

Current Awareness in Clinical Toxicology

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CURRENT AWARENESS PAPERS OF THE MONTH

Lipid emulsions in the treatment of acute poisoning: a systematic review of human and animal studies

Jamaty C, Bailey B, Larocque A, Notebaert E, Sanogo K, Chauny J-M. Clin Toxicol 2010; 48: 1-27.

Objective

To assess the evidence regarding the efficacy and safety of intravenous fat emulsion (IFE) in the management of poisoned patients.

Methods

We performed a systematic review of the literature with no time or language restriction. The electronic databases were searched from their inception until June 1, 2009 (Medline, EMBASE, ISI web of science, Biological abstract, LILACS, ChemIndex, Toxnet, and Proquest). We also examined the references of identified articles and the gray literature. The target interventions eligible for inclusion were administration of any IFE before, during, or after poisoning in human or animals. All types of studies were reviewed. Eligibility for inclusion and study quality scores, based on criteria by Jadad and the STROBE statement, were evaluated by independent investigators. The primary outcome was mortality. Secondary outcomes included neurologic, hemodynamic, and electrocardiographic variables, as well as adverse effects.

Results

Of the 938 publications identified by the search strategies, 74 met the inclusion criteria. We identified 23 animal trials, 50 human, and 1 animal case reports. Overall, the quality of evidence was weak and significant heterogeneity prevented data pooling. Available data suggest some benefits of IFE in bupivacaine, verapamil, chlorpromazine, and some tricyclic antidepressants and beta-blockers toxicity. No trial assessed the safety of IFE in the treatment of acute poisoning.

Conclusion

The evidence for the efficacy of IFE in reducing mortality and improving hemodynamic, electrocardiographic, and neurological parameters in the poisoned patients is solely based on animal studies and human case reports. The safety of IFE has not been established.

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Intravenous lipid emulsion as antidote beyond local anesthetic toxicity: a systematic review

Cave G, Harvey M. Acad Emerg Med 2009; 16: 815-24.

Objectives

The objective was to assess the efficacy of lipid emulsion as antidotal therapy outside the accepted setting of local anesthetic toxicity.

Methods

Literature was accessed through PubMed, OVID (1966-February 2009), and EMBASE (1947-February 2009) using the search terms "intravenous" AND ["fat emulsion" OR "lipid emulsion" OR "Intralipid"] AND ["toxicity" OR "resuscitation" OR "rescue" OR "arrest" OR "antidote"]. Additional author and conference publication searches were undertaken. Publications describing the use of lipid emulsion as antidotal treatment in animals or humans were included.

Results

Fourteen animal studies, one human study, and four case reports were identified. In animal models, intravenous lipid emulsion (ILE) has resulted in amelioration of toxicity associated with cyclic antidepressants, verapamil, propranolol, and thiopentone. Administration in human cases has resulted in successful resuscitation from combined bupropion/lamotrigine-induced cardiac arrest, reversal of sertraline/quetiapine-induced coma, and amelioration of verapamil- and beta blocker-induced shock.

Conclusions

Management of overdose with highly lipophilic cardiotoxic medications should proceed in accord with established antidotal guidelines and early poisons center consultation. Data from animal experiments and human cases are limited, but suggestive that ILE may be helpful in potentially lethal cardiotoxicity or developed cardiac arrest attributable to such agents. Use of lipid emulsion as antidote remains a nascent field warranting further preclinical study and systematic reporting of human cases of use.

Incidence of adverse drug reactions induced by N-acetylcysteine in patients with acetaminophen overdose

Zyoud S, Awang R, Sulaiman SAS, Sweileh WM, Al-Jabi SW. Hum Exp Toxicol 2010; online early: doi: 10.1177/0960327109359642: 1-8.

Background

Intravenous N-acetylcysteine (IV-NAC) is widely recognized as the antidote of choice for acetaminophen overdose. However, its use is not without adverse drug reactions (ADR) that might affect therapeutic outcome or lead to treatment delay.

