LITERATURE

TACTICAL-CBRN

Journal Watch

Q1 & Q2 2024

CRISIS MEDICINE®

A quarterly collection of literature topics clinically related to Tactical CBRN.

Posting of articles are for information only and does not imply agreement or disagreement with the contents nor constitute a change in practices or training. Links are provided to respective publications for further reading and research. Additional log-in requirements may be required at various websites. The blue link at the end of each article will take you to the journal article on the publisher's page, which may be behind a pay wall. Crisis Medicine does not provide downloadable articles or free access to journal sites.

Looking for medical evidence to support the management of CBRN casualties is challenging. There are few studies on actual casualties and therefore for these topics, we have to look at animal and "bench" research. Unfortunately (or fortunately?) this is the best data we have on these topics.

Cyanide

Hydroxocobalamin is not associated with methemoglobinemia in patients with inhalation injury and suspected cyanide toxicity and a proposed algorithm for hydroxocobalamin administration. Eloise Wood Stanton 1, Sarah Wang 2, Kenneth Han 2, Claudia Nevarez 3, Priya Srihari 4, Haig A Yenikomshian 1, Fiona Garlich 4, Justin Gillenwater 5. Burns. 2024 Apr 24:S0305-4179(24)00140-2. DOI: 10.1016/j.burns.2024.04.007.

Abstract

Background: Cyanide poisoning poses a significant threat to burn patients exposed to smoke in residential or workplace fires, leading to central nervous system dysfunction, hemodynamic instability, cardiovascular collapse, and death. Prompt administration of an effective antidote is critical. Hydroxocobalamin, a form of vitamin B12, is the gold standard treatment for cyanide toxicity, by binding to cyanide molecules and converting them into non-toxic cyanocobalamin that is eliminated by the kidneys. This mechanism is distinct from previous cyanide antidotes, which induce the formation of methemoglobin to bind to cyanide. Recent case studies have reported elevated methemoglobin levels after hydroxocobalamin administration, raising concerns regarding its safety. The current study investigates smoke inhalation patients treated with hydroxocobalamin at a single institution Burn Unit in hopes of enhancing our understanding of the complexities surrounding cyanide antidote therapy.

Methods: After Institutional Board Approval, a retrospective cohort study was conducted. Our sample comprised burn patients with inhalation injury admitted to a single institution from 2013 to 2023 and treated with hydroxocobalamin for suspected cyanide toxicity. We also analyzed a matched control cohort of similar patients with inhalation injury not treated with hydroxocobalamin. We analyzed changes and peaks in methemoglobin levels, lactate levels, blood urea nitrogen (BUN) and creatinine, ventilator days, % total body surface area (TBSA), various types of medications and dressings, and mortality. Statistical analyses included t-tests, chi-square, linear and logistic regressions, and correlation analysis.

Results: In the study, 36 patients with suspected inhalation injury were treated with hydroxocobalamin at the Los Angeles General (LAG) Burn Unit from 2013 to 2023, who were matched to 32 control patients with inhalation injury who were not treated with hydroxocobalamin. Demographic and baseline characteristics showed no statistically significant differences between the groups, including age, gender, BMI, and %TBSA. No significant differences were found in initial, final, peak, or change in methemoglobin levels. The study also revealed no significant disparities in initial lactate levels, mortality, kidney function tests, ventilator days, surgeries, or use of medications/treatments (e.g., Silvadene dressings, Vitamin C) between the two groups. When controlling for covariates, multiple linear regression analysis (age, gender, and %TBSA) indicated that hydroxocobalamin administration was not significantly associated with changes in methemoglobin or mortality. Increased %TBSA, however, was linked to elevated lactate levels.

Conclusions: Our investigation sought to assess the potential risks associated with hydroxocobalamin administration in burn patients with concomitant inhalation injury. Contrary to our initial hypothesis, we found no statistically significant differences in methemoglobinemia, lactate levels, mortality, or kidney function. The influence of other

factors, such as methemoglobinemia-inducing drugs or hydroxocobalamin's interference with co-oximetry, adds complexity. Although elevated methemoglobin levels were observed in some cases, their clinical significance was limited. However, this study's limitations, particularly the rarity of inhalation injury cases with concern for cyanide toxicity, warrant consideration. Further research is required to comprehensively elucidate the impact of hydroxocobalamin administration on burn patients' outcomes.

Evaluation of hydroxocobalamin use for the treatment of suspected cyanide toxicity secondary to smoke inhalation. Jeff Kamta 1, Kaylee Maynard 2, Rachel F Schult 3, Derek E Bell 4, Courtney M C Jones 5, Nicole M Acquisto 3. Burns. 2024 Feb;50(1):157-166. DOI: 10.1016/j.burns.2023.08.020.

Abstract
Hydroxocobalamin is used for cyanide toxicity after smoke inhalation, but diagnosis is challenging. Retrospective studies have associated hydroxocobalamin with acute kidney injury (AKI). This is a retrospective analysis of patients receiving hydroxocobalamin for suspected cyanide toxicity. The primary outcome was the proportion of patients meeting predefined appropriate use criteria defined as ≥1 of the following: serum lactate ≥8 mmol/L, systolic blood pressure (SBP) <90 mmHg, new-onset seizure, cardiac arrest, or respiratory arrest. Secondary outcomes included incidence of AKI, pneumonia, resolution of initial neurologic symptoms, and in-hospital mortality. Forty-six patients were included; 35 (76%) met the primary outcome. All met appropriate use criteria due to respiratory arrest, 15 (43%) for lactate, 14 (40%) for SBP, 12 (34%) for cardiac arrest. AKI, pneumonia, and resolution of neurologic symptoms occurred in 30%, 21%, and 49% of patients, respectively. In-hospital mortality was higher in patients meeting criteria, 49% vs. 9% (95% CI 0.16, 0.64). When appropriate use criteria were modified to exclude respiratory arrest in a post-hoc analysis, differences were maintained, suggesting respiratory arrest alone is not a critical component to determine hydroxocobalamin administration. Predefined appropriate use criteria identify severely ill smoke inhalation victims and provides hydroxocobalamin treatment guidance.

Hyperbaric Evaluation and Treatment of Cyanide Toxicity. Mary E. Hanley 1, Heather M. Murphy-Lavoie 2. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan. 2023 Jun 26. Bookshelf ID: NBK482265.

Excerpt
Cyanide toxicity occurs commonly in patients with smoke inhalation who have been removed from burning structures. Cyanide forms as a result of incomplete combustion of materials containing nitrogen (plastics, vinyl, acrylics, nylon, neoprene, rubber, insulation). Patients presenting from structure fires with carbon monoxide poisoning should be assumed to have been exposed to toxic levels of cyanide as well since most modern buildings contain these materials. Other sources include workplace exposure, prolonged administration of sodium nitroprusside, insecticides, metalworking, bitter almonds, and the seeds of some fruits such as apricots. Hydrogen cyanide has also been used in chemical warfare (gas chambers in German concentration camps in World War II) because inhalation leads quickly to death.

Cyanide Toxicity. Jeremy Graham 1, Jeremy Traylor 2. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan. Bookshelf ID: NBK507796.

Excerpt

Cyanide is a rapidly acting substance that is traditionally known as a poison. Hydrogen cyanide was first isolated from Prussian blue dye in 1786, and cyanide first extracted from almonds around 1800. Cyanide can exist as a gas, hydrogen cyanide, a salt, potassium cyanide. Natural substances in some foods such as lima beans, almonds can release cyanide. Cyanide is also found in manufacturing and industrial sources such as insecticides, photographic solutions, and jewelry cleaners. It has been used as a poison in mass homicides and suicides. During World War II, the Nazis used cyanide as an agent of genocide in gas chambers.

Nerve Agents

Baseline physiological data from anesthetized pigs in a VX intoxication model. R Goulay 1, F Fémy 2, A Nervo 1, S Valentino 1, M Madi 1, A-L Joly 1, A Servonnet 1, F Nachon 1, C Reymond 1, N Jaffré 3. Toxicol Lett. 2024 Jun:397:117-128. DOI: 10.1016/j.toxlet.2024.05.012.

