Current Awareness in Clinical Toxicology

Editors: Damian Ballam MSc and Allister Vale MD

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CURRENT AWARENESS PAPERS OF THE MONTH

Adult clonidine overdose: prolonged bradycardia and central nervous system depression, but not severe toxicity

Isbister GK, Heppell SP, Page CB, Ryan NM. Clin Toxicol 2017; 55: 187-92.

Context

There are limited reports of adult clonidine overdose. We aimed to describe the clinical effects and treatment of clonidine overdose in adults.

Methods

This was a retrospective review of a prospective cohort of poisoned patients who took clonidine overdoses (>200 μg). Demographic information, clinical effects, treatment, complications (central nervous system and cardiovascular effects) and length of stay (LOS) were extracted from a clinical database or medical records.

Results

From 133 admissions for clonidine poisoning (1988–2015), no medical record was available in 14 and 11 took staggered ingestions. Of 108 acute clonidine overdoses (median age 27 years; 14–65 years; 68 females), 40 were clonidine alone ingestions and 68 were clonidine with co-ingestants. Median dose taken was 2100 μg (interquartile range [IQR]: 400–15,000

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μg). Median LOS was 21h (IQR: 14–35 h) and there were no deaths. Glasgow coma score [GCS] <15 occurred in 73/108 (68%), and more patients taking co-ingestants (8/68; 12%) had coma (GCS <9) compared to clonidine alone (2/40; 5%). Miosis occurred in 31/108 (29%) cases. Median minimum HR was 48 bpm (IQR: 40–57 bpm), similar between clonidine alone and co-ingestant overdoses. There was a significant association between dose and minimum HR for clonidine alone overdoses (p = 0.02). 82/108 (76%) had bradycardia, median onset 2.5 h post-ingestion (IQR: 1.7–5.5 h) and median duration 20 h (2.5–83 h), similar for clonidine alone and co-ingestant overdoses. There were no arrhythmias. Three patients ingesting 8000–12,000 μg developed early hypertension. Median minimum systolic BP was 96 mmHg (IQR: 90–105 mmHg) and hypotension occurred in 26/108 (24%). 12/108 patients were intubated, but only 2 were clonidine alone cases. Treatments included activated charcoal (24), atropine (8) and naloxone (23). The median total naloxone dose was 2 mg (IQR: 1.2-2.4 mg), but only one patient given naloxone was documented to respond with partial improvement in GCS.

Discussion

Clonidine causes persistent but not life-threatening clinical effects. Most patients develop mild central nervous system depression and bradycardia. Naloxone was not associated with improved outcomes.

Full text available from: http://dx.doi.org/10.1080/15563650.2016.1277234

Long-term mortality after poisoning with antipsychotics

Toft S, Horwitz H, Dalhoff KP. Clin Toxicol 2017; 55: 267-74.

Introduction

The objective of this study was to investigate the long-term mortality and cause of death after deliberate self-poisoning with antipsychotics. Furthermore, we investigated the risk of repeated self-poisoning after a first episode of poisoning with antipsychotics.

Methods

We identified patients with antipsychotic poisoning from the Danish Poison Information Centre Database and correlated their personal identification number with four Danish national registries related to health aspects.

Results

From August 2006 to December 2013 we identified 2289 patients poisoned with antipsychotic agents. The average age of the patients was 35.6 years (SD 14.3) and 68.5% were women. Eleven patients died during the first 30 days, and at the end of follow-up in March 2014, 150 patients were deceased, leading to a mortality rate of 2.1 per 100 person-years and a standardized mortality ratio of 9.0. The most common causes of death were poisoning (29%) and violent suicide (18%) – however half of the patients died from natural reasons. 643 patients (28%) repeated the poisoning once or more.

Conclusions

Poisoning with antipsychotics was associated with an increased risk of death. Most of these deaths were preventable, and this highlights the need for secondary prophylaxis following a suicide attempt.

Full text available from: http://dx.doi.org/10.1080/15563650.2017.1284328

Leukotriene-mediated neuroinflammation, toxic brain damage, and neurodegeneration in acute methanol poisoning

Zakharov S, Kotikova K, Nurieva O, Hlusicka J, Kacer P, Urban P, Vaneckova M, Seidl Z, Diblik P, Kuthan P, Navratil P, Pelclova D. Clin Toxicol 2017; 55: 249-59.

Context

The role of neuroinflammation in methanol-induced toxic brain damage has not been studied.

Objective

We studied acute concentrations and the dynamics of leukotrienes (LT) in serum in hospitalized patients with acute methanol poisoning and in survivors.

Methods

Series of acute cysteinyl-LT and LTB4 concentration measurements were performed in 28/101 hospitalized patients (mean observation time: 88 ± 20 h). In 36 survivors, control LT measurements were performed 2 years after discharge.

