Current Awareness in Clinical Toxicology

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CONTENTS

CURRENT AWARENESS PAPERS OF THE MONTH

Efficacy and effectiveness of anti-digoxin antibodies in chronic digoxin poisonings from the DORA study (ATOM-1)

Chan BS, Isbister GK, O'Leary M, Chiew A, Buckley NA. Clin Toxicol 2016; online early: doi: 10.1080/15563650.2016.1175620:

Context

We hypothesized that in chronic digoxin toxicity, anti-digoxin antibodies (Fab) would be efficacious in binding digoxin, but this may not translate into improved clinical outcomes.

Objective

This study aims to investigate changes in free digoxin concentrations and clinical effects on heart rate and potassium concentrations in chronic digoxin poisoning when anti-digoxin Fab are given.

Materials and methods

This is a prospective observational study. Patients were recruited if they have been treated with anti-digoxin Fab for chronic digoxin poisoning. Data was entered into a standardised prospective form, supplemented with medical records. Their serum or plasma was collected, analysed for free and bound digoxin and free anti-digoxin Fab concentrations.

Results

From September 2013 to February 2015, 36 patients (median age, 78 years; 22 females)

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were recruited from 18 hospitals. Median heart rate (HR) was 49 beats/min. Initial median digoxin and potassium concentrations were 4.7 nmol/L (3.6 µg/L) (range: 2.3–11.2 nmol/L) and 5.3 mmol/L (range: 2.9–9.2 mmol/L) respectively. Beta-blockers (n = 18), calcium antagonists (n = 6), spironolactone and/or angiotensin blocking agents (n = 24) were also used concomitantly. Renal impairment and gastrointestinal symptoms were present in 31 (86%) and 22 (63%) patients respectively. Five patients died from conditions unrelated to digoxin toxicity. Median change in HR was 8 beats/min post-Fab with no effect on blood pressure; they were 4, 10 and 17 beats/min for the 1, 2 and ≥3 vials of anti-digoxin Fab groups respectively. Concomitant treatments with potassium lowering agents (12/36) and inotropic drugs (7/36) were used. Gastrointestinal effects resolved in all 22 patients. The median decrease for potassium was 0.3 mmol/L. Digoxin concentration reduced from 3.8 to 0 nmol/L post-Fab. There was a rebound observed in the free digoxin concentration in 25 patients but none had associated clinical deterioration.

Conclusions

One to two vials of anti-digoxin Fab initially bound all free digoxin confirming Fab efficacy. However, this was associated with only a moderate improvement in HR and potassium, suggesting bradyarrhythmia and hyperkalaemia may be from other co-morbidities.

Full text available from: http://dx.doi.org/10.1080/15563650.2016.1175620

A systematic analysis of methylene blue for drug-induced shock

Warrick BJ, Tataru AP, Smolinske S. Clin Toxicol 2016; online early: doi: 10.1080/15563650.2016.1180390:

Context

Pharmacologically induced shock can be refractory to standard resuscitation. Methylene blue (MB) acts to prevent nitric oxide-mediated vasodilation and may be a potential treatment for refractory shock.Objective: A systematic analysis of the literature to evaluate MB in pharmacologically induced shock. Primary outcome was survival and secondary outcome was hemodynamic improvement.

Materials and methods

A search of MedLine/PubMed, EMBASE, Cochrane Library, TOXLINE, Google Scholar and Google was performed 10 August 2015 using a combination of text words and keywords related to MB, shock and specific drugs. We included primary literature articles reporting clinical outcomes in humans.