Objective

The aim of this study was to investigate the type and incidence of ADR induced by IV-NAC in patients treated for acetaminophen overdose.

Methods

This is a retrospective study of patients admitted to the hospital for acute acetaminophen overdose over a period of 4 years (1 January 2005 to 31 December 2008). The primary outcome of interest in this study was the occurrence of ADR during NAC administration. Pearson chi-square test or Fisher's exact test, student's t test, and Mann-Whitney U test were used in univariate analysis. SPSS 15 was used for data analysis.

Results

Two hundred and fifty five patients were studied. Different types of ADR were observed in 119 (46.7%) cases. Of those patients, 83 (69.7%) had been treated with IV-NAC versus 36 (30.3%) who had not ($p < 0.001$). The following ADR were significantly associated with IV-NAC administration: vomiting ($p = 0.001$), flushing ($p < 0.001$), rash ($p < 0.001$), pruritus ($p < 0.001$), chest pain ($p = 0.001$), bronchospasm ($p = .03$), coughing ($p = .01$), headache ($p = .001$),

dizziness ($p < .001$), convulsion ($p = 0.03$), and hypotension ($p = 0.001$). ADR were mild in 54 (43.2%), moderate in 17 (13.6%), and severe in 12 (9.6%) patients. There were no ADR in 42 (33.6%) patients. Comparative results of the characteristics of patients who reacted to IV-NAC and non-reactors showed that patients with ADR had no significant difference in age, gender, ethnicity, amount ingested, latency time, and acetaminophen level than nonreactors.

Conclusion

ADR to IV-NAC were common among patients with acetaminophen overdose, but mostly minor and all reported adverse reactions were easily managed.

Cost minimization analysis comparing enteral *N*-acetylcysteine to intravenous acetylcysteine in the management of acute acetaminophen toxicity

Martello JL, Pummer TL, Krenzelok EP. Clin Toxicol 2010; 48: 79-83.

Context

Acetaminophen poisoning is one of the most common exposures and causes of poisoning-related fatalities as reported to US poison information centers. Acetylcysteine is indicated for the antidotal treatment of acetaminophen poisoning to prevent or minimize acetaminophen-related hepatotoxicity. Available as either an enteral or intravenous (IV) formulation, both forms of acetylcysteine have been proven to be efficacious. Because of the differences in the acquisition costs and the length of treatment, it is unclear which treatment route is the most cost-effective.

Objective

The purpose of this study was to compare the total hospitalization charges associated with patients who received either enteral or IV acetylcysteine therapy.

Materials and methods

A retrospective, IRB-approved cohort study of patients treated with either enteral or IV acetylcysteine at a university-related hospital for the treatment of acute acetaminophen overdose was conducted. Patients included were over 18 years of age, admitted during the 5-year periods of 1996-2000 (enteral) and 2004-2008 (IV), had an ICD-9 discharge diagnosis for acetaminophen overdose, had no transplant history, and were admitted within 24 h of the overdose. The primary endpoint was the total cost associated with the hospital stay. The Consumer Price Index (CPI) inflation calculator from the US Bureau of Labor Statistics was used to adjust all monetary values to 2008 dollars.

Results

Of a total of 1647 patients, 261 met the inclusion criteria with 70 patients being treated with enteral acetylcysteine and 191 patients treated with IV acetylcysteine. The associated cost was greater in the enteral group than in the IV group (\$18287.63 vs. \$7607.82; $p < 0.001$). The average length of stay was longer in the enteral group compared to the IV group (7 days vs. 4 days; $p < 0.001$).

Conclusions

Patients who were treated with IV acetylcysteine had a decreased length of stay and cost of hospitalization compared with those patients who were treated with enteral acetylcysteine.

What's new in... Toxicity of drugs of abuse

Hill SL, Thomas SHL. Medicine 2009; 37: 621-6.

Abstract

Toxicity caused by drugs of abuse is a frequent reason for presentation to hospital.