Abstract

Over the past fifty years, swine models have been used for organophosphorus intoxication studies. Among these studies and others on the swine model in general, some physiological data, especially cholinesterase activity highly impacted by organophosphorus compounds like nerve agent VX, still need to be completed. To support and compare our model to others, we have published the experimental protocol, the physiological values of 31 juvenile anesthetized pigs, and the 6 h-follow-up of six supplementary anesthetized control animals and 7 VX-intoxicated pigs. We reported hemodynamics and respiratory parameters, blood levels in several biochemical parameters, blood gas, and complete blood count and compared them to the literature. We also focused on tissue and blood cholinesterase activities and detailed them for acetylcholinesterase and butyrylcholinesterase. After establishing a broad physiological data set consistent with the literature, we reported several cardio-respiratory parameters that seem more affected by an organophosphate intoxication, like heart rate, arterial blood pressure, cardiac output, and respiratory rate. Within the blood, oxygen saturation (SpO_2), lactatemia, base excess, and glycemia can also be measured and associated with the other parameters to evaluate the life-threatening status. This swine model is currently used to develop and evaluate medical countermeasures against organophosphate nerve agent intoxications.

Acetohydroxamic acid salts: mild, simple and effective degradation reagents to counter Novichok nerve agents. Boris Smolkin 1, Victoria Nahum 1, Eugenia Bloch-Shilderman 2, Uri Nili 2, Gil Fridkin 1, Nissan Ashkenazi 1 3. RSC Adv. 2024 May 8;14(21):14904-14909. DOI: 10.1039/d4ra02038c.

Abstract

Novichoks is the latest known class of organophosphorus nerve agents to be developed. These highly lethal persistent agents, which exert their toxicity mainly through dermal exposure, pose new major challenges in mitigating their effect, mainly in respect to decontamination and medical countermeasures. Herein we report on the effective degradation of Novichok agents (A-230, A-232 and A-234) by hydroxamic acid salts. This class of α-nucleophiles, with emphasis on the FDA approved drug acetohydroxamic acid, were found to promote rapid hydrolysis of these extremely toxic agents. Using ^{31}P NMR the Novichoks degradation rates were determined to be in time scale of minutes with the following order of reactivity A-230>A-232>A-234. The degradation efficiency was found to be dependent on the nucleophiles, their counter-cations and the specific solvent mixture used. Hence, these scavengers can serve as efficient and mild decontaminants in various scenarios including surfaces, dermal decontamination (as an alternative to active lotions such as the RSDL® kit) and also as a medical countermeasure in the form of "catch-up therapy".

Hypothermia as potential therapeutic approach to attenuating soman-induced seizure, neuropathology, and mortality with an adenosine A1 receptor agonist and body cooling. Crystal Munoz 1, Cindy Acon-Chen 1, Zora-Maya Keith 1, Tsung-Ming Shih 2. Neuropharmacology. 2024 Aug 1:253:109966. DOI: 10.1016/j.neuropharm.2024.109966. Abstract

Abstract

Organophosphorus nerve agents, such as soman (GD), produce excitotoxic effects resulting in sustained status epilepticus (SSE) and brain damage. Previous work shows that neuronal inhibitory effects of A_1 adenosine receptor (A_1AR) agonists, such as N^6- Bicyclo (2.2.1)-hept-2-yl-5'-chloro-5'-deoxyadenosine (Cl-ENBA), suppresses GD-induced SSE and improves neuropathology. Some other physiologic effects of these agonists are hypothermia, hypotension, and sedation. Hypothermia may also shield the brain from injury by slowing down chemical insults, lessening inflammation, and contributing to improved neurological outcomes. Therefore, we attempted to isolate the hypothermic effect from ENBA by assessing the neuroprotective efficacy of direct surface body cooling in a rat GD-induced SSE model, and comparing the effects on seizure termination, neuropathology, and survival. Male rats implanted with a body temperature (T_b) transponder and electroencephalographic (EEG) electrodes were primed with asoxime (HI-6), exposed to GD 30 min later, and then treated with Cl-ENBA or had T_b lowered directly via body cooling at 30 min after the onset of seizure activity. Afterwards, they were either allowed to develop hypothermia as expected, or received thermal support to maintain normothermic T_b for a period of 6-h. Neuropathology was assessed at 24 h. Regardless of Cl-ENBA or surface cooling, all hypothermic GD-exposed groups had significantly improved 24-h survival compared to rats with normothermic T_b (81% vs. 39%, $p < 0.001$). Cl-ENBA offered neuroprotection independently of hypothermic T_b. While hypothermia enhanced the overall efficacy of Cl-ENBA by improving survival outcomes, body cooling didn't reduce seizure activity or neuropathology following GD-induced SSE.

Persistence of A-234 nerve agent on indoor surfaces. Tomáš Rozsypal 1. Chemosphere. 2024 Jun:357:141968. DOI: 10.1016/j.chemosphere.2024.141968.

Abstract
Understanding the fundamental physical characteristics of extremely toxic compounds and their behavior across different environments plays a crucial role in assessing their danger. Additionally, this knowledge informs the development of protocols for gathering forensic evidence related to harmful chemicals misuse. In 2018, former Russian spy Sergei Skripal and his daughter were poisoned in Salisbury, England, with a substance later identified as the unconventional nerve agent A-234. Contamination with the compound was found on items inside Skripal's home. The aim of this paper was to determine the persistence of A-234 on selected indoor surfaces. Ceramics, aluminum can, laminated chipboard, polyvinyl chloride (PVC) floor tile, polyethylene terephthalate (PET) bottle, acrylic paint and computer keyboard were used as matrices. The decrease in surface contamination and further fate of the compound was monitored for 12 weeks. Persistence determination involved optimizing the wipe sampling method. Simultaneously, evaporation from the surface and permeation of the contaminant into the matrix were closely monitored. The experimental findings indicate that the nerve agent exhibits remarkable persistence, particularly on impermeable surfaces. Notably, the process of A-234 evaporation plays a minor role in determining its fate, with detectable concentrations observed solely above solid, non-porous surfaces such as ceramics and aluminum can. The surface persistence half-life varied significantly, ranging from 12 min to 478 days, depending on the material. The article has implications for emergency response protocols, decontamination strategies, public health and crime scene investigations.

The estimation of acute oral toxicity (LD50) of G-series organophosphorus-based chemical warfare agents using quantitative and qualitative toxicology in silico methods. Maciej Noga 1, Agata Michalska 2, Kamil Jurowski 3 4. Arch Toxicol. 2024 Jun;98(6):1809-1825. DOI: 10.1007/s00204-024-03714-5.

Abstract
The idea of this study was the estimation of the theoretical acute toxicity (t-LD_{50}, rat, oral dose) of organophosphorus-based chemical warfare agents from the G-series (n = 12) using different in silico methods. Initially identified in Germany, the G-type nerve agents include potent compounds such as tabun, sarin, and soman. Despite their historical significance, there is a noticeable gap in acute toxicity data for these agents. This study employs qualitative (STopTox and AdmetSAR) and quantitative (TEST; CATMoS; ProTox-II and QSAR Toolbox) in silico methods to predict LD_{50} values, offering an ethical alternative to animal testing. Additionally, we conducted quantitative extrapolation from animals, and the results of qualitative tests confirmed the acute toxicity potential of these substances and enabled the identification of toxicophoric groups. According to our estimations, the most lethal agents within this category were GV, soman (GD), sarin (GB), thiosarin (GBS), and chlorosarin (GC), with t-LD_{50} values (oral administration, extrapolated from rat to human) of 0.05 mg/kg bw, 0.08 mg/kg bw, 0.12 mg/kg bw, 0.15 mg/kg bw, and 0.17 mg/kg bw, respectively. On the contrary, compounds with a cycloalkane attached to the phospho-oxygen linkage, specifically methyl cyclosarin and cyclosarin, were found to be the least toxic, with values of 2.28 mg/kg bw and 3.03 mg/kg bw. The findings aim to fill the knowledge gap regarding the acute toxicity of these agents, highlighting the need for modern toxicological methods that align with ethical

considerations, next-generation risk assessment (NGRA) and the 3Rs (replacement, reduction and refinement) principles.

