Accuracy of the paracetamol-aminotransferase product to predict hepatotoxicity in paracetamol overdose treated with a 2-bag acetylcysteine regimen


Introduction
Paracetamol concentration is a highly accurate risk predictor for hepatotoxicity following overdose with known time of ingestion. However, the paracetamol-aminotransferase multiplication product can be used as a risk predictor independent of timing or ingestion type. Validated in patients treated with the traditional, "three-bag" intravenous acetylcysteine regimen, we evaluated the accuracy of the multiplication product in paracetamol overdose treated with a two-bag acetylcysteine regimen.

Methods
We examined consecutive patients treated with the two-bag regimen from five emergency departments over a two-year period. We assessed the predictive accuracy of initial multiplication product for the primary outcome of hepatotoxicity (peak alanine aminotransferase \( \geq 1000 \text{IU/L} \)), as well as for acute liver injury (ALI), defined peak alanine aminotransferase \( 2\times \) baseline and above 50IU/L).
Results
Of 447 paracetamol overdoses treated with the two-bag acetylcysteine regimen, 32 (7%) developed hepatotoxicity and 73 (16%) ALI. The pre-specified cut-off points of 1500 mg/L × IU/L (sensitivity 100% [95% CI 82%, 100%], specificity 62% [56%, 67%]) and 10,000 mg/L × IU/L (sensitivity 70% [47%, 87%], specificity of 97% [95%, 99%]) were highly accurate for predicting hepatotoxicity. There were few cases of hepatotoxicity irrespective of the product when acetylcysteine was administered within eight hours of overdose, when the product was largely determined by a high paracetamol concentration but normal aminotransferase.

Conclusions
The multiplication product accurately predicts hepatotoxicity when using a two-bag acetylcysteine regimen, especially in patients treated more than eight hours post-overdose. Further studies are needed to assess the product as a method to adjust for exposure severity when testing efficacy of modified acetylcysteine regimens.

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Analysis of an 8-hour acetylcysteine infusion protocol for repeated supratherapeutic ingestion (RSTI) of paracetamol

Objectives
In Australia, the treatment guideline for patients with repeated supratherapeutic ingestion (RSTI) of paracetamol recommends an abbreviated acetylcysteine regimen if the paracetamol concentration is low (<10 mg/L) and alanine aminotransferase (ALT) is normal or static after 8 hours of infusion. There are currently no studies of this recommendation.

Method
A retrospective review of paracetamol overdose presentations from October 2009 to August 2016 in two hospital toxicology networks was performed. All cases of RSTI treated with acetylcysteine were extracted.

Results
Of the 2249 paracetamol overdose presentations, 91 cases of RSTI were treated with acetylcysteine. Median time to initial blood tests was 6 hours post-last paracetamol dose (IQR 4–6). Sixty-three (69%) presentations had an initial detectable paracetamol concentration, median 30 mg/L (IQR 18–60). Median ALT on presentation was 48 IU/L (IQR 18–109). After 8 hours of acetylcysteine infusion, median ALT was 34 IU/L (IQR 16–71) in those receiving abbreviated treatment and 74 IU/L (IQR 40–231) in those continuing acetylcysteine. Thirty-nine presentations (43%) had an abbreviated regimen. Nine (10%) patients had an initial ALT ≥50 IU/L and subsequently developed hepatotoxicity (ALT >1000 IU/L). No patients with an initial ALT <50 IU/L developed hepatotoxicity. Median duration of acetylcysteine infusion for those receiving a non-abbreviated regimen was 20 hours (IQR 20–25) vs. 10.4 hours (IQR 4.8–12.0) who received an abbreviated regimen. There were no re-presentations with hepatotoxicity.

Conclusions
An 8-hour acetylcysteine infusion regimen for treatment of paracetamol RSTI may be safe and is likely to reduce length of stay for patients at low risk of hepatotoxicity. Larger prospective studies are needed to examine the efficacy of this abbreviated acetylcysteine protocol.

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Increased acetaminophen related calls to Finnish PIC better reflect acetaminophen sales than serious poisonings

Objective
Acetaminophen (APAP) or paracetamol is a commonly encountered medicine in poisonings. We studied the changes in APAP related calls to the Finnish poison information centre (FPIC), and serious intoxications, involving hepatotoxicity or death in 2001–2014. These data were compared with paracetamol sales in Finland.

Methods
This is a retrospective analysis of the FPIC database calls, national cause of death registry, registries of liver transplantations and molecular adsorbent recycling system (MARS)-treated patients from Helsinki University Hospital together with the National Institute of Health and Welfare registry of patients hospitalized. Data on APAP sales were obtained from the Finnish Medicines Agency.

