MEDICAL PROPHYLAXIS TO MITIGATE CHEMICAL THREATS

Cannabinoids For Prophylaxis, Enhanced Neuroprotection And Therapy Against Organophosphate (OP) Chemical War Nerve Agents

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Background Information: Organophosphate (OP) toxicity remains a significant DTRA concern due to potential hazards of OPs from terrorism, warfare, or industrial accidents. FDA-approved, atropine-centered, injection-based OP toxicity treatments provide acute symptomatic relief, but lack significant neuroprotection, and don't promote neuroregeneration. Pharmacologically augmenting of the endocannabinoid system (ECS), has been identified by US government scientists as a potential therapeutic intervention for neuroprotection and OP treatment.1,2 Cannabinoids and cannabinomimetics demonstrated efficacy in several preclinical studies by CN Pope's group.3 Furthermore, it is not feasible to effectively manage an unexpected mass casualty event involving organophosphates using ATNAA, DuoDote, and CANA auto-injectors, or their generic, less restricted, non-autoinjector generic drug components.
Purpose and Objective: Evaluate SYNDROS (dronabinol) and CBD's neuroprotective and other therapeutic efficacies against acute OP-induced cholinergic toxicities and neurological sequelae. Compare FDA-approved cannabinoids with standard treatments, assessing safety, efficacy, and feasibility in acute and chronic OP exposure models4,5. Aim for supplemental FDA approval of SYNDROS for acute OP toxicity and/or military medical use of non-psychoactive cannabinoids like AgroDefend™ (CBD, CBG, CBC) for prophylaxis and prolonged therapy, potentially preventing/reducing OP induced delayed neuropathy (OPIDN).
Rationale and Relationship to Other Studies: Previous studies by Pope3 and Hoffman1 show augmenting the ECS (CB1R) reduces toxic effects of OPs and vice versa. Cannabinoids are broadly neuroprotective (e.g. Traumatic Brain Injury), and possess desirable antiemetic, analgesic, antispastic, bronchodilator, antioxidant, anticholinergic, and anti-inflammatory properties.2
Methods: Multiple rat groups, including controls, FDA standard treatment group, and several groups receiving different cannabinoid formulations, for different intervals after DFP. Behavioral toxicity, pain, survival, and histopathological markers will be used to evaluate outcomes. Study starts Aug 2024.
Preliminary Results: Multiple oral doses of Atropine (0.2 mg) and SYNDROS 12 mg with and without AgroDefend™ have been used safely together in healthy human volunteers. AgroDefend™ (CBD nutraceutical blend) has been successfully taken 2x daily by human volunteers (for three months) with subjective improvement in focus, mental clarity and information processing.
Preliminary Conclusions: Evaluating SYNDROS and CBD in OP-exposed rats is a practical next step for R&D of cannabinoids for OP toxicities. Our plan builds upon US Army Medical Research Institute of Chemical Defense findings that "exogenous potentiation of CB1R activity may provide a novel therapeutic approach to mitigate central OP toxicity"1 suggesting a promising avenue for developing broader and nonparenteral neuroprotective therapies.
Impact to the DTRA, JSTO Mission, Joint Force: If successful, this research could lead to the development of nonparenteral therapeutic agents to improve survival and quality of life for victims of OP poisoning. And enhance military effectiveness by protecting cognitive and physical health of personnel exposed to OPs. Oral SYNDROS and CBD could offer an alternative to injections for low level OP exposure. CBD could be used as prophylaxis, or cannabinoids as adjuncts to standard injection therapies. And perhaps the first treatment ever for OP-induced delayed neuropathy.
Future Directions: Government grants and collaborations to conduct definitive trials for approval in military medicine. Additionally, studies to explore the chronic effects of OP exposure and the potential of cannabinoids in treating conditions like Gulf War Illness and other aspects of military medicine, e.g, TBI and pain.

1. KM Hoffman, P.M. McNutt, et al. Retrograde activation of CB1R by muscarinic receptors protects against central organophosphorus toxicity." Neuropharmacol Sep, 2019; Vol 155, Pages 113-120. 2. A Hampson, J Axelrod, et al Cannabinoids as antioxidants and neuroprotectants, US Patent US6630507B1 assigned to US Dept of Health & Human Services. 3. L Wright, CN Pope, et al. Behavioral sequelae following acute DFP intoxication in rats: comparative effects of atropine and cannabinomimetics. Neurotoxicol Teratol. 2010; 4. Phillips KF, Deshpande LS. Chronic Neurological Morbidities and Elevated Hippocampal Calcium Levels in a DFP-Based Rat Model of Gulf War Illness. Mil Med. 2018 Mar 1; 183 (suppl_1): 552-555. 5. Deshpande LS, Phillips K, Huang B, DeLorenzo RJ. Chronic behavioral and cognitive deficits in a rat survival model of paraoxon toxicity. Neurotoxicology. 2014 Sep;44:352-7. We thank our partner Benuvia for providing SYNDROS and synthetic Pharma-grade CBD. We thank Carey N. Pope and Laxmikant Deshpande for serving as advisors to Kotzker Phfarma.