Insight in differences in venom and antivenom pharmacokinetics in sera of *V. ammodytes* bitten patients treated by currently available therapies

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INTRODUCTION

Due to current shortage in Zagreb antivenom availability, in Slovenia *V. ammodytes* venomous bites have recently been treated with antivenoms of French and UK producers. In Croatia, for therapeutic purposes the remaining doses of Zagreb antivenom have still been used. Composition differences between these three antivenoms exist. First, they differ slightly in specificity. Zagreb antivenom has been raised against *V. a. ammodytes* venom, but is clinically effective and used against all European venomous snakes (*V. ammodytes*, *V. berus*, *V. aspis*, *V. lebetina* and *V. xanthina*). Viperfav from the French producer has been raised against the mixture of *V. aspis*, *V. berus* and *V. ammodytes* venoms, but was mostly used against *V. aspis* and *V. berus*. ViperaTAb from the UK has been raised against *V. berus* venom solely, and used so far only to treat envenomations caused by *V. berus*. Second, they differ in type of the active drug component. Namely, Zagreb antivenom and Viperfav are F(ab')$_2$-based preparations, while ViperaTAb is formulated of Fab fragments. And third, investigated antivenoms have differently prescribed administration routes - intravenous for ViperaTAb and Viperfav or intramuscular for Zagreb antivenom.

AIM

Aim was to reveal pharmacokinetic profiles of currently available antivenoms in *V. ammodytes* envenomations and their influence on venom level decrement. In sera of envenomed and antivenom-treated patients pharmacokinetic behavior of *V. ammodytes* (*Va*) venom, ammodytoxins (Atxs) - its neurotoxic component, and Fab or F(ab')$_2$ fragments was evaluated.

MATERIALS AND METHODS

The study represents prospective case series of consecutive patients envenomed by *V. ammodytes* snakebite and mostly treated with Zagreb antivenom (9 patients) or ViperaTAb (6 patients) in University Hospital of Split or Ljubljana since 2015. In serum samples concentrations of F(ab')$_2$ or Fab fragments, venom and neurotoxic ammodytoxins (Atxs) were determined by the respective in-house ELISA assays. Pharmacokinetic analysis of antivenoms was performed whenever possible using PKSolver add-in software for Microsoft Excel. Concentration-time data was fitted either to non- or two-compartment model.