Results

The acute maximum (C_{max}) LT concentrations were higher than concentrations in survivors: C_{max} for LTC4 was 80.7 ± 5.6 versus 47.9 ± 4.5 pg/mL; for LTD4, 51.0 ± 6.6 versus 23.1 ± 2.1 pg/mL; for LTE4, 64.2 ± 6.0 versus 26.2 ± 3.9 pg/mL; for LTB4, 59.8 ± 6.2 versus 27.2 ± 1.4 pg/mL (all $p < 0.001$). The patients who survived had higher LT concentrations than those who died (all $p < 0.01$). Among survivors, patients with CNS sequelae had lower LTE4 and LTB4 than did those without sequelae (both $p < 0.05$). The LT concentrations increased at a rate of 0.4–0.5 pg/mL/h and peaked 4–5 days after admission. The patients with better outcomes had higher cys-LTs (all $p < 0.01$) and LTB4 ($p < 0.05$). More severely poisoned patients had lower acute LT concentrations than those with minor acidemia. The follow-up LT concentrations in survivors with and without CNS sequelae did not differ (all $p > 0.05$). The mean decrease in LT concentration was 30.9 ± 9.0 pg/mL for LTC4, 26.3 ± 8.6 pg/mL for LTD4, 37.3 ± 6.4 pg/mL for LTE4, and 32.0 ± 8.8 pg/mL for LTB4.

Conclusions

Our findings suggest that leukotriene-mediated neuroinflammation may play an important role in the mechanisms of toxic brain damage in acute methanol poisoning in humans. Acute elevation of LT concentrations was moderate, transitory, and was not followed by chronic neuroinflammation in survivors.

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Self-poisoning with baclofen in alcohol-dependent patients: national reports to French Poison Control Centers, 2008–2013

Pelissier F, de Haro L, Cardona F, Picot C, Puskarczyk E, Sapori J-M, Tournoud C, Franchitto N. Clin Toxicol 2017; 55: 275-84.

Background

Alcohol use disorders are frequently associated with self-intoxication in attempted suicide. In France since 2008, the off-label use of baclofen for treatment of alcohol dependence has greatly increased, leading to temporary regulation of use of the drug. At the request of the national authorities, the French Poison Control Centers carried out a retrospective survey to give an overview of baclofen exposure in this population.

Methods

A retrospective study was carried out from January 2008 to December 2013, focusing on baclofen exposures in alcohol-dependent patients managed by the nine national French Poison Control Centers.

Results

294 observations of baclofen exposures in alcohol-dependent patients were identified in our database. Of these, 220 were suicide attempts by self-poisoning and 74 were unintentional. The mean age of patients was 41.7 years, with a sex-ratio of 1.6. Patients attempting suicide with baclofen were younger than those with unintentional exposures, and 43.6% of them were women (vs 22.9%, $p < 0.01$). The mean supposed ingested dose was higher (480.7 mg) in patients who attempted suicide (vs 192.5 mg, $p < 0.0001$). 21.8% of intentional exposures involved baclofen alone. Psychiatric comorbidity (50.4%) was more frequent in the group of self-poisoning ($p < 0.001$). 132 patients were coded as severely exposed (60.0%). Nine victims died, but the causal link between self-poisoning with baclofen and fatal outcome should be interpreted with particular caution.

Conclusions

Baclofen self-poisoning by alcohol-dependent patients is a serious concern for the French health authorities. Our results are similar to those previously published, suggesting that most patients with baclofen overdose should be admitted to an intermediate or intensive care unit as the clinical course requires close monitoring. Because suicidal ideation and suicide attempts are more prevalent in people with substance use disorders than in the general population, and because of the lack of recommendations governing baclofen prescription in such a situation, its use needs to be better controlled.

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L-Arginine in the treatment of valproate overdose – Five clinical cases

Schrettl V, Felgenhauer N, Rabe C, Fernando M, Eyer F. Clin Toxicol 2017; 55: 260-6.

Background

Valproic acid and its metabolites – particularly valproyl-CoA – are inhibitors of the enzyme *N*-acetylglutamate synthetase. The amino acid L-arginine can stimulate *N*-acetylglutamate synthetase activity and could be potentially used therapeutically to correct hyperammonemia caused by valproate therapy or overdose. Severely valproic-acid-poisoned patients are usually treated with L-carnitine or hemodialysis in order to decrease hyperammonemia. We herein report of five cases, in which L-arginine was administered.

Methods

Observational study on five cases. Patients with hyperammonemia (i.e., ammonia 80 > µg/dL) and symptoms consistent with valproate overdose (i.e., drowsiness, coma) were selected for treatment with L-arginine. Data was collected retrospectively.