Cannabis is the most widely used recreational agent. Although not often associated with acute toxicity requiring hospital admission, there is increasing recognition of its cardiovascular, respiratory and central effects. Strong opioids like heroin and methadone are still the most common causes of fatal recreational drug poisoning, but morbidity and mortality caused by

cocaine has been increasing. Numerous hospital presentations continue to occur following ecstasy use. Although less common, episodes of toxicity relating to other drugs of abuse, such as newer stimulants (e.g. piperazines), gamma hydroxybutyrate and its precursors, and ketamine, are increasingly encountered by medical staff.

This article is an update on the toxicity of recreational drugs, concentrating on recent research findings and emerging issues.

Acute caffeine ingestion: clinical features in patients attending the emergency department and Scottish poison centre enquiries between 2000 and 2008

Waring WS, Laing WJ, Good AM, Malkowska AM. *Scott Med J* 2009; 54: 3-6.

Background and aims

Little information is available regarding the healthcare burden associated with deliberate caffeine ingestion. The present study sought to establish the impact of caffeine ingestion on hospital attendances and Poisons Centre enquiries in Scotland.

Methods

Retrospective analyses of clinical data from patients attending the Royal Infirmary of Edinburgh after acute caffeine ingestion, and TOXBASE enquiries from Scotland regarding caffeine poisoning between 2000-2008 inclusive. Cochran-Armitage trend tests were used to evaluate changes in annual admissions and TOXBASE enquiries.

Results

There were 43 hospital attendances due to deliberate caffeine ingestion, representing 0.2% of all poisoning cases. The median (interquartile range) stated dose was 1040 mg (600-1500 mg). Minor gastrointestinal symptoms were common, and no patient developed features of severe toxicity. There were 1418 enquiries to TOXBASE concerning caffeine poisoning, representing 0.2% of all poisoning enquiries from Scotland. The proportions of hospital admissions and TOXBASE enquiries due to caffeine ingestion have remained constant.

Conclusion

Caffeine ingestion is uncommon, and results in only a small number of hospital attendances and Poisons Centre enquiries. In contrast to patterns reported elsewhere, the prevalence of caffeine abuse has not increased in Scotland over recent years.

The functional outcome and recovery of patients admitted to an intensive care unit following drug overdose: a follow-up study

O'Brien BP, Murphy D, Conrick-Martin I, Marsh B. *Anaesth Intensive Care* 2009; 37: 802-6.

Abstract

Patients who have overdosed on drugs commonly present to emergency departments, with only the most severe cases requiring intensive care unit (ICU) admission. Such patients typically survive hospitalisation. We studied their longer term functional outcomes and recovery patterns which have not been well described.

All patients admitted to the 18-bed ICU of a university-affiliated teaching hospital following drug overdoses between 1 January 2004 and 31 December 2006 were identified. With ethical approval, we evaluated the functional outcome and recovery patterns of the surviving patients 31 months after presentation, by telephone or personal interview. These were recorded as Glasgow outcome score, Karnofsky performance index and present work status.

During the three years studied, 43 patients were identified as being admitted to our ICU because of an overdose. The average age was 34 years, 72% were male and the mean APACHE II score was 16.7. Of these, 32 were discharged from hospital alive. Follow-up data was attained on all of

them. At a median of 31 months follow-up, a further eight had died. Of the 24 surviving there were 13 unemployed, seven employed and four in custody. The median Glasgow outcome score of survivors was 4.5, their Karnofsky score 80.

Admission to ICU for treatment of overdose is associated with a very high risk of death in both the short- and long-term. While excellent functional recovery is achievable, 16% of survivors were held in custody and 54% unemployed.

Which cyanide antidote?

Hall AH, Saiers J, Baud F. Crit Rev Toxicol 2009; 39: 541-52.

Abstract

Cyanide has several antidotes, with differing mechanisms of action and diverse toxicological, clinical, and risk/benefit profiles. The international medical community lacks consensus about the antidote or antidotes with the best risk/benefit ratio. Critical assessment of cyanide antidotes is needed to aid in therapeutic and administrative decisions that will improve care for victims of cyanide poisoning (particularly poisoning from enclosed-space fire-smoke inhalation), and enhance readiness for cyanide toxic terrorism and other mass-casualty incidents.

