Articles You May Have Missed

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Mégarbane B, Buisine A, Jacobs F, et al. Prospective comparative assessment of buprenorphine overdose with heroin and methadone: Clinical characteristics and response to antidotal treatment. J Subst Abuse Treat 2010;38:403–7

Background: Buprenorphine is a partial opioid agonist with a reported “ceiling effect” for respiratory depression. Despite implied safety, it has been associated with significant overdoses. Conflicting data exist regarding the response to naloxone.

Research Question: How do the clinical characteristics and response to naloxone following buprenorphine overdose compare with those of heroin and methadone overdose?

Methods: Consecutive patients admitted to two teaching hospitals with Glasgow Coma Score (GCS) <12 and at least two of the following three criteria were included in this 4-year prospective.

Observational Study: History suggestive of opioid overdose, pinpoint pupils, or initial respiratory rate <12/min. Demographics, intent, initial GCS, respiratory rate, oxygen saturation (SpO₂), and vital signs were collected. Urine toxicological screening was performed and only overdoses involving the exclusive presence of 6-monoacetylmorphine, buprenorphine, or methadone were included. Cases involving multiple opioids were excluded, but cases with benzodiazepine coingestion were allowed. Patients were treated with naloxone and/or flumazenil. Antidote dose and order were at the discretion of

the attending physician. Response to naloxone was considered “positive” if full awakening occurred or intubation avoided.

Results: During the study, 160 patients were admitted for opioid overdose and 84 met inclusion criteria. These 84 were divided into three groups: heroin (*n*=26), buprenorphine (*n*=39), and methadone (*n*=19). Initial GCS, respiratory rate, SpO₂, and blood gas analysis were similar between groups. Benzodiazepine coingestion was more common in the buprenorphine vs heroin group and suicide more common in the methadone vs buprenorphine group. Naloxone was administered in 65% of 84 patients. Buprenorphine-poisoned patients did not respond to 0.4–0.8 mg intravenous naloxone (0/19).

Conclusion: Buprenorphine overdose induced a typical opioid syndrome that was not reversed with naloxone.

Critique: The strength of the study was a large number of patients and confirmation of toxins. Weaknesses include lack of data on pinpoint pupils (an inclusion criteria), subjective endpoints, preponderance of benzodiazepine co-ingestions, and lack of detailed naloxone dosing information.

Implication for Toxicologists: This study gives further evidence that buprenorphine overdose produces a typical opioid toxidrome. If naloxone is used to treat suspected buprenorphine overdose, doses of 0.4 to 0.8 mg may be insufficient to reverse the clinical effects. Benzodiazepines are common coingestants.

Taheri MS, Moghaddam HH, Moharamzad Y, et al. The value of brain CT findings in acute methanol toxicity. Eur J Radiol 2010;73:211–214

Background: Neuroimaging may play an important role in diagnosing methanol poisoning and predicting mortality. In prior case reports, radiological findings have included a variety of lesions.

Research Question: What are the brain CT findings in patients with acute, significant methanol poisoning and what is the association between the CT findings and death?

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Methods: Consecutive patients presenting to a large academic hospital were included in the study if their relatives reported a history of illicit alcohol ingestion or if they had a toxic blood methanol level (>20 mg/dL). Additionally, patients had to have an anion gap metabolic acidosis and osmolar gaps. All patients received ethanol therapy, intravenous sodium bicarbonate, and hemodialysis. During treatment, non-contrast head CT scans were obtained on all patients and were interpreted by a neuroradiologist. Data included radiological findings, demographics, estimated time between consumption and admission, clinical and laboratory findings, and final outcomes.

Results: Forty-two patients were included: 2/3 had consumed homemade alcohol and 1/3 had consumed industrial alcohol. The estimated mean time from ingestion to admission was 48 h (range, 24–72). At the time of presentation, 62% had blood methanol levels >20 mg/dL (mean 30 and range 22–67). All patients had an osmolar gap, anion gap, and acidemia (mean serum pH 6.9 with range 6.3–7.2). Six patients (14%) died. One third of cases had normal CT scans and 2/3 had a total of 55 pathologic findings on brain CT scans. Bilateral symmetric putaminal necrosis as a single lesion or in the company of other lesions was the predominant finding in 96% of cases, followed by insular necrosis (21%) and hemorrhage (16%; majority putaminal). Putaminal hemorrhage (OR=8; 95% CI 1.2–54) and insular necrosis (OR=11; 95% CI 1.5–80) were associated with mortality.

Conclusion: Putaminal necrosis was the predominant pattern found in methanol-intoxicated patients. Putaminal hemorrhage and insular subcortical white matter necrosis were associated with death.

Critique: This study is the first extensive clinical series of brain CT findings in a cohort of patients with significant methanol toxicity. Limitations of this report include lack of long-term clinical or radiographic follow-up and poorly described timing of the scans. Additionally, the authors do not comment on treatment implications of the CT results. Lastly, the value of the study may have been enhanced by calculating predictive values based on CT results vs metabolic data. Given these limitations, the authors were able to delineate the prevalence of a variety of abnormal head CT findings following delayed presentation in methanol toxicity.

