ARTICLES YOU MIGHT HAVE MISSED

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Article Title

Atsmon J, Brill-Amon E, Nadri-Shay C, et al. Preclinical and first-in-human evaluation of PRX-105, a PEGylated plant-derived, recombinant human acetylcholinesterase-R. *Toxicology and Applied Pharmacology* 2015;287:202–209.

Background

Organophosphate (OP) compounds, including potential terrorism agents, are associated with significant morbidity and mortality. Atropine and pralidoxime are the classic antidotes and utilized by the military via autoinjectors. Exogenous cholinesterase molecules are a potential alternative therapy when used as OP bio-scavengers.

Research Question

What are the pharmacokinetics and safety of PXR-105, a recombinant acetylcholinesterase-R, in animals and humans? What are its effects as a prophylactic and post-exposure treatment agent against OP poisoning?

Methods

PRX-105, a PEGylated, plant-derived, recombinant human acetylcholinesterase-R was expressed from a modified cell line of tobacco cells (*Nicotiana tabacum*). It was chemically conjugated to polyethylene glycol (PEG) to prolong its residence time and increase its efficacy as a bio-scavenger of OP agents. Multiple experiments were performed on mice, minipigs, and humans to determine the pharmacokinetics, effect, and safety of PRX-105. DEPQ (7-[(diethoxyphosphinyl)oxy]-1-methylquinolinium methyl sulfate) was selected as the OP agent since its LD50 is established.

Assessment of Prophylaxis

First study: 4 mice were pretreated with 50 nmol/mouse PRX-105 and subsequently challenged with 100 nmol/kg of DEPQ ($1.33 \times \text{LD}_{50}$). A control group of 4 mice was pretreated with normal saline followed by DEPQ challenge. Second study: 6 mice were pretreated with PXR-105 at doses of 40, 45, 50, and 60 nmol/kg and 2 min later, were challenged with DEPQ at a dose of 112.5 nmol/kg ($1.5 \times \text{LD}_{50}$). Two control groups received either saline followed by DEPQ or saline only. All groups were monitored for toxicity and mortality over 24 h.

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Assessment of Post-exposure Treatment

First study: 8–12 mice were challenged with DEPQ at a dose of 75 mcg/kg SQ ($1.5 \times \text{LD}_{50}$) and then at 10, 15, or 20 min, were administered PRX-105. Dosing of PRX-105 was either 50 or 70 nmol/kg. A control group received saline, and both groups were monitored for 24 h for signs of toxicity and mortality. Plasma concentrations and pharmacokinetic parameters were determined.

Second study: 2 mini-pigs were given a micro-dose of PRX-105 at a dose of 0.0144 mg/kg and then an IV injection of 0.0288 mg/kg, 1 week later, in order to mimic the intended clinical dosing of an exploratory human phase 1 study.

Safety and toxicity in mice were determined by administering PRX-105 at doses of 50, 100, and 200 mg/kg and comparing these to a saline control.

Third study: a repeat study was performed on 5 mice with corresponding doses of 3.2 and 16 mg/kg of PRX-105 or saline. Safety parameters included mortality, clinical signs of toxicity, body weight, food consumption, ophthalmoscopy, clinical chemistry and urinalysis, gross pathology, organ weights, and histopathology.

Fourth study: a safety study was also performed in 2 mini-pigs with similar parameters. Initially, they received 0.0144 mg/kg of PRX-105 followed by a dose of 0.0288 mg/kg 1 week later.

First in-human clinical trial: an exploratory phase 1, open-label, non-randomized, single-dose study was conducted on 10 healthy volunteers. One participant was given 0.025 mg IV, a second received 0.9 mg IV, and 8 subjects received 1.8 mg IV. Subjects were evaluated 7–10 days after drug administration for safety assessment.

Results

Assessment of prophylaxis: in the first part, all animals pretreated with 100 nmol/kg of PRX-105 survived, while all those pretreated with saline died. In the second part, all of the animals that received >50 nmol/kg of PRX-105 survived; those receiving saline control or PRX-105 at doses of 40 and 45 nmol/kg died. In both studies, no symptoms were observed in animals that survived 24 h after exposure to DEPQ.

Assessment of post-exposure treatment: all mice treated with saline died within 30 min of exposure to DEPQ. Treatment with PRX-105 was time dependent with no animals surviving when it was administered 20 min after exposure. Two of 8 survived at 15 min post exposure, and 14 of 16 survived at 10 min post exposure. PRX-105 was found to be safe and well tolerated in both mice and mini-pigs.

Human clinical study: in the first in-human trial, PRX-105 was found to be safe and well tolerated, without signs of anticholinergic toxicity or local adverse events. A 0.9 mg dose of

PRX-105 had a proportionally smaller area under the curve (AUC) than the 1.8 mg dose. For subjects receiving 1.8 mg/dose, the mean C_{max} was 335 ± 47 ng/mL. Mean t_{max} was 0.25 h, mean AUC was 2639 ± 592 ng $\times$ h/mL, and mean $t_{1/2}$ was 26.7 h.

