

# TOXICOLOGY TODAY



## ANASCORP®: A F(ab')<sub>2</sub> Scorpion Antivenom For The Treatment of *Centruroides* Envenomations

by Logan Kelly, PharmD

### Introduction

In 2008, 15 522 scorpion envenomations were reported to the National Poison Data System, with one fatality in a 2 year old child.<sup>1</sup> In the United States, *Centruroides sculpturatus*—commonly known as the Arizona bark scorpion—is the only species whose venom is toxic to humans.<sup>2</sup> While most *Centruroides* stings in adults are tolerated with only minor effects, pediatric patients are susceptible to significant morbidity from the venom.<sup>3,4</sup>

Traditional management of severe symptoms involves sedation and supportive care, resulting in hospital stays that may exceed 24 hours.<sup>5</sup> The first widely available antivenom for scorpion envenomation was initially devel-

oped in Mexico under the tradename Alacramyn®. Renamed Anascorp®, it is an equine F(ab')<sub>2</sub> antibody fragment antivenom, that was approved by the FDA in August 2011 for the treatment of *Centruroides* envenomations.<sup>6</sup> This new antivenom promises to shorten the duration of symptoms and hospital stay length in envenomated patients, with particular benefit to the pediatric population.

### Background

*Centruroides sculpturatus* is a scorpion native to southwestern United States. *Centruroides* venom contains a neurotoxin involved in sodium channel blockade that causes peripheral nervous system excitation and subsequent uncontrolled motor activity.<sup>7</sup>

Envenomations are graded on a scale of I to IV (Table 1), with symptoms ranging from local pain and numbness at grade I, to neuromuscular and respiratory compromise in



Credit: © Luisar | Dreamstime.com

grades III and IV. Grade III to IV symptoms are most commonly experienced in pediatric patients, and require medical observation and treatment.<sup>4</sup>

Historically, a whole IgG goat antivenom was available for use solely in Arizona as a treatment option for grade III and IV symptoms. This antivenom never received FDA approval, and eventually Arizona State University ended production in 2000, with all remaining stockpiles used by 2004.<sup>3</sup>

Traditional management of patients with severe symptoms in areas without antivenom available involves sedation with benzodiazepines.<sup>5</sup> Intubation and ventilation may be required, and these treatments complicate hospital stays and require long

## IN THIS ISSUE

### Anascorp®

#### Outreach Education:

- Deaths from Poisoning Continue to Rise

#### Poison Pearls:

- Single-Use Laundry Detergent Packs

#### Meet the UPCC Staff:

- Zane Horowitz, MD

observation periods.<sup>7</sup> The need for an effective antidote spurred the pursuit of creating a F(ab')<sub>2</sub> scorpion antivenom.

### Development

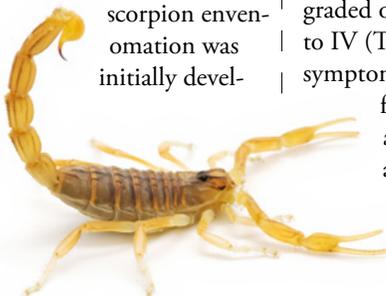
Anascorp® is produced from equine IgG antibodies. Due to the initial development and use of this product in Mexico, venoms from several *Centruroides* species endemic to Mexico are pooled and diluted. This diluted mixture is then injected into horses to produce an IgG mediated immune

response. The equine IgG is separated from the plasma, and digested with pepsin to release the F(ab')<sub>2</sub> complex of the IgG antibody. The sample is then purified via fractionation and other methods.<sup>9</sup> The final product is lyophilized and packaged in sterile 10 mL vials. Each vial of antivenom contains 85% F(ab')<sub>2</sub> antibodies and at least 120 mg of total protein, which is the equivalent of 150 LD<sub>50</sub> neutralizing units in mice.<sup>6</sup>

(cont. on pg. 3)

Table 1. *Centruroides* envenomation symptom grading scale<sup>8</sup>

Envenomation Grade	Associated Symptoms
Grade I	Pain and numbness at site of injection
Grade II	Remote pain or numbness in addition to local reaction
Grade III	Cranial nerve OR neuromuscular symptoms
Grade IV	Cranial nerve AND neuromuscular symptoms

