementation

- Current paracetamol overdose guidelines[5] (and imminently the updated guidelines) and links to the two-bag NAC recommendations from Austin Health and Sydney's Children's hospital are available on the Emergency Care Institute website https://www.aci.health.nsw.gov.au/networks/eci/clinical/clinical-resources/clinical-tools/toxicology/paracetamol
- The new Therapeutic Guidelines, Toxicology and Toxinology version 3 will align with new recommendations
- An updated Paracetamol overdose treatment poster for Emergency Departments has been prepared
- NSW PIC have already implemented these changes to our current advice.

Further Information

1. Cairns R, Brown JA, Wylie C etal ,2019, Paracetamol poisoning-related hospital admissions and deaths in Australia, 2004–2017 Med J Aust; 211 (5): 218-223.
2. Wong A, Graudins A. 2016 ,Simplification of the standard three-bag intravenous acetylcysteine regimen for paracetamol poisoning results in a lower incidence of adverse drug reactions. Clin Tox; 54:2, 115-119.
3. Chiew AL, Isbister GK, Page CB, et al, 2017, Massive paracetamol overdose: an observational study of the effect of activated charcoal and increased acetylcysteine dose. (ATOM-2) Clin Tox ;Dec;55(10):1055-1065.
4. Chiew AL, Isbister GK, Page CB, et al , 2018, Modified release paracetamol overdose: a prospective observational study (ATOM-3). Clin Tox; 56: 810–819.
5. Chiew AL, Fountain JS, Graudins A, Isbister GK, Reith D and Buckley NA , 2015, Guidelines for the management of paracetamol poisoning in Australia and New Zealand — explanation and elaboration Med J Aust; 203 (5): 215-218.
6. DBL Acetylcysteine injection Product Information ,available from www.tga.gov.au. Accessed 10/10/2019

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