WG 1 (Chemical, Biological, Radiological and Nuclear materials)

Computational Identification of Repurposed Combinatorial Treatments for CBRN Threats: A Text Mining Approach to Evidence-Based Countermeasure Development

Yosi Shamay.
Faculty of Biomedical Engineering, Technion IIT.

This study presents a novel computational approach for identifying repurposing opportunities of existing treatments against chemical, biological, radiological, and nuclear (CBRN) threats. Utilizing advanced text mining methodologies through the SPIKE platform for extractive search, CoreMine Medical, Embase, and Clinical Queries, we developed a structured framework for mapping hazardous agents to potential therapeutic interventions. Our approach involved constructing specialized threat categories and cross-referencing them with comprehensive drug databases to identify evidence-based connections. To enhance precision, we employed contextual keyword enhancement and AI-driven (LLM) validation strategies, effectively filtering irrelevant associations. The methodology can identify promising treatment candidates for toxic industrial gases, nerve agents, opioid toxicity, and radiation exposure, with specific emphasis on combinatorial interventions. This systematic approach bridges critical gaps in CBRN preparedness by leveraging existing medical knowledge and provides a scalable framework for future countermeasure development. Our approach demonstrates the value of computational text mining in accelerating the identification of viable treatment options for complex threat scenarios while minimizing resource expenditure.

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Novel Approaches for Developing New Oxime Reactivators of OPNA-Inhibited Cholinesterase

Gavriel Amitai, Alexander Plotnikov, Rellie Gez, Ariel Gore, Khriesto A. Shurrush, Helaneh Salameh, Galit Cohen, Shlomi Lazar, Haim Barr.
The Wohl Drug Discovery Institute, G-INCPM, Weizmann Institute of Science.
Department of Pharmacology, Israel Institute for Biological Research (IIBR).

There are three components in the antidotal medical mixture used toward organophosphorus nerve agents (OPNA) poisoning: 1. oxime reactivator of OPNA-inhibited acetylcholinesterase (AChE), (e.g. 2-PAM, HI-6), 2. Anticholinergic drug (e.g. atropine, scopolamine) and 3. anti-convulsant (e.g. diazepam, midazolam). Despite extensive translational research over the last 50 years only few antidotal drugs were introduced to clinical use and there are still efficacy gaps to surmount in the treatment of certain OPNA intoxications. In particular, insufficient recovery, long term neurotoxic effects and fatalities have been observed during treatment of respiratory and skin-exposure to the A-series Novichoks nerve agents. We believe that the key component of the antidotal mixture is the oxime reactivator that displaces the OPNA from the covalent OPNA-AChE complex. Based on HTS-driven approach, we have recently discovered new non-quaternary oximes that are efficient and safe reactivators of sarin- and VX-inhibited BChE (Amitai et al. Comms. Biol. 2021). These non-quaternary oximes could potentially penetrate through the blood-brain barrier (BBB) and reactivate brain ChEs. In addition, during the last two years we have been focused on the development of new ketoximes rather than clinically approved aldoximes. The notion is that the spontaneous degradation of Phosphoryl-Ketoxime intermediate formed during reactivation of OPNA-AChE is catalytic, allowing turnover of the oxime for multiple reactivation cycles, effectively reducing the dose required for reactivation. In contrast, aldoximes reactivators produce a nitrile upon hydrolysis of their respective phosphoryl-oxime intermediate, an irreversible process. Therefore, we have prepared new ketoximes with enhanced nucleophilic potency. This project involves newly synthesized compounds that include substitution of aromatic rings by halogens (e.g. F and Cl) as an electron withdrawing group (EWG) as well as lipophilic group. The EWG effect is expected to lower the pKa of the ketoxime group and lipophilic efficiency is predicted to increase by Chlorine (Cl) substitution. Lower pKa values could induce higher concentration of oximate anion at physiological pH (7.4). The oximate anion is an active nucleophilic species that attacks the bound OP during reactivation. Indeed, calculated pKa and log P values (ACD Labs) demonstrate decrease in pKa values from 9-10 to pKa 7-8 together with increase in log P of Cl-substituted ketoximes compared to non-

Cl ketoixmes. Notably, some newly synthesized Cl-Ketoximes demonstrated enhanced in vitro reactivation kinetics of sarin- and/or VX-inhibited AChE compared to 2-PAM and TMB-4.

WG 1 (Chemical, Biological, Radiological and Nuclear materials)

Whole-Body Exposure of Rats to High Concentration Chlorine Gas: Clinical and Histological Evaluation

Adi Neufeld-Cohen, Hila Gutman, Shlomit Dachir, Mordi Hotoveli, Shlomy Maimon, Maayan Cohen, Tamar Kadar, Tamar Klapholtz, Eldar Peretz, Inbal Egoz, Rellie Gez, Eyal Dor, Ariel Gore, Vered Horwitz.
Israel Institute for Biological Research, Department of Pharmacology.

Chlorine is a corrosive irritant widely used in the chemical industry. Since it was first used as a chemical warfare agent in World War I in the battle of Ypres, Belgium, hundreds of attacks were reported, many of which in the last two decades in Syria. Acute exposure to chlorine gas due to industrial accidents or military activity may cause severe airway irritation and inflammation, respiratory distress and pulmonary edema injury, and in severe cases respiratory failure and death. Survivors of acute chlorine exposure present long-term effects such as bronchitis, emphysema, airway obstruction, encephalopathy and cardiac pathology. Currently, the treatments of acute inhalation of chlorine gas are supportive and symptom oriented.

Our work aims to characterize a rat model of acute and chronic injuries following a whole-body exposure to high concentrations of chlorine gas, which can serve for evaluations of emerging treatments.

Groups of awake adult Sprague-Dawley rats were exposed to 500ppm or 600ppm chlorine gas for 20-30 minutes in 70% humidified whole-body exposure system. Clinical evaluations including body weight, clinical severity score, respiratory functions, circadian activity and changes in blood count were performed for a period of 16 days after the exposure. Following euthanasia, lung and trachea tissues were processed for histological evaluation.

Exposed rats developed chlorine acute intoxication symptoms including skin injuries, changes in white blood cells counts, breathing difficulties, impaired circadian activity and weight loss. Death rates after 24 hours were 11% and 25% for 600ppm for 20 min and 500ppm for 30 min, respectively. Although gradual healing process was seen clinically, respiratory measurements using plethysmography presented ongoing dysfunction during the 16 days of monitoring. In addition, skin injuries around the eyes, nose and tail, did not heal during the follow-up period. Histological analysis revealed inflammatory cell infiltration and airways obstruction in the lungs, tracheal obstruction and severe damage to tracheal cilia and epithelium.

This study presents a model of an acute injury following a whole-body exposure of rats to a high concentration of chlorine, as expected in a real scenario. A comprehensive characterization of various clinical and histological parameters of acute chlorine induced injury was performed. This model will serve as a tool for emerging treatment evaluation.