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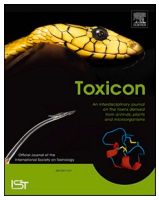

Neurotoxic respiratory failure absent following Arizona rattlesnake bites

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ABSTRACT

Warnings of neurotoxic respiratory paralysis following envenomation by rattlesnakes (*Crotalus* sp.) have been included in numerous scholarly publications over the past 60 years, resulting in fear and anxiety in the public and among clinicians. We examine the validity of the widespread belief that rattlesnakes in the arid southwestern United States, and particularly the Mohave Rattlesnake (*Crotalus scutulatus*), pose a significant risk of medically relevant respiratory weakness and paralysis in humans. A retrospective review of 3440 suspected rattlesnake bites reported to the Arizona Poison and Drug Information Center between 1999 and 2020 produced no evidence of respiratory weakness in a region with three species known to express significant amounts of neurotoxin in their venoms: *Crotalus concolor*, *C. tigris*, and the more widely distributed *C. scutulatus*. A literature review produced numerous warnings regarding respiratory paralysis following envenomation by rattlesnakes in our region that either lacked references or cited sources that did not contain strong supportive data. We found no case reports of neurotoxic respiratory weakness following Arizona rattlesnake bites in the literature and such reports in surrounding states were scant. We conclude that neurotoxic respiratory failure in this region following rattlesnake envenomation is extraordinarily rare. All rattlesnake bites should receive the same consideration and critical care, and warnings about significant risk of respiratory failure are unwarranted, regardless of species involved.

1. Introduction

For more than half a century, numerous references have warned of the potential for respiratory muscle weakness and paralysis following North American rattlesnake bites, sometimes delayed following an initially innocuous presentation (e.g., Shannon, 1957; Russell, 1962, 1969, 1973; Dowling et al., 1971; Minton et al., 1976; Wingert and Wainschel, 1975, 1977; Wingert, 1980; Wingert and Chan, 1988; Bush and Siedenburg, 1999; Stebbins, 2003; Lavonas et al., 2011; Kanaan et al., 2015; Schield et al., 2018; Greene et al., 2021; Patel et al., 2022; Clark, 2022).

In particular, a potential identification of Mohave Rattlesnake (Crother et al., 2017) has become widely considered a prognosticator of dire outcomes following a bite, including potentially significant neurotoxic respiratory paralysis. Known as *Crotalus scutulatus* to biologists and "Mojave green" to many others, Mohave Rattlesnakes have been repeatedly characterized as being among the most lethal of North American snakes and capable of producing paralysis and respiratory failure, with one reference commenting:

"Venom from southwestern United States populations of *C. s. scutulatus* has long drawn the interest of researchers and laymen alike. Amongst the latter, largely due to popular media coverage of the snakes' toxicity, *C. s. scutulatus* origins, resurrection capabilities, and reported venom toxicity have reached mythological proportions." (Dobson et al., 2018)

1.1. History

Early studies reported that rattlesnake venoms with "a so-called neurotoxin" produced paralysis, "beginning in the forelegs of animals (or wings of birds), extending to the hind legs and finally to the muscles of respiration. When these are involved, death follows quickly" (Githens, 1931). A subsequent report compared the average median lethal dose (MLD) of venoms from 27 North American pitvipers that caused "acute, paralytic death" in 350 g pigeons. In these trials, Tiger Rattlesnakes, *Crotalus tigris*, and Mohave Rattlesnakes were ranked highest in lethality, with average MLDs of 0.004 mg and 0.007 mg, respectively

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(Githens, 1935). Then, it was reported that five North American rattlesnakes (Tiger; Mohave; "Bleached," *C. mitchelli*, aka *C. pyrrhus*; "Green," *C. lepidus*; and the Massasauga, *Sistrurus catenatus*) had "highly neurotoxic" effects in pigeons, producing "slow paralytic action" and death from "respiratory paralysis" (Githens and Wolff, 1939a, 1939b, 1939c). However, these investigators also noted that "none of the North American rattlesnakes whose venoms cause delayed paralysis are important as the cause of accidents in man" (Githens and Wolff, 1939b).

