A case series of patients with lamotrigine toxicity at one center from 2003 to 2012

Introduction
Lamotrigine is a phenyltriazine compound that inhibits voltage-gated sodium channels, decreasing release of glutamate and aspartate, and inhibits serotonin, norepinephrine and dopamine reuptake. Reports of toxicity in the literature are limited to case reports and primarily involve coingestants. This case series is intended to report the clinical manifestations of lamotrigine toxicity.

Methods
his retrospective case series from 2003 to 2012 studies the effects of lamotrigine toxicity when not confounded by coingestants. Admission records at an inpatient toxicology center were reviewed for lamotrigine-only exposure based on history with supporting laboratory data when available. After identification, these charts were reviewed again to characterize vital signs, neurological examination findings, specific laboratory and electrocardiography parameters, and complications.

Results
Fifty-seven patients were identified with possible lamotrigine toxicity. Nine patients, including three toddlers, had lamotrigine-only ingestions. Three of these patients had seizures, four were hypertensive, five were tachycardic, and four experienced tachypnea. Mental status was altered in all nine (depressed (n = 4), agitated (n = 5) or both (n = 3)). Five patients were hyperreflexic and experienced intermittent myoclonus, and two had inducible clonus. On electrocardiogram, two patients experienced QRS prolongation (114–116 ms), and four had QTc prolongation (463–586 ms). No patient had life-threatening symptoms or signs. Serum levels of lamotrigine were available in seven patients, and averaged 35.4 mg/L (17–90 mg/L). The therapeutic range for sLTG is 3–14 mg/L.
Conclusions
Lamotrigine toxicity manifested with minor–moderate neurologic and/or electrocardiographic effects. Toxicity reflects the known pharmacologic actions of lamotrigine: serotonin, norepinephrine and dopamine reuptake inhibition, and sodium channel blockade.

Full text available from: http://dx.doi.org/10.3109/15563650.2013.818685

Polymorphisms in CYP2D6 may predict methamphetamine related heart failure

Background
Methamphetamine (METH) has been associated with a dilated cardiomyopathy. The first and rate-limiting step of metabolism is dependent on the polymorphic enzyme CYP2D6.

Objectives
To evaluate if polymorphisms in CYP2D6 can be associated with the development of a methamphetamine-induced cardiomyopathy.

Methods
We performed a prospective case-control pilot study. Cases were defined by a urinary drug screen positive for amphetamine and evidence of heart failure by beta natriuretic peptide (BNP) greater than 300 pg/ml and symptoms of heart failure. Controls were defined with urinary drug screens positive for amphetamines but without evidence of heart failure defined by a BNP lesser than 300 pg/ml or symptoms of heart failure. Exclusion criteria were less than 18 years or greater than 60 years of age, urinary toxicology screen positive for additional stimulants, known coronary artery disease (CAD) defined by greater than 50% stenosis on catheterization or previous myocardial infarction, known cardiomyopathy of alternative etiology or inability to provide consent. Patients underwent gas chromatography confirmation-mass spectroscopy for methamphetamine, genotyping of CYP2D6, limited echocardiography, and participated in a modified 2007 National Survey of Drug Use and Health Stimulant Survey. Genotype results were analyzed with traditional classifications and "Activity Scores".

Results
Fifty-six patients completed the study with 19 cases and 37 controls. There was no statistically significant difference in days of use in a month, age, gender, or ethnicity between cases and controls. While not statistically significant, age and days of use did trend higher in cases. CYP2D6 genotype demonstrated that the lower the activity score/poor metabolizer group had less heart failure than extensive metabolizers/higher activity score. However, it did not reach statistical significance. When adjusting for higher days of use, extensive metabolizers had the highest odds of developing a dilated cardiomyopathy. (OR: 2.33, 95% CI: 0.54–10.13). Echo findings in all cases showed reduced ejection fractions with a mean of 18.6% (range: 10–35%) and 70% had a dilated cardiomyopathy. No cardiomyopathies were seen in the controls. Mean ejection fraction was 56.75% (range: 45–70%). The odds ratio of having a dilated cardiomyopathy in extensive metabolizers was 1.62 (95% CI: 0.47–5.5).

Conclusion
Our study demonstrates a trend that individuals with decreased metabolic activity were less
likely to develop heart failure. While not statistically significant, a signal is present that extensive metabolizers may be at increased risk for the development of a cardiomyopathy.

