Articles You Might Have Missed

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Article #1: Pettie JM, Caparrotta TM, Hunter RW, et al. Safety and efficacy of the SNAP 12-h acetylcysteine regimen for the treatment of paracetamol overdose. *EClinicalMedicine* 2019; 11:11–17

Background: Standard protocols for treatment of paracetamol (acetaminophen, APAP) poisoning include administration of 300 mg/kg of n-acetylcysteine (NAC), via three different bag solutions, over a 21-h period. However, this treatment regimen is labor intensive, associated with dosing errors, and can result in adverse drug events (ADEs) such as anaphylactoid reactions. In 2015, a 12-h NAC protocol (Scottish and Newcastle anti-emetic pre-treatment for paracetamol poisoning study; the SNAP regimen) was instituted to administer equivalent total doses (300 mg/kg) of NAC. This regimen had previously been demonstrated to cause fewer ADEs compared with the 21-h protocol.

Research Questions: What is the effectiveness of the 12-h SNAP regimen compared with the standard 21-h NAC regimen for the treatment of APAP poisoning? And, as hypothesized, did the 12-h SNAP regimen perform better in patients presenting > 8 h from ingestion?

Methods: This was a mixed methods study comparing the efficacy of the SNAP and standard 21-h regimens at three hospitals (the Royal Infirmary of Edinburgh, St. Thomas' Hospital and the Royal Victorian Infirmary) in the UK. The study was a prospective cohort study including patients admitted over a 4-year period (2013 to 2017) for APAP toxicity, 2 years before the introduction of the SNAP regimen and 2 years after. Patients received a total of 300 mg/kg of intravenous NAC according to either the standard 21-h protocol (150 mg/kg over 1 h, then 50 mg/kg over 4 h, and followed by 100 mg/kg over 16 h) or the SNAP protocol

(100 mg/kg over 2 h followed by 200 mg/kg over 10 h). The same 21-h and SNAP protocols were utilized at all three study sites, although stop criteria and patient monitoring differed between the Scottish site and two English sites. During the 21-h protocol, repeat blood tests were performed 1 h prior to NAC completion to ensure that liver function, creatinine, and INR values supported stopping NAC. At the end of the SNAP (12-h) protocol, liver function, creatinine, INR, and a repeat APAP level were checked to support stopping NAC. If the SNAP protocol was stopped within 24-h of the ingestions, these same blood tests were performed at the 24-h mark. The NAC treatments were continued (or restarted) for any of the following: ALT > two times the upper limit of normal or doubled from admission, INR > 1.3, or 24-h APAP concentration > 10 mcg/mg.

Data were analyzed from each site separately and were subsequently combined. Rates of hepatotoxicity (as defined by ALT > 1000 U/L) were compared between the protocols. Multivariate logistical regression was performed to assess the strength of association between hepatotoxicity, synthetic dysfunction (as defined by INR > 2.0), a combination of patient variables (including age, gender, weight, dose ingested, and weight-based ingestion), and presentation ALT and INR. Two separate subset analyses were performed to compare NAC protocols regarding acute single-dose ingestions versus staggered ingestions and patients presenting before and after 8 h since ingestion. The Scottish data were analyzed for additional outcomes including hospital readmission at 7 and 30 days due to liver failure, transfer to liver transplant unit, and death (for APAP or otherwise) within 7 or 30 days.

Results: Scottish data: 1075 patients were treated with the 21-h NAC protocol and 1137 with the SNAP regimen. Patients were demographically similar, although more patients in the 21-h NAC group had treatment initiated after 8 h from the time of ingestion and more patients in the SNAP group had staggered APAP ingestions. Hepatotoxicity occurred in 4.4% of patients with 21-h NAC and 3.9% of those treated with SNAP regimen (absolute difference 0.5%; 95% CI, −2.2 to 1.2). The SNAP regimen had an anaphylactoid rate of 1.6%

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compared with 11.8% in the 21-h group (absolute risk reduction (ARR) 10.2%; 95% CI, 8.2 to 12.4).

London and Newcastle Data: 413 patients received the 21-h protocol, and 715 were treated with the SNAP regimen. The rates of hepatotoxicity were 4.1% and 3.1%, respectively (ARR 0.9%; 95% CI, −3.5 to 1.3%). Anaphylactoid reactions occurred in 8.7% of patients treated with the 21-h protocol and 2.7% of those treated with the SNAP regimen (ARR 6.1%; 95% CI, 3.3 to 9.3).