Implication for Toxicologists: This study shows a high prevalence of brain CT abnormalities associated with methanol toxicity, some of which carry prognostic value. Toxicologists should have a low threshold for obtaining cranial imaging in serious cases.

Craig DGN, Ford AC, Hayes PC, Simpson KJ. Systematic review: Prognostic tests of paracetamol-induced acute liver failure. *Aliment Pharmacol Ther* 2010;31:1064–76.

Background: Acetaminophen (paracetamol) toxicity remains the leading cause of acute liver failure (ALF) in

the developed world. Over recent years, a plethora of prognostic variables have been proposed in an attempt to improve or replace the King's College Criteria (KCC) for predicting need for transplant.

Research Question: What are the existing prognostic criteria for predicting death without transplantation in acetaminophen-induced ALF and what are their accuracies?

Methods: The authors conducted a systematic review of the medical literature to identify studies of adult patients that evaluated prognostic markers of acetaminophen-induced ALF. All potential articles were assessed independently by two researchers according to predefined criteria. Structured data extraction was performed by two separate reviewers and any discrepancies were resolved by consensus.

Results: The search strategy identified 6,507 studies of which 105 were retrieved for detailed review. Fourteen were considered eligible for inclusion. The eligible studies evaluated a total of 1,960 acetaminophen-ALF patients and analyzed 22 prognostic markers or combinations thereof, focusing on the KCC. Sensitivity and specificity for the KCC in 1,929 pooled patients were 58% (95% CI 53–63) and 95% (95% CI 93–96), respectively. The KCC diagnostic odds ratio (DOR) was 28 (95% CI 9–84). Predictive values were greater for King's College Hospital patients compared to non-KCH patients (DOR 44 vs 17). Modified KCC criteria that included a post-resuscitation lactate >3 were inconsistent between three studies. Other markers, including alpha-feto-protein, APACHE II score, interleukin, MELD score, and serum phosphate, had better scores than the KCC but were evaluated in only single studies.

Conclusion: This systematic review and meta-analysis demonstrated that in pooled analysis, the original KCC have high specificity, but low sensitivity in determining prognosis in acetaminophen-induced ALF. One study included a lactate modification that improved sensitivity, but this has been unable to be replicated in subsequent studies and calls into question the benefit of this modification. Other markers need further prospective study.

Critique: This study provides an extensive review of the existing prognostic criteria for predicting death due to acetaminophen-ALF and hence which patients may benefit from transplant. One would question the value of the DOR as a variable since the upper end of this calculation is infinity. Because a value of infinity cannot be obtained, a subjective decision remains in deciding what threshold value less than infinity is clinically acceptable.

Implication for Toxicologists: The decision to recommend transplant following acetaminophen-induced ALF remains difficult. Numerous criteria have been suggested in various studies, and toxicologists must be aware of the limitations of each criterion.

Akdur O, Durukan P, Ozkan S, et al. Poisoning severity score, Glasgow coma scale, corrected QT interval in acute organophosphate poisoning. *Hum Exp Toxicol* 2010;29:419–25.

Background: Human poisoning with organophosphates (OP) is a worldwide problem. According to the World Health Organization, there are one million serious accidental and two million suicidal poisonings annually with approximately 200,000 deaths. A number of systems have been proposed for predicting outcome in OP poisoning.

Research Question: What is the effectiveness of the Poisoning Severity Score (PSS), Glasgow coma scale (GCS), and QTc interval in predicting outcomes in OP poisoning?

Methods: This was a prospective observational study of OP poisoned patients with defined inclusion and exclusion criteria. All patients received standard medical treatment that included atropine and pralidoxime. Clinical and demographic data were recorded in a standardized software program. GCS and PSS were calculated for each patient. ECG recordings were obtained prior to atropine treatment.

Results: Over a period of 2 years, 62 patients with OP poisoning were admitted and 54 were included for analysis. Patients ranged in age from 17 to 80 years (mean 34). The average time lapse between exposure and initial ED evalua-

tion was 4.4 h (range 2–24). Most cases were suicidal (40), but there were 12 accidental and two occupational exposures. There were three deaths. Prolongation of the QTc interval (defined as 0.41 s in men and 0.42 s in women) was the most common ECG abnormality, occurring in 54%. Mean PSS score was 1.8. No statistically significant correlation was found between the PSS and clinical parameters or EKG findings. A significant correlation was determined between the GCS and PSS.

Conclusion: The authors determined that QTc interval is not effective in the determination of short-term prognosis of OP poisoned patients but concluded that the PSS and GCS may be effective tools for determination of the severity.

Critique: Unfortunately, the methodological weaknesses of this study preclude acceptance of the author's conclusion that the PSS and GCS are useful prognostic tools. First, there is no independent analysis for GCS versus outcome, only GCS in context of the PSS. Second, analysis did not include true correlation studies for GCS, PSS, or EKG abnormalities. Third, relatively low QTc values were considered abnormal compared with FDA standards. Lastly, low prevalence of mortality and lack of significant cardiac manifestations predisposed to failure to find positive predictors.

Implication for Toxicologists: The author's findings cannot be adopted for routine use.