SPIDER BITE

CLINICAL SYNDROMES AND ROLE OF ANTIVENOM

Geoff Isbister
Calvary Mater Newcastle
SUMMARY

• Spider myths
• Spiders and Drugs
• Latrodectism
  • Widow spider bite
• Loxoscelism
• Other spiders:
  • Funnel-web spider bite

Isbister and Fan. Spider bite Lancet 2011
BUT IN ALL HONESTY….

• Last talk of the day….

1. Most spider bites cause minor effects
2. In general, antivenom appears to not be effective for most spider envenoming…
3. Spiders are lovely creatures
4. Spiders are attributed with almost every clinical effect!
5. Too little research on the effects of drugs in spiders
QUANTIFYING SPIDER (ARANAEAE) BITES: A FIELD AND LABORATORY STUDY

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Abstract. Spiders (Araneae) are often blamed for various infectious wounds, yet to date there have been few studies directly assessing the actual risk of being bitten by a spider. Using human subjects, we quantified the probability of receiving a spider bite (and subsequent infection) in both the field and laboratory. The field study involved releasing naked human subjects (10 male, 10 female) into 1) a forest in central Kansas, 2) rangeland in central Texas; and 3) human dwellings in Wichita, Kansas. Subjects were released, and asked to wander freely for a period of 90 minutes. If bitten, subjects were asked to bring the suspected spider back in a 3 dram vial. After this time period, a team of professional arachnologists searched the subject’s and all spiders found were identified to species. The experiment was conducted in the spring and autumn of 1995, and repeated once and twice during the day. Out of 240 individual trials, spiders were blamed for only one bite: this was due to the human subject directly antagonizing a black widow spider (Latrodectus mactans) found on the underside of an outhouse in central Texas. The reason for the human’s interest in the outhouse remains largely unknown. Wasp stings occurred in 24 of 240 trials, all in either the forest or rangeland habitats. Six of 80 trials in the residence in Wichita resulted in hospitalization due to lacerations resulting from stepping on broken beer bottles in the night trials; numerous cuts and bruises also resulted from the inability of human’s to walk carefully in the wilderness. The laboratory experiment involved human subjects placing one foot (without socks or shoes) in a terrarium that was subject to one of the following treatments: 1) control, 2) one live specimen of the black widow spider (L. mactans), 3) one live specimen of the brown recluse spider (Loxosceles reclusa), and 4) one specimen of Erigone atra. Each treatment was replicated 10 times, using different human subjects. Any bites, and subsequent pain and discomfort, were recorded by either the authors or by the medical staff at a nearby hospital. The results showed that spiders never bite humans unless they are directly stepped upon. In two trials, the human inadvertently placed their foot on a black widow, and brown recluse spider, and these resulted in injury to both the spider and human. Erigone atra never hit a human subject, nor was it later recovered from the terrarium. Due to its small size, it is doubtful this species could puncture the human epidermis. Interestingly, there were significantly more injuries caused by the control ($P = 0.024$); in 7 trials, the humans became alarmed when their feet were in the terrarium, resulting in rapid exits through the plate glass, and later hospitalization. In summary, spiders do not bite humans (unless directly stepped upon) and the stupidity exemplified by the human subjects is the main cause of injury and subsequent infection.
Spiderbite Myths
ARACHNOPHOBIA

- In a study of 261 adults
  - 32% of females
  - 18% of males
- Reported that spiders made them feel anxious, nervous or very frightened
RATIONAL EXAMINATION... in Australia

- **Spider fatalities:**
  - 26 recorded (1900+): 13 FWS, 13 RBS
  - No deaths since 1980
- **Hymenoptera deaths (mainly anaphylaxis):**
- **Motor vehicles**
  - In 2001 there were 1183 motor vehicle deaths (drivers/passengers) in Australia
MIDDLE AGES

• the belief that spiders were the harbingers of the Great Plagues

• the cause of the mass hysterical reaction, “tarantism”, blamed on spiderbites
“The treatment of tarantism involved patients dancing to special tunes in lively 3/8 or 6/8 time, until they dropped. This is preserved today in the popular dance ‘tarantella’. They would fall completely exhausted to the ground and sleep;”
NECROTIC ARACHNIDISM:
The mythology of a modern plague

Attacked by 250 spiders

By KAMAH COGDON

A MAN bitten more than 350 times by an army of spiders is haunted by nightmares of his brush with death.

