Current Awareness in Clinical Toxicology

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CONTENTS

CURRENT AWARENESS PAPERS OF THE MONTH

Treatment for calcium channel blocker poisoning: a systematic review

St-Onge M, Dubé P-A, Gosselin S, Guimont C, Godwin J, Archambault PM, Chauny J-M, Frenette AJ, Darveau M, Le sage N, Poitras J, Provencher J, Juurlink DN, Blais R. Clin Toxicol 2014; online early: doi: 10.3109/15563650.2014.965827:

Context

Calcium channel blocker poisoning is a common and sometimes life-threatening ingestion.

Objective

To evaluate the reported effects of treatments for calcium channel blocker poisoning. The primary outcomes of interest were mortality and hemodynamic parameters. The secondary outcomes included length of stay in hospital, length of stay in intensive care unit, duration of vasopressor use, functional outcomes, and serum calcium channel blocker concentrations.

Methods

Medline/Ovid, PubMed, EMBASE, Cochrane Library, TOXLINE, International pharmaceutical abstracts, Google Scholar, and the gray literature up to December 31, 2013 were searched

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without time restriction to identify all types of studies that examined effects of various treatments for calcium channel blocker poisoning for the outcomes of interest. The searchstrategy included the following Keywords: [calcium channel blockers OR calcium channel antagonist OR calcium channel blocking agent OR (amlodipine or bencyclane or bepridil or cinnarizine or felodipine or fendiline or flunarizine or gallopamil or isradipine or lidoflazine or mibefradil or nicardipine or nifedipine or nimodipine or nisoldipine or nitrendipine or prenylamine or verapamil or diltiazem)] AND [overdose OR medication errors OR poisoning OR intoxication OR toxicity OR adverse effect]. Two reviewers independently selected studies and a group of reviewers abstracted all relevant data using a pilot-tested form. A second group analyzed the risk of bias and overall quality using the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) checklist and the Thomas tool for observational studies, the Institute of Health Economics tool for Quality of Case Series, the ARRIVE (Animal Research: Reporting In Vivo Experiments) guidelines, and the modified NRCNA (National Research Council for the National Academies) list for animal studies. Qualitative synthesis was used to summarize the evidence. Of 15,5577 citations identified in the initial search, 216 were selected for analysis, including 117 case reports. The kappa on the quality analysis tools was greater than 0.80 for all study types.

Results

The only observational study in humans examined high-dose insulin and extracorporeal life support. The risk of bias across studies was high for all interventions and moderate to high for extracorporeal life support.

High-dose insulin

High-dose insulin (bolus of 1 unit/kg followed by an infusion of 0.5–2.0 units/kg/h) was associated with improved hemodynamic parameters and lower mortality, at the risks of hypoglycemia and hypokalemia (low quality of evidence).

Extracorporeal life support

Extracorporeal life support was associated with improved survival in patients with severe shock or cardiac arrest at the cost of limb ischemia, thrombosis, and bleeding (low quality of evidence).

Calcium, dopamine, and norepinephrine

These agents improved hemodynamic parameters and survival without documented severe side effects (very low quality of evidence).

4-Aminopyridine

Use of 4-aminopyridine was associated with improved hemodynamic parameters and survival in animal studies, at the risk of seizures.

Lipid emulsion therapy

Lipid emulsion was associated with improved hemodynamic parameters and survival in animal models of intravenous verapamil poisoning, but not in models of oral verapamil poisoning.

Other studies

Studies on decontamination, atropine, glucagon, pacemakers, levosimendan, and plasma exchange reported variable results, and the methodologies used limit their interpretation. No trial was documented in humans poisoned with calcium channel blockers for Bay K8644, CGP 28932, digoxin, cyclodextrin, liposomes, bicarbonate, carnitine, fructose 1,6-diphosphate, PK 11195, or triiodothyronine. Case reports were only found for charcoal hemoperfusion, dialysis, intra-aortic balloon pump, Impella device and methylene blue.

