Current Awareness in Clinical Toxicology

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CURRENT AWARENESS PAPERS OF THE MONTH

Comparison of F(ab')$_2$ versus Fab antivenom for pit viper envenomation: a prospective, blinded, multicenter, randomized clinical trial

Bush SP, Ruha AM, Seifert SA, Morgan DL, Lewis BJ, Arnold TC, Clark RF, Meggs WJ, Toschlog EA, Borron SW, Figge GR, Sollee DR, Shirazi FM, Wolk R, de Chazal I, Quan D, García-Ubbelohde W, Alagón A, Gerkin RD, Boyer LV. Clin Toxicol 2014; online early: doi: 10.3109/15563650.2014.974263:

Background

Crotalidae Polyvalent Immune Fab (Ovine) has been the only antivenom commercially available in the US since 2007 for treatment of Crotalinae envenomation. Late coagulopathy can occur or recur after clearance of Fab antivenom, often after hospital discharge, lasting in some cases more than 2 weeks. There have been serious, even fatal, bleeding complications associated with recurrence phenomena. Frequent follow-up is required, and additional intervention or hospitalization is often necessary. F(ab')$_2$ immunoglobulin derivatives have longer plasma half life than do Fab. We hypothesized that F(ab')$_2$ antivenom would be superior to Fab in the prevention of late coagulopathy following treatment of patients with Crotalinae envenomation.

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Methods

We conducted a prospective, double-blind, randomized clinical trial, comparing late coagulopathy in snakebitten patients treated with $F(ab')_2$ with maintenance doses [$F(ab')_2$/$F(ab')_2$], or $F(ab')_2$ with placebo maintenance doses [$F(ab')_2$/placebo], versus Fab with maintenance doses [Fab/Fab]. The primary efficacy endpoint was coagulopathy (platelet count < 150 K/mm^3, fibrinogen level < 150 mg/dL) between end of maintenance dosing and day 8.

Results

121 patients were randomized at 18 clinical sites and received at least one dose of study drug. 114 completed the study. Of these, 11/37 (29.7%) in the Fab/Fab cohort experienced late coagulopathy versus 4/39 (10.3%, $p < 0.05$) in the $F(ab')_2$/$F(ab')_2$ cohort and 2/38 (5.3%, $p < 0.05$) in the $F(ab')_2$/placebo cohort. The lowest heterologous protein exposure was with $F(ab')_2$/placebo. No serious adverse events were related to study drug. In each study arm, one patient experienced an acute serum reaction and one experienced serum sickness.

Conclusions

In this study, management of coagulopathic Crotalinae envenomation with longer-half-life $F(ab')_2$ antivenom, with or without maintenance dosing, reduced the risk of subacute coagulopathy and bleeding following treatment of envenomation.

Full text available from: http://dx.doi.org/10.3109/15563650.2014.974263

Czech mass methanol outbreak 2012: epidemiology, challenges and clinical features

Zakharov S, Pelclova D, Urban P, Navratil T, Diblik P, Kuthan P, Hubacek JA, Miovsky M, Klempir J, Vaneckova M, Seidl Z, Pilin A, Fenclova Z, Petrik V, Kotikova K, Nurieva O, Ridzon P, Rulisek J, Komarc M, Hovda KE. **Clin Toxicol 2014; online early: doi: 10.3109/15563650.2014.974106:**

Objectives

Methanol poisonings occur frequently globally, but reports of larger outbreaks where complete clinical and laboratory data are reported remain scarce. The objective of the present study was to report the data from the mass methanol poisoning in the Czech Republic in 2012 addressing the general epidemiology, treatment, and outcomes, and to present a protocol for the use of fomepizole ensuring that the antidote was provided to the most severely poisoned patients in the critical phase.

Methods

A combined prospective and retrospective case series study of 121 patients with confirmed methanol poisoning.