Results

L-Arginine decreased ammonia levels in a close temporal relation (case I ammonia in EDTA-plasma [µg/dL] decreased from 381 to 39; case II from 281 to 50; case III from 669 to 74; case IV from 447 to 56; case V from 202 to 60). In cases I and II, hemodialysis was performed and l-carnitine was given before the administration of L-arginine. In case III, hemodialysis was performed after the administration of L-arginine was already started . In

cases IV and V, treatment with L-arginine was the sole measure to decrease ammonia levels in plasma.

Conclusion

The results suggest that L-arginine may be beneficial in selected cases of valproate overdose complicated by hyperammonemia. L-Arginine could extend our conventional treatment options for valproic acid overdose.

Full text available from: http://dx.doi.org/10.1080/15563650.2017.1284333

Poison exposures in young Israeli military personnel: a National Poison Center Data analysis

Lavon O, Bentur Y. Clin Toxicol 2017; online early: doi: 10.1080/15563650.2016.1278225:

context

To characterize poison exposures in young Israeli military personnel as reported to the national poison center.

Methods

Retrospective poison center chart review over a 14-year period. Cases included were Israeli soldiers aged 18–21 years, the compulsory military service age required by the Israeli law.

Results

1770 records of poison exposures in young military personnel were identified. Most exposed individuals involved males (*n* = 1268, 71.6%). Main routes of exposure were ingestion (*n* = 854, 48.3%), inhalation (*n* = 328, 18.6%) and ocular (*n* = 211, 11.9%). Accidents or misuse (*n* = 712, 40.2%) were the most frequently reported circumstances, followed by suicide attempts (370, 20.9%), and bites and stings (161, 9.1%). More than half of the cases involved chemicals (*n* = 939, 53.1%); hydrocarbons, gases and corrosives were the main causative agents. Pharmaceuticals (mainly analgesics) were involved in 519 (29.3%) cases, venomous animals (mainly scorpions, centipedes, and snakes) in 79 (4.5%). Clinical manifestations were reported in 666 (37.6%) cases, mostly gastrointestinal, neurologic, and respiratory. The vast majority of cases (1634, 92.3%) were asymptomatic or mildly affected; no fatalities were recorded. In 831 (46.9%) cases the clinical toxicologist recommended referral to an emergency department; ambulatory observation was recommended in 563 (31.8%) cases, and hospitalization in 86 (4.9%).

Conclusions

Our data show that poison exposures among young soldiers involve mainly males, accidents, misuse and suicides, oral route and chemicals; most exposures were asymptomatic or with mild severity. Repeated evaluations of poison center data pertaining to military personnel is advised for identifying trends in poison exposure and characteristics in this particular population.

Full text available from: http://dx.doi.org/10.1080/15563650.2016.1278225

Evaluation of antivenom therapy for *Vipera palaestinae* bites in children: experience of two large, tertiary care pediatric hospitals

Pivko-Levy D, Munchnak I, Rimon A, Balla U, Scolnik D, Hoyte C, Voliovitch Y, Glatstein M. Clin Toxicol 2017; 55: 235-40.

Background

Antivenom has been successfully used to treat systemic and progressive, local manifestations of envenomation inflicted by *Vipera (V.) palaestinae*, the most common venomous snake in Israel. The objective of this study was to evaluate the fixed dose *V. palaestinae* monovalent (equine) immunoglobulin G antivenom used in two pediatric emergency departments. In particular, we wanted to assess the need for repeated antivenom administration and the rate of adverse antivenom effects in children.

Methods

A retrospective chart review was performed for all children admitted with definite or probable signs of *V. palaestinae* envenomation to Chaim Sheba Medical Center and Kaplan Medical Center between 1 March 2008 and 1 March 2014. Extracted data included: age, location of bite, time to hospital arrival, time to antivenom administration if indicated, outcomes, and complications of the envenomation and adverse effects to the antivenom.

Results

57 patients met inclusion criteria; they ranged from 1 to 17 years in age and median age was 9.5 years. Clinical manifestations were evident in 55 (96.4%) of victims: 18 presented with minimal local signs and 37 showed marked progressive, local features (rapidly progressing edema) and signs of systemic envenomation: tachycardia (20), vomiting (17), abdominal pain (11) and hypotension (6). Two patients developed compartment syndrome and underwent surgical decompression (both received only a loading dose of antivenom with no subsequent maintenance dose). One patient developed thrombocytopenia and three patients presented with mild coagulopathy. *Antivenom* was administered to 25 (42%) children. Indications for antivenom administration included moderate to severe local signs (19 patients) and systemic signs (6 patients). None of these patients developed adverse reactions, serum sickness, or other side effects to the antivenom. One patient received a single additional 30mL dose of antivenom, due to hypotension and syncope, with good response.