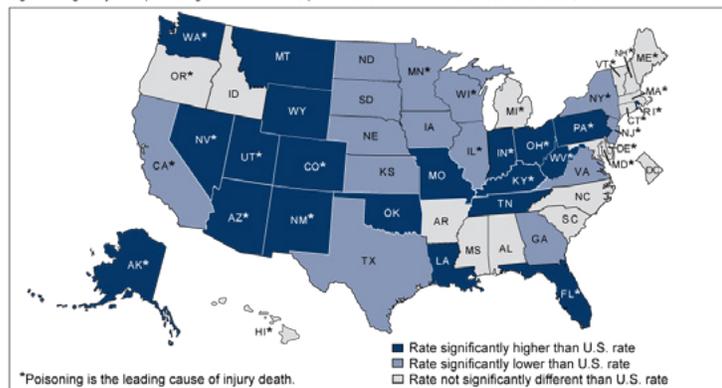


Credit: © Luisar | Dreamstime.com

## UNINTENTIONAL INJURY DEATHS FROM POISONING CONTINUE TO RISE

The National Center for Health Care Statistics (NCHS) recently published a brief on drug poisoning deaths in the US (NCHS 2011). Nationally, unintentional injury death due to poisoning has outpaced motor vehicle crash (MVC) deaths since 2009. In Utah, this trend started in 2005 when there were 282 deaths from MVCs compared to 308 deaths from poisoning. In 2008, poisoning was the leading cause of death from injury in 30 states.

Figure 1. Age-adjusted poisoning death rates: Comparison of state and U.S. rates: United States, 2008



NOTES: The poisoning death rate for Georgia may not be based on the final numbers of poisoning deaths. See "Data source and methods" for details. Figure 2 at [http://www.cdc.gov/nchs/data/databriefs/db81\\_tables.pdf#2](http://www.cdc.gov/nchs/data/databriefs/db81_tables.pdf#2). SOURCE: CDC/NCHS, National Vital Statistics System.

Five states with the highest poisoning death rates were New Mexico (30.8), West Virginia (27.6), Alaska (24.2), Nevada (21.0), and **Utah (20.8)**. At the Utah Poison Control Center, the number of emergency calls for prescription opioid exposures tripled over the past decade – from 486 in 1998 to 1502 in 2008.

During the years 1997-2004 deaths attributed to poisoning by drugs increased 128% in Utah. Methadone was the most common drug identified in poisoning deaths, with oxycodone, hydrocodone,

and fentanyl also contributing significantly. More recent data in Utah indicates that oxycodone is now the most common drug in poisoning deaths.

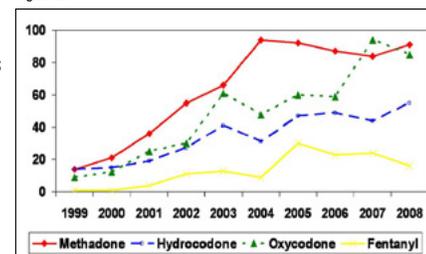
In Utah, rates of death are similar for males and females (51.3% vs 48.7%).

The average age at death was 42 years old, with the ages ranging from 16-80 years old. This closely mirrors the national picture where the death rate was highest in the 45-54 year age group. The final report from the Utah Prescription Pain Medication program noted that 50% of individuals who died of an overdose of methadone had a valid prescription at the time of death.

While the MVC death rate decreased over the past 2 decades, poisoning deaths from prescription drugs have experienced an exponential increase. Measures to prevent misuse and abuse of prescription medication should be reinforced:

- Promote safe use of prescription medication – only use/prescribe the lowest effective dose.
- Promote safe storage practices – out of reach of children and visitors.
- Promote safe disposal – take used and expired medicines to collection bins located in law enforcement offices. Access safe disposal information at [UseOnlyAsDirected.org](http://UseOnlyAsDirected.org).

Figure 2.



Credit: Utah Department of Health

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## POISON PEARLS

### SINGLE-USE LAUNDRY DETERGENT PACKS



Credit: Iowa Statewide Poison Control Center

Adapted from a paper by Jason Morris, PharmD Candidate 2013

Laundry detergent has long been a source of unintentional poisoning, especially in

young children. Most of these exposures do not result in symptoms. Typically, minor symptoms manifest quickly and resolve.

Recently, poison centers are reporting an uptick in calls about exposures in children to laundry detergents packaged in small, single-use packets with more severe clinical effects compared to traditional laundry detergent products. These packs are quick to dissolve in water, or even with moisture present on hands. The packets easily burst when squeezed. Exposure to this concentrated detergent can happen by ingestion, inhalation, eye and/or skin contact.