Results

From a total of 121 intoxicated subjects, 20 died outside the hospital and 101 were hospitalized. Among them, 60 survived without, and 20 with visual/CNS sequelae, whereas 21 patients died. The total and hospital mortality rates were 34% and 21%, respectively. Multivariate regression analysis found pH < 7.0 (OR 0.04 (0.01-0.16), $p < 0.001$), negative serum ethanol (OR 0.08 (0.02-0.37), $p < 0.001$), and coma on admission (OR 29.4 (10.2-84.6), $p < 0.001$) to be the only independent parameters predicting death. Continuous hemodialysis was used more often than intermittent hemodialysis, but there was no significant difference in mortality rate between the two [29% ($n = 45$) vs 17% ($n = 30$), $p = 0.23$]. Due to limited stockpiles of fomepizole, ethanol was administered more often; no

difference in mortality rate was found between the two [16% (n = 70) vs. 24% (n = 21), p = 0.39]. The effect of folate administration both on the mortality rate and on the probability of visual sequelae was not significant (both $p > 0.05$).

Conclusions

Severity of metabolic acidosis, state of consciousness, and serum ethanol on admission were the only significant parameters associated with mortality. The type of dialysis or antidote did not appear to affect mortality. Recommendations that were issued for hospital triage of fomepizole administration allowed conservation of valuable antidote in this massive poisoning outbreak for those patients most in need.

Full text available from: http://dx.doi.org/10.3109/15563650.2014.974106

Cardiac conduction disturbance after loperamide abuse

Marraffa JM, Holland MG, Sullivan RW, Morgan BW, Oakes JA, Wiegand TJ, Hodgman MJ. Clin Toxicol 2014; 52: 952-7.

Context

Prescription opioid abuse is a major public health concern and an ongoing epidemic in the United States. Loperamide is a widely available and inexpensive over-the-counter antidiarrheal with peripheral mu-opioid receptor activity. Online resources discuss the use of loperamide for the amelioration of withdrawal symptoms or recreational abuse. We describe the clinical course of 5 patients abusing loperamide, 3 of whom had life-threatening cardiac arrhythmias.

Methods

In this observational case series, patients with cardiac arrhythmias or history of loperamide abuse with cardiac arrhythmias were identified; 5 patients were identified and 4 of the 5 patients were seen directly at the bedside. Clinical profile and outcome of patients is reported.

Results

We report 5 patients with history of loperamide abuse; 3 of the 5 patients had life-threatening cardiac arrhythmias. One of the patients experienced a second life-threatening arrhythmia after he resumed loperamide abuse. Loperamide levels were obtained in 4 of the 5 patients and were at least one order of magnitude greater than therapeutic concentrations. Discontinuation of loperamide resulted in complete resolution of cardiac conduction disturbances.

Conclusion

This case series describes several patients with cardiac conduction abnormalities and life-threatening ventricular arrhythmias temporally related to loperamide abuse. With the recent efforts to restrict the diversion of prescription opioids, increasing abuse of loperamide as an opioid substitute may be seen. Toxicologists should be aware of these risks and we urge all clinicians to report such cases to FDA Medwatch®.

Full text available from: http://dx.doi.org/10.3109/15563650.2014.969371

Patterns of presentation and clinical features of toxicity after reported use of ([2-aminopropyl]-2,3-dihydrobenzofurans), the 'benzofuran' compounds. A report from the United Kingdom National Poisons Information Service

Kamour A, James D, Lupton DJ, Cooper G, Eddleston M, Vale JA, Thompson JP, Thanacoody HKR, Hill SL, Thomas SHL. Clin Toxicol 2014; online early: doi: 10.3109/15563650.2014.973115:

Objective

To characterise the patterns of presentation and clinical features of toxicity following reported recreational use of benzofuran compounds ((2-aminopropyl)-2,3-dihydrobenzofurans) in the UK, as reported to the National Poisons Information Service (NPIS), and to compare clinical features of toxicity with those after reported mephedrone use.

Methods

NPIS patient-specific telephone enquiries and user sessions for TOXBASE®, the NPIS online information database, related to (2-aminopropyl)-2,3-dihydrobenzofurans and associated synonyms were reviewed from March 2009 to August 2013. These data were compared with those of mephedrone, the recreational substance most frequently reported to NPIS, collected over the same period.