A-series agent A-234: initial in vitro and in vivo characterization. Martina Hrabinova, Jaroslav Pejchal, Vendula Hepnarova 2, Lubica Muckova 1 3, Lucie Junova 1 3, Jakub Opravil 1, Jana Zdarova Karasova 1 3, Tomas Rozsypal 4, Alzbeta Dlabkova 1, Helena Rehulkova 1, Tomas Kucera 5, Zbyněk Vecera 1, Filip Caisberger 6, Monika Schmidt 3 7, Ondrej Soukup 3, Daniel Jun 8. Arch Toxicol. 2024 Apr;98(4):1135-1149. DOI: 10.1007/s00204-024-03689-3

Abstract
A-series agent A-234 belongs to a new generation of nerve agents. The poisoning of a former Russian spy Sergei Skripal and his daughter in Salisbury, England, in March 2018 led to the inclusion of A-234 and other A-series agents into the Chemical Weapons Convention. Even though five years have already passed, there is still very little information on its chemical properties, biological activities, and treatment options with established antidotes. In this article, we first assessed A-234 stability in neutral pH for subsequent experiments. Then, we determined its inhibitory potential towards human recombinant acetylcholinesterase (HssAChE; EC 3.1.1.7) and butyrylcholinesterase (HssBChE; EC 3.1.1.8), the ability of HI-6, obidoxime, pralidoxime, methoxime, and trimedoxime to reactivate inhibited cholinesterases (ChEs), its toxicity in rats and therapeutic effects of different antidotal approaches. Finally, we utilized molecular dynamics to explain our findings. The results of spontaneous A-234 hydrolysis showed a slow process with a reaction rate displaying a triphasic course during the first 72 h (the residual concentration 86.2%). A-234 was found to be a potent inhibitor of both human ChEs (HssAChE IC_{50} = 0.101 ± 0.003 μM and HssBChE IC_{50} = 0.036 ± 0.002 μM), whereas the five marketed oximes have negligible reactivation ability toward A-234-inhibited HssAChE and HssBChE. The acute toxicity of A-234 is comparable to that of VX and in the context of therapy, atropine and diazepam effectively mitigate A-234 lethality. Even though oxime administration may induce minor improvements, selected oximes (HI-6 and methoxime) do not reactivate ChEs in vivo. Molecular dynamics implies that all marketed oximes are weak nucleophiles, which may explain the failure to reactivate the A-234 phosphorus-serine oxygen bond characterized by low partial charge, in particular, HI-6 and trimedoxime oxime oxygen may not be able to effectively approach the A-234 phosphorus, while pralidoxime displayed low interaction energy. This study is the first to provide essential experimental preclinical data on the A-234 compound.

Acholinergic established status epilepticus following a sarin nerve agent insult in rats. Shlomi Lazar 1, Adi Neufeld-Cohen 2, Inbal Egoz 2, Shlomi Baranes 2, Rellie Gez 2, Pnina Glick 2, Maayan Cohen 2, Hila Gutman 2, Shira Chapman 2, Ariel Gore 3 Toxicol Appl Pharmacol. . 2024 Mar:484:116870. DOI: 10.1016/j.taap.2024.116870

Abstract
The development of refractory status epilepticus (SE) following sarin intoxication presents a therapeutic challenge. Here, we evaluated the efficacy of delayed combined double or triple treatment in reducing abnormal epileptiform seizure activity (ESA) and the ensuing long-term

neuronal insult. SE was induced in rats by exposure to 1.2 LD_{50} sarin followed by treatment with atropine and TMB4 (TA) 1 min later. Double treatment with ketamine and midazolam or triple treatment with ketamine, midazolam and levetiracetam was administered 30 min post-exposure, and the results were compared to those of single treatment with midazolam alone or triple treatment with ketamine, midazolam, and valproate, which was previously shown to ameliorate this neurological insult. Toxicity and electrocorticogram activity were monitored during the first week, and behavioral evaluations were performed 2 weeks post-exposure, followed by biochemical and immunohistopathological analyses. Both double and triple treatment reduced mortality and enhanced weight recovery compared to TA-only treatment. Triple treatment and, to a lesser extent, double treatment significantly ameliorated the ESA duration. Compared to the TA-only or the TA+ midazolam treatment, both double and triple treatment reduced the sarin-induced increase in the neuroinflammatory marker PGE_2 and the brain damage marker TSPO and decreased gliosis, astrocytosis and neuronal damage. Finally, both double and triple treatment prevented a change in behavior, as measured in the open field test. No significant difference was observed between the efficacies of the two triple treatments, and both triple combinations completely prevented brain injury (no differences from the naïve rats). Delayed double and, to a greater extent, triple treatment may serve as an efficacious delayed therapy, preventing brain insult propagation following sarin-induced refractory SE.

AChE reactivation in precision-cut lung slices following organophosphorus compound poisoning. Fee Gölitz[1], Julia Herbert[2], Franz Worek[3], Timo Wille[4]. Toxicol Lett. 2024 Feb:392:75-83. DOI: 10.1016/j.toxlet.2023.12.014.

Abstract
Precision-cut lung slices (PCLS) are a suitable model for analyzing the acetylcholinesterase (AChE) activity and subsequent effects after exposure to organophosphorus (OP) compounds. In this study, the AChE activity was determined in intact PCLS for the first time. Since the current standard therapy for OP poisoning (atropine + oxime + benzodiazepine) lacks efficiency, reliable models to study novel therapeutic substances are needed. Models should depict pathophysiological mechanisms and help to evaluate the beneficial effects of new therapeutics. Here PCLS were exposed to three organophosphorus nerve agents (OPNAs): sarin (GB), cyclosarin (GF), and VX. They were then treated with three reactivators: HI-6, obidoxime (OBI), and a non-oxime (NOX-6). The endpoints investigated in this study were the AChE activity and the airway area (AA) change. OPNA exposure led to very low residual AChE activities. Depending on the reactivator properties different AChE reactivation results were measured. GB-inhibited PCLS-AChE was reactivated best, followed by VX and GF. To substantiate these findings and to understand the connection between the molecular and the functional levels in a more profound way the results were correlated to the AA changes. These investigations underline the importance of reactivator use and point to the possibilities for future improvements in the treatment of OPNA-exposed victims.

Irritant Gases

Phosgene Toxicity Clinical Manifestations and Treatment: A Systematic Review. Alireza Asgari 1, Mohammadreza Parak 1, Yazdan Hasani Nourian 1, Mostafa Ghanei 2. Cell J. 2024 Feb 1;26(2):91-97. DOI: 10.22074/cellj.2024.2011864.1405

Abstract
Exposure to phosgene, a colourless poisonous gas, can lead to various health issues including eye irritation, a dry and burning throat, vomiting, coughing, the production of foamy sputum, difficulty in breathing, and chest pain. This systematic review aims to provide a comprehensive overview of the clinical manifestations and treatment of phosgene toxicity by systematically analyzing available literature. The search was carried out on various scientific online databases to include related studies based on inclusion and exclusion criteria with the use of PRISMA guidelines. The quality of the studies was assessed using the Mixed Methods Appraisal Tool (MMAT). Thirteen articles were included in this study after the screening process. Inhalation was found to be the primary health problem of phosgene exposure with respiratory symptoms such as coughing and dyspnea. Chest pain and pulmonary oedema were also observed in some cases. Furthermore, pulmonary crackle was the most common reported physical examination. Beyond respiratory tract health issues, other organs involvements such as cardiac, skin, eye, and renal were also reported in some studies. The symptoms can occur within minutes to hours after exposure, and the severity of symptoms depends on the amount of inhaled phosgene. The findings showed that bronchodilators can alleviate symptoms of bronchoconstriction caused by phosgene. Oxygen therapy is essential for restoring oxygen levels and improving respiratory function in cases of hypoxemia. In severe cases, endotracheal intubation and invasive mechanical ventilation are used for artificial respiration, along with the removal of tracheal secretions and pulmonary oedema fluid through suctioning as crucial components of supportive therapy.

