Current Awareness in Clinical Toxicology

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CONTENTS

CURRENT AWARENESS PAPERS OF THE MONTH

Cannabinoid hyperemesis syndrome: potential mechanisms for the benefit of capsaicin and hot water hydrotherapy in treatment

Richards JR, Lapoint JM, Burillo-Putze G. Clin Toxicol 2017; online early: doi: 10.1080/15563650.2017.1349910:

Introduction

Cannabinoid hyperemesis syndrome is a clinical disorder that has become more prevalent with increasing use of cannabis and synthetic cannabinoids, and which is difficult to treat. Standard antiemetics commonly fail to alleviate the severe nausea and vomiting characteristic of the syndrome. Curiously, cannabinoid hyperemesis syndrome patients often report dramatic relief of symptoms with hot showers and baths, and topical capsaicin.

Objectives

In this review, we detail the pharmacokinetics and pharmacodynamics of capsaicin and explore possible mechanisms for its beneficial effect, including activation of transient receptor potential vanilloid 1 and neurohumoral regulation. Putative mechanisms responsible for the benefit of hot water hydrotherapy are also investigated.

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Methods

An extensive search of PubMed, OpenGrey, and Google Scholar from inception to April 2017 was performed to identify known and theoretical thermoregulatory mechanisms associated with the endocannabinoid system. The searches resulted in 2417 articles. These articles were screened for relevant mechanisms behind capsaicin and heat activation having potential antiemetic effects. References from the selected articles were also hand-searched. A total of 137 articles were considered relevant and included.

Capsaicin

Topical capsaicin is primarily used for treatment of neuropathic pain, but it has also been used successfully in some 20 cases of cannabinoid hyperemesis syndrome. The pharmacokinetics and pharmacodynamics of capsaicin as a transient receptor potential vanilloid 1 agonist may explain this effect. Topical capsaicin has a longer half-life than oral administration, thus its potential duration of benefit is longer.

Capsaicin and transient receptor potential vanilloid 1

Topical capsaicin binds and activates the transient receptor potential vanilloid 1 receptor, triggering influx of calcium and sodium, as well as release of inflammatory neuropeptides leading to transient burning, stinging, and itching. This elicits a novel type of desensitization analgesia. Transient receptor potential vanilloid 1 receptors also respond to noxious stimuli, such as heat (>43 °C), acids (pH <6), pain, change in osmolarity, and endovanilloids. The action of topical capsaicin may mimic the effect of heat-activation of transient receptor potential vanilloid 1.Endocannabinoid system and transient receptor potential vanilloid 1: Cannabinoid hyperemesis syndrome may result from a derangement in the endocannabinoid system secondary to chronic exogenous stimulation. The relief of cannabinoid hyperemesis syndrome symptoms from heat and use of transient receptor potential vanilloid 1 agonists suggests a complex interrelation between the endocannabinoid system and transient receptor potential vanilloid 1.

Temperature regulation

Hot water hydrotherapy is a mainstay of self-treatment for cannabinoid hyperemesis syndrome patients. This may be explained by heat-induced transient receptor potential vanilloid 1 activation.

"Sensocrine" antiemetic effects

Transient receptor potential vanilloid 1 activation by heat or capsaicin results in modulation of tachykinins, somatostatin, pituitary adenylate-cyclase activating polypeptide, and calcitonin gene-related peptide as well as histaminergic, cholinergic, and serotonergic transmission. These downstream effects represent further possible explanations for transient receptor potential vanilloid 1-associated antiemesis.

Conclusions

These complex interactions between the endocannabinoid systems and transient receptor potential vanilloid 1, in the setting of cannabinoid receptor desensitization, may yield important clues into the pathophysiology and treatment of cannabinoid hyperemesis syndrome. This knowledge can provide clinicians caring for these patients with additional treatment options that may reduce length of stay, avoid unnecessary imaging and laboratory testing, and decrease the use of potentially harmful medications such as opioids.