Traditional laundry detergents contain mild anionic and nonionic detergents and builders. Ingestion of these products generally produces mild GI upset and possibly vomiting. Some young children who swallowed the

new single-use packets have become very ill including several children who rapidly became obtunded and required intubation. Several reports of corneal abrasions after eye exposures in children have also been reported. At this time it is not yet clear how these new products differ from the traditional detergents. However, a heightened awareness to potential for toxicity from these products is warranted.

As of July 1, 2012, 1 464 exposures in children 5 and younger to highly concentrated liquid laundry detergent packets have been reported to US poison centers.

These new products are squishy and colorful, which makes them very attractive to small children. They look like candy or something fun to play with. As with all household cleaners, it's important to keep these out of children's reach.

(cont. from pg. 1)

## Anascorp®

### Mechanism of Action

Equine F(ab')<sub>2</sub> scorpion antivenom fragments bind to and neutralize free venom in the bloodstream, resulting in enhanced venom elimination. Additionally, the antivenom creates a venom concentration gradient between plasma and target tissues, allowing for redistribution out of affected tissues and rapid resolution of symptoms.<sup>3</sup>

### Dosing

Initial dosing of Anascorp® is the same for every patient. Three vials of antivenom (360 mg) are reconstituted in normal saline to a total volume of 50 mL. This preparation is administered intravenously over 10 minutes. The patient should be observed over the next 60 minutes to evaluate for resolution of symptoms. If symptoms are still present after 60 minutes, 1 additional vial of drug should be infused in 50 mL of normal saline over 10 minutes. This additional 1 vial dose can be repeated every 60 minutes until symptoms have resolved.<sup>6</sup> The mean number of vials needed for resolution of symptoms in the 1534 patients included in the safety analysis was 3.59 vials.<sup>3</sup>

### Pharmacokinetics

F(ab')<sub>2</sub> scorpion antivenom rapidly distributes from the bloodstream into extracellular space, where it binds quickly to venom. The mean duration of symptoms reported once the antivenom is infused is 1.42 hours. Serum venom levels drop below the level of detection within 1 hour of administration of antivenom. The average half life of the antivenom is 159 hours, and mean residence time—the average amount of time a molecule of antivenom spends in the body—is 10.4 days. The half life and mean residence time are important when considering how long to monitor a patient for delayed hypersensitivity reactions. Renal clearance of the F(ab')<sub>2</sub>/venom complex is 83.5 mL/hr.<sup>9</sup>

### Adverse Reactions

The majority of data for adverse reactions comes from open-label clinical trials of F(ab')<sub>2</sub> scorpion antivenom conducted in Arizona since 2007. The effects seen to date have been mild (Table 2). Out of the 1534 patients

reported in the adverse reaction data, 39 patients reported a serious adverse reaction; however, the reactions reported can also be caused by *Centruroides* envenomation, so the true cause is uncertain. Serious adverse reactions reported include: hypoxia, respiratory distress, aspiration pneumonia, swelling of the eyes, and ataxia. No anaphylactic reactions to the antivenom have been reported to date.<sup>6</sup> Out of all the clinical trial data reported for the antivenom, a total of 8 patients developed symptoms of a type III hypersensitivity reaction (serum sickness) within 14 days of follow up, but never developed the full syndrome.<sup>3</sup>

Table 2. Adverse reactions reported in > 1% of patients treated with antivenom

ADVERSE REACTION	NUMBER OF EVENTS [N=1534] (%)
Vomiting	72 (4.7)
Pyrexia	63 (4.1)
Rash	41 (2.7)
Pruritus	31 (2.0)
Headache	29 (1.9)
Rhinorrhea	28 (1.8)
Myalgia	25 (1.6)
Fatigue	25 (1.6)
Cough	22 (1.4)
Diarrhea	20 (1.3)
Lethargy	17 (1.1)

### Evidence for Use

Approval of Anascorp® by the FDA was principally based on 4 unpublished open label studies, with an additional unpublished retrospective study to establish a control baseline.<sup>3</sup> One randomized double blind placebo controlled trial was made public, and conducted in Arizona from May 2004 to October 2005.<sup>7</sup>