Full text available from: http://dx.doi.org/10.3109/15563650.2013.818684

Behavioral and physiologic adverse effects in adolescent and young adult emergency department patients reporting use of energy drinks and caffeine


Introduction

This pilot study assessed the prevalence of physiologic and behavioral adverse effects among adolescent (13–17 years) and adult (18–25 years) emergency department patients who reported energy drink and/or caffeinated-only beverage use within the 30 days prior to emergency department presentation. It was hypothesized that energy drink users would report more adverse effects than those who used only traditional caffeinated beverages such as coffee, tea, or soft drinks.

Methods

This cross-sectional pilot study was conducted in two urban emergency departments, one adult and one pediatric. Eligible patients were enrolled during a 6-week period between June and August 2010. Participants completed a tablet computer-based, self-administered, anonymous questionnaire about their past 30-day energy drink and/or caffeinated-only beverage use, substance use, and experience of 10 physiologic and 10 behavioral symptoms. Multivariable logistic regression and negative binomial regression models, adjusted for age, gender, and substance use, were created to compare the occurrence of each adverse effect between energy drink and caffeinated-only beverage users. Odds ratios (ORs) and incidence rate ratios (IRRs) were estimated.

Results

Of those enrolled, 53.3% reported consuming energy drinks, 39.1% caffeinated-only beverages, and 7.6% no energy drinks or caffeinated-only beverages within the past 30 days. In multivariable logistic regression models, energy drink users were more likely than caffeinated-only beverage users to report having "gotten into trouble at home, school, or work" in the past 30 days (OR: 3.12 [1.24–7.88]). In the negative binomial regression multivariable models, more behavioral effects were reported among drug users (IRR: 1.50 [1.18–1.93]), and more physiologic effects were reported among tobacco users (IRR: 1.42 [1.13–1.80]) and females (IRR: 1.48 [1.21–1.80]), but not among energy drink users.

Conclusions

Energy drink users and substance users are more likely to report specific physiologic and behavioral adverse effects. Emergency department clinicians should consider asking patients about energy drink and traditional caffeine usage and substance use when assessing patient symptoms.

Full text available from: http://dx.doi.org/10.3109/15563650.2013.820311
An analysis of energy-drink toxicity in the National Poison Data System

Context
Small studies have associated energy drinks-beverages that typically contain high concentrations of caffeine and other stimulants-with serious adverse health events.

Objective
To assess the incidence and outcomes of toxic exposures to caffeine-containing energy drinks, including caffeinated alcoholic energy drinks, and to evaluate the effect of regulatory actions and educational initiatives on the rates of energy drink exposures.

Methods
We analyzed all unique cases of energy drink exposures reported to the US National Poison Data System (NPDS) between October 1, 2010 and September 30, 2011. We analyzed only exposures to caffeine-containing energy drinks consumed as a single product ingestion and categorized them as caffeine-containing non-alcoholic, alcoholic, or "unknown" for those with unknown formulations. Non-alcoholic energy drinks were further classified as those containing caffeine from a single source and those containing multiple stimulant additives, such as guarana or yerba mate. The data were analyzed for the demographics and outcomes of exposures (unknown data were not included in the denominator for percentages). The rates of change of energy drink-related calls to poison centers were analyzed before and after major regulatory events.

Results
Of 2.3 million calls to the NPDS, 4854 (0.2%) were energy drink-related. The 3192 (65.8%) cases involving energy drinks with unknown additives were excluded. Of 1480 non-alcoholic energy drink cases, 50.7% were children < 6 years old; 76.7% were unintentional; and 60.8% were males. The incidence of moderate to major adverse effects of energy drink-related toxicity was 15.2% and 39.3% for non-alcoholic and alcoholic energy drinks, respectively. Major adverse effects consisted of three cases of seizure, two of non-ventricular dysrhythmia, one ventricular dysrhythmia, and one tachypnea. Of the 182 caffeinated alcoholic energy drink cases, 68.2% were < 20 years old; 76.7% were referred to a health care facility. Educational and legislative initiatives to enhance understanding of the health consequences of energy drink consumption were significantly associated with a decreased rate of energy drink-related cases (p = 0.036).

Conclusions
About half the cases of energy drink-related toxicity involved unintentional exposures by children < 6 years old. Educational campaigns and legal restrictions on the sale of energy drinks were associated with decreasing calls to poison centers for energy drink toxicity and are encouraged.

Full text available from: http://dx.doi.org/10.3109/15563650.2013.820310
**Effect of intravenous lipid emulsion in patients with acute glyphosate intoxication**


**Background**

Although glyphosate intoxication has been considered minimally toxic in animals, severe toxicity has been observed in humans due to surfactant. We aimed to examine the potential therapeutic effects of intravenous lipid emulsion (ILE) on the patients with acute glyphosate intoxication.

