

To the editor:

Clinical relevance of brown snake (*Pseudonaja* spp) factor V escaping hemostatic regulation

Despite the work by Bos et al¹ reported in *Blood* and by other researchers on the structure and function of the procoagulant molecules,^{2,3} the pathophysiology of venom-induced consumption coagulopathy (VICC) associated with human envenoming by these snakes remains unclear.⁴ Although it would appear that the presence of a factor Va–like toxin in brown snake (*Pseudonaja* spp) venom that is impervious to regulation by the hemostatic system provides a potent biologic weapon against prey and in human envenoming, clinical research does not fully support this.^{4,5}

It is useful to compare the effects of Australian tiger snake group (genera *Notechis*, *Tropidechis*, and *Hoplocephalus*) venoms, which all contain factor Xa–like prothrombin activators (without a factor Va–like part),⁴ to that of brown snake venom, which contains the factor Xa–Va–like prothrombin activator. A recent study of severe coagulopathy in 167 envenomed patients demonstrated that the coagulopathy was similar irrespective of the snake, characterized by complete consumption of fibrinogen, very high D-dimers and unrecordable international normalized ratio.⁵ Importantly, the time course of the recovery of the consumption coagulopathy or VICC was the same for tiger and brown snakes.⁵ Therefore, the coagulopathy seen clinically appears to be similar irrespective of the use of human factor Va by the tiger snake group venoms or the presence of brown snake derived factor Va–like toxin and its ability to avoid hemostatic regulation as shown by Bos et al.¹

Interestingly, it may be more clinically relevant and unique that the brown snake–derived factor Va–like molecule does not require activation, so that the prothrombin activator (Xa–Va–like toxin) is able to rapidly induce clotting activation in vivo. Some recent work by our group on the onset of VICC showed that, in a series of 112 patients, there was a discernible delay in the development of the coagulopathy with tiger snake group envenoming compared with brown snake.⁶ Serial clotting factor assays indicated that fibrinogen, factor V, and factor VIII concentration dropped to low concentrations or zero almost immediately after the bite in brown snake cases compared with the tiger snake group, in which there was a delay of 1 to 2 hours. This would support the findings of Bos et al,¹ which would in turn explain the delayed clotting activation by the tiger snake group factor Xa–like toxins: the factor Xa–like toxin by itself will convert only a small amount of prothrombin to thrombin, the thrombin will then lead to activation of human factor V, and finally, the combination of human factor Va with toxin Xa will lead to the observed massive consumption. Brown snake avoids this delay by supplying its own factor Va.

Response

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We thank Isbister and colleagues for their interest in our paper detailing the procoagulant properties of venom-derived factor V (pt-FV) from the common brown snake, *Pseudonaja textilis*.¹ In their letter, they contend that the presence of pt-FV is not a contributing factor to the coagulopathy seen clinically. The studies in reference suggest that the final extent of coagulopathy after

Bos et al¹ have highlighted one of the pitfalls of conducting toxin research in an isolated in vitro system. Although the molecular structures of molecules can be deciphered, this does not always readily translate to their clinical effects in vivo.

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References

1. Bos MH, Boltz M, St Pierre L, et al. Venom factor V from the common brown snake escapes hemostatic regulation through procoagulant adaptations. *Blood*. 2009;114(3):686-692.
2. Rao VS, Kini RM. Pseutarin C, a prothrombin activator from *Pseudonaja textilis* venom: its structural and functional similarity to mammalian coagulation factor Xa–Va complex. *Thromb Haemost*. 2002;88(4):611-619.
3. St Pierre L, Masci PP, Filippovich I, et al. Comparative analysis of prothrombin activators from the venom of Australian elapids. *Mol Biol Evol*. 2005;22(9):1853-1864.
4. Isbister GK. Procoagulant snake toxins: laboratory studies, diagnosis, and understanding snakebite coagulopathy. *Semin Thromb Hemost*. 2009;35(1):93-103.
5. Isbister GK, Duffull SB, Brown SG, ASP Investigators. Failure of antivenom to improve recovery in Australian snakebite coagulopathy. *Q J Med*. 2009;102(8):563-568.
6. Isbister GK, Scorgie F, Brown SGA, et al. Coagulation factor deficiencies associated with venom induced consumption coagulopathy in Australian snake envenoming [abstract]. *Clin Toxicol*. 2009;47(5):462.

envenomation by either the brown or tiger snake (no venom FV) was comparable.²⁻⁴ Masci et al made a similar observation investigating the time course of snake bite envenomation by these snakes.^{5,6} To a certain extent the observation that there are no differences in the final coagulopathy and time course of recovery is not surprising. Laboratory measurements (> 3 INR, undetectable