Results

The searches yielded 928 citations, with 255 exact duplicates. Of the 673 entries screened, 16 citations met study criteria and comprised 17 cases. Calcium channel blockers (CCBs) represented ten cases (six amlodipine, two verapamil, and two diltiazem), atenolol three cases as coingestant with amlodipine, five metformin, one ibuprofen, and one multidrug (quetiapine, carbamazepine, valproic acid, oxazepam, and fluoxetine). Twelve patients survived and nine had hemodynamic improvement following MB administration. Four did not respond to MB but survived with other advanced resuscitative measures. None of the seven cases had BP improvement and four died when lipid was given prior to MB, compared to one death and nine cases of BP improvement when lipid was not given. In all cases, MB was used after failing several other treatments. Bolus doses ranging from 1 to 3 mg/kg, with repeat boluses or maintenance infusions. Reported adverse events were temporary self-limited blue discolorations.

Conclusion

While there are compelling cases describing an improved hemodynamic status following MB,

there are also several cases without observed change. Currently, there is not enough evidence available to recommend the routine administration of MB in refractory pharmacologically induced shock.

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Epidemiology and clinical features of toxicity following recreational use of synthetic cannabinoid receptor agonists: a report from the United Kingdom National Poisons Information Service

Waugh J, Najafi J, Hawkins L, Hill SL, Eddleston M, Vale JA, Thompson JP, Thomas SHL. Clin Toxicol 2016; online early:

doi: 10.3109/15563650.2016.1171329:

Context

Toxicity from the use of synthetic cannabinoid receptor agonists (SCRAs) has been encountered increasingly frequent in many countries.

Objective

To characterise presentation rates, demographic profiles and reported clinical features for users of SCRAs referred by health professionals in the United Kingdom to the National Poisons Information Service (NPIS), to compare reported toxicity between commonly used branded products, and to examine the impact of legal control measures on enquiry numbers.

Methods

NPIS telephone enquiry records were searched for SCRA-related terms for the 8-year period 1st January 2007 to 31st December 2014, consolidating multiple enquiries about the same case into a single record. Demographic data, reported exposure details, clinical features and poisoning severity were analysed, excluding cases where SCRA exposure was unlikely.

Results

Enquiries to the NPIS were made concerning 510 individuals relating to probable SCRA use, with annual numbers increasing year on year. Most patients were male (80.8%) and <25 years old (65.1%). Common clinical features reported in the 433 (84.9%) patients reporting SCRA use without other substances included tachycardia (*n* = 73, 16.9%), reduced level of consciousness (*n* = 70, 16.2%), agitation or aggression (*n* = 45, 10.4%), vomiting (*n* = 30, 6.9%), dizziness (*n* = 26, 6.0%), confusion (*n*= 21, 4.8%), mydriasis (*n* = 20, 4.6%) and hallucinations (*n* = 20, 4.6%). The Maximum Poisoning Severity Score (PSS) indicated severe toxicity in 36 cases (8.3%). Legal control of "second generation" SCRAs did not affect the rate of growth in enquiry numbers or the proportion with severe toxicity. The three most commonly reported products were "Black Mamba" (*n*= 88, 20.3%), "Pandora's Box" *(n*= 65, 15.0%) and "Clockwork Orange" (*n*= 27, 6.2%). Neurological and general features were recorded more often with "Clockwork Orange" than for "Black Mamba" and "Pandora's Box", but moderate or severe toxicity was significantly less common after reported use of this product.

Conclusions

Enquiries about SCRA-related toxicity have become increasingly frequent in the UK in spite of legal controls and commonly involve younger males. Differences in the patterns of toxicity associated with different branded preparations may occur, although further work with larger patient numbers is needed to confirm this.

Full text available from: http://dx.doi.org/10.3109/15563650.2016.1171329

Four analytically confirmed cases of use of third-generation synthetic cannabinoid receptor agonists incorporating an adamantyl group

Rook W, Ford L, Vale A. Clin Toxicol 2016; online early: doi: 10.1080/15563650.2016.1175005:

Full text available from: http://dx.doi.org/10.1080/15563650.2016.1175005

Difference of the clinical course and outcome between dapsone-induced methemoglobinemia and other toxic-agent-induced methemoglobinemia

Kim Y-J, Sohn CH, Ryoo SM, Ahn S, Seo DW, Lee Y-S, Lee JH, Oh BJ, Lim KS, Kim WY. Clin Toxicol 2016; online early:

doi: 10.1080/15563650.2016.1178759:

Context

Acquired methemoglobinemia is a potentially fatal condition that leads to tissue hypoxia. Although the clinical features of methemoglobinemia depend on the methemoglobin levels, the clinical course would differ depending on the causative agents.