Results
Between 2001 and 2014, the number of calls/year related to human APAP exposures to the FPIC increased from 227 to 1058. No change in the age distribution of enquiries was seen. Most calls involved minors: 58% (range 52–64%) for children under 6 years old, and 9% (range 6–14%) for children of 6–15 years. In Finland, APAP related fatalities have gradually increased from an average of 7/year (range 4–10) in 2000–2005 to an average of 11/year (range 6–17) in 2010–2013, whereas the number of liver transplantations remained low, average 0.6/year (range 0–2). For patients in need of MARS-treatment, a slight decrease was seen. Total APAP sales increased from 5.6 (47% prescription, 53% OTC) to 29.7 (81% prescription, 19% OTC). DDD/1000 inhabitants/day from 2001 to 2014 is recorded. Best linear relationship (R² = 0.97; p < .001) was observed between total FPIC calls and total sales of APAP in 2001-2014. Fatalities show a weaker relationship with sales (R² = 0.317; p = .045).

Conclusions
During the study period, we see an increase in FPIC exposure calls accompanied by an increase in APAP sales. Changes in the chosen indicators for serious poisonings show only a weak association. Despite an evident trend between sales and fatalities, the correlation with fatality remains weak due to the small number of fatalities.

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Retrospective review of SGLT2 inhibitor exposures reported to 13 poison centers

Background
SGLT2 inhibitors are a new class of oral antidiabetics prescribed in the United States since 2013. They act by inhibiting reabsorption of glucose in the proximal convoluted tubule of the kidney, allowing excess glucose to be excreted. Little has been reported regarding effects of non-therapeutic exposure to this class of medication.

Methods
Retrospective records from 13 poison centers were examined for human exposures to SGLT2 inhibitors between 1st January 2013 and 31st December 2016. Exclusion criteria
included multi-substance exposures and exposures without any follow-up call. Data examined included patient age, chronicity of exposure, clinical effects, management site, treatments administered, duration of follow-up, and outcome.

**Results**

Eighty-eight cases met inclusion criteria. Patient age ranged from 1 to 75 years; 49 were evaluated in a health care facility with 18 admissions. No symptoms developed in 80 (91%) patients, 6 (7%) developed minor symptoms, and 2 (2%) developed moderate symptoms. Hypoglycemia was not observed. Mean time to final follow-up was 9.3 h, ranging from 1 to 42 h; median was 6 h. Of the two patients who developed moderate symptoms, one was a 65 year old male who developed metabolic acidosis and hypokalemia while taking canagliflozin therapeutically; the other a 43-year-old female who developed tachycardia and mild hypertension following the intentional ingestion of 6000 mg of canagliflozin.

**Discussions**

The number of patients evaluated in a health care facility is most likely reflective of a cautious approach to dealing with a new class of drug. Exposures were generally well-tolerated and managed with minimal intervention.

**Conclusions**

In this retrospective series, acute ingestions of SGLT2 inhibitors were well-tolerated with no hypoglycemia and only minor effects. For young children with unintentional ingestions, a reasonable approach to home management would include at least one follow-up for signs and symptoms of possible toxicity including mental status changes, polyuria, or tachypnea.

Full text available from: [http://dx.doi.org/10.1080/15563650.2017.1357824](http://dx.doi.org/10.1080/15563650.2017.1357824)

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**Recreational drug use at a major music festival: trend analysis of anonymised pooled urine**


**Objective**

The spread of new psychoactive substances (NPS) has expanded rapidly in the last decade. The complexity of the pharmacological effects of NPS challenges the traditional treatment guidelines, and information of the emergence of new arrivals is valuable. Our knowledge on the actual range of recreational drugs used and NPS available in Denmark is limited as identification is possible only when consumers become patients in the healthcare system or through drug seizures. We aimed to detect classical recreational drugs and NPS in the urine of music festival attendees and evaluate if the use of NPS could have been predicted by comparing study data with drug seizure data from the previous year published by European and Danish health authorities.

**Methods**

In a cross-sectional study, 44 urine samples were collected from three urinals at Roskilde Festival 2016—the largest Danish music festival. Two urinals were placed at music stages with late-night concerts, and one urinal was placed at a camp site. Samples were prepared using enzymatic hydrolysis followed by cationic and anionic solid phase extraction, and analysed using ultra performance liquid chromatography-high-resolution time-of-flight mass spectrometry (UPLC-HR-TOF-MS). Data were processed using an in-house library of 467 target substances, including legal and illegal drugs and metabolites. Urine drug-screening immunoassays were also evaluated and results were compared to UPLC-HR-TOF-MS results.
Results
In total, 77 drugs, including metabolites, were qualitatively identified in the 44 urine samples. The recreational drugs identified were amphetamine (n = 30), cocaine (n = 44), MDA (n = 40), MDMA (n = 44), THC-COOH (n = 19) and ketamine (n = 17). No NPS were identified. Sample testing using the urine drug-screening immunoassays showed presence of cocaine (n = 27), methamphetamine/MDMA (n = 4), THC (n = 7), "Spice" (n = 7) and methylphenidate (n = 1). These discrepancies might be caused by differences in cut-off values between the analytical methods, limited specificity or cross-reactivity of the urine drug-screening immunoassays compared to UPLC-HR-TOFMS results.