Successful treatment of 1 patient with chlorine-induced ARDS using awake self-prone positioning and nasal high-flow oxygen: A case report. Fugui Wang 1, Fangfang Liu, Houqing Lu. Medicine (Baltimore) . 2024 Jan 19;103(3):e36995. DOI: 10.1097/MD.0000000000036995

Abstract
Rationale: Accidents involving chlorinated compounds in the context of cleaning are not uncommon. However, improving the treatment success rate for acute respiratory distress syndrome (ARDS) patients caused by chlorine gas presents significant challenges.

Patient concerns: A 28-year-old female was admitted to the intensive care unit after accidental inhalation of chlorine gas resulting in ARDS.

Diagnoses: The patient was diagnosed with ARDS attributed to chlorine gas exposure.

Interventions: The intervention involved utilizing a combination of awake self-prone positioning (ASPP) and high-flow nasal oxygen therapy for treatment.

Outcomes: After continuous ASPP and high-flow nasal oxygen therapy, the patient quickly recovered and was transferred out of the intensive care unit on the 6th day without any adverse events.

Lessons: ASPP combined with high-flow nasal oxygen therapy can improve patients' hypoxemia, prevent the need for intubation, avoid rapid deterioration of the condition, reduce treatment complexity, and lower mortality rate.

An in-silico porcine model of phosgene-induced lung injury predicts clinically relevant benefits from application of continuous positive airway pressure up to 8 h post exposure. Sonal Mistry 1, Timothy E Scott 2, Bronwen Jugg 3, Rosi Perrott 3, Sina Saffaran 1, Declan G Bates. Toxicol Lett. 2024 Jan:391:45-54. DOI: 10.1016/j.toxlet.2023.12.005

Abstract
We present the first computational model of the pathophysiological consequences of phosgene-induced lung injury in porcine subjects. Data from experiments previously performed in several cohorts of large healthy juvenile female pigs (111 data points from 37 subjects), including individual arterial blood gas readings, respiratory rate and heart rate, were used to develop the computational model. Close matches are observed between model outputs (PaO_2 and $PaCO_2$) and the experimental data, for both terminally anaesthetised and conscious subjects. The model was applied to investigate the effectiveness of continuous positive airway pressure (CPAP) as a pre-hospital treatment method when treatment is initiated at different time points post exposure. The model predicts that clinically relevant benefits are obtained when 10 cmH_2O CPAP is initiated within approximately 8 h after exposure. Supplying low-flow oxygen (40%) rather than medical air produced larger clinical benefits than applying higher CPAP pressure levels. This new model can be used as a tool for conducting investigations into ventilation strategies and pharmaceutical treatments for chemical lung injury of diverse aetiology, and for helping to refine and reduce the use of animals in future experimental studies.

Countermeasures against Pulmonary Threat Agents. Jacqui Marzec 1, Srikanth Nadadur 2. J Pharmacol Exp Ther. 2024 Jan 17;388(2):560-567. DOI: 10.1124/jpet.123.001822

Abstract
Inhaled toxicants are used for diverse purposes, ranging from industrial applications such as agriculture, sanitation, and fumigation to crowd control and chemical warfare, and acute exposure can induce lasting respiratory complications. The intentional release of chemical warfare agents (CWAs) during World War I caused life-long damage for survivors, and CWA use is outlawed by international treaties. However, in the past two decades, chemical warfare use has surged in the Middle East and Eastern Europe, with a shift toward lung toxicants. The potential use of industrial and agricultural chemicals in rogue activities is a major concern as they are often stored and transported near populated areas, where intentional or accidental release can cause severe injuries and fatalities. Despite laws and regulatory agencies that regulate use, storage, transport, emissions, and disposal, inhalational exposures continue to cause lasting lung injury. Industrial irritants (e.g., ammonia) aggravate the upper respiratory tract, causing pneumonitis, bronchoconstriction, and dyspnea. Irritant gases (e.g., acrolein, chloropicrin) affect epithelial barrier integrity and cause tissue damage through reactive intermediates or by direct adduction of cysteine-rich proteins. Symptoms of CWAs (e.g., chlorine gas, phosgene, sulfur mustard) progress from airway obstruction and pulmonary

edema to acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), which results in respiratory depression days later. Emergency treatment is limited to supportive care using bronchodilators to control airway constriction and rescue with mechanical ventilation to improve gas exchange. Complications from acute exposure can promote obstructive lung disease and/or pulmonary fibrosis, which require long-term clinical care. SIGNIFICANCE STATEMENT: Inhaled chemical threats are of growing concern in both civilian and military settings, and there is an increased need to reduce acute lung injury and delayed clinical complications from exposures. This minireview highlights our current understanding of acute toxicity and pathophysiology of a select number of chemicals of concern. It discusses potential early-stage therapeutic development as well as challenges in developing countermeasures applicable for administration in mass casualty situations.

Dermal Exposure to Vesicating Nettle Agent Phosgene Oxime: Clinically Relevant Biomarkers and Skin Injury Progression in Murine Models. Dinesh G Goswami 1, Satyendra K Singh 1, Ebenezar O M Okoyeocha 1, Andrew K Roney 1, Omid Madadgar 1, Rick Tuttle 1, William Sosna 1, Poojya Anantharam 1, Claire R Croutch 1, Rajesh Agarwal 1, Neera Tewari-Singh 2. Pharmacol Exp Ther. 2024 Jan 17;388(2):536-545. DOI: 10.1124/jpet.123.001718

Abstract
Phosgene oxime (CX), categorized as a vesicating chemical threat agent, causes effects that resemble an urticant or nettle agent. CX is an emerging potential threat agent that can be deployed alone or with other chemical threat agents to enhance their toxic effects. Studies on CX-induced skin toxicity, injury progression, and related biomarkers are largely unknown. To study the physiologic changes, skin clinical lesions and their progression, skin exposure of SKH-1 and C57BL/6 mice was carried out with vapor from 10 μl CX for 0.5-minute or 1.0-minute durations using a designed exposure system for consistent CX vapor exposure. One-minute exposure caused sharp (SKH-1) or sustained (C57BL/6) decrease in respiratory and heart rate, leading to mortality in both mouse strains. Both exposures caused immediate blanching, erythema with erythematous ring (wheel) and edema, and an increase in skin bifold thickness. Necrosis was also observed in the 0.5-minute CX exposure group. Both mouse strains showed comparative skin clinical lesions upon CX exposure; however, skin bifold thickness and erythema remained elevated up to 14 days postexposure in SKH-1 mice but not in C57BL/6 mice. Our data suggest that CX causes immediate changes in the physiologic parameters and gross skin lesions resembling urticaria, which could involve mast cell activation and intense systemic toxicity. This novel study recorded and compared the progression of skin injury to establish clinical biomarkers of CX dermal exposure in both the sexes of two murine strains relevant for skin and systemic injury studies and therapeutic target identification. SIGNIFICANCE STATEMENT: Phosgene oxime (CX), categorized as a vesicating agent, is considered as a potent chemical weapon and is of high military and terrorist threat interest since it produces rapid onset of severe injury as an urticant. However, biomarkers of clinical relevance related to its toxicity and injury progression are not studied. Data from this study provide useful clinical markers of CX skin toxicity in mouse models using a reliable CX exposure system for future mechanistic and efficacy studies.

Chlorine Gas Toxicity. Ashkan Morim 1, Gregory T. Guldner. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan. Bookshelf ID: NBK537213

Excerpt
Gaseous chlorine is poisonous and classified as a pulmonary irritant. It has intermediate water solubility with the capability of causing acute damage to the upper and lower respiratory tract. Chlorine gas has many industrial uses, but it was also once used as a chemical weapon in World War I. Today, most incidents of chlorine exposure are through accidental industrial or household exposures. As for industrial exposures, there have been several instances of train accidents carrying liquid chlorine that caused the release of chlorine gas to the surrounding environment. At home, a mixture of chlorine bleach with other household products that contain acid or ammonia is a common source of exposure to chlorine gas.

Toxicity to chlorine gas depends on the dose and duration of exposure. At concentrations of 1 to 3 ppm, chlorine gas acts as an eye and oral mucous membrane irritant; at 15 ppm, there is an onset of pulmonary symptoms, and it can be fatal at 430 ppm within 30 minutes.

Because of its strong odor, chlorine gas can be detected easily. Symptoms of chlorine gas exposure include burning of the conjunctiva, throat, and the bronchial tree. Higher concentrations can produce bronchospasm, lower pulmonary injury, and delayed pulmonary edema.