This paper reviews preclinical and clinical data on available cyanide antidotes and considers the profiles of these antidotes relative to properties of a hypothetical ideal cyanide antidote. Each of the antidotes shows evidence of efficacy in animal studies and clinical experience. The data available to date do not suggest obvious differences in efficacy among antidotes, with the exception of a slower onset of action of sodium thiosulfate (administered alone) than of the other antidotes. The potential for serious toxicity limits or prevents the use of the Cyanide Antidote Kit, dicobalt edetate, and 4-dimethylaminophenol in prehospital empiric treatment of suspected cyanide poisoning. Hydroxocobalamin differs from these antidotes in that it has not been associated with clinically significant toxicity in antidotal doses.

Hydroxocobalamin is an antidote that seems to have many of the characteristics of the ideal cyanide antidote: rapid onset of action, neutralizes cyanide without interfering with cellular oxygen use, tolerability and safety profiles conducive to prehospital use, safe for use with smoke-inhalation victims, not harmful when administered to non-poisoned patients, easy to administer.

Protective effects of fomepizole on 2-chloroethanol toxicity

Chen YT, Liao JW, Hung DZ. Hum Exp Toxicol 2010; online early: PM:20056735:

Abstract

2-Chloroethanol (2-CE) is a widely used industrial solvent. In Taiwan, Taiwanese farmers apply 2-CE on grapevines to accelerate grape growth, a practice that in some cases have caused poisoning in humans. Thus, there is strong interest in identifying antidotes to 2-CE.

This study examines the protective role in 2-CE intoxicated rats. Alcohol dehydrogenase and glutathione were hypothesized to be important in the metabolism of 2-CE. This study used fomepizole, an alcohol dehydrogenase inhibitor, and chemicals that affected glutathione metabolism to study 2-CE toxicity.

Notably, fomepizole 5 mg/kg significantly increased median lethal dose (LD50) of 2-CE from 65.1 to 180 mg/kg and reduced the production of a potential toxic metabolite chloroacetaldehyde (CAA) in animal plasma. In contrast, disulfiram (DSF), an aldehyde dehydrogenase inhibitor, increased the toxicity of 2-CE on the lethality in rats. Additional or pretreatment with N-acetylcysteine (NAC) and fomepizole significantly reduced plasma CAA concentrations. Fomepizole also significantly reduced 2-CE-inhibited glutathione activity. Otherwise, pretreatment with NAC for 4 days followed by co-treatment with fomepizole significantly decreased formation of the metabolic CAA.

These results indicated that its catalytic enzyme might play a vital role during 2-CE intoxication, and the combination of fomepizole and NAC could be a protective role in cases of acute 2-CE intoxication.

Acute renal failure owing to paraphenylenediamine hair dye poisoning in Sudanese children

Abdelraheem MB, El-Tigani MAA, Hassan EG, Ali MAM, Mohamed IA, Nazik AE. Ann Trop Paediatr 2009; 29: 191-6.

Introduction

Paraphenylenediamine (PPD) has traditionally been used as a dark-coloured hair dye. In Sudan, it is used by women to colour their hair and as a body dye when added to henna (*Lawsonia alba*). Accidental or deliberate ingestion causes severe systemic toxicity. Although a wide variety of complications has been described, there are few reports in children.

Aim

To describe the clinical features, management and outcome of PPD intoxication in Sudanese children. Methods: Data for a 3-year period (2006-2008) were extracted from the medical records of the Paediatric Nephrology Unit, Soba University Hospital. Information included the circumstances of poisoning, gender, age distribution, clinical presentation, biochemical findings and outcome.