Conclusion

PRX-105 may be a candidate for prophylaxis and post-exposure treatment for OP poisoning. Further investigations are required to better understand human dosing, efficacy, and side effects.

Critique

The study was a preliminary analysis of PRX-105 involving multiple small studies; larger human studies are needed. Pretreatment with PRX-105 will be difficult outside of military settings, extrapolation to civilian populations is difficult. No animals survived when PRX-105 was administered 20 min post-exposure. If these results can be extrapolated to the field, it would make timely administration to affected patients very difficult. There was minimal mention of the aging process and if this compound would address that effect. Lastly, there was a potential conflict of interest, as the manufacture of the compound funded the study.

Implication for Toxicologists

Although bio-scavengers are not currently used for OP toxicity, this work suggests a novel therapy. More research is needed before these agents enter into our treatment regimen.

Article Title

Geller A, Shehab N, Weidle NJ, et al. Emergency department visits for adverse events related to dietary supplements. *New England Journal of Medicine* 2015;373:1531–1540.

Background

The dietary supplement industry is a growing market with limited regulation and surveillance. Data on adverse events (AEs) is often voluntary and underreported.

Research Question

How many emergency department (ED) visits for AEs are related to dietary supplements? What are the associated characteristics of the patients, products, and types of AEs?

Methods

Trained abstractors reviewed clinical records of ED visits at 63 hospitals in the USA from 2004 to 2013. The hospitals were all participants in the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance project. Physician-diagnosed AEs were identified, and narrative descriptions recorded, including preceding circumstances, testing, treatments administered, and patient outcome. Cases were identified for events that were attributed to the use of dietary supplements by the treating clinician. Dietary supplements included botanicals, microbial additives, amino acids, vitamins, and minerals. Products that are typically considered food, such as energy drinks and herbal teas, were excluded. Adverse events were categorized as adverse reactions, allergic reactions, excess doses, unsupervised ingestion by children, or other events like choking. Deaths prior to or after ED arrival, as well as visits involving self-harm, drug abuse, therapeutic failures, non-adherence, or withdrawal were excluded from the analysis. National estimates (calculated as the sum of the number of cases multiplied by their respective weights) and corresponding 95 % confidence intervals (CIs) were developed by using SAS® software's SURVEYMEANS.

Results

A total of 3667 cases were identified during the 10-year study period. This corresponded to a yearly average of 23,005 (CI, 18,611 to 27,398) ED visits in the US for AEs related to dietary supplements. These visits were estimated to result in an average of 2154 (CI, 1342 to 2967) hospitalizations annually. The mean age of patients was 32 years, and those >64 years of age were more likely to be hospitalized (16.4 vs 8.4 %; $p = .003$). One fifth of ED visits was for AEs involving unsupervised children.

Products: most AEs among unsupervised children were due to micronutrient products (such as multivitamins or iron), weight loss supplements, or sleep, sedation, and anxiolytic aides (61.9 %; CI 56.5 to 67.3). After the exclusion of childhood events, weight loss supplements were implicated in 25.5 % of ED visits and energy products in 10 %. When analyzed by gender, women were more likely to have been exposed to weight loss products (30.4 %; CI 27.4 to 33.4) compared to men (17.6 %, CI 14.3 to 20.9) while men were more likely to have been exposed to sexual enhancement or

bodybuilding products (14.1 %; CI 10.5 to 17.7). Among adults >64 years or older, three specific micronutrients (iron, calcium, and potassium) were implicated in almost one third of ED visits.

Symptoms: cardiac symptoms (palpitations, chest pain, or tachycardia) were the most common symptoms associated with weight loss (42.9 % of patients), energy (46.0 % of patients), body building (49.8 %), and sexual enhancement products (37.3 %). Most patients with these symptoms were discharged from the ED (89.9 %; CI 87.2 to 92.6). Mild to moderate allergic reactions (40.6 %) and swallowing problems (41 %; CI 32.4 to 49.7) were the most common AEs associated with micronutrients (excluding iron, calcium, and potassium). Swallowing problems were most common with calcium; abdominal pain, nausea, and vomiting were associated with iron and potassium products. Among patients >64 years of age, 83.1 % (CI 73.3 to 92.9) of ED visits were due to swallowing problems from micronutrients.

Conclusion

An estimated 23,000 ED visits and 2100 hospitalizations annually in the USA from 2004 to 2013 were due to AEs associated with dietary supplements. They commonly involved cardiovascular symptoms from weight loss or energy products in young adults, unintentional ingestions among unsupervised children, and swallowing problems associated with micronutrients among older adults.

Critique

Limitations of this study include the inability to identify specific ingredients, missing fatality data, and reporting biases. The lack of laboratory analysis prevented analysis of the products' listed versus actual ingredients. There were no known biological samples taken, and confirmation of the exposures was not reported. Finally, the authors failed to mention poison centers as a possible resource for recording, and managing, such exposures.

Implication for Toxicologists

As more people utilize over-the-counter dietary supplements, the incidence of ED utilization for AEs associated with these products will increase. Toxicologists need to be aware of the potential AEs associated with dietary supplements. The findings in this study can serve as groundwork to institute public health interventions to reduce the risk of these AEs.

