Pharmacokinetic evaluation of *Vipera ammodytes* snakebites treated with currently available antivenoms

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INTRODUCTION

Due to shortage in Zagreb antivenom availability, in Slovenia *V. ammodytes* bites have been treated with French and UK antivenoms in the recent years. In Croatia, the remaining doses of Zagreb antivenom have still been used for therapeutic purposes. Composition differences between these three antivenoms exist. First, they differ in specificity. Zagreb antivenom (Croatia) is raised against *V. ammodytes* venom, but is clinically effective and used against all European venomous snakes. Viperfav (France) 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 (UK) has been raised against *V. berus* venom solely, and used so far only to treat *V. berus* envenomations. Second, they differ in type of the active drug. Namely, Zagreb antivenom and Viperfav are F(ab')$_2$-based products, 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

The aim of the study was to reveal pharmacokinetic profiles of currently available antivenoms that are being used in *V. ammodytes* (*Va*) envenomations and their influence on venom level decrement. Pharmacokinetic behavior of *Va* venom, its neurotoxins (Atxs), and Fab or F(ab')$_2$ fragments was evaluated in serum samples of patients.

MATERIALS & METHODS

The study represents prospective case series of consecutive patients envenomed by *Va* snakebite and mostly treated with Zagreb antivenom (9 patients) or ViperaTAb (6 patients one of which received Viperfav also) in University Hospital of Split (Croatia) or Ljubljana (Slovenia) since 2015. Concentrations of F(ab')$_2$ or Fab fragments, *Va* venom and Atxs in serum samples 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 to non- or two-compartment model.

RESULTS

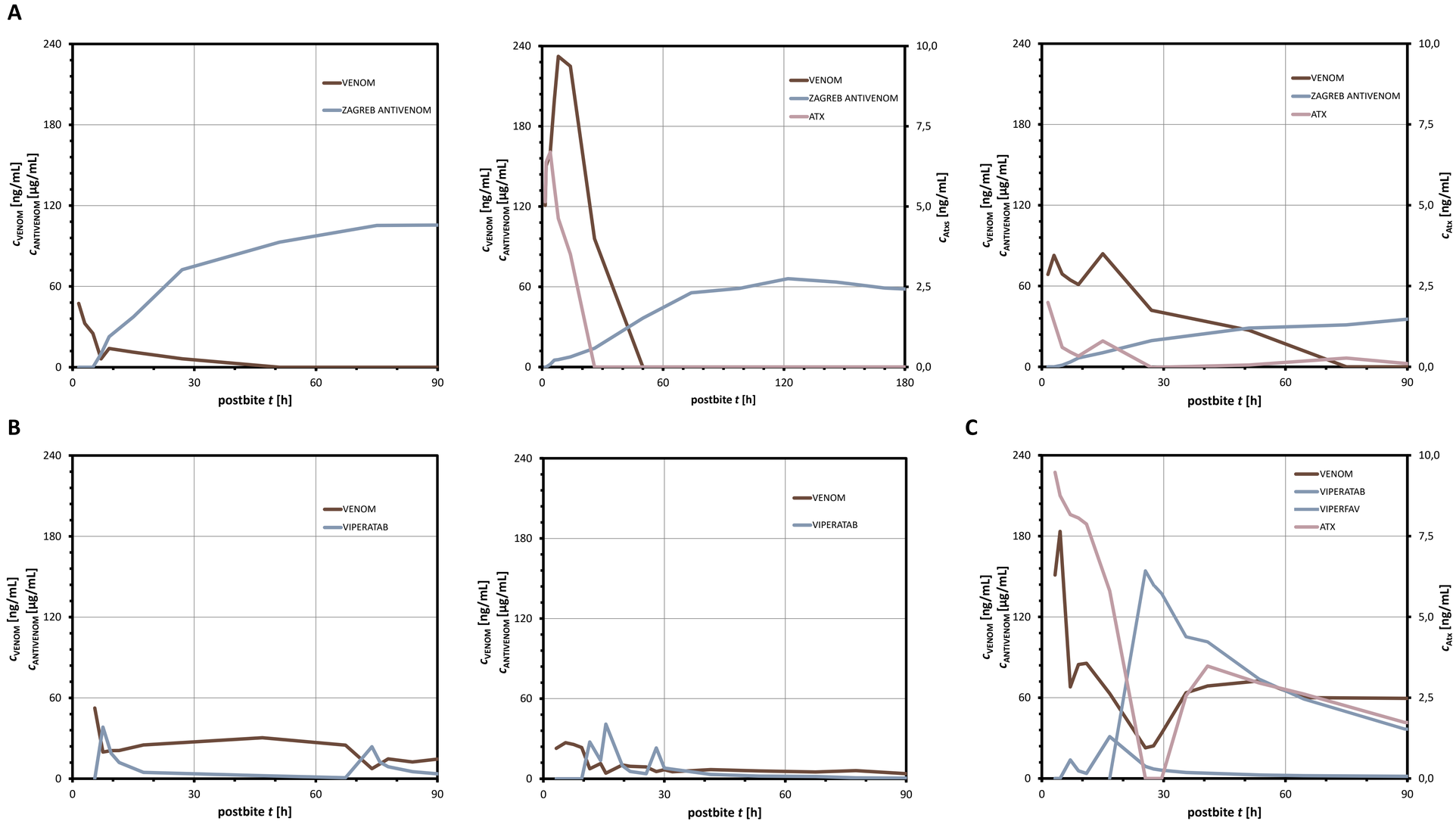

Figure 1. Representative pharmacokinetic profiles of antivenom, venom and Atxs in patients bitten by *V. ammodytes* and treated with Zagreb antivenom (single dose *i.m.*) (A), ViperaTAb (two or three doses *i.v.*) (B) or ViperaTab (two doses *i.v.*) in combination with Viperfav (single dose *i.v.*).