Joe Smith, 46, said he was given little chance of survival when he was attacked by what he believed were dangerous white-tailed spiders.

The spiders crawled under his clothes and into his boots and socks as he worked in his shed.

Blisters emerged on his skin while multitudes swarmed by the time he got to hospital. The police had stopped his car and left about every continent of his body reddened with venom.

But Museum of Victoria spider expert Ken Walker yesterday said the white-tailed spiders didn't need; alike any spiders which often sheltered in family groups in burrows and were encountered by digging or weeding.

Mr Smith, of Beveridge, and a friend were digging up a palm tree when they disturbed spiders living in its branches last October.

Mr Smith ran to his house nearby and called 000. "I grabbed the leaves and branches and as I was pulling it out, they came out from everywhere," Mr Smith said.

"They were all over me, literally all over me, spiders upon hundreds.

He ran in hospital and was transferred by ambulance to Melbourne Medical Centre in a critical condition.

"I was on morphine for the pain and I couldn't move. But I could hear everything that was going on around me," he said.

There is no real reason for white-tailed spiders, which are common in urban gardens and homes.

Mr Smith was in hospital for three months.

Isbister Lancet 2004
AUSTRALIAN SPIDER BITE

A prospective study of 750 definite bites, with expert spider identification
CONCLUSIONS

• Medically important spiders:
  • Redback spider
  • Funnel web spider

• Majority of bites caused minor effects

• Specific effects/syndromes
  • **NO cases of necrosis or ulceration**
  • no allergic reactions
  • 1% with probable secondary infection
WHITE-TAIL SPIDER BITE VS. NECROTIC ARACHNIDISM

130 definite white-tail spider-bites

- Clinical syndromes DIFFERED
- No ulceration or necrosis occurred 0% [97.5% C.I.; 0 – 2.8%]

Isbister and Gray Med J Aust 2003
ANTIVENOM

Is it effective?
**EFFICACY VS. EFFECTIVENESS**

**Antivenom efficacy:**
- Ability to bind toxins/venoms
- To neutralise venom effects *IN VITRO*
- To reverse venom effects *IN VITRO*
- To neutralise venom effects *IN VIVO*
- To reverse venom effects *IN VIVO*
- To change patient outcomes from envenoming: Either preventing further or persistent effects OR reversing established effects

**Antivenom effectiveness:**
- Venom Pharmacokinetics
  - Central Compartment
    - Eg. coagulant toxin
  - Peripheral Compartment
    - Eg. neurotoxin, myotoxin

- Biological Reversibility
- Antivenom Pharmacokinetics
- Premixture prevents clinical effects
- Premixture prevents OR reverses clinical effects
ANTIVENOM

• Efficacy = BINDS to toxins
  • STOPS
  • PREVENTS
  • REVERSES
  • CURES

• Effectiveness = patient gets better
MECHANISMS OF “STOPPING” TOXICITY

• How does antivenom binding to toxins “stop” toxicity ➔ effectiveness
• Possible mechanisms:
  • Neutralisation:
    • Blocks active site
    • Prevents toxin active site interacting with target tissue/cell
  • Trapping:
    • Traps toxin in central compartment ➔ cannot reach target site
  • Elimination:
    • Removes toxins from the body - ? mechanism
Absorption / Distribution
Venom and Antivenom

Trapping

Elimination

Lymphatics
Latrodectism

RED-BACK SPIDER BITE
WIDOW SPIDER BITE
EPIDEMIOLOGY

- Differs throughout the world
- Poorly described in many places.
- Examples
  - Australia bites occur in and around the house in dry dark areas, and includes shoes, bike helmets and garden equipment
  - Some South American countries bites occur in rural workers and mainly outdoors.
CLINICAL SYNDROME

“... so characteristic that any experienced physician would be able to make the diagnosis on first sight,...”