Conclusions

The treatment for calcium channel blocker poisoning is supported by low-quality evidence drawn from a heterogeneous and heavily biased literature. High-dose insulin and

extracorporeal life support were the interventions supported by the strongest evidence, although the evidence is of low quality.

Full text available from: http://dx.doi.org/10.3109/15563650.2014.965827

An 11-year review of levetiracetam ingestions in children less than 6 years of age

Lewis JC, Albertson TE, Walsh MJ. Clin Toxicol 2014; online early: doi: 10.3109/15563650.2014.965828:

Background

Levetiracetam is a new anticonvulsant, which works to block high-voltage-activated Ca^{++} channels in children, for partial-onset seizures. Reports of clinical experience with pediatric ingestions are minimal. The purpose of this study was to characterize the toxicity of accidental levetiracetam exposures in children less than 6 years of age.

Methods

This was an 11-year retrospective observational case series of pediatric (< 6 years old) levetiracetam ingestions reported to a Poison Control System from 2002 to 2013. Case narratives were individually reviewed to collect desired information on exposure and clinical course. Inclusion criteria were levetiracetam as a single ingested medication, age less than 6 years, treatment in a health care facility, and followed to a known outcome.

Results

Eighty-two cases met inclusion criteria with 55% female patients and overall median age of 2.0 years (range: 1–60 months). The levetiracetam dose ingested was reported in 69 (84.1%) cases, with exact dose (median dose, 45.0 mg/kg; range, 10.5–1429 mg/kg) reported in 33 cases (40.2%). Of these, twenty-nine cases (88%) involved the oral solution formulation and 28 cases (85%) had unintentional therapeutic error as the cause of the exposure. No dose–response relationship was demonstrated; however, the odds of a levetiracetam-naive patient, (median dose, 26.9 mg/kg; *N* = 15) with an unintentional exposure, developing drowsiness or ataxia was 6 times that of a patient who was not naïve to levetiracetam (median dose, 70.1 mg/kg; *N* = 20) (Odds ratio [OR], 6.0; 95% confidence interval [CI], 1.03–35.91).Of the 82 cases, 17 (20.7%) developed untoward clinical effects of drowsiness and/or ataxia. Eighty patients (97.6%) were treated and discharged from the emergency department, and two patients (2.4%) were admitted. The two patients admitted included a two-month old who was accidentally given a dose 10 times that of her usual dose and a 3-year old who was lethargic on arrival to the hospital after ingestion of an unknown dose. Of all patients, 66 patients (80.5%) had no effect from the drug exposure. The medical outcome was considered to be minor in 15 cases (18.3%), and moderate in 1 case (1.2%). There were no cases with major outcomes and no deaths.

Conclusions

Pediatric levetiracetam exposures were associated with few transient clinical effects. Poison Control Centers may wish to consider acuity of ingestion when developing send-in protocols.

Full text available from: http://dx.doi.org/10.3109/15563650.2014.965828

An 11-year review of bupropion insufflation exposures in adults reported to the California Poison Control System

Lewis JC, Sutter ME, Albertson TE, Owen KP, Ford JB. Clin Toxicol 2014; online early: doi: 10.3109/15563650.2014.969372:

Background

Seizures of both immediate and delayed onset after ingestion of bupropion SR and bupropion XL formulations are well documented, but are less well characterized after insufflation. Bupropion is crushed and insufflated to experience a high similar to that from amphetamines and cocaine. We sought to characterize the abuse of bupropion via insufflation in cases reported to the California Poison Control System (CPCS) and the incidence of seizures.

Methods

An 11-year (2002–2012) retrospective observational case series of insufflated bupropion exposures evaluated in a health care facility (HCF) were reviewed after searching our database for all bupropion insufflation exposures. Patients with coingestants, multiple exposure routes, or age less than 18 were excluded. Data included age, gender, estimated bupropion dose, occurrence of pre-HCF seizures, symptoms and vital signs reported to the CPCS, treatments, and adverse events that occurred until time of discharge.