Objective

We attempted to clarify this issue by comparing the clinical course of methemoglobinemia caused by dapsone and that caused by other toxic agents.

Materials and methods

A retrospective case–control study was performed. All patients with methemoglobinemia and who were admitted to the emergency department (ED) of our hospital from 1 January 2002 to 31 December 2014 were included.

Results

Of the 34 patients with methemoglobinemia, 15 ingested dapsone (14 with acute overdose and one with chronic therapeutic use) and 19 had been exposed to other toxic agents, such as sodium nitrites, indoxacarb, primaquine, and lidocaine. The clinical characteristics and the course of dapsone-induced and other toxic-agent-induced methemoglobinemia were compared. There was no significant difference in clinical presentation and methemoglobin level (38.5% vs. 35.0%, p = 0.456) upon their ED arrival between the two groups. However, the methemoglobin level after use of methylene blue and the total dose of methylene blue were higher in patients with dapsone-induced methemoglobinemia than in those with other agent-induced methemoglobinemia (11.9% vs. 1.7%, p = 0.001, 455 mg vs. 144 mg, p = 0.006). The majority of dapsone-induced methemoglobinemia (93.3%) required more than 72 h for normalization of the methemoglobin level, despite the use of methylene blue. Five of the study patients died due to multiorgan failure, and all of whom were inpatients with dapsone-induced methemoglobinemia.

Conclusion

The clinical course of dapsone-induced methemoglobinemia was worse than that of other toxic-agent-induced methemoglobinemia despite no significant difference in their initial clinical presentation. Continuous treatment with serial monitoring of the serum methemoglobin is necessary for patients with dapsone-induced methemoglobinemia.

Full text available from: http://dx.doi.org/10.1080/15563650.2016.1178759

A prospective study of ketamine versus haloperidol for severe prehospital agitation

Cole JB, Moore JC, Nystrom PC, Orozco BS, Stellpflug SJ, Kornas RL, Fryza BJ, Steinberg LW, O'Brien-Lambert A, Bache-Wiig P, Engebretsen KM, Ho JD. Clin Toxicol 2016; online early:

doi: 10.1080/15563650.2016.1177652:

Context

Ketamine is an emerging drug for the treatment of acute undifferentiated agitation in the prehospital environment, however no prospective comparative studies have evaluated its effectiveness or safety in this clinical setting.

Objective

We hypothesized 5 mg/kg of intramuscular ketamine would be superior to 10 mg of intramuscular haloperidol for severe prehospital agitation, with time to adequate sedation as the primary outcome measure.

Methods

This was a prospective open label study of all patients in an urban EMS system requiring chemical sedation for severe acute undifferentiated agitation that were subsequently transported to the EMS system's primary Emergency Department. All paramedics were trained in the Altered Mental Status Scale and prospectively recorded agitation scores on all patients. Two 6-month periods where either ketamine or haloperidol was the first-line therapy for severe agitation were prospectively compared primarily for time to adequate sedation. Secondary outcomes included laboratory data and adverse medication events.

Results

146 subjects were enrolled; 64 received ketamine, 82 received haloperidol. Median time to adequate sedation for the ketamine group was 5 minutes (range 0.4-23) vs. 17 minutes (range 2–84) in the haloperidol group (difference 12 minutes, 95% CI 9–15). Complications occurred in 49% (27/55) of patients receiving ketamine vs. 5% (4/82) in the haloperidol group. Complications specific to the ketamine group included hypersalivation (21/56, 38%), emergence reaction (5/52, 10%), vomiting (5/57, 9%), and laryngospasm (3/55, 5%). Intubation was also significantly higher in the ketamine group; 39% of patients receiving ketamine were intubated vs. 4% of patients receiving haloperidol.