In his 1956 tome, highly regarded rattlesnake authority Laurence Klauber quoted Githens, concluding that "if future tests of the quality of the venom of *C. s. scutulatus* corroborate the m.l.d. figures now available, this may prove to be a very dangerous rattler" (Klauber, 1956:788). Subsequent toxicity comparisons of rattlesnake venoms have corroborated those of Tiger and Mohave Rattlesnakes as among the most lethal to mice (e.g., Glenn and Straight, 1978; Russell, 1980; Minton, 1987). In particular, warnings about Mohave Rattlesnakes' extreme lethality have subsequently abounded in popular, biological, and medical literature. At the same time, warnings have proliferated about the species' ability to produce delayed respiratory paralysis, despite a lack of supporting data after the early animal studies.

1.2. Mohave toxin

Beginning in the 1970s, considerable research was focused specifically on the venom of the Mohave Rattlesnake. The component responsible for the species' high lethality in test animals was isolated in 1975 and named "Mojave toxin" (Bieber et al., 1975). Shortly thereafter, a large area in south-central Arizona was identified where Mohave Rattlesnakes lack this presynaptic β-neurotoxin, instead producing venom similar to other species, rich in hemorrhagic and proteolytic snake venom metalloproteinases (SVMPs; Glenn and Straight, 1978; Glenn et al., 1983; Glenn and Straight, 1989; Wilkinson et al., 1991; Massey et al., 2012; Zancolli et al., 2019). The neurotoxic variant has been labeled venom A (Glenn and Straight, 1978) and type II (Mackessy, 2010) and the hemorrhagic variant venom B (Glenn and Straight, 1978) and type I (Mackessy, 2010).

Some individual Mohave Rattlesnakes in the intergrade zone between Arizona's venom A and B populations express both Mojave toxin and SVMPs (venom A+B; Glenn and Straight, 1978). Occasional individuals expressing venom B or A+B have since been detected (Bush et al., 2012) or identified far from central Arizona (Strickland et al., 2018). The hemorrhagic variant lacking Mojave toxin (venom B/type I) failed to produce extreme lethality in test animals (Glenn and Straight, 1978).

Following the early lethality comparisons, subsequent investigators identified significant expression of neurotoxic venom components closely related to Mojave toxin in the Tiger Rattlesnake (Weinstein et al., 1985) and in the Midget Faded Rattlesnake, *C. viridis concolor* (Pool and Bieber, 1981), among others.

1.3. Distribution and abundance of neurotoxic species in Arizona

Midget Faded Rattlesnakes are restricted in Arizona to a small and sparsely populated area of northern Coconino County around the southern end of Lake Powell, while Tiger Rattlesnakes are more widely distributed but restricted to arid rocky hillsides in southern Arizona and encounters with people appear to be uncommon for both species. But Mohave Rattlesnakes are distributed across most of the southwestern half of the state, south of the Mogollon Rim. In our experience, of the approximately 16 species of rattlesnakes in Arizona, Mohave Rattlesnakes are second only to Western Diamond-backed Rattlesnakes, *Crotalus atrox*, in frequency of human encounters, owing to the ubiquitous distribution of both species in the broad desert valleys and bajadas where most people live, work, and recreate. The percentage of bites attributed to these species in southern Arizona was once estimated as 60% *C. atrox*, 30% *C. scutulatus*, and 10% all others (Hardy, 1988). A recent query of "research grade" observations of these species in Arizona logged at the citizen science website www.inaturalist.org (and validated by curators and other taxon experts) during the 22-year period of our case review yielded 637 (23%) *C. scutulatus* and 2135 (77%) *C. atrox*.

Our collective experience led us to hypothesize that neurotoxic respiratory weakness is quite rare following rattlesnake bites in Arizona and the goal of these analyses was to test this hypothesis.

2. Methods

We retrospectively reviewed 3440 suspected human rattlesnake exposures reported to the Arizona Poison and Drug Information Center (APDIC; covering the entire state except Maricopa County, which is served by a different poison center) between January 1, 1999, and December 31, 2020. All cases coded as "rattlesnake" envenoming reported to the APDIC during this period were evaluated. Cases that involved bites to animals (i.e. pets or livestock), bites by non-native captive snakes, and out-of-state consults, as well as cases where subsequent information clearly indicated the case should not have been coded as a rattlesnake exposure, were excluded. For example, one case was a patient with Munchausen Syndrome who had overdosed on warfarin in an effort to receive medical care for a snakebite.

Each case was read in its entirety by one of six researchers who entered the data on a spreadsheet containing >120 columns designed to tabulate all the clinically significant information available. One of us (GS) then reviewed the researchers' submitted data for accuracy, consistency, and completeness. All concerns were resolved through direct communication with the researcher and any areas of confusion were proactively clarified to the entire research team. All cases with critical findings such as intubation were sent to a second reviewer that was blinded of the first reviewer's submission. Submissions from both reviewers were compared for discrepancies and any clarification needed was obtained directly from the medical record by the lead investigator (GS).