Results

Over the 3-year period, 17 children (16 female) were admitted to the Paediatric Nephrology Unit with PPD intoxication. Mean age was 13.8 yrs (range 2-18). Thirteen (76.4%) had attempted suicide, three (17.6%) were poisoned as a result of attempted murder and one poisoning (5.8%) was accidental. Eight children (47%) required tracheostomy for severe angioneurotic oedema. Of 12 (71%) who developed acute renal failure (ARF), nine required dialysis and three were managed conservatively. Two children (12%) died and the other 15 recovered with normal renal function.

Conclusion

PPD intoxication is a life-threatening condition with significant morbidity and mortality in children. Clinical manifestations and outcome are similar to those in adults. Mortality can be reduced by early recognition, prompt referral and aggressive supportive treatment.

Early molecular adsorbents recirculating system treatment of Amanita mushroom poisoning

Kantola T, Koivusalo A-M, Hockerstedt K, Isoniemi H. Ther Apheresis Dial 2009; 13: 399-403.

Abstract

Acute poisoning due to ingestion of hepatotoxic *Amanita* sp. mushrooms can result in a spectrum of symptoms, from mild gastrointestinal discomfort to life-threatening acute liver failure. With conventional treatment, *Amanita phalloides* mushroom poisoning carries a substantial risk of mortality and many patients require liver transplantation. The molecular adsorbent recirculating system (MARS) is an artificial liver support system that can partly compensate for the detoxifying function of the liver by removing albumin-bound and water-soluble toxins from blood. This treatment has been used in acute liver failure to enable native liver recovery and as a bridging treatment to liver transplantation.

The aim of the study is to evaluate the outcome of 10 patients with *Amanita* mushroom poisoning who were treated with MARS. The study was a retrospectively analyzed case series. Ten adult patients with accidental *Amanita* poisoning of varying severity were treated in a liver disease specialized intensive care unit from 2001 to 2007. All patients received MARS treatment and standard medical therapy for mushroom poisoning. The demographic, laboratory, and clinical data from each patient were recorded upon admission. The one-year survival and need for liver transplantation were documented.

The median times from mushroom ingestion to first-aid at a local hospital and to MARS treatment were 18 h (range 14-36 h) and 48 h (range 26-78 h), respectively. All 10 patients survived longer than one year. One patient underwent a successful liver transplantation. No serious adverse side-

effects were observed with the MARS treatment.

In conclusion, MARS treatment seems to offer a safe and effective treatment option in Amanita mushroom poisoning.

Syndromic approach to treatment of snake bite in Sri Lanka based on results of a prospective national hospital-based survey of patients envenomed by identified snakes

Ariaratnam CA, Rezvi Sheriff MH, Arambepola C, Theakston RDG, Warrell DA. Am J Trop Med Hyg 2009; 81: 725-31.

Abstract

Of 860 snakes brought to 10 hospitals in Sri Lanka with the patients they had bitten, 762 (89%) were venomous. Russell's vipers (*Daboia russelii*) and hump-nosed pit vipers (*Hypnale hypnale*) were the most numerous and *H. hypnale* was the most widely distributed. Fifty-one (6%) were misidentified by hospital staff, causing inappropriate antivenom treatment of 13 patients.

Distinctive clinical syndromes were identified to aid species diagnosis in most cases of snake bite in Sri Lanka where the biting species is unknown. Diagnostic sensitivities and specificities of these syndromes for envenoming were 78% and 96% by *Naja naja*, 66% and 100% by *Bungarus caeruleus*, 14% and 100% by *Daboia russelii*, and 10% and 97% by *Hypnale hypnale*, respectively. Although only polyspecific antivenoms are used in Sri Lanka, species diagnosis remains important to anticipate life-threatening complications such as local necrosis, hemorrhage and renal and respiratory failure and to identify likely victims of envenoming by *H. hypnale* who will not benefit from existing antivenoms.

The technique of hospital-based collection, labeling and preservation of dead snakes brought by bitten patients is recommended for rapid assessment of a country's medically-important herpetofauna.

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CHEMICAL WARFARE, BIOLOGICAL WARFARE AND RIOT CONTROL AGENTS

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