Conclusions

Ketamine is superior to haloperidol in terms of time to adequate sedation for severe prehospital acute undifferentiated agitation, but is associated with more complications and a higher intubation rate.

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Plasma paracetamol concentration at hospital presentation has a dose-dependent relationship with liver injury despite prompt treatment with intravenous acetylcysteine

Cairney DG, Beckwith HKS, Al-Hourani K, Eddleston M, Bateman DN, Dear JW. Clin Toxicol 2016; 54: 405-10.

Context

Paracetamol (acetaminophen) overdose is a common reason for emergency hospital admission in the UK and the leading cause of acute liver failure in the Western world.

Currently, the antidote acetylcysteine (NAC) is administered at a dose determined only by body weight without regard for the body burden of paracetamol.

Objective

To determine whether higher plasma paracetamol concentrations are associated with increased risk of liver injury despite prompt treatment with intravenous NAC.

Methods

Patients admitted to hospital for treatment with intravenous NAC following a single acute paracetamol overdose entered the study if NAC was commenced within 24 h of drug ingestion (N = 727 hospital presentations). Based on the plasma paracetamol concentration at first presentation to hospital, a series of nomograms were created: 0-100, 101-150, 151-200, 201-300, 301-500 and over 501 mg/L. The primary endpoints were acute liver injury (ALI – peak serum ALT activity >150 U/L and double the admission value) and hepatotoxicity (peak ALT >1000 U/L).

Results

ALI and hepatotoxicity were more common in patients with higher admission plasma paracetamol concentrations despite NAC treatment (ALI: nomogram 0–100: 6%, 101–150: 3%, 151–200: 3%, 201–300: 9%, 301–500: 13%, over 501 mg/dL: 27%. $p < 0.0001$). This dose-response relationship between paracetamol concentration and ALI persisted even in patients treated with NAC within 8 h of overdose (nomogram 0–100: 0%, 101–150: 0.8%, 151–200: 2%, 201–300: 3.6%, 301–500: 12.5%, over 501mg/L: 33%. $p < 0.0001$) and in patients with normal ALT activity at first presentation (nomogram: 0–100: 0%, 101–150: 1.2%, 151–200: 1.5%, 201–300: 5.3%, 301–500: 10.8% $p < 0.0001$).

Discussion

Patients with increased concentrations of plasma paracetamol at hospital presentation are at higher risk of liver injury even when intravenous NAC is promptly administered before there is biochemical evidence of toxicity.

Conclusion

This study supports theoretical concerns that the current intravenous dose of NAC may be too low in the setting of higher paracetamol exposure.

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Outcomes of patients with premature discontinuation of the 21-h Intravenous N-acetylcysteine protocol after acute acetaminophen overdose

Lucyk SN, Yarema MC, Sivilotti MLA, Johnson DW, Nettel-Aguirre A, Victorino C, Bailey B, Dart RC, Heard K, Spyker DA, Rumack BH. J Emerg Med 2016; 50: 629-37.

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A review of pitfalls and progress in chelation treatment of metal poisonings

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Reactivation of nerve agent-inhibited human acetyl-cholinesterase by obidoxime, HI-6 and obidoxime+HI-6: kinetic in vitro study with simulated nerve agent toxicokinetics and oxime pharmacokinetics

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Neurologic, psychiatric, and other medical manifestations of nitrous oxide abuse: a systematic review of the case literature

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Maternal use of selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn

Alwan S, Bandoli G, Chambers CD. Clin Pharmacol Ther 2016; online early: doi: 10.1002/cpt.376:

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Ondansetron use in pregnancy and birth defects: a systematic review

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CHEMICAL WARFARE, BIOLOGICAL WARFARE AND RIOT CONTROL AGENTS

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INDEX

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