Combined data: Hepatotoxicity occurred in 4.3% of the 21-h patients and 3.6% of the SNAP patients in those receiving the 21-h NAC protocol and SNAP protocols, respectively (absolute difference −0.7%; 95% CI, −2.1 to 0.6). Anaphylactoid reactions occurred in 11% of the 21-h patients compared with 2.0% in the SNAP group (ARR 9%; 95% CI, 7.3 to 10.7). Multivariable logistical regression showed no difference between treatment regimens and the development of hepatotoxicity or synthetic dysfunction in patients with either a single dose or staggered ingestion.

The combined database was then analyzed to evaluate for differences in treatment efficacy based on overdose patterns associated with a higher risk of developing liver injury: staggered overdose and those starting treatment > 8 h after ingestion. Patients starting treatment > 8 h were less likely to develop hepatotoxicity if they received the 21-h protocol compared with the SNAP regimen (absolute difference 3.7%; 95% CI, 0.5 to 7.2). Patients treated for staggered ingestions did better with the SNAP regimen (absolute difference −2.9%; 95% CI, −6.0 to 0.6%). However, all differences were not statistically significant after accounting for baseline characteristics.

Conclusion: The 21-h and SNAP NAC protocols have similar efficacy in managing APAP patients. There were decreased rates of anaphylactoid reactions among patients receiving the SNAP regimen.

Critique: This study represents an extension of the original SNAP data with inclusion of consecutive patients with a wide range of clinical presentations. The ability to decrease length of treatment (and stay) while decreasing ADEs is intriguing. The paper, however, has limitations. The primary outcome was not explicit and involved several subgroup analyses. Power analyses were not performed making it difficult to determine if the regimens were equivalent (or non-inferior) in efficacy. Some other variables were not analyzed, including co-ingestions such as ethanol (which may protect against APAP toxicity via CYP2E1 interference). And while the paper stated similar efficacy for the protocols, there were subsets of patients who appeared to do worse with the 12-h treatment, including those presenting after 8 h. Lastly, since 2012, the UK has used a modified (more conservative) protocol for establishing need for NAC therapy, including a 4-h APAP concentration > 100 mcg/mL at 4 h and patients presenting with staggered ingestions.

Implication for Toxicologists: This paper supports future investigations regarding efficacy of the SNAP (12-h) NAC protocol for APAP toxicity. Once prospectively validated to demonstrate non-inferiority, this regimen may change the current practice pattern for treating some APAP overdoses.

Article #2: Calgar B, Serin S, Yilmaz G, Torun A, Parlak I: The impact of treatment with continuous positive airway pressure on acute carbon monoxide poisoning. *Prehospital & Disaster Med* 2019; 34(6): 588–591

Background: The mainstay of treatment in carbon monoxide (CO) poisoning is supplemental, normobaric oxygen via a non-rebreather mask (NRB) or hyperbaric oxygen (HBO) therapy. Although HBO significantly reduces CO elimination half-life, and has debatable benefits in terms of reducing delayed neurological sequelae, it is not easily accessible in many regions. Continuous positive airway pressure (CPAP), by comparison, is readily available in many healthcare facilities and may be beneficial for CO poisoning.

Research Questions: Can CPAP therapy reduce carboxyhemoglobin (COHb) percentages faster than oxygen via NRB? Additionally, can CPAP provide a more rapid reduction of CO poisoning symptoms compared with NRB?

Methods: This was a prospective study of patients presenting with CO poisoning as defined as an arterial blood gas with COHb > 10%. Patients were randomized into two treatment arms: group 1 (NRB group, $n = 40$) received oxygen at FiO₂ 1.0 via 15 L/min NRB at room temperature, and group 2 (CPAP group, $n = 37$) received FiO₂ 1.0 oxygen at 12 cm H₂O via oronasal CPAP mask. Both groups were treated for at least 30 min. Exclusion criteria included age < 18 years, pregnancy, unstable vital signs, GCS < 15 or history of somnolence, syncope, seizure, chest pain, or shortness of breath.

Primary outcomes included COHb percentages and report of severity of headache, nausea, dizziness, and weakness (on a 10-point Likert scale) at time zero and 30 min. The change in scores within groups was tested for statistical significance via Wilcoxon signed-rank test. Differences in COHb percentage and symptoms between NRB and CPAP groups were compared using Pearson Chi-square test.

