

Current Awareness in Clinical Toxicology

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CURRENT AWARENESS PAPERS OF THE MONTH

Digoxin-specific antibody fragments in the treatment of digoxin toxicity

Chan BSH, Buckley NA. Clin Toxicol 2014; online early:

doi: [10.3109/15563650.2014.943907](https://doi.org/10.3109/15563650.2014.943907):

Context

Digoxin-specific antibody fragments (digoxin-Fab) are widely regarded as a safe and effective treatment for the management of acute and chronic digoxin poisoning. Calculated equimolar doses of digoxin-Fab are high, very expensive, and infrequently used.

Objective

To review the pharmacology, efficacy, effectiveness, indications, safety and the dosage of digoxin-specific antibody fragments.

Methods

Pubmed, Embase, Medline and Cochrane were searched from 1946 to May 2013 using the terms digoxin, digoxin-specific Fab, and digoxin antibody.

Pharmacology and kinetics of digoxin and digoxin-Fab

Digoxin acts via inhibition of Na⁺/K⁺ ATPase. It has a narrow therapeutic index. Digoxin has 60–80% bioavailability, a mean plasma half-life of 40 h and a volume of distribution (Vd) of 5–10 L/kg and low protein binding (20%). A 40-mg vial of digoxin-Fab (DigiFab) binds 0.5 mg digoxin. Digoxin-Fab has a mean plasma half-life of 19–30 h and a Vd of 0.4 L/kg. The half-lives of both digoxin and digoxin-Fab are prolonged in renal failure to over 100 h.

Efficacy and effectiveness of digoxin-Fab

There were no randomised clinical trials examining the use of digoxin-Fab for acute or chronic digoxin poisonings. Ten case series with a total of 2,080 patients have reported on the use of digoxin-Fab in digoxin poisoning. In three large case series of 430 acute and 1308 chronic poisonings, response rates to digoxin-Fab vary from 80–90% to 50%. The time for reversal of digoxin toxicity is reported to be 30–45 min. Studies with pharmacokinetic data showed that free digoxin concentration fell to almost zero within a few minutes following the administration of digoxin-Fab. Digoxin-Fab was used more frequently in acute

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than chronic digoxin poisoning with a higher reported success rate when used in acute overdose. It is sometimes recommended to use full neutralisation doses (based on serum concentration \times Vd or ingested dose). It has also been proposed to use half this dose.

Indications for digoxin-Fab

Patients who have life-threatening tachy-bradyarrhythmias, hyperkalaemia (> 6 mmol/L) or haemodynamic instability with an elevated digoxin concentration (> 2 μ g/L or 2.6 nmol/L). The lowest effective digoxin-Fab dosing regimen has not been established.

Safety of digoxin-Fab

Adverse events such as exacerbation of heart failure, increased ventricular rate and hypokalaemia are uncommon ($< 10\%$). Recrudescence of digoxin toxicity and allergic reactions are infrequent.

Digoxin-Fab dosing in acute poisoning

Digoxin load based on ingested dose will generally overestimate digoxin-Fab doses as bioavailability is 60–80%, and further reduced by vomiting and activated charcoal. Digoxin load based on concentration also will be overestimated when the concentration is taken before distribution is complete (around 6 h). Much smaller doses of digoxin-Fab can eliminate the digoxin in the central compartment (Vd \approx 55 L). In imminent cardiac arrest, it may be justified to give a full neutralising dose. Otherwise, based on pharmacokinetic modelling, it is recommended to give 80 mg bolus digoxin-Fab, repeated as required according to clinical parameters because the onset of clinical response is usually rapid. Most patients would be expected to require a total of less than half of the calculated neutralising dose using this strategy.

Digoxin-Fab dosing in chronic poisoning

Even if digoxin load is estimated following distribution (> 6 h), excessive neutralisation doses may still be calculated because of variation in Vd due to equations failing to account for lean body weight, age and renal failure. In practice, it is suggested to give 40 mg (1 vial) digoxin-Fab at a time and repeat after 60 min if patient is still symptomatic, sooner if patient is clinically unstable. In general, 40–120 mg (1–3 vials) should be sufficient.

