Jimson Weed Extract as a Protective Agent in Severe Organophosphate Toxicity

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Abstract

Treatment of patients following an organophosphate (OP) exposure can deplete a hospital’s entire supply of atropine. Given the possibility of multiple severe exposures after a terrorist attack using OP nerve agents, there exists a need for either greater atropine stores or the development of alternative antidotes. Jimson weed (Datura stramonium) contains atropine and other anticholinergic compounds and is common and readily available. It is used recreationally for its central anticholinergic effects and is made easily into an extract by boiling the crushed seeds. The extract has rapid onset of effects and may be useful for treatment of OP poisoning. Objectives: To determine whether pretreatment with an easily stored and prepared Datura seed extract (DSE) will increase survival following a severe OP poisoning. Methods: Datura stramonium seeds were collected, crushed, and then heated in water to make a 2-mg/mL atropine solution (100 seeds contain approximately 6 mg of atropine or 0.007 mg/seed). Male rats were randomized to pretreatment with either saline (n = 10) or 7.5 mg/kg DSE (n = 10) given as a single intraperitoneal injection 5 minutes prior to a subcutaneous injection of 25 mg/kg of dichlorvos. The endpoint was time to death recorded by a blinded observer. Results: The Kaplan-Meier estimates of the 24-hour survival rate was 90% (95% CI = 56% to 100%) for the DSE-pretreated group and 10% (95% CI = 0% to 45%) for the control group. The log-rank test revealed a statistically significant longer survival for the Datura-treated animals (p = 0.0002). Median survival time was 22 minutes 30 seconds for the control group and greater than 24 hours for the DSE-pretreated group. Conclusions: Pretreatment with DSE significantly increases survival following severe dichlorvos exposure. Key words: organophosphate toxicity; antidotes; Datura stramonium. ACADEMIC EMERGENCY MEDICINE 2004; 11:335–338.

The possibility of a terrorist attack involving “nerve agents” or weaponized organophosphate (OP) compounds is a constant threat. Local, state, and federal emergency management organizations and hospitals are preparing for this possibility by stocking large amounts of the antidotes atropine and pralidoxime. However, current supplies of these antidotes may not be adequate because each exposed patient may require a large amount of the antidote or because the number of patients in an OP attack could overwhelm resources. For these reasons, there exists a need for either more antidote stores or an alternative to these traditional antidotes. Datura stramonium (also known as Jimson weed, Jamestown weed, Loco weed, or Devil’s weed) contains numerous anticholinergic compounds such as atropine, scopolamine, and hyoscyamine. Datura is used recreationally for its anticholinergic effects, resulting in hallucinations. The entire plant has anticholinergic compounds, but the seeds contain the highest concentration. An extract made by boiling crushed seeds retains the anticholinergic activity, has a rapid onset of action, and thus may be potentially useful as an alternative to atropine for the treatment of the muscarinic symptoms of OP toxicity and some of the central anticholinergic effects. We examined the protective effect of a Datura stramonium (Jimson weed) seed extract on severe OP toxicity in rats. Our hypothesis was that there would be a protective effect of the Datura seed extract on mortality from severe OP poisoning.

METHODS

Study Design. This was a randomized, controlled, blinded laboratory investigation. The animal care and use committee of the institution approved this protocol, and handling of the animals was in accord with the National Institutes of Health and Food and Drug Administration guidelines.

Animal Subjects and Preparation. Twenty adult male Sprague-Dawley rats were used in the study. Adult male Sprague-Dawley rats were chosen because they have been used to study OP toxicity and therapy. A pre-exposure model was chosen because it has been used previously in rats to study OP toxicity and therapy. The animals were housed in...
plastic cages with 12-hour light and dark cycles and were allowed free access to food and water.

**Study Protocol.** Animals were randomized to receive intraperitoneal pretreatment with either Jimson weed extract (at a dose equivalent to 7.5 mg/kg of atropine intraperitoneal) or an equivalent volume of 0.9% saline. Five minutes later, both groups received dichlorvos (Pestaloid, Sigma-Aldrich, St. Louis, MO) at a dose of 25 mg/kg subcutaneously. Following the dichlorvos administration, a blinded observer determined the time of death in minutes when cardiac activity was no longer palpated in the subcostal area. The animals were observed continuously for the first two hours, and an observation was made at 24 hours. The rats were euthanized at 24 hours using carbon dioxide.

*Datura stramonium* (Jimson weed) seeds were collected in the summer of 2002, and the identity was confirmed by two certified toxicologists. During the summer, the plants are flowering, which means the seeds collected were from the 2001 growth season.