The placebo controlled trial consisted of pediatric patients aged 1-10 years, who exhibited both abnormal eye movements and limb thrashing within 5 hours of being stung. 8 patients were randomized to receive antivenom, and 7 patients were randomized to receive normal saline as a control. The baseline characteristics were similar between both groups, including: baseline midazolam use, plasma venom level, and time to presentation. At 4 hours, zero patients in the antivenom group exhibited any signs of envenomation, versus 6 patients in the control group (p < 0.001). Cumulative midazolam use was significantly higher in the placebo group (4.61 mg/kg

versus 0.07 mg/kg, p < 0.01). At 1 hour, 6 patients in the placebo group had a detectable plasma venom level, versus zero in the antivenom group (p < 0.001). A total of 2 adverse reactions were reported in the antivenom group, versus 1 adverse reaction in the placebo group.<sup>7</sup>

The results from the open label trials reported in an FDA review corroborate the results from the randomized controlled trial, with 98% of patients exhibiting complete resolution of symptoms within 4 hours of antivenom administration.<sup>3</sup>

### Conclusion

Anascorp® is a newly approved F(ab')<sub>2</sub> antivenom therapy for *Centruroides* envenomations in the United States. The F(ab')<sub>2</sub> antivenom has demonstrated ability to shorten duration of symptoms and decrease hospital stay length in envenomated patients compared to current management practices. The ease of dosing and low rate of adverse effects suggests that Anascorp® will become the treatment of choice in severe *Centruroides* envenomations. We recommend contacting the poison center for assistance with management of scorpion envenomations.

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Check our website for more poison prevention information at [www.utahpoisoncontrol.org](http://www.utahpoisoncontrol.org)

## TOXINS IN THE NEWS

**Cefepime** is often used for neutropenic fever in patients on chemotherapy. However the FDA wants to alert physicians about the potential for seizures in patients with renal impairment. After a review of the FDA's Adverse Event Reporting System (AERS) database through February 2012, they discovered 59 cases of non-convulsive status epilepticus during cefepime therapy; 56% of these cases involved patients over 65 years old. One commonality was renal impairment in 58 patients, and in 56 of these cases cefepime dosing was not adjusted for renal status. The dosage of cefepime should be adjusted in patients with creatinine clearance less than or equal to 60 mL/min. Nonconvulsive status epilepticus resolved in 43 patients. While 16 of these patients died, 13 deaths were attributed to the patient's underlying illness.

**Antiplatelet therapy** is good for patients who have had myocardial infarctions or cardiac stents placed, and often is used in combination with aspirin. However, more may not be better. The FDA issued a warning about high dose aspirin (> 100 mg/day) with ticagrelor, a P2Y12 platelet inhibitor, indicated to reduce the rate of thrombotic events in patients with acute coronary syndrome. Ticagrelor has been shown to reduce the rate of a combined endpoint of cardiovascular death, myocardial infarction or stroke, but new warnings suggest that use with aspirin greater than 100 mg a day diminishes, rather than enhances this effect.

## MEET THE UPCC STAFF



**DR. ZANE HOROWITZ** has joined the Utah Poison Control Center as of July 1, 2012, as its new medical director. He currently is a professor of emergency medicine at the Oregon Health & Sciences University in Portland, Oregon and the Medical Director of the Oregon-Alaska-Guam Poison Center. We will be sharing Doctor Horowitz's time and effort between the two poison centers as he "super-commutes" back and forth, spending 1 week each month here in Utah. Doctor Horowitz did residencies in Emergency Medicine at Georgetown University, and in Internal Medicine - with an emphasis in critical care - at U.C. Davis Medical Center in Sacramento California, where he was also on faculty for 14 years in the department of emergency medicine. During his years at U.C. Davis he also worked with the California Poison Control System. After moving to Oregon in 1997 he started a fellowship in medical toxicology, and shepherded it through accreditation by the Accreditation Council for Graduate Medical Education, at the Oregon Poison Center. He has trained a dozen fellows there, some of which are now medical directors of other poison centers and faculty in emergency medicine around the country. He looks forward to continuing the growth of the Utah Poison Control Center and providing education to pharmacy students, nurses, medical students, paramedics, and emergency medicine residents interested in toxicology.

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## THANK YOU

*The Utah Poison Control Center expresses its sincere thanks to the health care professionals, public health officials and toxicology colleagues that work together to treat and prevent poisonings.*



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