Results

74 cases were identified (1 excluded due to age, 5 excluded due to additional oral ingestion of bupropion, and 1 excluded due to being unable to follow). A total of 67 cases met inclusion criteria. The median age was 36 (range, 18–65) years. The total dose of bupropion insufflated was reported in 52 pts; median dose of 1500 (range, 100–9000) mg. Eighteen cases (27%) involved staggered or chronic exposures. Of the 67 patients, 20 (30%) experienced a seizure prior to arrival at the HCF. Of these, 19 patients (95%) presented with tachycardia. None of these patients had a second seizure in the emergency department. There were no major medical outcomes and no deaths. Of the 67 patients, 9 patients received benzodiazepines and 6 patients received single-dose activated charcoal.

Conclusion

The abuse of bupropion by crushing and insufflating through the nose is uncommon (67/2270 or 3.0%) compared with that by oral bupropion exposures reported to CPCS. Seizures are common but are self-limited. Delayed seizures (more than 8 h after exposure) appear to be rare. Tachycardia is present in almost all patients who have seizures.

Full text available from: http://dx.doi.org/10.3109/15563650.2014.969372

Expanding access to naloxone in the United States

Doyon S, Aks SE, Schaeffer S. Clin Toxicol 2014; online early: doi: 10.3109/15563650.2014.968657:

Background

Drug overdose deaths have increased steadily in the United States (U.S.) since 1979. During the past three decades, drug overdose deaths have tripled. In 2008, the number of unintentional poisoning deaths exceeded the number of motor vehicle deaths for the first time. Of the 38,329 drug overdose deaths in the United States in 2010, 22,134 (60%) were related to pharmaceuticals, with 75% of those deaths involving prescription opioid analgesics. Concomitantly, heroin deaths have risen by 55% between 2000 and 2010. Deaths from use of fentanyl-laced or acetyl fentanyl-laced heroin were reported in multiple states in 2013. In 2012, the Centers for Disease Control characterized opioid overdose

deaths as an epidemic. Most of these deaths are preventable.

Overdose of opioids, including morphine, oxycodone, hydrocodone, methadone, and fentanyl, cause respiratory depression that can lead to hypoxia and, if untreated, death. The exact neuronal mechanisms by which opioids depress respiration in humans are complex. Opioids reduce the sensitivity of the medullary chemoreceptors to hypercapnia. In addition, opioids depress the ventilatory response to hypoxia. The combined losses of hypercarbic and hypoxic drives deprive the victim of the stimulus to breathe. This results in a disruption of the respiratory pattern with prolongation of inspiration and, at higher doses, reduction of chest wall compliance, decrease in tidal volume, and slowing of respiratory rate and apnea.

Naloxone is a medication that displaces the opioid agonist from the mu receptor. Timely administration of naloxone reverses opioid-induced respiratory depression-that is, its primary clinical indication. Naloxone is very effective, inexpensive, and has been used since 1970 in hospitals and by emergency medical systems (EMS) for this purpose. The Food and Drug Administration (FDA) has approved the intravenous, intramuscular, and subcutaneous routes of administration of naloxone for opioid reversal; onset of action is rapid via any of these routes. While not specifically approved by FDA for intranasal administration, multiple scientific studies support this route of administration. Intranasal administration has been routinely used in many pediatric emergency departments for years. Currently in the U.S., naloxone is principally administered in the health care setting, but use by laypersons is becoming more common.

Full text available from: http://dx.doi.org/10.3109/15563650.2014.968657

Description of 3,180 courses of chelation with dimercaptosuccinic acid in children ≤5 y with severe lead poisoning in Zamfara, Northern Nigeria: a retrospective analysis of programme data

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Systematic review of potential health risks posed by pharmaceutical, occupational and consumer exposures to metallic and nanoscale aluminum, aluminum oxides, aluminum hydroxide and its soluble salts

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