While interpreting details in the included cases, we sought to identify signs of significant neurotoxic weakness of the respiratory muscles exclusive of other signs of neurotoxicity like fasciculations, myokymia, paresthesias, and ptosis.

Any record indicating intubation or fatality received particular scrutiny. The most common syndromes requiring intubation in our dataset were angioedema, anaphylaxis or anaphylactoid reactions. Anaphylaxis and anaphylactoid reactions result from the release of mast cell mediators and are indicated by signs and symptoms such as urticaria or rash, airway swelling, and bronchospasm; while β-neurotoxins like Mojave toxin and its homologs decrease acetylcholine binding at the neuromuscular junction, resulting in weakness (Gopalakrishnakone et al., 1980; Ho and Lee, 1981). Thus, we searched for neurotoxic respiratory failure requiring intubation resulting from impaired ventilation due to weakness of the diaphragm and intercostal muscles and/or weakness of the oropharyngeal muscles causing accumulation of secretions and upper airway obstruction (Gnanathasan and Rodrigo, 2014). In reviewing our case data, as well as in our literature review, we distinguished these clinical syndromes based on careful review of the available clinical information in its entirety.

We searched the medical and biological literature for mentions of envenomation, neurotoxicity, and respiratory paralysis/weakness/failure associated with rattlesnake bites in the southwestern United States and we examined any references cited in those papers.

3. Results

Review of our 3440 cases does not demonstrate neurotoxic respiratory failure in humans and evidence of this effect in the literature is scant.

3.1. Case review

None of our Arizona rattlesnake bite cases described respiratory failure resulting from weakness of the muscles of respiration or upper airway obstruction caused by weakness of oropharyngeal muscles. Fifteen patients were intubated: 12 because of angioedema or anaphylactic/anaphylactoid reactions, 2 following iatrogenic sedation for agitation, and 1 patient was intubated during complications from a newly placed pacemaker. Intubations in our dataset did not include any cases of respiratory weakness or paralysis (Fig. 1). Of the 12 patients intubated for angioedema or anaphylactic/anaphylactoid reactions, 11 cases specifically mention facial or airway swelling; in the case where such swelling was not noted, the patient developed hives and throat itching after receiving CroFab. Two deaths were identified: one due to an immediate severe allergic reaction (included in intubations above) and the other suffered severe skin necrosis and profound sepsis following a very significant delay in reaching medical care.

Six of the 15 intubation cases contained snake identification comments but only one was confirmed (by an APDIC herpetologist): a Mohave bite that produced an immediate anaphylactic/anaphylactoid reaction. The other five tentative identifications consisted of two Western Diamond-backed Rattlesnakes and three Mohave Rattlesnakes, including the anaphylaxis-associated fatality following a bite by an animal identified by "friends, experienced with snakes, hobbyists" as a Mohave Rattlesnake.

3.2. Literature review

David Hardy Sr., a physician and competent herpetologist based in Tucson, published a prospective investigation of fifteen rattlesnake bites in southern Arizona in the 1980s that he could confirm were caused by Mohave Rattlesnakes and found no clinical evidence of respiratory muscle weakness and no fatalities. His literature search at that time produced no documentation of respiratory paralysis in humans (Hardy, 1983). Of the nine deaths between 1969 and 1984 in which snakebite was listed on the Arizona Certificate of Death, two were reportedly caused by captive Mohave Rattlesnakes. Neither victim sought medical care and "probably died of untreated hypotension and cardiopulmonary collapse." The other seven snakes were not identified and were presumably not captives, but all were in areas inhabited by both Western Diamond-backed and Mohave Rattlesnakes. (Hardy, 1986).

Our own recent literature search disclosed no cases of neurotoxic respiratory weakness following rattlesnake bites in Arizona but two cases were found in surrounding states (both in southern California): In one case (Jansen et al., 1992), the biting animal was identified as a Mohave Rattlesnake by a local museum naturalist (Jansen, pers comm). In the other (Richardson et al., 2007), the snake was subsequently obtained and "determined to be a Southern Pacific rattlesnake (*Crotalus viridis helleri*)" (a species not found in Arizona). A 2002 retrospective chart review of 289 rattlesnake envenomations reported to the poison center in Maricopa County (the Arizona county not covered by our poison center) revealed 13 cases requiring intubation, but none were attributed to neurotoxic effects (Brooks et al., 2002).

