SOCOM213-002: Concentrated Atropine Sulfate Formulations

MODERNIZATION PRIORITIES:

Biotechnology, Space

TECHNOLOGY AREA(S):

Bio Medical, Chem Bio Defense

OBJECTIVE:

Develop a novel stable, injectable, high concentration atropine sulfate (AS) formulation in a multi-dose vial to facilitate ease of treatment for severely poisoned nerve agent casualties in austere settings

DESCRIPTION:

Organophosphorus nerve agents are highly toxic chemicals and difficult to treat. Exposure to nerve agents occurs through multiple routes, including dermal, ocular, ingestion, inhalation and mucous membranes. Severe effects from nerve agent exposure include respiratory failure and death. Nerve agent casualties require immediate and rapid administration of medical countermeasures (MCM). The current Service member-carried MCM therapeutic regimen for nerve agent exposure includes autoinjectors containing atropine (an anticholinergic), the cholinesterase reactivator, 2-PAM (2-pyridine aldoxime methyl chloride (pralidoxime)), and an anticonvulsant, to decrease morbidity and mortality. The Antidote Treatment Nerve Agent Autoinjector (ATNAA) sequentially delivers atropine (2.1 mg) and 2-PAM (600 mg) via intramuscular injection through a single needle. The ATNAA is designed for automatic self- and buddy-aid administration by military personnel as soon as possible after the onset of symptoms of nerve agent exposure. The Service Member will receive 3 ATNAAs if exhibiting severe signs of nerve agent exposure. Additional atropine can be administered by a medic or physician to block severe and life-threatening muscarinic effects of nerve agent poisoning. In severe cases, 50 to 100 mg of atropine may be needed over a period of 24 hours to control cholinergic symptoms. Using commercially available 0.4 mg/ml atropine vials would require approximately 13 vials to treat a single severely poisoned casualty.

The United States Special Operations Command (SOCOM) is interested in a concentrated vialed atropine formulation to ease administration of large amounts of atropine to control cholinergic symptoms of poisoned individuals under operational conditions. Formulations of sufficient concentration to make dosing 2 mg atropine bolus injections easy is desired. For example, a 4.0 mg/ml solution would require 0.5 ml to deliver a 2.0 mg dose. A multi-dose vial containing a higher concentration of AS would significantly decrease the logistical burden associated with having to use multiple vials to treat a single nerve agent casualty, thereby simplifying dosing, and decreasing material costs, medical waste, and storage needs. As atropine solutions are light sensitive, vials should be of appropriately sealed, pharmaceutical grade light restricting glass, as is routinely used for injectable drug formulations. Suitable vial sizes amenable to being carried by medical personnel into operational conditions range from 10 to 20 ml. Appropriate consideration for the inclusion of bacteriostatic and antimicrobial agents for use in austere, non-sterile environments is desired. Commercial formulations of AS for injection are marketed with a shelf-life of 2 years at 25 ± 2°C / 60% ± 5% RH and transient excursions. Given the nature of military operations, improvements in formulation stability to endure prolonged excursions are of interest.

PHASE I:

Demonstrate the feasibility of a concentrated AS formulation in a multi-dose vial, developed under International Conference on Harmonization (ICH) Pharmaceutical Development Guidelines, to meet stability and quality requirements. Employing USP grade AS for preliminary studies is acceptable. Formulations should be evaluated against a U. S. Food and Drug Administration (FDA)-approved, AS formulation, which is available as USP sterile, non-pyrogenic isotonic solution of atropine sulfate monohydrate in water for injection. Stability assessments could employ forced degradation and initial real time testing for measuring the atropine drug substance and development of degradants at targeted temperatures and relative humidity conditions: refrigerated (2-8°C), room temperature (25 ± 2°C / 60% ± 5% RH), stressed (40 ± 2°C / 75% ± 5% RH), and transient excursions as required to comply with FDA regulations.

PHASE II:

Conduct further evaluation, improvements, and stability enhancements of the novel candidate formulations. Analytical testing may be performed to determine the presence and concentrations of extractables and leachables. Studies may determine the effects of potential stability enhancement techniques as needed, such as utilization of head-space nitrogen purge, vacuum seal, or others as needed to promote controlled stoUSrage stability to two years,

as well as operational stability. Operational stability could be demonstrated by exposing the vial to temperature extremes. A syringe needle puncture study may be performed to evaluate up to 28-day drug stability (28 days at 2-8°C and 25 ± 2°C / 60% ± 5% RH). If indicated, the performer may evaluate the alternative use of lyophilization as dry powder stability enhancer after reconstitution with bacteriostatic saline, sterile water for injection or other appropriate solution. Antimicrobial agents may also be assessed. The performer may determine the shelf-life stability of the lyophilized powder if indicated under vacuum seal or nitrogen purge. A 28-day stability study might be conducted to determine shelf-life after reconstitution.

PHASE III DUAL USE APPLICATIONS:

Develop scale-up processes and technology transfer protocol for pilot lot and GMP production. Develop regulatory strategy for commercialization and initiate interactions with the FDA. A more concentrated, multi-dose vialed atropine could reduce the logistical burden associated emergency medical personnel having to use multiple lower concentration vials to treat nerve agent casualties in the civilian sector, as well as the Department of Defense. Successful completion of all three phases under this solicitation will support small business valuation by confirming technical merit that invites further investment. This award mechanism will bridge the gap between laboratory-scale innovation and entry into a recognized FDA regulatory pathway leading to approval and commercialization.

REFERENCES:

1) Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use. Guidance for Industry. Division of Drug Information, Center for Drug Evaluation and Research, FDA. FDA-2015-D-343 2018;

2) Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products. Guidance for Industry. Division of Drug Information, Center for Drug Evaluation and Research, FDA. June 2015 Pharmaceutical Quality/CMC. 2015;

3) International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonized Tripartite Guideline. Pharmaceutical Development Q8 (R2). 2009 ;

4) Lee et al. 2010;

5) Single versus Multi-Dose Vaccine Vials: An Economic Computational Model. Vaccine. 2020 July 19;

6) 28(32): 5292-5300.

KEYWORDS:

atropine; chemical nerve agent; medical countermeasure; drug formulation

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