• Appears to be significant variation between species:
  • predominantly a pain syndrome in Australasia
  • systemic illness with the European widow spider where myocardial effects are reported
  • South Africa difference between *L. indistinctus* and *L. geometricus*. 
CLINICAL SYNDROME... Redback spider

Local and regional effects
- Local pain: increasing pain at the bite site over a period of minutes to hours. The pain may last for well over 24 hours
- Radiating pain: from the bite site to the proximal limb, trunk or local lymph nodes
- Local sweating
- Regional sweating: unusual distributions of diaphoresis, usually associated with the site of the bite
- Piloerection
- Local erythema

Systemic effects
- Remote or generalised pain or generalised myalgia
- Abdominal pain (differential diagnosis: acute abdomen)
- Nausea, vomiting and headache
- Malaise and lethargy
- Hypertension
- Irritability and agitation*
- Fever
- Paraesthesia
- Chest pain (differential diagnosis: acute MI)
- Muscle spasms
- Patchy paralysis
LATRODECTISM

- Is antivenom effective?
- Is there venom delivery to the central compartment?
- Does antivenom distribute to the site
- Effects:
  - Local and regional pain
  - Systemic symptoms
- “PAIN” ... rarely objective
Elimination

Toxin in local compartment

Trapping

130 kDa toxin

Elimination
REDBACK SPIDER ANTIVENOM: IN VITRO

- Premix neutralisation studies:
  - Antivenom prevents neurotoxicity for:
    - redback spider venom
    - other latrodectus venoms
    - α-latrotoxin
- Antivenom is efficacious

BUT
- Does this neurotoxicity represent clinical effects
- Requires pre-mixing

RANDOMISED CONTROLLED TRIALS

• Ellis et al 2005
  - RCT / blinded treatment - IM versus IV – small study
  - No difference in pain at 1h or antivenom dose
  - 2° outcome - IV more ‘pain free’ at 24 hrs

• Isbister et al 2008
  - RCT / blinded treatment - IM versus IV
  - No difference in pain at 2 hours
  - No difference in systemic effects

• Stanford et al 2007 (abstract)
  - 24 patients – placebo controlled – small study
  - ΔVAS greater for AV group

<table>
<thead>
<tr>
<th>Outcome</th>
<th>IV</th>
<th>IM</th>
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</thead>
<tbody>
<tr>
<td>Improved pain at 2h</td>
<td>62%</td>
<td>53%</td>
</tr>
<tr>
<td>Improved pain at 24h</td>
<td>84%</td>
<td>71%</td>
</tr>
<tr>
<td>Systemic Effects</td>
<td>58%</td>
<td>65%</td>
</tr>
</tbody>
</table>
EFFECTIVE...BUT?

- There was not a clinically significant difference between the IV and IM route of administration of RBS AV in reducing pain.
- Two interpretations:
  - Equally effective
  - Equally ineffective
- Subgroup of 19 patients had:
  - serial AV concentrations measured using ELISA.
  - **IM 10 patients:** no antivenom could be detected
  - **IV 9 patients:** antivenom detected in all patients

Isbister et al 2008
IS REDBACK ANTIVENOM EFFECTIVE?

• Antivenom is efficacious – bind venom/toxins

• Problems:
  • Pharmacokinetics
    • Does venom reach the central compartment
    • Can antivenom reach the toxin target site
  • RCT suggest no difference in IM versus IV
  • BUT, only IV antivenom present in the central compartment

• Placebo controlled trial is required
  • Currently underway with 150 patients recruited
CURRENT PRACTICE

• PIC Recommendation until RCT finished:
  • IV administration
  • Dose = 2 vials

• Analgesia: should be given to all patients:
  • Oral paracetamol/NSAIDS/opiates
    • 1g paracetamol
    • 800mg ibuprofen (400mg tds)
    • 5 – 10mg oxycodone
  • Parenteral opiates
Loxoscelism
WHAT CAN I SAY?
CLINICAL EFFECTS

- **Cutaneous Form**
- **Systemic or viscerocutaneous form (≥ 1 to 10%)**
  - Fever, malaise, vomiting, headache and rash
  - Intravascular haemolysis
    - Autoimmune haemolysis, +ve to direct antiglobulin to C3, IgG, IgM, IgA

Day 1 - 2  Day 9  Day 16  Day 25
TREATMENT

- Antivenom
- Corticosteroids
- Dapsone
- Antihistamines
- Antibiotics
- Analgesics

- Hyperbaric oxygen therapy
- Electric shock
- Surgical excision

Very little evidence to support any of these therapies
ANTIVENOM… THEORETICAL

- Small amount of toxin
- Irreversible toxicity:
  - Cutaneous injury/necrosis
  - Intravascular haemolysis
- Delayed presentation
  - Often > 24hr
- ? Toxin in circulation
ANTIVENOM… EVIDENCE

• No clinical trials

• Animal studies are conflicting
  • Gomez et al 1999: must be given within 4 hours
  • Pauli et al 2009: benefit for up to 48 hours