Twenty seeds were weighed, and the average weight of each seed was 0.0072 g (95% CI = 0.0069 to 0.0075). It is estimated that 100 seeds contain 6 mg of atropine equivalent. The authors estimated that 1 g of seeds contained 8.34 mg of atropine.5,11,12 The authors estimated that 1 g of seeds contained 8.34 mg of atropine. Datura seeds were weighed, crushed, and then diluted in 0.9% saline to make 2 mg/mL of atropine equivalent.

The seeds were heated to a boil and then cooled. The effect of this method of extraction on the pharmacologic agents was not assessed; however, anticholinergic activity is still present since this is the method used to make Jimson weed tea that is then ingested intentionally for recreational purposes.8,9 A dose of 7.5 mg/kg atropine equivalent was used because a dose of 5 mg/kg of atropine resulted in 88% survival (95% CI = 0.55 to 0.95) in a pre-exposure male Wistar rat model of OP poisoning using 25 mg/kg of dichlorvos.10

**Data Analysis.** Twenty-four-hour mortality rates were compared using the chi-square test. The times to the development of death were compared using the Kaplan-Meier method, and the two groups were compared using the log-rank test. Alpha was set at 0.05. Data were analyzed using SPSS statistical software (Version 8.0; SPSS Inc., Chicago, IL).

**RESULTS**

All deaths occurred within 32 minutes of the dichlorvos administration. Nine of ten animals pretreated with the Datura seed extract survived (90% survival, 95% CI = 56 to 100), while only one of ten animals in the control group survived at 24 hours (10% survival, 95% CI = 0 to 45) (p < 0.001). The median survival time for the animals pretreated with the Datura seed extract was >24 hours, and the median survival time for the control group was 23 minutes. The survival curve for the animals pretreated with the Datura seed extract was longer than the survival curve for the control (p < 0.0002) (Figure 1).

**DISCUSSION**

Within each hospital, there should exist enough atropine and pralidoxime to treat several cases of severe OP toxicity. In response to the terrorist attack of September 11, 2001, local hospital and regional stores of atropine and pralidoxime have been increased in preparation for a potential OP attack. Still, it is unknown whether even these increased stores will be adequate following a large exposure.

One option is to obtain atropine powder from pharmaceutical manufacturers and commercial supply houses. This can be easily obtained in bulk, stored, and reconstituted rapidly based on a previously derived formula.13

Alternative anticholinergic medications have also been evaluated as potential substitutes for atropine if supplies are inadequate. Diphenhydramine, given as a 30-mg/kg intramuscular injection, increased survival in a rat model of severe OP toxicity.10 Additional studies are needed before diphenhydramine can be used, and it is doubtful that there would be adequate supplies in each hospital to treat more than a few cases of OP toxicity.

The *Datura* species of plants contains a variety of tropane alkaloids such as atropine (dl-hyoscyamine), scopolamine, and l-hyoscyamine. All have a long duration of effect, cross the blood–brain barrier, and have central anticholinergic effects and antagonize the peripheral muscarinic receptor.5 The high concentrations of these anticholinergic alkaloids in the Datura seeds make an extract of this plant a potentially useful agent for the treatment of OP toxicity. In this study, we demonstrated that pretreating mice with a Datura...
seed extract subcutaneously significantly increased survival following a severe dichlorvos exposure. These preliminary pretreatment results suggest the possibility that a Datura extract may be used as a posttreatment antidote for mild OP poisonings, such as the chemical warfare agents. Clearly Datura extract would not address any significant nicotinic or central nervous system symptoms, or assist in reactivation of the cholinesterase enzyme (as does pralidoxime or related compounds) in the management of more severe OP poisoning.

The use of a plant extract at this time for OP poisoning is impractical. Several obstacles need to be overcome before it can be considered for use. The extract is unfiltered and not sterile. The process of purification, sterilization, and filtering of the Datura extract to make an intravenous preparation is not a reasonable option since this would be just as expensive and time-consuming as making additional atropine.

Gastric administration is a potentially safe alternative route that could be studied to overcome the issues needed to make an intravenous preparation. It is one of the routes used when the Datura extract is taken intentionally for recreational purposes. Gastric administration has been proposed as an alternative route of administration for atropine and pralidoxime because in a mouse model gastric administration is effective against OP toxicity. The oral route of administration would be limited to mild cases of OP poisoning since more severe cases would not be able to swallow the antidotes, and these cases would be complicated by vomiting, altered mental status, and seizures.