RESULTS

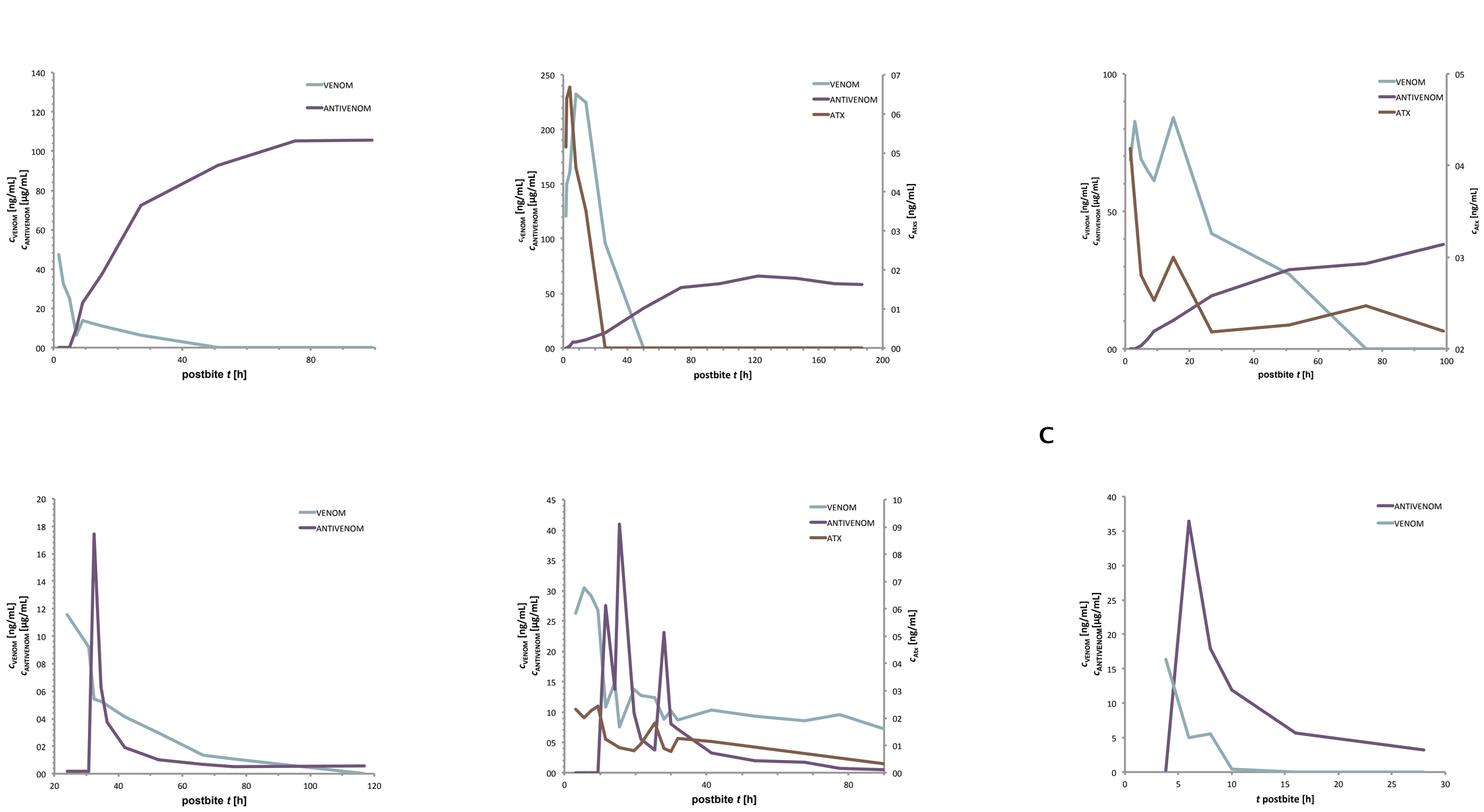

Figure 1. Representative pharmacokinetic profiles of antivenom, venom and Atxs in patients bitten by *V. ammodytes* and treated either with (A) Zagreb antivenom intramuscularly or (B) ViperaTAb (one or three doses) intravenously. (C) Pharmacokinetic profiles of ViperaTAb and venom in *V. berus*-bitten patient.

CONCLUSIONS

Pharmacokinetic profile differences between Zagreb antivenom and ViperaTAb were revealed.

Systemic clearance of ViperaTAb was between 4.3 and 23.2 (mL h^{-1}) / kg. Its distribution and elimination half-lives were in range of 0.4-3.2 h and 12.9-55.9 h, respectively.

In the case of Zagreb antivenom, due to prolonged residence time, even the sampling period of 96 h post-treatment was not sufficient for estimation of pharmacokinetic parameters. The exception was 8 days hospitalized patient, revealing systemic clearance of 0.42 (mL h^{-1}) / kg and half-life of 317.2 h.

Venom was detected in serum of all patients, in contrary to Atxs. Measured concentrations inversely correlated with the F(ab')$_2$/Fab level.

Antivenom level was highly dependent on the fabotherapics type and administration route, significantly affecting reappereance and systemic clearance of *V. ammodytes* venom and its neurotoxic component as well.

The treatment of patients with Zagreb antivenom did not required additional doses, in contrast to ViperaTAb treatment. This effect might be due to higher specificity of Zagreb antivenom for *V. ammodytes* venom, but also due to differences in administration route and antivenom pharmacokinetics.

This work was fully financially supported by Croatian Science Foundation (IP-2014-09-4915). Any opinions, findings or recommendations expressed in this material are those of the authors and do not necessarily reflect the views of Croatian Science Foundation.