• Anecdote/observation
  • Reduce the extent of cutaneous lesions
  • Possible prevent systemic toxicity
RECOMMENDED TREATMENT

• Brazilian Ministry of Health
  • Antivenom for extensive cutaneous and systemic loxoscelism
  • Corticosteroids
  • Timing – not recommended more than 72h post-bite

• Whatever therapy is chosen:
  • Wound care is paramount
SYDNEY FUNNEL-WEB SPIDER
CLINICAL EFFECTS

• Local
  • Pain: usually severe pain from large fangs
  • Local muscle fasciculation and paraesthesia

• Systemic Symptoms:
  • nausea, vomiting, abdominal pain
  • Pulmonary oedema
    • non-cardiogenic or cardiogenic
CLINICAL EFFECTS

• Autonomic Effects

  • Cholinergic: diaphoresis, salivation, lacrimation, miosis, bradycardia
  • Catecholaminergic: tachycardia, mydriasis

• Neuromuscular Excitation:
  • Muscle fasciculations – eg. tongue spasms
  • Paraesthesia: often perioral tingling (early)

• Central Nervous System:
  • Usually agitated and anxious initially
  • Coma (late or in children)
## DEATHS SINCE 1927

<table>
<thead>
<tr>
<th>Date</th>
<th>Sex</th>
<th>Age</th>
<th>Bite Site</th>
<th>Interval to death</th>
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<tr>
<td>1927</td>
<td>M</td>
<td>2</td>
<td>finger</td>
<td>90 min</td>
</tr>
<tr>
<td>1929</td>
<td>F</td>
<td>5</td>
<td>lower arm</td>
<td>80 min</td>
</tr>
<tr>
<td>1930</td>
<td>F</td>
<td>47</td>
<td>thumb</td>
<td>9 hrs</td>
</tr>
<tr>
<td>1933</td>
<td>F</td>
<td>25</td>
<td>buttock</td>
<td>13 hrs</td>
</tr>
<tr>
<td>1949</td>
<td>M</td>
<td>14</td>
<td>toe</td>
<td>12 hrs</td>
</tr>
<tr>
<td>1951</td>
<td>F</td>
<td>8</td>
<td>finger</td>
<td>23 hrs</td>
</tr>
<tr>
<td>1953</td>
<td>M</td>
<td>7</td>
<td>finger</td>
<td>90 min</td>
</tr>
<tr>
<td>1958</td>
<td>F</td>
<td>2</td>
<td>not seen</td>
<td>15 min</td>
</tr>
<tr>
<td>1958</td>
<td>M</td>
<td>1</td>
<td>both hands</td>
<td>90 min</td>
</tr>
<tr>
<td>1961</td>
<td>F</td>
<td>60</td>
<td>finger</td>
<td>5 hrs</td>
</tr>
<tr>
<td>1970</td>
<td>F</td>
<td>17</td>
<td>breast</td>
<td>16 hrs</td>
</tr>
<tr>
<td>1979</td>
<td>F</td>
<td>31</td>
<td>wrist</td>
<td>6 days</td>
</tr>
<tr>
<td>1980</td>
<td>M</td>
<td>2½</td>
<td>upper arm</td>
<td>3 days</td>
</tr>
</tbody>
</table>
ANTIVENOM ... DOES IT WORK?
THEORETICAL

- Small toxin
  - Slows Na channel inactivation
- Large mass of venom:
  - Fangs larger than brown snake
  - Easily milk large amounts
- Clear systemic effects
- Early antivenom likely to bind toxin centrally;
  - Prevents and possibly reverse neurotoxicity

MW 4800 Da
CIRCUMSTANTIAL AND ANECDOTAL

- No deaths since 1980
  - Two deaths in modern intensive care units
- 1980: Last death of a 3 y.o.
  - 6 days with multiorgan failure
- 1983: same age, same hospital, similar severity initially
  - Given antivenom, well, discharged within 24 hours
- BUT still the “haven’t given enough” dosing phenomena:
  - Repeat dosing common for non-progressive toxicity
  - Huge doses given in some patients?
FUNNEL ANTIVENOM

• Indicated for treatment
  • Dose ? 2 vials was the initial recommendation

• Clinical trial
  • Unlikely, would need to be N=1 cross-over design
  • Too rare

• Sensible approach to re-dosing
  • May be seeing irreversible effects
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