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Pharmacologic Management of Crotalid Envenomation

Introduction

1. Around 9,000 Americans are treated for snake bites and 5 die each year. Most are bitten by members of the *Crotalinae* subfamily (a.k.a. crotalids) of the pit viper family which includes copperheads, water moccasins, and rattlesnakes.
2. Crotalid envenomation's can cause broad range of adverse effects, including local tissue, hematologic, and/or systemic effects including shock and life-threatening bleeding.
3. Use symptom progression such as swelling beyond 1 major joint or hematologic effects (decreased fibrinogen, thrombocytopenia, or increased PT) as an indicator for initial or additional doses of antivenom. Identification of the snake can be helpful but should not determine decision to initiate or continue therapy in place of symptom progression.
4. Patients can develop delayed or recurrent hematologic symptoms up to a week after treatment cessation, especially following a severe envenomation.

PHARMACOLOGY		
	Crotalidae Polyvalent Immune Fab (Ovine) **(*Crofab*®)**	Crotalidae Immune F(ab')2 (Equine) **(*Anavip*®)**
Mechanism of Action	Fab fragment of IgG antibody isolated from sheep serum; antibody binds to venom and removes it from tissue	$F(ab')_2$ fragment of IgG antibody isolated from horse serum; antibody binds to venom and removes it from tissue

Dose	• Initial Dose
	  o **Progressing tissue/hematologic effects: 4 – 6 vials**
	  o **Systemic effects including shock: 8 – 12 vials**
	  ▪ May repeat every hour as needed until initial control of local, hematological, and systemic symptoms is achieved
	• Maintenance: 2 vials q6h x 3 after control is achieve
		• **Initial dose: 10 vials**
		  o May repeat every hour as needed until initial control of local, hematological, and systemic symptoms is achieved
		• Maintenance: 4 vials as needed; may administer for any re-emerging symptoms

Administration	• Inject ≥18 mL NS (or SWFI) into each vial; more volume will speed up dissolution • **Gently swirl or roll vials in hand or combine all vials in bag to roll simultaneously; DO NOT SHAKE** • Add/QS solution to 250 mL bag of NS admin over 1 hour • NOTE: Many clinicians choose a slower initial rate to allow for assessment of allergic reaction	• **Reconstitute each vial with 10 mL NS** • **Gently swirl or roll vials in hand or combine all vials in bag to roll simultaneously; DO NOT SHAKE** • Solution should be clear to yellow/green and opalescent; do not use if otherwise discolored • Add/QS solution to 250 mL bag of NS • Administer total volume over 1 hour • NOTE: Many clinicians choose a slower initial rate to allow for assessment of allergic reaction
Formulation	**IV only; each box contains 2 vials (~$5000/box)**	**IV only; each vial costs ~$1220**
PK/PD	T½: 12 – 23 hours	T½: ~5.5 days
Adverse Effects	• Hypersensitivity reactions ranging from pruritus/urticaria to anaphylaxis • Serum sickness (rare)	• Nausea (23%), arthralgia (11%), peripheral edema (8%) • Hypersensitivity reactions ranging from pruritus/urticaria to anaphylaxis • Serum sickness (rare)
Drug Interactions	No known drug interactions	No known drug interactions
Compatibility	NS or SWFI for reconstitution; NS for infusion	NS
Comments	**Approved for treatment of any North American crotalid envenomation**	**Recently approved any North American crotalid envenomation**

Overview of Evidence			
Author, year	**Design/ sample size**	**Intervention & Comparison**	**Outcome**
Dart RC, 1997	Prospective, multicenter trial (n = 11)	Patients received 4 vials of *Crofab*® for initial control of symptoms following minimal or moderate crotalid envenomation	**Ten of 11 patients were deemed to have a clinical response and reduction in snakebite** severity score; one patient required 4 addition vials
Dart RC, 2001	Multicenter, randomized, prospective, open-label trial (n = 31)	Initial 6 vials of *Crofab*® patients were randomized to receive either 2 vials PRN vs 2 vials Q6h x 18 hours	**No statistical difference between groups in snakebite severity score**; Overall severity was reduced from 4.35 to 2.39 ($p < 0.001$)
Boyer LV, 2013	Phase 2, RCT for rattlesnake bites in Tuscon, AZ (n = 12)	*Crofab*® vs *Anavip*® for reduction in serum venom levels at various pre-defined times following crotalid envenomation	Venom levels were **insignificantly lower** following initial control in the *Crofab*® group, but **significantly lower following maintenance and during follow-up** in the *Anavip*® group ($p = 0.004$); No difference between groups in safety outcomes
Bush SP, 2015	RCT at 18 sites in the US (n = 123)	*Crofab*® vs *Anavip*® for the prevention of late coagulopathy following crotalid envenomation	**More patients in the Crofab® group vs the Anavip group ® experienced late coagulopathy versus** • 29.7% vs 10.3% • $p < 0.05$, NNT = 5
Gerardo CJ, 2017	RCT in 18 ED in the US (n = 74)	*Crofab*® versus placebo to measure limb function 14 days after envenomation using Patient-Specific Functional Scale	**Crofab reduced limb disability** measured by the Patient-Specific Functional Scale 14 days after copperhead envenomation. • 8.6 in the treatment group vs 7.4 in the control group (95% CI 0.1 – 2.3; $p = 0.04$)
Gerardo CJ, 2020	Post-hoc analysis (N=21)	Group 1: Anavip 10 Vials + Anavip 4 vials q6 x 3 Group 2: Anavip 10 vials + Placebo Group 3: Crofab 5 vials + 2 vials q6h x 3	In Copperhead bites (n=21) there was no difference between Anavip® and Crofab® in o Time to achieve initials control o Patient requiring PRN or unscheduled doses

Conclusions

- *Crofab*® and *Anavip*® seem to be comparable for initial symptom control, although due to the longer half-life, *Anavip*® may have a larger role in prevention of late-onset or recurrent coagulopathy.
- Each health-system will likely need to make a formulary decision on which agent to use. This decision should be based on which snake species are endemic to that region, preparation time, agent costs, and the prevalence of recurring coagulopathy in their patient population.

References

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