Full text available from: http://dx.doi.org/10.1080/15563650.2017.1349910

Evaluation of toxicity after acute accidental methotrexate ingestions in children under 6 years old: a 16-year multi-center review

Hays H, Beuhler MC, Spiller HA, Weber J, Mowry JB, Ryan ML, Spiller NE, Webb A. Clin Toxicol 2017; online early: doi: 10.1080/15563650.2017.1349319:

Context

There is little data on the frequency of adverse events following acute methotrexate ingestions in pediatric patients. Likewise, recommendations for observation length, site and management strategies in this population are not well established. Therefore, most recommendations are modeled after management of chronic overdose in patients with underlying medical conditions.

Objective

The primary objective of this study is to determine the frequency of acute toxicity after acute methotrexate accidental unsupervised ingestions in patients less than six years. In addition, we describe the frequency of late toxicity and characterize the management site and approaches.

Materials and Methods

This is a retrospective cohort study of pediatric accidental unsupervised methotrexate ingestions reported to six poison centers in the United States over a 16 year period. Demographic information, exposure details, signs, symptoms, treatments, length and location of observation and outcomes were collected.

Results

103 patients met inclusion criteria. Methotrexate dose was reported in 86 patients (84%) and ranged from 1.3 mg–75 mg. The majority of cases (97%) ingested a dose ≤20 mg. The significant majority of cases experienced no clinical effects (99 of 103 cases; 96%). Three children experienced minor outcome (3%). There were no patients with a major outcome or death.

Conclusions

The incidence of toxicity from pediatric single, acute ingestions of methotrexate is rare and when it occurs is generally limited to no or only minimally concerning effects. Because concentrations from single ingestions were consistent with low subtoxic exposures, we believe that home monitoring without hospital referral and without methotrexate specific therapy is reasonable in those with acute ingestions up to 20 mg.

Full text available from: http://dx.doi.org/10.1080/15563650.2017.1349319

Evaluation of dose and outcomes for pediatric vilazodone ingestions

Gaw CE, Spiller HA, Russell JL, Chounthirath T, Smith GA. Clin Toxicol 2017; online early: doi: 10.1080/15563650.2017.1347263:

Background

Selective serotonin reuptake inhibitor (SSRI) exposures among children younger than 6 years of age are generally well tolerated. Vilazodone is an SSRI with partial agonism at the 5-HT_{1A} receptor with demonstrated clinical efficacy for depression whose off-label usage is likely to increase. Recent evidence suggests that unintentional ingestion of vilazodone in children under 6 years old is associated with more severe clinical effects than other SSRIs. We chose to evaluate dose and outcomes for pediatric vilazodone ingestions.

Methods
A retrospective analysis of single-substance exposures associated with vilazodone among children younger than 6 years of age from 2011 through 2016 was conducted using data from the National Poison Data System.

Results
During 2011–2016, 753 vilazodone ingestions among children <6 years old were reported to US poison control centers. A near majority (49.0%, *n* = 369) experienced one or more clinical effects. The dose ingested was reported for 596 children (79%). The median dose associated with major effects was 50.0mg (Mean: 106.0) compared with 40.0mg (Mean 81.1) for moderate effects. Half (50.0%) of children with a major effect and 54.0% with a moderate effect ingested ≤40 mg of vilazodone. As the dose of vilazodone ingested increased, the proportions of exposures admitted to a healthcare facility (HCF) ($p < .001$) and with serious outcomes ($p < .001$) both increased. Children ≤2 years had higher proportions of HCF admission (33.8% vs 23.1%) and serious outcomes (27.0% vs 17.7%) than children 3–5 years of age. Clinical effects, such as coma, seizures, ataxia, and hallucinations/delusions, were observed among children ingesting doses of vilazodone as low as 10 mg.

Conclusions
Exposure to vilazodone poses a unique and potentially serious threat to children <6 years of age. Children in this age group who are exposed to vilazodone should be evaluated promptly in a clinical setting. Off-label use of vilazodone in children under 6 years should be discouraged until further research is conducted regarding its safety in this population.

Full text available from: http://dx.doi.org/10.1080/15563650.2017.1347263

Safety and effectiveness of physostigmine: a 10-year retrospective review

Arens AM, Shah K, Al-Abri S, Olson KR, Kearney T. Clin Toxicol 2017; online early: doi: 10.1080/15563650.2017.1342828:

Background
Physostigmine has long been recognized as an antidote to reverse anticholinergic delirium. However, its effectiveness, safety profile, and dosing have been disputed.