Title

Manini AF, Stimmel B, Hoffman RS, et al. Utility of cardiac troponin to predict drug overdose mortality. *Cardiovascular Toxicology*; (online) November 2015.

Background

Drug overdose is currently the leading cause of injury-related deaths in the USA. Clinical predictors of mortality related to overdose may be useful in predicting outcomes, risk stratification, and optimizing management of these patients.

Research Question

Can in-hospital mortality be predicted by cardiac troponin I (cTnI) following drug overdose?

Methods

This was a prospective, observational cohort study of suspected acute (duration <24 h of exposure) drug overdoses presenting to two urban tertiary care hospitals. Trained research assistants screened patients by rounding with an emergency department (ED) attending, several times a day during normal business hours, or by reviewing telephone referrals to the regional Poison Control Center (PCC). Following screening, subjects with any of the following were excluded: alternative diagnosis, nondrug overdose, dermal or inhalational exposures, age <18 years, incomplete outcome data, prisoners, pre-hospital cardiac arrest, or DNR orders. Subjects who did not have cTnI drawn as part of their initial workup were also excluded. Trained abstractors (95 % agreement of a random sampling of ten test charts) reviewed charts for necessary information. Traditional cardiac biomarkers, cTnI, were drawn upon initial presentation to the ED, with a detection limit of 0.01 ng/mL. Repeat cardiac biomarkers were drawn at the discretion of the primary clinical team. Peak troponin was defined as the highest measured cTnI at any point during the admission. Myocardial injury was defined as cTnI >0.09 ng/mL at any point in the hospital course. Chi-squared and *t* tests were used for categorical and continuous variables, respectively. Logistic regression analysis was used to assess the prognostic utility of cTnI. Odds ratios (ORs) were calculated with 95 % confidence intervals (CIs). Sample size was calculated a priori, assuming 5 % incidence of myocardial injury. A total of 435 subjects were needed to show, with 80 % power, a 5 % difference between fatal and nonfatal overdoses.

Results

A total of 1058 subjects were screened during the study period, and 625 were included for analysis. Of these, 437 (69.9 %) subjects had a cTnI ordered while 188 lacked cTnI data. Of those with a cTnI ordered, 14 % had a previous history of coronary artery disease (CAD), and 64 % were men. Abnormal vital signs were not significantly different in subjects with elevated cTnI or mortality. Clinicians were less likely to order troponins in patients with cocaine-positive urine toxicology screens. The proportion of death between groups was not significantly different; 20 deaths among those with cTnI testing ($n=437$; 4.6 %) versus 4 deaths among those without cTnI testing ($n=188$; 2.1 %). The most common classes of drug overdoses were benzodiazepines, opioids, sympathomimetics, acetaminophen, and antidepressants. The median number of cTnI ordered on patients was 2, with 20 patients having 3 or more. Elevated initial cTnI and peak cTnI occurred in 50 and 60 patients, respectively; both were associated with mortality. Mean initial troponin was significantly higher in fatal overdoses (1.2 vs. 0.06 ng/mL; $p<0.001$), but peak cTnI was not (1.3 vs. 0.38 ng/mL; $p=0.3$). A sensitivity analysis (excluding subjects with a history of CAD) showed that an elevated cTnI was an independent predictor of mortality (adjusted OR 25.2; CI 8.6 to 73.6) regardless of gender or age. Elevated cTnI significantly predicted mortality; OR 21.1 (CI, 6.2 to 71.4). Peak cTnI also predicted mortality; OR 25 (CI, 6.7 to 93.9). The optimal receiver operating characteristic cutpoints for initial cTnI was >0.02 ng/mL (85 % sensitive and 83 % specific) and >0.05 ng/mL (85 % sensitive and 86 % specific) for peak cTnI. Test characteristics were best for the initial cTnI (90 % specificity and 99 % negative predictive value). Initial cTnI was only normal in one death out of the entire cohort.

Conclusion

In acute drug overdoses, the initial cTnI result was strongly associated with in-hospital mortality but subsequent cTnI did not improve upon the diagnostic test characteristics.

Critique

This study was conducted at two urban tertiary care centers and involved mostly men; the results may not be valid in other patient populations. Likewise, over 90 % of cases involved one of only five different drug-class overdoses. Results may differ when other overdoses are studied. Also, about 30 % of subjects did not have a cTnI ordered. While these cases may represent the lowest risk patients, we cannot assume that this factored into clinicians' decision making. Finally, while the

initial cTnI demonstrated prognostic value over trended values, not all patients had repeated troponin levels.

Implications for Toxicologists

A presenting troponin level in the setting of a drug overdose may help toxicologists risk stratify patients and guide man-

agement. Overdose patients presenting with elevated cTnI, and those with ischemic EKG changes, should be admitted to intensive care units and may warrant further testing (i.e., echocardiograms, serial troponins).

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Conflicts of Interest None

Previous presentation of data at meetings or in abstract form None