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PROCEEDINGS

ACMT/IST 2019 American-Israeli Medical Toxicology Conference Abstracts—Haifa, Israel

American College of Medical Toxicology[1]

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Introduction

The American College of Medical Toxicology (ACMT) in conjunction with the Israeli Society of Toxicology (IST) is presenting the Third Joint American-Israeli Medical Toxicology Conference in Haifa, Israel, on November 19–20, 2019. ACMT and IST previously held joint conferences in 2010 and in 2013. This work would not be possible without the hard work and diligence of our conference organizers and abstract reviewers: Didi Bentur, Yaron Finklestein, Lewis Nelson and Paul Wax. Equally significant is the contribution of the ACMT staff (Adrienne Dunavin) and the Israel Poison Information Center staff (Vered Steiner) who helped manage the process. Congratulations to all the contributors whose work will be presented in Haifa.

Day 1

The Medical Challenge at the Chemical Terror Scene

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Since the 1995 Tokyo subway sarin attack, terrorist attacks involving weapons of mass destruction or other industrial chemicals present worldwide security and health concerns. On-scene medical triage and treatment in such events is crucial to save lives and minimize the deleterious effects of the toxic agent involved. The challenges facing the emergency medical service (EMS) teams on scene include recognizing the event as a non-conventional attack involving a chemical agent, recognizing the nature of the agent and at last, treating the casualties accordingly. The wide range of potential chemicals that may be used in terror attacks and their diverse toxidromes render diagnosis extremely difficult. Taking in account that the medical treatment is usually supportive, the question that EMS personnel should be asking is not "what chemical was used" but "does the offending agent have an antidote." This relevant question may change the treatment and prognosis of the patients.

Treatment of Acute Cyanide Poisoning: Time to Move Forward

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Cyanide continues to pose a major threat for single and mass poisonings. Better and safer antidotes for cyanide poisoning are needed, especially for out-of-hospital treatment. After decades of lack of significant progress, the recent years are rich with studies evaluating novel compounds as counter measures for acute cyanide poisoning. Yet, there are still obstacles in the way to improve therapy and outcome and the road for an available and effective treatment is still long. Mechanisms of cyanide toxicity are more complex than previously recognized. While the inhibition of cellular respiration through cytochrome oxidase C and the development of metabolic acidosis are considered the main mechanism, more data from animal models indicate earlier central effect leading to mortality before acidosis is evident. Better understanding of the full acute insults of cyanide is cardinal to direct studies for new countermeasures, aimed to improve morbidity and mortality. New pathways for antidotal effect should be explored

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Weaponized Opioids

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The use of chemical weapons in areas of conflict has been a concern since antiquity. While the main focus of attention and preparation has been on agents such as nerve gases, sulfur mustards, and asphyxiants, opioids can be incapacitating and deadly when targeting people in a confined setting. Weaponized opioids have been used on a large scale at least once, most notably in 2002, by Russian special forces during the Dubrovka Theater hostage crisis in Moscow. During that incident, a chemical was administered through the theater ventilation system prior to the armed entry of special forces. Over 100 hostages were killed by the gas. While Russian authorities never officially identified the chemicals, residue collected from survivors isolated remifentanil and carfentanil. Before it became a scheduled substance in 2017, several companies in China exported carfentanil cheaply for about $2750 per kilogram. At 100 times, the potency of fentanyl the easy distribution of such a potent opioid has been a concern of the US Department of Defense. It has gained international attention as well and is banned from the battlefield under the Chemical Weapons Convention. Human symptoms are consistent with toxicity due to other opioids including depressed mental status, ventilatory depression, and death. In carfentanil, exposures due to contaminated heroin large doses of naloxone were required for reversal. Public agencies appreciate the threat posed by weaponized opioids and industry contracts for the development of a nasal nalmefene, a long-acting opioid antagonist, have been awarded by the US Department of Health and Human Services under the Biomedical Advanced Research and Development Authority. Medications with opioid antagonism such as naloxone, naltrexone, nalmefene, and possibly buprenorphine can be considered when preparing for a response to this threat.

Dipyrone—a Good Medication with a Bad Reputation

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Dipyrone, a weak NSAID, is used as analgesic and antipyretic medication in many countries worldwide. It is being marketed for almost 100 years. Its mechanism of action is probably by inhibition of a central COX-3, activation of the opioidermic system and cannabinoid system. More than 50% of the drug is protein-bound, with short half-life, and its elimination is mostly renal.

Dipyrone is registered in Israel from 3 months of age, and it is being sold as OTC. There are countries where it is a prescribed medication. Several studies have been performed with dipyrone showing its efficacy and safety in fever reduction in children and adults, post-operative pain, migraine, and headaches. Rare adverse effects of dipyrone are anaphylaxis and agranulocytosis. Recently, the EMA issued a warning on dipyrone use during pregnancy and lactation, claiming that there is no information in these conditions. However, a consensus statement of several drug consultation centers in Israel, opposed EMA's decision, determining that the medication is compatible with pregnancy and lactation.

Data Sources Supporting Food and Drug Administration Drug Safety Communications

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Introduction: Drug safety communications (DSCs) are the Food and Drug Administration's (FDA) primary tool for communicating important new post-marketing safety information to patients and healthcare professionals [1]. Our objective was to describe the sources of the initial safety signals that leads to DSCs and examine their associations with drug characteristics and subsequent label changes.

Methods: The study included all DSCs issued between January 29, 2010, when DSCs first became publicly available, and December 31, 2018, identified from the FDA's website [2]. We excluded DSCs for over-the-counter drugs. For each DSC, we determined the information source that served as the basis of the initial safety signal, categorized as data from the FDA's Adverse Event Reporting System (FAERS) [3], RCTs, and other sources. We used Fisher's exact test for categorical variables and Wilcoxon rank sum test for continuous variables to examine associations between information source and initial regulatory approval pathways, time between initial approval and DSC posting, characteristics of clinical studies included in the most recent drug label prior to DSC publication, and subsequent safety-related changes to drug label. We used Spearman's correlation testing to examine for changes in the number of DSCs issued annually. Analyses were performed using SAS, version 9.4 (SAS Institute, Cary NC). Statistical significance was defined as a 2-sided $p < 0.05$.

Results: There were 228 DSCs issued by the FDA from 2010 through 2018. DSCs characteristic are shown in Table 1. The number of DSCs decreased with time ($\rho = -0.9$, $p = 0.005$). The most frequent information source that served as the basis of the initial safety signal were FAERS ($n = 87.38\%$) and RCTs ($n = 81.36\%$). Time from initial approval to DSC posting was significantly shorter for DSCs triggered by FAERS or RCTs versus other sources ($p < 0.001$) (Table 2). Common subsequent changes to drug labels included additional warnings and precautions and boxed warning.

Discussion: The leading initial sources of DSCs were the FAERS program and RCTs. Despite known under-reporting