Results: A total of 80 patients were enrolled, but three CPAP patients were excluded due to inability to tolerate the mask. There were statistically significant differences in the reduction of (interquartile range; IQR) COHb fractions over 30 min: 19 to 14% (6% change) for group 1 (NRB) and 22 to 9% (13% change) for CPAP group. The symptomatic (Likert) severity score for headache between the NRB and CPAP groups was also statistically significant: initially 8 for both groups, reduced by 2 for group 1, and 5 for group 2. Both groups saw a decrease in self-reported severity of nausea and dizziness but without statistical significance.

Conclusion: CPAP reduced COHb percentages nearly twice as fast as NRB; CPAP had a COHb half-life similar to

HBO (15–30 min). Subjective headache improved more with CPAP, but there were no differences in reports of nausea, dizziness, and weakness.

Critique: This study followed a small number of patients for a short duration of time. The initial COHb percentages were modestly elevated (group 1 = 19%; group 2 = 22%) and used interquartile range for comparison. The numeric (Likert scale) changes in subjective symptoms were of limited clinical relevance, and delayed symptoms or neurological sequelae were not evaluated. More studies will need to be performed to evaluate the effectiveness of CPAP in preventing delayed neurological sequelae.

Implication for Toxicologists: Non-invasive CPAP appears to be a potentially useful adjunct in the treatment of CO poisoning for selected patients who are alert and cooperative.

Article #3: Sheta AA, El-Banna AS, Elmeguid RA, Mohamed HE, Gad NH: A study of the predictive factors of mortality in acute poisoning with aluminum phosphide with special reference to echocardiography and SOFA score. *Environ Sci & Pollution Res* 2019; 26(32):33135–45

Background: Aluminum phosphide (AIP) is a common cause of serious poisoning in many countries with a high mortality rate due to acid-base disturbance and cardiogenic shock. Few studies have focused on the utility of the sequential organ failure assessment (SOFA) score and echocardiographic (ECHO) parameters to predict the mortality of AIP poisoning.

Research Question: What are the prognostic factors contributing to mortality and the outcomes of acute AIP poisoning?

Methods: This study included acute AIP poisoning patients admitted to a single academic hospital in Egypt between November 2017 and April 2018. Diagnosis was made by history alone; “unconfirmed” cases were excluded. Vital signs, Glasgow coma scale (GCS), and systemic examination variables were recorded for all cases. Grading SOFA score, ECHO, arterial blood gas, and electrocardiogram were performed on all patients at time of admission. All patients received protocolized care including gastric lavage with potassium permanganate (1:10,000), 1 meq/kg intravenous (IV) sodium bicarbonate (NaHCO_3), and proton pump inhibitors. Patients were given either IV crystalloid fluids (up to 3 L per day) if the ejection fraction (EF) was $> 40\%$ or norepinephrine $5 \mu\text{g}/\text{min}$ if the EF $< 40\%$. An initial univariate binary logistic regression analysis was performed to compare the prognostic factors for mortality.

Results: Thirty patients were admitted during the study period; of these, 22 (73%) were female, and the mean age was 22.77 ± 12.79 years (range, 3–60 years). Most exposures were from rural areas ($n = 29$; 96.6%) and involved intentional exposures ($n = 28$; 27 ingestions and 1 intravaginal). Half of these patients were students. Overall, 43.3% ($n = 13$) of the

patients died. The mean amount of time between exposure and hospital admission was significantly higher in non-survivors (2.73 ± 2.09 h) compared with survivors (1.56 ± 1.64 h). The majority (94.1%) of surviving patients reported taking $\leq$ one tablet, while only one surviving patient (5.9%) reported ingesting $>$ one tablet. There was a statistically significant difference in the number of AIP tablets ingested between survivors and non-survivors ($p = 0.025$).

Survivors had a significantly higher mean systolic blood pressure (SBP; 97.65 ± 17.86 mmHg vs. 71.67 ± 13.37 mmHg) and diastolic blood pressure (DBP; 64.71 ± 13.28 mmHg vs. 42.50 ± 11.38 mmHg) than non-survivors. A significant difference was found between survivors and non-survivors regarding acid-base abnormality ($p < 0.001$). Serum HCO_3 and pH were significantly lower in non-survivors (10.58 ± 4.16 and 7.23 ± 0.10 mEq/L) compared with survivors (19.13 ± 4.87 and 7.40 ± 0.07 mEq/L). Moreover, 92.3% of the non-survivors presented with metabolic acidosis on admission, while 58.8% of the survivors presented with either normal parameters or mixed metabolic acidosis and respiratory alkalosis (29.4% each).