Phosgene Toxicity. Matthew A. Von Zimmerman 1, Thomas C. Arnold 2. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan. Bookshelf ID: NBK589660

Excerpt
Phosgene dates back over 200 years to its conception in the laboratory of Cornish chemist John Davy. During WWI, it was known as 'Choky Gas' or 'CG.' Today it remains ubiquitous in the industrial landscape. Phosgene is a hydrophobic, volatile irritant that causes chemical pneumonitis and is a cause of acute respiratory distress syndrome (ARDS) that can be refractory.

Vesicants

A 39 Year mortality study of survivors exposed to sulfur mustard agent: A survival analysis. Hossein Amini 1, Masoud Solaymani-Dodaran 2 3, Mostafa Ghanei 4, Jamileh Abolghasemi 5, Mahmoud Salesi 4, Amir Vahedian Azimi 6, Mohammad Farjami 7, Amir Hosein Ghazale 8, Batool Mousavi 9, Amirhossein Sahebkar 10 11. Heliyon. 2024 Jan 17;10(2):e24535. DOI: 10.1016/j.heliyon.2024.e24535

Abstract
Background: The primary objective of this study was to analyze the long-term survival of 48,067 chemical warfare survivors who suffered from pulmonary, cutaneous, and ocular lesions in the decades following the Iran-Iraq war.

Methods: The data for this study were obtained from the Veterans and Martyr Affair Foundation (VMAF) database. The survivors were divided into two groups based on whether they were evacuated/admitted (EA) to a hospital or not evacuated/admitted (NEA) to a hospital. The proportional hazard (PH) assumption for age categories, gender, exposure

statuses, and eye severity was not satisfied. Therefore, we used a Generalized Gamma (GG) distribution with an Accelerated Failure Time (AFT) model for analysis.

Results: The study included a total of 48,067 observations, and among them, 4342 (9.03 %) died during the study period. The mean (SD) age of the survivors was 55.99 (7.9) years. The mortality rate increased with age, and higher rates were observed in males. Survival probabilities differed significantly among age categories, provinces, lung severity, and eye severity based on log-rank tests (p-value<0.05 for all). The GG model results showed that higher age and being male were associated with a shorter time to death. The study also found that the mortality rate was significantly higher in the EA group compared to the NEA group.

Conclusion: The present study showed no significant difference in survival time between the EA and NEA groups. The findings suggest that pulmonary lesions caused by mustard gas are more likely to be fatal compared to skin and eye lesions.

Dexamethasone targets actin cytoskeleton signaling and inflammatory mediators to reverse sulfur mustard-induced toxicity in rabbit corneas. Rama Kant 1, Neha Mishra 1, Kushal Kandhari 1, Laura Saba 1, Cole Michel 1, Richard Reisdorph 1, Neera Tewari-Singh 2, Mina B Pantcheva 3, J Mark Petrash 3, Chapla Agarwal 1, Rajesh Agarwal 4. Toxicol Appl Pharmacol. 2024 Feb:483:116834. DOI: 10.1016/j.taap.2024.116834

Abstract

Sulfur mustard (SM), a bi-functional alkylating agent, was used during World War I and the Iran-Iraq war. SM toxicity is ten times higher in eyes than in other tissues. Cornea is exceptionally susceptible to SM-injuries due to its anterior positioning and mucous-aqueous interphase. Ocular SM exposure induces blepharitis, photosensitivity, dry eye, epithelial defects, limbal ischemia and stem cell deficiency, and mustard gas keratopathy leading to temporary or permanent vision impairments. We demonstrated that dexamethasone (Dex) is a potent therapeutic intervention against SM-induced corneal injuries; however, its mechanism of action is not well known. Investigations employing proteomic profiling (LC-MS/MS) to understand molecular mechanisms behind SM-induced corneal injury and Dex efficacy were performed in the rabbit cornea exposed to SM and then received Dex treatment. PEAKS studio was used to extract, search, and summarize peptide identity. Ingenuity Pathway Analysis was used for pathway identification. Validation was performed using immunofluorescence. One-Way ANOVA (FDR < 0.05; p < 0.005) and Student's t-test (p < 0.05) were utilized for analyzing proteomics and IF data, respectively. Proteomic analysis revealed that SM-exposure upregulated tissue repair pathways, particularly actin cytoskeleton signaling and inflammation. Prominently dysregulated proteins included lipocalin2, coronin1A, actin-related protein2, actin-related protein2/3 complex subunit2, actin-related protein2/3 complex subunit4, cell division cycle42, ezrin, bradykinin/kininogen1, moesin, and profilin. Upregulated actin cytoskeleton signaling increases F-actin formation, dysregulating cell shape and motility. Dex reversed SM-induced increases in the aforementioned proteins levels to near control expression profiles. Dex aids corneal wound healing and improves corneal integrity.

Long-term health complications of chemical weapon exposure: a study on Halabja chemical attack survivors (Iraqi Kurds). Belal A Muhammad 1, Salih A Hama 1 2, Karzan A M Hawrami 3, Salar H Karim 4, Gasha S Ahmed 1, Hawbash M Rahim 1 5 6. Inhal Toxicol. 2024 Jan;36(1):26-30. DOI: 10.1080/08958378.2024.2301985

Abstract

Objective: In 1988, the Iraqi government used a range of chemical weapons (CWs) against the Iraqi Kurds of Halabja. Here, we aim to investigate the long-term health consequences in exposed survivors as they are not sufficiently studied.

Materials and methods: This was a retrospective study conducted from November 2019 to May 2020 assessing the health status of all exposed Halabja chemical attack survivors compared to non-exposed people from the same area.

Results and discussion: Two hundred thirty survivors and 240 non-exposed participants were enrolled in this study, with control participants matched to age, gender, and occupation. Among the survivors, females were more prevalent. The respiratory system was the most common single exposure route (83, 36.1%), with 138 (60%) of the survivors being exposed by multiple routes. The vast majority (88.7%) of survivors had activities of daily living (ADL) impairment. There was female predominance in mild and moderate cases, with more males in severe cases ($p < 0.01$). Respiratory and cardiac diseases were significantly more common in the survivors compared to the controls ($p < 0.001$). Survivors with multiple CW exposure routes had significantly higher rates of ADL impairment ($p < 0.001$) and cardiac disease, respiratory diseases, and miscarriage ($p < 0.01$), than those with a single exposure route.

Conclusion: In this study comparing CW survivors with a local control population, a single, high-dose exposure to CWs was associated with significant increases in chronic respiratory and cardiac conditions, in addition to high rates of ADL impairment. Similar studies are needed in other, more recent CW survivor cohorts.

A Murine Model of Vesicant-Induced Acute Lung Injury. Iram Zafar 1, Shajer Manzoor 1, Nithya Mariappan 1, Shama Ahmad 1, Mohammad Athar 1, Veena Antony 1, Aftab Ahmad 2. J Pharmacol Exp Ther. 2024 Jan 17;388(2):568-575. DOI: 10.1124/jpet.123.001780

Abstract

Burn injuries including those caused by chemicals can result in systemic effects and acute lung injury (ALI). Cutaneous exposure to Lewisite, a warfare and chemical burn agent, also causes ALI. To overcome the limitations in conducting direct research on Lewisite-induced ALI in a laboratory setting, an animal model was developed using phenylarsine oxide (PAO) as a surrogate for Lewisite. Due to lack of a reliable animal model mimicking the effects of such exposures, development of effective therapies to treat such injuries is challenging. We demonstrated that a single cutaneous exposure to PAO resulted in disruption of the alveolar-capillary barrier as evidenced by elevated protein levels in the bronchoalveolar lavage fluid (BALF). BALF supernatant of PAO-exposed animals had increased levels of high mobility group box 1, a damage associated molecular pattern molecule. Arterial blood-gas measurements showed decreased pH, increased $PaCO_2$, and decreased partial pressure of arterial O_2, indicative of respiratory acidosis, hypercapnia, and hypoxemia. Increased protein levels of

interleukin (IL)-6, CXCL-1, CXCL-2, CXCL-5, granulocyte-macrophage colony-stimulating factor, CXCL-10, leukemia inhibitory factor, leptin, IL-18, CCL-2, CCL-3, and CCL-7 were observed in the lung of PAO-exposed mice. Further, vascular endothelial growth factor levels were reduced in the lung. Pulmonary function evaluated using a flexiVent showed a downward shift in the pressure-volume loop, decreases in static compliance and inspiratory capacity, increases in respiratory elastance and tissue elastance. These changes are consistent with an ALI phenotype. These results demonstrate that cutaneous PAO exposure leads to ALI and that the model can be used as an effective surrogate to investigate vesicant-induced ALI. SIGNIFICANCE STATEMENT: This study presents a robust model for studying ALI resulting from cutaneous exposure to PAO, a surrogate for the toxic vesicating agent Lewisite. The findings in this study mimic the effects of cutaneous Lewisite exposure, providing a reliable model for investigating mechanisms underlying toxicity.