Conclusions

In children, 50 ml dosing of *V. palaestinae* antivenom is efficacious and safe for the treatment of systemic and progressive local manifestations of envenomation by *V. palaestinae*.

Full text available from: http://dx.doi.org/10.1080/15563650.2016.1277233

Vipera ammodytes bites treated with antivenom ViperaTAb: a case series with pharmacokinetic evaluation

Brvar M, Kurtovic T, Grenc D, Lang Balija M, Krizaj I, Halassy B. Clin Toxicol 2017; 55: 241-8.

Context

In clinical practice it is difficult to differentiate between *V. berus* and *V. ammodytes* venomous bites. In the past this was not a concern, but due to the current shortage in Viperfav™ and European viper venom antiserum availability, *V. a. ammodytes* venomous

bites have recently been treated with ViperaTAb®, which is a pharmaceutical formulation containing a monospecific ovine Fab fragments against the venom of *V. berus*.

Objective

To evaluate ViperaTAb® in *V. a. ammodytes* envenomations.

Materials and methods

This is a prospective case series of three consecutive patients envenomed by *V. a. ammodytes* snakebite treated with ViperaTAb®. *V. ammodytes* venom, neurotoxic ammodytoxins, and Fab fragment levels were determined in serum samples and a pharmacokinetic analysis of the antivenom Fab fragments was carried out.

Results

Three patients bitten by *V. a. ammodytes* with extensive local swelling, neurological symptoms and recurrent thrombocytopenia were treated with ViperaTAb®. *V. ammodytes* venom was detected in serum of all three patients. Ammodytoxins were detected in the serum of only the most severely envenomed patient who developed neurological symptoms. In the presented moderate cases, a dose of 8 mL of ViperaTAb® reduced swelling and improved systemic effects, such as thrombocytopenia. However, this dose of ViperaTAb® was not effective in the most severely envenomed patient with the highest serum values of *V. ammodytes* venom. In this case ViperaTAb® did not stop local swelling and it had no effect on neurological signs. ViperaTAb®'s systemic clearance, distribution and elimination half-lives were 4.3–13.4 mL/h/kg, 1.2–3.2 h and 14.1–55.4 h, respectively.

Conclusions

In patients envenomed by *V. a. ammodytes* venom, ViperaTAb® reduces moderate swelling and temporarily improves systemic effects, except neurological symptoms. ViperaTAb® application induces a decrement of *V. ammodytes* venom level in the blood, but did not affect serum concentration of neurotoxic ammodytoxins in the one patient with measurable concentrations.

Full text available from: http://dx.doi.org/10.1080/15563650.2016.1277235

Are vasopressors useful in toxin-induced cardiogenic shock?

Skoog CA, Engebretsen KM. Clin Toxicol 2017; 55: 285-304.

Objective

Overdoses with cardio-depressive medications can result in toxin-induced cardiogenic shock (TICS), a life-threatening condition characterized by severe hypotension and ineffective tissue perfusion. Vasopressors are often employed in the treatment of shock to increase heart rate and blood pressure. We sought to conduct a systematic review of the literature to evaluate the effectiveness of vasopressors in improving hemodynamic function and survival in the treatment of TICS.

Data sources

We searched PubMed, EMBASE, TOXLINE, and International Pharmaceutical Abstracts.

Study selection

We included studies evaluating the use of vasopressors in humans or animals with TICS. We limited human study types to randomized controlled trials, clinical trials, observational studies, and case reports.

Data extraction

Our search yielded 913 citations and 144 of these met our inclusion criteria. 130 were human case reports and 14 were animal studies.

Data synthesis

Human case report data showed vasopressors were ineffective more often than they were partially or fully effective. In the majority of animal studies, vasopressor treatment failed to improve hemodynamic parameters and resulted in decreased survival.

Conclusions

Human case reports and controlled animal experiments lead to different conclusions about vasopressors in TICS. Most animal studies indicate that vasopressors impair hemodynamic function and increase mortality. In contrast, human case reports suggest that vasopressors are often ineffective but not necessarily harmful.

Full text available from: http://dx.doi.org/10.1080/15563650.2017.1284329

An assessment of the variation in the concentration of acetylcysteine in infusions for the treatment of paracetamol overdose

Bailey GP, Wood DM, Archer JRH, Rab E, Flanagan RJ, Dargan PI. Br J Clin Pharmacol 2017; 83: 393-9.

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CHEMICAL WARFARE, BIOLOGICAL WARFARE AND RIOT CONTROL AGENTS

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