CONCLUSIONS

Pharmacokinetic profile differences between ViperaTAb, Zagreb antivenom and Viperfav were revealed (**Fig 1**). Systemic clearance of ViperaTAb was between 4.3 and 23.2 (mL h^{-1}) / kg (**Fig 2**). Its elimination half-life was in the range of 12.9-55.9 h. Viperfav, which has also been administered *i.v.*, exhibited much longer retention in circulation. 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 elimination half-life of 317.2 h.

Venom was detected in serum of all patients (**Fig 1**). Its concentration correlated with the F(ab')$_2$/Fab level, revealing inverse trend in venom-antivenom circulation behavior. Atxs appeared in measurable quantity only in samples with high venom level.

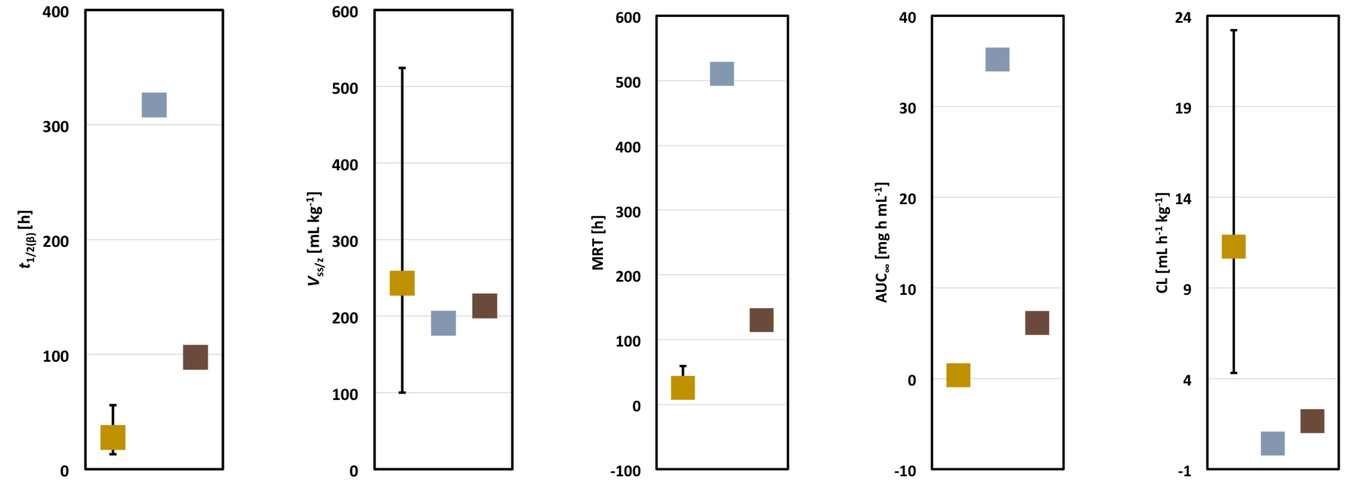

Figure 2. Pharmacokinetic parameters of ViperaTAb, Zagreb antivenom and Viperfav in *V. ammodytes*-bitten patients. For ViperaTAb mean values (■) as well as minimal and maximal values (bars) obtained for six patients are indicated. For Zagreb antivenom (■) and Viperfav (■) pharmacokinetic parameters were determined for only one patient.

$t_{1/2}$, elimination half-life in non-compartment model, $t_{1/2\beta}$, elimination half-life in two-compartment model; V_{ss}, volume of distribution at steady-state in two-compartment model; V_z, volume of distribution during terminal phase in non-compartment model; MRT, mean residence time; AUC_∞, area under the curve at $t = \infty$; CL, clearance time.

Antivenom concentration was dependent on fabotherapics type and administration route, affecting re-appereance and clearance of venom and Atxs as well (**Fig 1**). In contrast to Zagreb antivenom treatment, therapy with ViperaTAb in half of patients required additional dose(s) because of difficulties in resolution of clinical signs (Brvar *et al*., 2017), although some of them had low serum quantity of venom. Discrepancy in efficiency between Zagreb antivenom and ViperaTAb might be due to higher specificity of the former one for *Va* venom, but also due to differences in antivenom dose, administration route or pharmacokinetics.

REFERENCE

Brvar M, Kurtović T, Grenc D, *et al*. Vipera ammodytes bites treated with antivenom ViperaTAb: a case series with pharmacokinetic evaluation. Clin Toxicol. 2017;55:241–248

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