There were significant differences in ECHO values between groups. All non-survivors had EF% $< 40\%$, while two-thirds (64.7%) of survivors had EF% $> 40\%$. Also, there was a significant difference between survivors and non-survivors regarding regional wall motion abnormality (RWMA; $p < 0.001$). All non-survivors, but only 5 (29.4%) survivors, had RWMA.

The mean GCS score was significantly higher in survivors versus non-survivors (14.24 ± 0.97 vs. 7.62 ± 5.33 ; $p < 0.001$). There was a significant difference between survivors and non-survivors regarding the SOFA score. In the survivor group, the SOFA score ranged from 0 to 6 with a mean of 1.24 ± 1.60 and median of 1. For the non-survivor group, the SOFA score ranged from 4 to 15 with a mean value of 10 ± 3.49 and median value of 10 ($p < 0.001$). Nineteen patients had a SOFA score of 0 to 6, 17 of whom survived, and two patients died. The mortality rate was higher ($n = 9$) in those with a SOFA score of 7 to 14. Both patients with a presenting SOFA score of 15 died. Non-survivors were more likely to need mechanical ventilation (76.9% versus 17.6%). Also, non-survivors had a more prolonged need for mechanical ventilation. Multivariate logistic regression analysis showed that SOFA score was the only (minimally) statistically significant predictor of death ($p = 0.03$; OR = 1.57, 95%CI 1.045–2.361).

Conclusion: Data from this small study suggest the following findings in AIP poisoning: metabolic acidosis was the most prevalent metabolic disturbance; low ($< 40\%$) EF, RWMA and dysrhythmia, were common cardiac findings in non-survivors; and SOFA score and presenting pH were the best predictors of death.

Critique: The study's small size and reliance on patient report of data (timing, amount and intention) limited the study

significantly. Also, other ingestions and pre-existing medical conditions were not completely evaluated.

Implication for Toxicologists: This study suggests that presenting arterial pH, SOFA score, and ECHO findings may assist in predicting outcome.

Article #4: Evoy R, Kincl L: Evaluation of pesticides found in Oregon cannabis from 2016 to 2017. *Ann Work Expo Health* 2019, 1–5. doi:<https://doi.org/10.1093/annweh/wxz075>

Background: Legalization of cannabis provided an opportunity to study pesticide exposures within the cannabis industry, mainly the type of pesticides used and the potential hazards they pose to cannabis workers.

Research Questions: What types of pesticides are being used in the cannabis industry in Oregon and what health hazards do these pesticides present?

Methods: Data were obtained from Oregon state agricultural and health regulatory agencies from 2016 and 2017 and only included cannabis samples that failed mandatory pesticide testing. Failure was defined as cannabis that contained pesticide concentrations above the state established action level or cannabis containing a pesticide not on the Oregon Department of Agriculture (ODA) recommended list. The data was stratified by recreational and medicinal cannabis. The identified pesticides and their associated toxicity were classified using the World Health Organization (WHO) pesticide classification system.

Results: Of the 50 pesticides identified, three were extremely hazardous, six were highly hazardous, 22 were moderately hazardous, four were slightly hazardous, and 15 were non-hazardous. Only three of the identified pesticides were on the ODA's list of recommended pesticides. The mean level of residual pesticides in recreational cannabis was 68 ppm (PPM; SD 610.1) compared with 260 ppm (SD 186.1) in medicinal cannabis. Concentrated recreational cannabis products had the lowest mean level of pesticides (11 ppm, SD 39.53), whereas

medicinal useable cannabis contained the highest mean level of pesticides (98.58 ppm, SD 554.54). Approximately 6.7% of all recreational cannabis samples failed state pesticide testing. Recreational cannabis extracts had the highest percent of failure at 47%. Data were not available (or none provided) concerning the failure rates among medicinal products.

Conclusion: Pesticides not recommended by the ODA are detected in Oregon cannabis samples collected between 2016 and 2017. Some of the pesticides detected are considered slightly to extremely hazardous according to WHO classification.

Critique: The extent of cannabis worker exposure to pesticides was not evaluated in this study. The implications for pesticide effects among workers, or consumers, could not be meaningfully explored. No data concerning the failure rates for medical products were provided, which was a significant limitation. Additionally, the methods used to detect and quantify the pesticide concentration were not detailed.

Implication for Toxicologists: Pesticides used in the cannabis industry do not appear to follow state regulatory agency recommendations. Some of these pesticides may pose a health risk to cannabis workers or consumers, but these risks remain unknown.

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