Conclusions

Digoxin-Fab is safe and indicated in all patients with life-threatening arrhythmias and an elevated digoxin concentration. However, calculated full neutralising doses of digoxin-Fab are expensive and may not be required. In acute poisoning, a small bolus of 80 mg, repeat if necessary, titrated against clinical effect, is likely to achieve equivalent benefits with much lower total doses. With chronic poisoning, it may be simplest to give 40 mg (1 vial) digoxin-Fab at a time and repeat after 60 min if there is no response.

Full text available from: <http://dx.doi.org/10.3109/15563650.2014.943907>

Features of myocardial injury in severe organophosphate poisoning

Cha YS, Kim H, Go J, Kim TH, Kim OH, Cha KC, Lee KH, Hwang SO. Clin Toxicol 2014; online early: doi: 10.3109/15563650.2014.944976:

Background

In organophosphate (OP) poisoning cardiac complications may occur. However, the current body of knowledge largely consists of limited studies, and case reports are mainly on electrocardiogram (ECG) abnormalities. As definite myocardial injury is difficult to assess through ECG, we investigated the prevalence of myocardial injury through cardiac biochemical markers such as troponin I (TnI) in severe OP poisoning.

Methods

We conducted a retrospective review of 99 consecutive OP insecticide poisoning cases that were diagnosed and treated at the emergency department of the Wonju Severance Christian Hospital between March 2008 and December 2013.

Results

Based on Namba classification for OP poisoning, there were no patients with mild toxicity, 9 patients (9.1%) with moderate toxicity and 90 patients (90.9%) with severe toxicity. On ECG, normal sinus rhythm was most common, and ST depression and elevation were seen in 11 patients (11.1%). Elevation of TnI within 48 h was seen in 34 patients (34.3%). The median peak level and peak time of TnI were 0.305 (IQR, 0.078–2.335) ng/mL and 15 (IQR 6.9–34.4) hours, respectively. There were differences between patients with normal TnI and elevated TnI in terms of age (yrs), number of patients who were exposed to OP via the oral route, and initial Glasgow Coma Scale (GCS; 58 ± 17 vs. 66 ± 16 , $p = 0.015$, 56 [87.5%] vs. 33 [97.1%], $p = 0.048$ and 12.0 [IQR, 8.0–15.0] vs. 9.0 [IQR, 5.8–12.0], $p = 0.019$).

Conclusions

OP can cause direct myocardial injury during the acute early phase in severe OP poisoning. Monitoring of TnI may be needed in severe OP poisoning.

Full text available from: <http://dx.doi.org/10.3109/15563650.2014.944976>

Acute kidney injury associated with smoking synthetic cannabinoid

Buser GL, Gerona RR, Horowitz BZ, Vian KP, Troxell ML, Hendrickson RG, Houghton DC, Rozansky D, Su SW, Leman RF. Clin Toxicol 2014; 52: 664-73.

Context and objectives

Synthetic cannabinoids are illegal drugs of abuse known to cause adverse neurologic and sympathomimetic effects. They are an emerging health risk: 11% of high school seniors reported smoking them during the previous 12 months. We describe the epidemiology of a toxicologic syndrome of acute kidney injury associated with synthetic cannabinoids, review the toxicologic and public health investigation of the cluster, and describe clinical implications of the cluster investigation.

Materials and methods

Case series of nine patients affected by the toxicologic syndrome in Oregon and southwestern Washington during May–October 2012. Cases were defined as acute kidney injury (creatinine > 1.3 mg/dL) among persons aged 13–40 years without known renal disease who reported smoking synthetic cannabinoids. Toxicology laboratories used liquid chromatography and time-of-flight mass spectrometry to test clinical and product specimens for synthetic cannabinoids, their metabolites, and known nephrotoxins. Public health alerts informed clinicians, law enforcement, and the community about the cluster and the need to be alert for toxidromes associated with emerging drugs of abuse.

Results

Patients were males aged 15–27 years (median, 18 years), with intense nausea and flank or abdominal pain, and included two sets of siblings. Peak creatinine levels were 2.6–17.7 mg/dL (median, 6.6 mg/dL). All patients were hospitalized; one required dialysis; none died. No alternate causes of acute kidney injury or nephrotoxins were identified. Patients reported easily purchasing synthetic cannabinoids at convenience, tobacco, and adult bookstores. One clinical and 2 product samples contained evidence of a novel synthetic cannabinoid, XLR-11 ([1-(5-fluoropentyl)-1H-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone).