Countermeasures against Pulmonary Threat Agents. Jacqui Marzec 1, Srikanth Nadadur 2. J Pharmacol Exp Ther. 2024 Jan 17;388(2):560-567. DOI: 10.1124/jpet.123.001822

Abstract
Inhaled toxicants are used for diverse purposes, ranging from industrial applications such as agriculture, sanitation, and fumigation to crowd control and chemical warfare, and acute exposure can induce lasting respiratory complications. The intentional release of chemical warfare agents (CWAs) during World War I caused life-long damage for survivors, and CWA use is outlawed by international treaties. However, in the past two decades, chemical warfare use has surged in the Middle East and Eastern Europe, with a shift toward lung toxicants. The potential use of industrial and agricultural chemicals in rogue activities is a major concern as they are often stored and transported near populated areas, where intentional or accidental release can cause severe injuries and fatalities. Despite laws and regulatory agencies that regulate use, storage, transport, emissions, and disposal, inhalational exposures continue to cause lasting lung injury. Industrial irritants (e.g., ammonia) aggravate the upper respiratory tract, causing pneumonitis, bronchoconstriction, and dyspnea. Irritant gases (e.g., acrolein, chloropicrin) affect epithelial barrier integrity and cause tissue damage through reactive intermediates or by direct adduction of cysteine-rich proteins. Symptoms of CWAs (e.g., chlorine gas, phosgene, sulfur mustard) progress from airway obstruction and pulmonary edema to acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), which results in respiratory depression days later. Emergency treatment is limited to supportive care using bronchodilators to control airway constriction and rescue with mechanical ventilation to improve gas exchange. Complications from acute exposure can promote obstructive lung disease and/or pulmonary fibrosis, which require long-term clinical care. SIGNIFICANCE STATEMENT: Inhaled chemical threats are of growing concern in both civilian and military settings, and there is an increased need to reduce acute lung injury and delayed clinical complications from exposures. This minireview highlights our current understanding of acute toxicity and pathophysiology of a select number of chemicals of concern. It discusses potential early-stage therapeutic development as well as challenges in developing countermeasures applicable for administration in mass casualty situations.

Dermal Exposure to Vesicating Nettle Agent Phosgene Oxime: Clinically Relevant Biomarkers and Skin Injury Progression in Murine Models. Dinesh G Goswami 1, Satyendra K Singh 1, Ebenezar O M Okoyeocha 1, Andrew K Roney 1, Omid Madadgar 1, Rick Tuttle 1, William Sosna 1, Poojya Anantharam 1, Claire R Croutch 1, Rajesh Agarwal 1, Neera Tewari-Singh 2. Pharmacol Exp Ther. 2024 Jan 17;388(2):536-545. DOI: 10.1124/jpet.123.001718.

Abstract
Phosgene oxime (CX), categorized as a vesicating chemical threat agent, causes effects that resemble an urticant or nettle agent. CX is an emerging potential threat agent that can be deployed alone or with other chemical threat agents to enhance their toxic effects. Studies on CX-induced skin toxicity, injury progression, and related biomarkers are largely unknown. To study the physiologic changes, skin clinical lesions and their progression, skin exposure of SKH-1 and C57BL/6 mice was carried out with vapor from 10 μl CX for 0.5-minute or 1.0-minute durations using a designed exposure system for consistent CX vapor exposure. One-minute exposure caused sharp (SKH-1) or sustained (C57BL/6) decrease in respiratory and heart rate, leading to mortality in both mouse strains. Both exposures caused immediate blanching, erythema with erythematous ring (wheel) and edema, and an increase in skin bifold thickness. Necrosis was also observed in the 0.5-minute CX exposure group. Both mouse strains showed comparative skin clinical lesions upon CX exposure; however, skin bifold thickness and erythema remained elevated up to 14 days postexposure in SKH-1 mice but not in C57BL/6 mice. Our data suggest that CX causes immediate changes in the physiologic parameters and gross skin lesions resembling urticaria, which could involve mast cell activation and intense systemic toxicity. This novel study recorded and compared the progression of skin injury to establish clinical biomarkers of CX dermal exposure in both the sexes of two murine strains relevant for skin and systemic injury studies and therapeutic target identification.
SIGNIFICANCE STATEMENT: Phosgene oxime (CX), categorized as a vesicating agent, is considered as a potent chemical weapon and is of high military and terrorist threat interest since it produces rapid onset of severe injury as an urticant. However, biomarkers of clinical relevance related to its toxicity and injury progression are not studied. Data from this study provide useful clinical markers of CX skin toxicity in mouse models using a reliable CX exposure system for future mechanistic and efficacy studies.

Establishing a Dexamethasone Treatment Regimen To Alleviate Sulfur Mustard-Induced Corneal Injuries in a Rabbit Model. Neha Mishra 1, Rama Kant 1, Kushal Kandhari 1, Neera Tewari-Singh 1, Poojya Anantharam 1, Claire R Croutch 1, Mina B Pantcheva 1, J Mark Petrash 1, Houmam Araj 1, Chapla Agarwal 1, Rajesh Agarwal 2 3. Pharmacol Exp Ther. 2024 Jan 17;388(2):469-483. DOI 10.1124/jpet.123.001680

Abstract
Sulfur mustard (SM) is an ominous chemical warfare agent. Eyes are extremely susceptible to SM toxicity; injuries include inflammation, fibrosis, neovascularization (NV), and vision impairment/blindness, depending on the exposure dosage. Effective countermeasures against ocular SM toxicity remain elusive and are warranted during conflicts/terrorist activities and accidental exposures. We previously determined that dexamethasone (DEX) effectively counters corneal nitrogen mustard toxicity and that the 2-hour postexposure therapeutic window is most beneficial. Here, the efficacy of two DEX dosing frequencies [i.e., every 8 or 12

hours (initiated, as previously established, 2 hours after exposure)] until 28 days after SM exposure was assessed. Furthermore, sustained effects of DEX treatments were observed up to day 56 after SM exposure. Corneal clinical assessments (thickness, opacity, ulceration, and NV) were performed at the day 14, 28, 42, and 56 post-SM exposure time points. Histopathological assessments of corneal injuries (corneal thickness, epithelial degradation, epithelial-stromal separation, inflammatory cell, and blood vessel counts) using H&E staining and molecular assessments (COX-2, MMP-9, VEGF, and SPARC expressions) were performed at days 28, 42, and 56 after SM exposure. Statistical significance was assessed using two-way ANOVA, with Holm-Sidak post hoc pairwise multiple comparisons; significance was established if $P < 0.05$ (data represented as the mean ± S.E.M.). DEX administration every 8 hours was more potent than every 12 hours in reversing ocular SM injury, with the most pronounced effects observed at days 28 and 42 after SM exposure. These comprehensive results are novel and provide a comprehensive DEX treatment regimen (therapeutic-window and dosing-frequency) for counteracting SM-induced corneal injuries. SIGNIFICANCE STATEMENT: The study aims to establish a dexamethasone (DEX) treatment regimen by comparing the efficacy of DEX administration at 12 versus 8 hours initiated 2 hours after exposure. DEX administration every 8 hours was more effective in reversing sulfur mustard (SM)-induced corneal injuries. SM injury reversal during DEX administration (initial 28 days after exposure) and sustained [further 28 days after cessation of DEX administration (i.e., up to 56 days after exposure)] effects were assessed using clinical, pathophysiological, and molecular biomarkers.