Objectives
To describe effectiveness, adverse events, and dosing associated with the use of physostigmine to reverse anticholinergic delirium.

Methods
A retrospective cohort study of hospitalized patients reported to a regional poison center system between 2003 and 2012 who received physostigmine to reverse an anticholinergic toxidrome. Data extraction of *a priori* defined variables were recorded with concurrence of investigators. The cases were stratified by the primary ingestant as the presumed causative agent and associations for response were performed using odds ratios (ORs), 95% confidence intervals (CI's), and p values.

Results
Of the 1422 cases identified, 191 met the inclusion criteria. Patients exposed to non-diphenhydramine antihistamines (*n* = 14), antipsychotics (*n* = 4), and tricyclic anti-depressants (*n* = 3) had 100% response to physostigmine, whereas anticholinergic plants (*n* = 46/67; 68.7%, OR: 0.70; CI: 0.36–1.35), diphenhydramine (*n* = 43/56; 64.2%, OR: 1.30; CI: 0.63–2.68), and combination products (*n* = 8/10; 80%, OR: 1.48; CI: 0.30–7.24) had partial response rates. Of the included patients, 142 (74.3%) were treated with

physostigmine alone, and 16 (8.4%) of these patients were discharged directly from the emergency department (ED).

Discussion

Most patients, 182 (95.3%), had no documented adverse effects. Four patients (2.1%) experienced emesis, two experienced QTc prolongation (1.0%), and two experienced seizures (1.0%). There was a single fatality 6 h after physostigmine administration. Average initial total doses of physostigmine ranged from 1.0 to 1.75 mg. Most patients were admitted to the ICU (*n* = 110; 57.6%), however, 36 (18.8%) patients were discharged directly from the ED.

Conclusions

In this retrospective cohort study, physostigmine administration to reverse anticholinergic delirium had a good safety profile, and often improved or resolved anticholinergic delirium when administered in doses less than 2 mg.

Full text available from: http://dx.doi.org/10.1080/15563650.2017.1342828

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Simplifying the hemodialysis prescription in patients with ethylene glycol poisoning

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Approaches to prevent bleeding associated with anticoagulants: current status and recent developments

Kalathottukaren MT, Haynes CA, Kizhakkedathu JN. Drug Deliv Transl Res 2017; online early: doi: 10.1007/s13346-017-0413-4:

Abstract and full text available from: http://dx.doi.org/10.1007/s13346-017-0413-4

Incomplete dabigatran reversal with idarucizumab

Steele AP, Lee JA, Dager WE. Clin Toxicol 2017; online early: doi: 10.1080/15563650.2017.1349911:

Context

With increasing use of direct oral anticoagulants (DOACs), urgent reversal of these agents becomes a growing concern. Idarucizumab is a humanized monoclonal antibody fragment that specifically binds to dabigatran with higher affinity than thrombin, rapidly neutralizing its anticoagulant effect without increased risk of thrombosis.

Case details

We describe two cases in which the recommended dose of idarucizumab was unsuccessful in completely reversing the anticoagulant effects of dabigatran. Both of these patients were noted to have supratherapeutic international normalized ratios (INRs) and high dabigatran concentrations. In the first case, an 86-year-old male underwent an emergent procedure and experienced excessive hemorrhaging refractory to blood product repletion, idarucizumab, and factor eight inhibitor bypass activity (FEIBA). In the second case, a 62-year-old female in shock was found to have elevated dabigatran concentrations despite two doses of idarucizumab, continuous renal replacement therapy (CRRT), blood product repletion, and FEIBA. Both patients ultimately expired from their coagulopathies.

Discussion

These cases illustrate the potential for incomplete reversal of dabigatran with the recommended 5 g of idarucizumab and emphasize the importance of early detection of dabigatran toxicity. While direct dabigatran serum concentrations are not readily available, the INR may be a useful surrogate marker for supratherapeutic dabigatran concentrations.

Full text available from: http://dx.doi.org/10.1080/15563650.2017.1349911

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INDEX

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