**Methods**

This study enrolled 64 glyphosate-intoxicated patients with allocation to two groups: those treated with ILE (ILE group, n = 22), and control patients treated with only supportive (conservative) care. Control patients were selected by matching for the amount ingested and time since ingestion. Twenty-two control patients were separately selected from the 42 patients receiving supportive care only. In ILE group, 20% lipid emulsion product was injected intravenously at the rate of 20 mL/h for the patients who ingested less than 100 ml of glyphosate. In the patients who ingested more than 100 ml of glyphosate, the loading dose was 500 ml for 2–3 h according to the status of the patients, followed by a maintenance dose of 1000 ml for the next 24 h.

**Results**

Thirteen patients received high dose of ILE because the ingestion amount was more than 100 ml. None of the ILE group suffered from the complication of hypotension, while approximately 41% of the control group developed the complication. Additionally, arrhythmia was not observed in the ILE group. The incidence of mental change, respiratory failure, and acute kidney injury was similar between the two groups.

**Conclusions**

ILE administration was associated with lower incidence of hypotension and arrhythmia in patients with acute glyphosate intoxication. ILE administration seems to be an effective treatment modality in patients who ingested sufficient amount of glyphosate herbicide that is expected to bring about significant toxicity.

Full text available from: [http://dx.doi.org/10.3109/15563650.2013.821129](http://dx.doi.org/10.3109/15563650.2013.821129)

**With the benefit of hindsight: trials using retrospective controls versus randomized controlled trials in clinical toxicology**


For a clinician, a well-conducted randomised controlled trial (RCT) with standardised protocol-driven treatment in all its arms provides some of the best evidence to influence clinical practice, especially if the RCT examines important clinical outcomes and is supported by a plausible biological mechanism for the effect. For the patient enrolled in an RCT, even being in the placebo arm that utilises defined clinical guidelines is associated with improved outcomes, typically as a result of improved general care.

In clinical toxicology, RCTs are relatively rare compared with case reports and case series. Important reasons for this are the often very small number of cases in individual centres and the understandable reluctance of clinicians to potentially withhold specific treatments from seriously ill patients, even if the evidence for their benefit is weak or lacking. When a new
Intravenous lipid emulsion entraps amitriptyline into plasma and can lower its brain concentration – An experimental intoxication study in pigs
Abstract and full text available from: http://dx.doi.org/10.1111/bcpt.12082

Hump-nosed pit viper (Hypnale hypnale) envenoming causes mild coagulopathy with incomplete clotting factor consumption

**Context**
Limited information exists on the coagulopathy caused by hump-nosed pit viper (Hypnale hypnale) envenoming.

**Objectives**
This study aimed to characterise the coagulopathy in hump-nosed pit viper bites by measuring laboratory clotting times and factor studies.

**Materials and methods**
Cases of hump-nosed pit viper envenoming were included from a prospective cohort study of Sri Lankan snake-bite patients. Patient age, sex, snake identification, time of bite and clinical effects were recorded. Patients did not receive anti-venom because no specific anti-venom to hump-nosed vipers exists. All patients received supportive care and serial 20-min whole blood clotting tests (WBCT20). The prothrombin time (PT), international normalised ratio (INR), activated partial thromboplastin time (aPTT), coagulation factors I, II, V, VII, VIII, IX and X, von Willebrand factor (vWF) antigen and D-Dimer concentrations were measured. The median of highest or lowest test result for each patient was reported with interquartile range (IQR).

**Results**
There were 80 hump-nosed pit viper bites, median age was 37 years (IQR: 26–51 years) and 48 were male. The WBCT20 was positive in one patient. The median highest INR was 1.9 (1.5–2.2; Range: 1.3 to > 12) and median highest aPTT was 54 s (46–72 s; Range: 35–170 s). There was low fibrinogen [median: 1.3 g/L; 1, –1.8 g/L; Range: < 0.2–2.9], low factor VIII levels [median: 23%; 16–37%; Range: < 0.2–2.9], low factor VII levels [median: 23%; 16–37%; Range: < 0.2–2.9] and low factor V levels [median: 43%; 23–74%]. D-Dimer concentrations [median: 3.4 mg/L; 2–7.4 mg/L] were slightly elevated. Factors II, VII and X and vWF antigen concentrations were normal.

**Discussion and Conclusions**
Hump-nosed pit viper bites result in a mild coagulopathy which is usually not detected by a WBCT20. It is characterised by mild elevation of INR, low fibrinogen and Factors V and VIII...
which may be consistent with the venom containing a thrombin-like enzyme.

Full text available from: http://dx.doi.org/10.3109/15563650.2013.811589

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Abstract and full text available from: http://dx.doi.org/10.1016/j.toxicon.2013.07.010

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