Radiation and Chemical Program Research for Multi-Utility and Repurposed Countermeasures: A US Department of Health and Human Services Agencies Perspective.
Carmen I Rios 1, Efrain E Garcia 2, Thomas S Hogdahl 2nd 3, Mary J Homer 4, Narayan V Iyer 3, Judith W Laney 2, Shannon G Loelius 4, Merriline M Satyamitra 1, Andrea L DiCarlo 1. Disaster Med Public Health Prep. 2024 Feb 22:18:e35. DOI: 10.1017/dmp.2023.226

Abstract
Although chemical and radiological agents cause toxicity through different mechanisms, the multiorgan injuries caused by these threats share similarities that convene on the level of basic biological responses. This publication will discuss these areas of convergence and explore "multi-utility" approaches that could be leveraged to address common injury mechanisms underlying actions of chemical and radiological agents in a threat-agnostic manner. In addition, we will provide an overview of the current state of radiological and chemical threat research, discuss the US Government's efforts toward medical preparedness, and identify potential areas for collaboration geared toward enhancing preparedness and response against radiological and chemical threats. We also will discuss previous regulatory experience to provide insight on how to navigate regulatory paths for US Food and Drug Administration (FDA) approval/licensure/clearance for products addressing chemical or radiological/nuclear threats. This publication follows a 2022 trans-agency meeting titled, "Overlapping Science in Radiation and Sulfur Mustard Exposures of Skin and Lung: Consideration of Models, Mechanisms, Organ Systems, and Medical Countermeasures," sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), a part of the National Institutes of Health (NIH). Discussions from this meeting explored the overlapping nature of radiation and chemical injury and spurred increased interest in how preparedness for one threat leads to preparedness for the other.

Herein, subject matter experts from the NIAID and the Biomedical Advanced Research and Development Authority (BARDA), a part of the Administration for Strategic Preparedness and Response (ASPR), summarize the knowledge gained from recently funded biomedical research, as well as insights from the 2022 meeting. These topics include identification of common areas for collaboration, potential use of biomarkers of injury to identify injuries caused by both hazards, and common and widely available treatments that could treat damage caused by radiological or chemical threats.

Decon

Effective skin decontamination with RSDL® (reactive skin decontamination lotion kit) following dermal exposure to a Novichok class nerve agent. Alex S Cornelissen 1, Roland M van den Berg 1, Jan P Langenberg 1, Marco van Grol 1, Rowdy Bross 1, John Pittman 2, Laura Cochrane 2, Vladimir Savransky 3. Sem Biol Interact. 2024 May 25:395:111001. DOI: 10.1016/j.cbi.2024.111001

Abstract

In recent years, various poisoning incidents have been reported, involving the alleged use of the so-called Novichok agents, resulting in their addition to the Schedule I list of the Organisation for the Prohibition of Chemical Warfare (OPCW). As the physicochemical properties of these agents are different from the 'classical' nerve agents, such as VX, research is needed to evaluate whether and to what extent existing countermeasures are effective. Here, we evaluated the therapeutic potential of RSDL® (Reactive Skin Decontamination Lotion Kit) for the neutralization of percutaneous toxicity caused by Novichok agents, both in vitro and in vivo. Experiments showed the three selected Novichok agents (A230, A232, A234) could be degraded by RSDL lotion, but at a different rate. The half-life of A234, in the presence of an excess of RSDL lotion, was 36 min, as compared to A230 (<5 min) and A232 (18 min). Following dermal exposure of guinea pigs to A234, application of the RSDL kit was highly effective in preventing intoxication, even when applied up until 30 min following exposure. Delayed use of the RSDL kit until the appearance of clinical signs of intoxication (3-4 h) was not able to prevent intoxication progression and deaths. This study determines RSDL decontamination as an effective treatment strategy for dermal exposure to the Novichok agent A234 and underscores the importance of early, forward use of skin decontamination, as rapidly as possible.

Acetohydroxamic acid salts: mild, simple and effective degradation reagents to counter Novichok nerve agents. Boris Smolkin 1, Victoria Nahum 1, Eugenia Bloch-Shilderman 2, Uri Nili 2, Gil Fridkin 1, Nissan Ashkenazi 1 3. RSC Adv. 2024 May 8;14(21):14904-14909. DOI: 10.1039/d4ra02038c

Abstract

Novichoks is the latest known class of organophosphorus nerve agents to be developed. These highly lethal persistent agents, which exert their toxicity mainly through dermal exposure, pose new major challenges in mitigating their effect, mainly in respect to decontamination and medical countermeasures. Herein we report on the effective degradation of Novichok agents

(A-230, A-232 and A-234) by hydroxamic acid salts. This class of α-nucleophiles, with emphasis on the FDA approved drug acetohydroxamic acid, were found to promote rapid hydrolysis of these extremely toxic agents. Using ^{31}P NMR the Novichoks degradation rates were determined to be in time scale of minutes with the following order of reactivity A-230>A-232>A-234. The degradation efficiency was found to be dependent on the nucleophiles, their counter-cations and the specific solvent mixture used. Hence, these scavengers can serve as efficient and mild decontaminants in various scenarios including surfaces, dermal decontamination (as an alternative to active lotions such as the RSDL® kit) and also as a medical countermeasure in the form of "catch-up therapy".

Reactive skin decontamination lotion (RSDL) safety with clinical antiseptics and hemostatic agents. Jessica Franken 1, John Mikler 2. Toxicol Lett. 2024 May 1:395:11-16. **DOI:** 10.1016/j.toxlet.2024.02.014

Abstract

Reactive skin decontamination lotion (RSDL) is a Health Canada approved product used by the Canadian Armed Forces for removal and inactivation of toxic chemicals on skin. Although it is considered very safe when used as directed, questions have been raised regarding whether topical RSDL in the medical setting will react exothermically with antiseptic compounds on the casualty's epidermis that could result in thermal burns. Benchtop experiments were conducted to investigate reactivity of RSDL with various antiseptic compounds or hemostatic agents. Temperature changes were closely monitored in three different volume ratios, 1:10, 1:1, and 10:1 over a time course of 16 minutes. Chlorine based bleaches versus RSDL were included as a positive control and were the only combination that exhibited a significant exothermic reaction capable of causing minor thermal burns. RSDL was also evaluated with antiseptic solution applied to swine epidermal tissue without observation of visual irritation; then in lacerated skeletal muscle tissue which resulted in no measured temperature change. The conclusion of this study is that antiseptics and hemostatic agents can be used as required on a patient decontaminated with RSDL as no exothermic reaction will occur.

Immediate dry decontamination using efficient absorbent materials is beneficial following skin exposure to low-volatile toxic chemicals. Lina Thors 1, Elisabeth Wigenstam 1, Johanna Qvarnström 1, Pär Wästerby 1, Linda Öberg 1, Anders Bucht 1. J Appl Toxicol. 2024 May 10. DOI: 10.1002/jat.4627

Abstract

In a chemical mass casualty incident requiring skin decontamination, dry removal using absorbent materials may be beneficial to enable immediate decontamination. The efficacy of absorbent materials has therefore been evaluated, alone or procedures including both dry and wet decontamination, following skin exposure to two low volatile toxic chemicals using an in vitro human skin penetration model. Additionally, removal using active carbon wipes was evaluated with or without the Dahlgren Decon solution. All dry decontamination procedures resulted in a significantly decreased skin penetration rate of the industrial chemical 2-butoxyethanol compared to the control without decontamination. Wet decontamination following dry absorption significantly improved the efficacy compared to dry removal alone. Dry decontamination post-exposure to the chemical warfare nerve agent VX showed no

decontamination efficacy. However, dry and wet decontamination resulted in a decreased agent skin penetration rate during the last hour of the experiment. At -15°C, significantly reduced VX skin penetration rates were demonstrated for both dry decontamination alone and the dry and wet decontamination procedure. The Dahlgren Decon solution significantly reduced the amount of VX penetrating the skin, but the active carbon wipe alone did not impact the skin penetration rate. In conclusion, absorbent materials are beneficial for the removal of low-volatile chemicals from the skin, but the degree of efficacy varies between chemicals. Despite the variability, immediate dry decontamination using available absorbent materials prior to wet decontamination is recommended as a general procedure for skin decontamination. The procedure should also be prioritized in cold-weather conditions to prevent patient hypothermia.