Results

There were 63 telephone enquiries concerning 66 patients and 806 TOXBASE® user sessions regarding benzofuran compounds during the period of study. The first telephone enquiry was made in July 2010 and the highest numbers of enquiries were received in August 2010 (33 calls, 112 TOXBASE® sessions). Patients were predominantly male (82%) with a median age of 29 years; 9 reported co-ingestion of other substances. Comparing the 57 patients who reported ingesting benzofuran compounds alone with 315 patients ingesting mephedrone alone, benzofurans were more often associated with stimulant features, including tachycardia, hypertension, mydriasis, palpitation, fever, increased sweating, and tremor, (72% vs. 38%, odds ratio [OR] 4.2, 95% confidence interval [CI] 2.27-7.85, $P < 0.0001$) and mental health disturbances (58% vs. 38%, OR 2.3, 95% CI 1.29-4.07, $P = 0.006$). Other features reported after benzofuran compound ingestion included gastrointestinal symptoms (16%), reduced level of consciousness (9%), chest pain (7%), and creatinine kinase elevation (5%).

Conclusions

Reported ingestion of benzofuran compounds is associated with similar toxic effects to those of amphetamines and cathinones. Mental health disturbances and stimulant features were reported more frequently following reported ingestion of benzofuran compounds than after ingestion of mephedrone.

Full text available from: http://dx.doi.org/10.3109/15563650.2014.973115

Extracorporeal treatment for carbamazepine poisoning: systematic review and recommendations from the EXTRIP workgroup

Ghannoum M, Yates C, Galvao TF, Sowinski KM, Vo THV, Coogan A, Gosselin S, Lavergne V, Nolin TD, Hoffman RS. Clin Toxicol 2014; online early: doi: 10.3109/15563650.2014.973572:

Context

The Extracorporeal Treatments in Poisoning (EXTRIP) workgroup was created to provide evidence and consensus-based recommendations on the use of extracorporeal treatments (ECTRs) in poisoning.

Objectives

To perform a systematic review and provide clinical recommendations for ECTR in carbamazepine poisoning.

Methods

After a systematic literature search, the subgroup extracted the data and summarized the findings following a pre-determined format. The entire workgroup voted via a two-round modified Delphi method to reach a consensus on voting statements, using a RAND/UCLA Appropriateness Method to quantify disagreement. Anonymous votes were compiled, returned, and discussed in person. A second vote determined the final recommendations.

Results

Seventy articles met inclusion criteria. Articles included case reports, case series, descriptive cohorts, pharmacokinetic studies, and in-vitro studies; two poor-quality observational studies were identified, yielding a very low quality of evidence for all recommendations. Data on 169 patients, including 6 fatalities, were reviewed. The workgroup concluded that carbamazepine is moderately dialyzable and made the following recommendations: ECTR is suggested in severe carbamazepine poisoning (2D). ECTR is recommended if multiple seizures occur and are refractory to treatment (1D), or if life-threatening dysrhythmias occur (1D). ECTR is suggested if prolonged coma or respiratory depression requiring mechanical ventilation are present (2D) or if significant toxicity persists, particularly when carbamazepine concentrations rise or remain elevated, despite using multiple-dose activated charcoal (MDAC) and supportive measures (2D). ECTR should be continued until clinical improvement is apparent (1D) or the serum carbamazepine concentration is below 10 mg/L (42 µmol/L) (2D). Intermittent hemodialysis is the preferred ECTR (1D), but both intermittent hemoperfusion (1D) or continuous renal replacement therapies (3D) are alternatives if hemodialysis is not available. MDAC therapy should be continued during ECTR (1D).

Conclusion

Despite the low quality of the available clinical evidence and the high protein binding capacity of carbamazepine, the workgroup suggested extracorporeal removal in cases of severe carbamazepine poisoning.

Full text available from: http://dx.doi.org/10.3109/15563650.2014.973572

Extracorporeal treatment for barbiturate poisoning: recommendations from the EXTRIP workgroup

Mactier R, Laliberté M, Mardini J, Ghannoum M, Lavergne V, Gosselin S, Hoffman RS, Nolin TD, on behalf of the EXTRIP workgroup. Am J Kidney Dis 2014; 64: 347-58.

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CHEMICAL WARFARE, BIOLOGICAL WARFARE AND RIOT CONTROL AGENTS

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