Another obstacle that needs to be overcome before the Datura extract could be considered for use would be standardization and preparation. In this protocol, the authors did not measure the amount of atropine or scopolamine but used a generally accepted estimate and then calculated a dose of 8.34 mg of atropine per gram of seed. This may be an overestimate since others have reported much lower amounts of anticholinergic compounds in the seeds (5.8 mg atropine/g, 2.71 mg atropine, 0.66 mg scopolamine, 0.387 mg atropine/g, 0.089 mg scopolamine/g). Additionally, the effect of scopolamine, which is also found in the plant, would have to be assessed. Since the Datura plant is not readily available, it would have to be grown and prepared in advance and packaged as a powdered, dried standardized form that would then have to be easily reconstituted for oral administration.

Datura seed extract has several properties that make it a potentially useful antidote to store in preparation for a terrorist attack. The seeds contain a high concentration of anticholinergic alkaloids that are easily extracted from the seeds by simply crushing them and heating them to a boil. While other parts of the plant also contain anticholinergic alkaloids, they contain less of these compounds and are more likely than the seeds to decompose with storage.

Like all anticholinergic compounds, the toxicity depends on the amount of exposure. Mild toxicity would present with tachycardia, dilated pupils, and dry skin; however, an excess of Datura extract can cause severe anticholinergic effects such as hyperthermia, seizures, and rhabdomyolysis. These toxic anticholinergic effects would not be expected if appropriately administered to a patient with cholinergic toxicity following an OP exposure. The usual duration of anticholinergic effect following exposure to the Datura extract is 12–48 hours. This long duration of clinical effect has potential advantage in the treatment of OP toxicity since the effect of most OP will be long. Patients treated with this extract may not require additional doses of antidote.

Other plants contain a variety of anticholinergic compounds and may be potentially used like the Datura species. *Atropa belladonna* (deadly nightshade) contains atropine, and its seeds contain hyoscyamine. *Cestrum diurnum* (day-blooming jessamine) and *Cestrum nocturnum* (night-blooming jessamine) contain atropine but also solanine in the unripe berries, which is a gastrointestinal irritant and may limit its usefulness in this setting. Additionally, *Mandragora officinarum* (mandrake, Satan’s apple) contain scopolamine, and *Hyoscyamus niger* (henbane) contains hyoscymine and hyoscine.

Weaponized OP may result in a large number of toxic patients that can overwhelm a local supply of atropine and pralidoxime. There is a need for either an increase in atropine and pralidoxime supplies or alternative antidotes. The Datura seed contains a large concentration of anticholinergic agents and in this pretreatment animal model is protective against mortality from an OP poisoning. The appropriate route of administration and method to standardize, prepare, and store the extract are needed before a Datura seed extract is considered a potential alternative to atropine following a large OP exposure.

**LIMITATIONS**

In this study, the Datura seed extract was administered prior to the administration of the OP. The results of a pre-exposure model may not be similar to the results of a post-exposure model. A pre-exposure model may allow time for the antidote to penetrate to tissue binding sites, while in a post-exposure model there may not be enough time. Additionally, a pre-exposure model is rarely seen clinically; however, this type of model has been used previously as a first step to evaluate other antidotes. Future studies should evaluate the effect in a post-exposure model and other routes of administration of the extract such as via the intragastric, oral mucosal, or sublingual route.
This study did not evaluate any potential side effects or toxicity from the Datura seed extract. In addition to the anticholinergic toxicity that may develop if administered to patients who are not cholinergic, there may be additional unidentified compounds that could be toxic. This could be assessed by administering the extract to a third group of animals. However, there are no known long-term sequelae reported following the recreational use of Datura.5

The only endpoint measured in this experimental model is rat mortality. Other endpoints such as duration of symptoms, fasciculations, and prolonged neurologic effects should be assessed in future protocols.

It may also be difficult to standardize the dose of the extract since there may be varying concentrations of the anticholinergic compound in different plants. The age of the plant also affects the concentration of the anticholinergic compounds. Younger plants have less atropine and scopolamine content in the seed; these concentrations increase as the plant ages.18

The authors used a rodent model of subcutaneous dichlorvos poisoning. The result may be different when this therapy is used in humans; if other organophosphates are used such as the weaponized organophosphate; and if the organophosphate exposure is by dermal, inhalational, or gastrointestinal routes.

CONCLUSIONS

Pretreatment with Datura seed extract significantly increases survival in a rat model of severe OP poisoning.

References