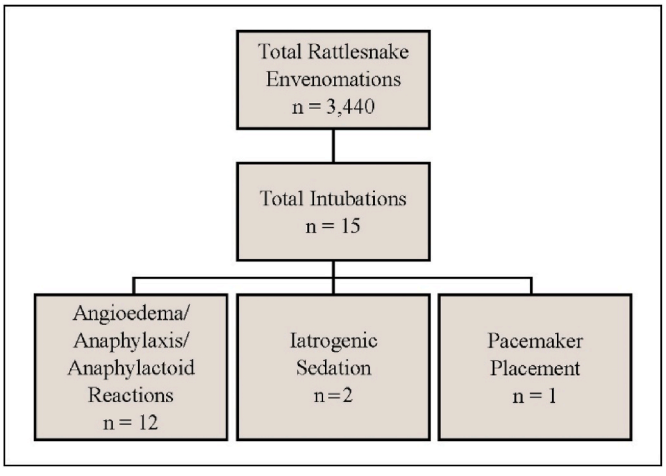

Fig. 1. Indications for intubation of reported rattlesnake bite patients in our dataset.

4. Discussion

It is rare for rattlesnake bite patients or their companions to bring evidence of the species of rattlesnake, such as photographs or the snake itself, to the hospital. And the ability of lay persons to accurately differentiate one rattlesnake species from another (especially Western Diamond-backed vs. Mohave Rattlesnakes) is problematic (Cardwell et al., 2022). Therefore, we cannot know the exact portion of Mohave Rattlesnake envenomations in our dataset. Nevertheless, based on Hardy's 1988 estimates and recent proportions of rattlesnake observations posted to www.inaturalist.org, we estimate that our dataset likely represents several hundred to over 1000 Mohave Rattlesnake envenomations.

5. Conclusions

Warnings that have proliferated over several decades regarding the potential for neurotoxic respiratory paralysis following rattlesnake envenomation in the arid southwestern United States are unwarranted. While our case review was restricted to Arizona, our literature search was not similarly restricted. We see a disconnect between often-mentioned life-threatening neurotoxicity, most often attributed to the Mojave Rattlesnake, and evidentiary support for these claims in the literature or in our more than two decades of data on rattlesnake envenomation in Arizona.

Patients bitten by any rattlesnake species in this region require the same critical care without extraordinary concern for respiratory paralysis or the species involved, despite frequent mentions of such clinical concerns in the snakebite literature.

5.1. Limitations

Our database was analyzed retrospectively and is limited in most cases by the clinical information gathered by telephone. We also rely on clinicians or patients to reach out to the poison center. There may, theoretically, be envenomations, especially severe envenomations resulting in intubation or death without medical attention, which are not captured in our data.

Although our dataset undoubtedly contains Mohave Rattlesnake bites from the venom B (non-neurotoxic) area in south-central Arizona, it contains copious data from the western, southern, and southeastern portions of the state populated with neurotoxic Mohaves, although we cannot identify the snakes responsible for individual cases.

Both case reviews and our literature search were complicated by the challenge of determining the cause of respiratory failure. There is overlap in the signs and symptoms such as shortness of breath and stridor. Distinguishing features of anaphylaxis would include visible swelling of the tongue or lips, rash, and wheezing. These features would be lacking in neurotoxic respiratory failure. The presence of other neurotoxic features such as ptosis, myokymia, and paresthesias would not be required but would bolster the case for neurotoxic respiratory failure. Presentations with simultaneous anaphylaxis and neurotoxic weakness or more subtle weakness of muscles of respiration would be difficult to detect.

There are no large-scale prospective studies addressing our questions specifically. Case reports are published when remarkable presentations are encountered. But many reputable sources have characterized

Mohave Rattlesnake envenomation as causing neurotoxic respiratory paralysis and, therefore, these cases may not be seen as remarkable and subsequently not published as case reports. Finally, there may be relevant data or cases that we did not find in our search, despite our best efforts.

Credit author statement

Geoffrey Smelski – Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – review & editing. Michael Cardwell – Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. Jaiva Larsen – Formal analysis, Investigation, Writing – review & editing.

Ethical statement

This study does not involve manipulation of human or animal subjects, only retrospective review of blinded case data and published literature.

The authors know of no similarity between this study/report and other studies, either published, reported at meetings, or underway elsewhere.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors do not have permission to share data.

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