RAD / NUC

Development of Drug Products for the Treatment of Acute Radiation Syndrome. Marzella Libero 1. Disaster Med Public Health Prep. 2024 Jan 2:17:e571. DOI: 10.1017/dmp.2023.227

Abstract

The Food and Drug Administration's (FDA) approval to market drug products for use as medical countermeasures, to prevent or mitigate injury caused by various threat agents, is commonly based on evidence of efficacy obtained in animals. Animal studies are necessary when human studies are not feasible and challenge studies are not ethical. The successful development of countermeasures to radio-nuclear threats that cause Acute Radiation Syndrome (ARS) provides the opportunity to explore potential areas of overlap in the scientific approaches to studies of injuries caused by radiation and sulfur mustard exposures in animals. The aim is to evaluate the available scientific knowledge for radiation threat agents and sulfur mustard for potential analogies of fundamental mechanisms of organ injury and dysfunction. This evaluation is needed to determine the applicability of regulatory strategies for product development and approval adopted by manufacturers of countermeasures for radiation threat agents. Key elements of an efficient development plan based on animal efficacy studies include characterizing the pathophysiology of organ injury and the mechanism of action (MOA) of the countermeasure; modeling the clinical condition in animals to establish the manifestations of the injury caused by various levels of exposures to the threat agent and the response to various doses of the countermeasure candidate; as well as selecting a maximally effective human dose.

Pediatric Medical Countermeasures: Antidotes and Cytokines for Radiological and Nuclear Incidents and Terrorism. Thom S Maciulewicz 1 2 3, Ziad Kazzi 3 4 5, Irene L Navis 3, Gregory J Nelsen 3 6, Theodore J Cieslak 3 7, Christopher Newton 3 8, Anna Lin 3 9, Doneen J West 3, Frank G Walter 1 2 3 10 11. Disaster Med Public Health Prep. 2024 Apr 23:18:e76. **DOI:** 10.1017/dmp.2024.35

Abstract

The war in Ukraine raises concerns for potential hazards of radiological and nuclear incidents. Children are particularly vulnerable in these incidents and may need pharmaceutical

countermeasures, including antidotes and cytokines. Searches found no published study comparing pediatric indications and dosing among standard references detailing pediatric medications for these incidents. This study addresses this gap by collecting, tabulating, and disseminating this information to healthcare professionals caring for children. Expert consensus chose the following references to compare their pediatric indications and dosing of medical countermeasures for radiation exposure and internal contamination with radioactive materials: *Advanced Hazmat Life Support (AHLS) for Radiological Incidents and Terrorism*, *DailyMed*, *Internal Contamination Clinical Reference*, *Medical Aspects of Radiation Incidents*, and *Medical Management of Radiological Casualties*, as well as Micromedex, *POISINDEX*, and *Radiation Emergency Medical Management (REMM)*. This is the first study comparing pediatric indications and dosing for medical countermeasures among commonly used references for radiological and nuclear incidents.

Decorporation dilemma: Interplay of prussian blue and potassium iodide in radioactive contamination. Riya Mahar 1, Nidhi Sandal 2. J Environ Radioact. 2024 Jul:277:107458. DOI: 10.1016/j.jenvrad.2024.107458

Abstract

The expansion of the nuclear industry has led to various radioactive effluents, originating from routine operations or catastrophic incidents such as those at Three Mile Island (USA), Chernobyl (Ukraine), and Fukushima (Japan). Research conducted after these events emphasizes Cesium-137 (137Cs) and iodine 131 (131I) as major contributors to harmful airborne dispersion and fallout. These isotopes infiltrate the human body via inhalation, ingestion, or wounds, posing significant health risks. Understanding contamination mechanisms and devising effective countermeasures are crucial in mitigating nuclear incident consequences. We propose that concurrent administration of Pru-Decorp™/Pru-Decorp-MG and potassium iodide (KI) could synergistically reduce the levels of 137Cs and block uptake of 131I, respectively, in nuclear incident scenarios. Pru-Decorp™ capsules contain insoluble ferric hexacyanoferrate(II) and are equivalent to USFDA-approved Radiogardase®-Cs, offering radiation exposure mitigation for Cs and Tl contamination. Pru-Decorp-MG capsules consist of insoluble PB and magnesium hydroxide, serving as a prophylactic measure to reduce the risk of internal Cs and Tl contamination for rescue responders. Pru-Decorp™/Pru-Decorp-MG binds Cs/Tl ions in the gastrointestinal tract, hindering absorption and promoting excretion, while KI saturates the thyroid gland with stable iodine, decreasing the uptake of radioactive iodine isotopes. Our hypothesis is supported by studies demonstrating the effectiveness of combination therapies, such as calcium alginate, iron(III) ferrocyanide, and KI, in decreasing the retention of radioisotopes in vital organs. To test this hypothesis, we propose a comprehensive research plan, including in vitro studies simulating gastrointestinal conditions, animal studies to evaluate the efficacy of both drugs simultaneously, and safety clinical trials comparing Pru-Decorp™/Pru-Decorp-MG alone, KI alone, and their combination. Expected outcomes include insights into the synergistic effects of Pru-Decorp™/Pru-Decorp-MG and KI, guiding the development of optimized treatment protocols for simultaneous administration during radioactive contamination incidents. This research aims to address significant critical gaps in nuclear incident preparedness by providing evidence-based recommendations for concurrent

antidote use in scenarios involving multiple isotope contamination. Ultimately, this will enhance public health and safety during nuclear emergencies.

CBRN General

Chemical and Biological Threats: Guidance for Breastfeeding Women, Infants, and Young Children. Sharon Leslie 1 2, Mija Ververs 3. Health Secur. 2024 Mar-Apr;22(2):172-181. **DOI:** 10.1089/hs.2023.0096

No abstract available

Progress and Challenges in Developing Medical Countermeasures for Chemical, Biological, Radiological, and Nuclear Threat Agents. Doodipala Samba Reddy [1]. Pharmacol Exp Ther. . 2024 Jan 17;388(2):260-267. DOI: 10.1124/jpet.123.002040

Abstract
This Commentary delves into the current progress and challenges on ongoing research on medical countermeasures (MCs) for chemical, biologic, radiologic, and nuclear (CBRN) threats. CBRN agents pose a serious risk to human health and safety, with the potential for mass casualties in both military and civilian settings. Chemical threats are toxic compounds that could be used in a terrorist attack, an accidental release, or chemical warfare. They include nerve agents, organophosphates, pulmonary agents, metabolic/cellular agents, vesicants, ocular toxicants, and opioid agents. Developing effective MCs is crucial for mitigating the acute and chronic effects of exposure to CBRN agents. The papers in this special issue of JPET highlights the latest advancements in MC research, showcasing insightful outcomes on experimental models, mechanisms, and translational research on MCs for CBRN threats. They portray several notable contributions, including the development of neurosteroid and combination anticonvulsant therapies for nerve agent poisoning, the exploration of chronic impacts and diagnostic tracers for OP neurotoxicity, the establishment of innovative pediatric OP models, the identification of novel molecules for ocular, pulmonary and vesicant injuries, and the repurposing of existing drugs for the treatment of botulism, cyanide, and OP poisoning. These crucial outcomes underscore the breadth of current research covering a variety of chemical threats. Overall, this collection of articles highlights the importance of ongoing research and development in the field of MCs, emphasizing the potential of these countermeasures to effectively treat and mitigate the effects of toxicant exposures and thereby enhance our preparedness for mass casualty incidents. SIGNIFICANCE STATEMENT: CBRN agents pose a significant threat to public health. Effective MCs exist for certain chemical threats, but there is a need for new and improved MCs for many others. The research presented in this special issue of JPET highlights the latest advancements in MCs for CBRN threats. This research has the potential to lead to the development of new and repurposed MCs that are more effective, broad-spectrum, and easier to administer to mitigate acute and long-term consequences of chemical exposures.