Discussion and conclusion

Whether caused by direct toxicity, genetic predisposition, or an as-yet unidentified nephrotoxin, this association between synthetic cannabinoid exposure and acute kidney injury reinforces the need for vigilance to detect new toxicologic syndromes associated with emerging drugs of abuse. Liquid chromatography and time-of-flight mass spectrometry are useful tools in determining the active ingredients in these evolving products and evaluating them for toxic contaminants.

Full text available from: <http://dx.doi.org/10.3109/15563650.2014.932365>

Comprehensive analysis of "bath salts" purchased from California stores and the internet

Schneir A, Ly BT, Casagrande K, Darracq M, Offerman SR, Thornton S, Smollin C, Vohra R, Rangun C, Tomaszewski C, Gerona RR. Clin Toxicol 2014; 52: 651-8.

Study objective

To analyze the contents of "bath salt" products purchased from California stores and the Internet qualitatively and quantitatively in a comprehensive manner.

Methods

A convenience sample of "bath salt" products were purchased in person by multiple authors at retail stores in six California cities and over the Internet (U.S. sites only), between August 11, 2011 and December 15, 2011. Liquid chromatography-time-of-flight mass spectrometry was utilized to identify and quantify all substances in the purchased products.

Results

Thirty-five "bath salt" products were purchased and analyzed. Prices ranged from \$9.95 to 49.99 (U.S. dollars). Most products had a warning against use. The majority (32/35, 91%) had one ($n = 15$) or multiple cathinones ($n = 17$) present. Fourteen different cathinones were identified, 3,4-methylenedioxypropylvalerone (MDPV) being the most common. Multiple drugs found including cathinones (buphedrone, ethcathinone, ethylone, MDPBP, and PBP), other designer amines (ethylamphetamine, fluoramphetamine, and 5-IAI), and the antihistamine doxylamine had not been previously identified in U.S. "bath salt" products. Quantification revealed high stimulant content and in some cases dramatic differences in either total cathinone or synthetic stimulant content between products with the same declared weight and even between identically named and outwardly appearing products.

Conclusion

Comprehensive analysis of "bath salts" purchased from California stores and the Internet revealed the products to consistently contain cathinones, alone, or in different combinations, sometimes in high quantity. Multiple cathinones and other drugs found had not been previously identified in U.S. "bath salt" products. High total stimulant content in some products and variable qualitative and quantitative composition amongst products were demonstrated.

Full text available from: <http://dx.doi.org/10.3109/15563650.2014.933231>

An Internet snapshot study to compare the international availability of the novel psychoactive substance methiopropamine

Vermette-Marcotte A-E, Dargan PI, Archer JRH, Gosselin S, Wood DM. Clin Toxicol 2014; 52: 678-81.

Context

With the increased use of novel psychoactive substances, there is an increasing availability of these substances from Internet-based suppliers. Methiopropamine, first reported in 2011, is a recreational drug available over the Internet. The aim of this study was to investigate availability and cost of methiopropamine in three different countries: the UK, France, and Canada.

Methods

Using the European Monitoring Centre for Drugs and Drug Addiction Internet snapshot methodology, this study, conducted in June 2013, was undertaken in two different languages: in English (the UK and Canada) and in French (France and Canada), using three Internet searching engines: "google.co.uk", "google.fr" and "google.ca".

Results

A total of 62 sites were found, most of them were found from the English searches. 45% of the suppliers seemed to originate from the UK. The prices of methiopropamine were comparable between suppliers, no matter which search engine or language was used. The cost of a unit of methiopropamine was inversely related to the purchased quantity, going from 19.49 ± 0.15 GBP per gram for a purchase amount of 500 mg to 3.54 ± 0.13 GBP per gram for a purchase amount of 1 kg.

Discussion

The results of the present study demonstrate that the sale of methiopropamine has the potential to reach users across the world. It also appears to support that snapshot studies could be used for toxicovigilance across different countries, by studying the Internet market of novel psychoactive substances.

Conclusion

To date, snapshot studies, used to monitor the Internet novel psychoactive substances market, have only been undertaken in Europe. We have shown that the flexibility of this methodology enables comparison of the online activity of drug sellers between different countries and continents and that, at least for methiopropamine, the UK is the predominant source for Internet supply.

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CHEMICAL WARFARE, BIOLOGICAL WARFARE AND RIOT CONTROL AGENTS

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