Conclusion
Widespread uses of classical recreational drugs were identified in pooled urine samples. The prevalence of NPS was not as comprehensive as expected based on the European and Danish health authorities reports on illegal drugs. Urine drug-screening immunoassays results are advised to be confirmed by chromatographic bioanalysis.

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Can elevated lactate and LDH produce a false positive enzymatic ethanol result in live patients presenting to the emergency department?

Background
There have been allegations in the courtroom that elevated serum lactic acid in trauma victims can yield a falsely elevated serum ethanol assay. Most hospitals utilize an indirect method of ethanol measurement where a serum sample is added to a mix of alcohol dehydrogenase and oxidized nicotinamide adenine dinucleotide (NAD+). This allows any ethanol in the patient's serum to be metabolized to acetaldehyde, and in the process results in the reduction of NAD+ to NADH. NADH is then measured using spectrophotometry. The courtroom allegation stems from the concept that oxidation of lactate to pyruvate by lactate dehydrogenase (LDH) results in the same molar-for-molar reduction of NAD+ to NADH, and could therefore theoretically cause patients with elevated lactate and LDH to have a falsely elevated ethanol concentration.

Methods
Patients with elevated lactic acid and LDH concentrations who presented to a university hospital from 20 April 2015 to 13 December 2015 were identified to provide possible test specimens. If a sufficient amount of serum was available, the sample was used to re-run the lactate and LDH concentration simultaneously with an enzymatic ethanol assay. Any samples that had elevated lactic acid and LDH concentrations on this retesting, and also yielded a positive ethanol concentration, were sent for confirmatory gas chromatography testing of ethanol concentrations. A control group of 20 samples with normal lactate and LDH were included.

Results
A total of 37 samples were included in the final analysis. Only 4 patients had an elevated enzymatic ethanol concentration, and all 4 also had a measurable GC ethanol concentration. The lactate in this dataset ranged from 2.4 to 24.2 mmol/L, with a mean of 6.53 mmol/L (normal value 0.5–2.2). The LDH ranged from 242 to 8838 U/L with a mean of 1695 U/L (normal value 122–225 U/L). Twenty control samples were run on patients with normal lactate and LDH, none of which yielded a positive enzymatic ethanol result.
Conclusions
This data does not support the contention that an elevated LDH and lactate can yield a false positive serum ethanol result as run by enzymatic ethanol assay in live patients presenting to the emergency department.

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Naja atra snakebite in Taiwan

Background
Naja atra snakebite is uncommon in Taiwan and causes distinct effects on its victims. Although the Taiwan government produces its own specific antivenom, little information on the management of N. atra snakebite is available.

Materials and methods
We retrospectively evaluated 183 patients admitted to two medical centers. Of these, 45 were identified as definite cases of N. atra snakebite, 86 as suspected cases, and 52 as clinical cases. Demographic data, symptomatology, and management were compared between these case groups.

Results
Symptomatology and management were similar in the three groups. Among the 183 patients, 10 (5.5%) were asymptomatic and nine (4.9%) had transient and partial ptosis or body weakness. The principal effects were local tissue swelling and pain in 173 patients (94.5%), followed by clinically suspected wound infection in 148 (80.9%), skin necrosis in 120 (65.6%), necrotizing soft tissue infection in 77 (42.1%), fever in 59 (32.2%), and gastrointestinal effects in 53 (29%). The median total dose of specific antivenom needed to treat N. atra envenoming was 10 vials. In the envenomed patients, debridement was required in 74 patients (42.8%), fasciotomy/fasciectomy in 46 (26.6%), and finger or toe amputation in seven (4%). The first operation was performed at a median of 3.5 days after the bite.

Discussion and conclusions
Based on these typical manifestations, clinical diagnosis of N. atra snakebites may be feasible and practical. In contrast to other snakes of Elapidae family, N. atra bite did not cause serious neurological effects. Early surgical consultation should be obtained because half of the patients underwent surgery due to infectious complications. Acute compartment syndrome was the surgical indication in rare cases; however, overestimation of the incidence may have occurred. This syndrome should be confirmed by serial intracompartmental pressure monitoring instead of only physical examination, and a sufficient dose of antivenom should be given prior to surgical decompression.

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