



PHARMACOKINETIC STUDY OF ANTIVENOMS, DEVIATION OF THERAPEUTIC EFFECTS.

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Introduction. The therapeutic effectiveness of the antivenom depends on the neutralizing potential of the venom, the rate at which it penetrates the venomous site and the adequate dosage. Today, the design of the therapeutic antibodies is based mainly on its optimal neutralization; however, a new concept of the design of antivenoms is focused on the Pharmacokinetics (PK). We previously studied the PK (Vazquez et al, 2010) of immunoglobulins and fragments in rabbits. It was shown that the profile of Fab and F(ab')₂ PK were well described by a three-exponential kinetics equation, while IgG and IgG(T) PK, presented deviations from the three-exponential kinetics at 120 h after injecting the bolus of the immunotherapeutics. The differences were explained as an effect of surge of anti-horse antibodies. After 120 h the profile shows a peak at 260 h and decaying slowly afterwards (Vázquez et al., 2010). The purpose of this work is the description of antivenom PK and anti-horse IgG production in rabbits receiving three boluses (300 µg/kg, I.V.) of Fab, F(ab')₂ or IgG separated by 21 days.

Methods. Blood samples from Four rabbits receiving three boluses (300 µg/kg, I.V.) of Fab, F(ab')₂ or IgG at intervals of 21 days, Each sample was evaluated by ELISA quantification. To evaluate anti-horse antibodies production, IgG titers were determined in samples taken on days 0, 10, 21, 31, 42 and 53, after the first 300 µg/kg bolus of each kind of Ig. The analysis of the generated data was performed using the algorithm "Simplex" to minimize the absolute values of the differences between the predicted values and the measured values, using different kinetic models (Vazquez et al, 2005).

Results. Values obtained were fitted to the kinetic equation using the profiles of the seric antivenom concentration vs time. After the first bolus Fab and F(ab')₂ were well described by a tri-exponential model; IgG was also fitted to three exponentials (Vázquez et al., 2010). After the 2nd and 3rd bolus it was

not possible to fit data setting. The only exception was one rabbit (registered as 49 in the experiment protocols). PK changes after successive boluses, and that the same kinetic model cannot be applied to the three situations. PK of 2nd and 3rd bolus were calculated and compared in a model independent. The figure 1 presents plots of anti-horse immunoglobulin seric titers after 300 µg/kg I.V. boluses of Fab, F(ab')₂ or IgG for 4 rabbits injected.

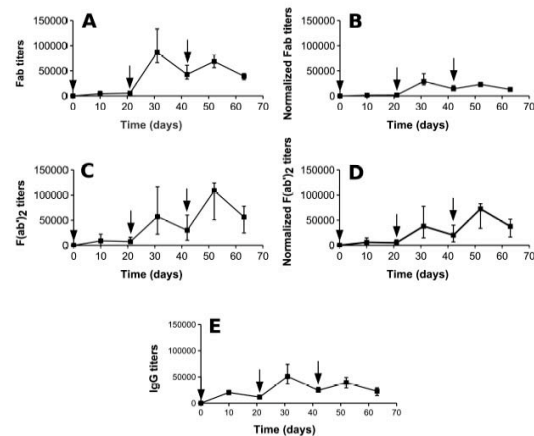


Figure 1. Seric titers.

Conclusions. We observed no adverse effects induced by the 2st and 3rd boluses in spite of the anti-horse IgG titers detected in our rabbits. However it can be a risk in the efficiency of subsequent antivenom treatments.

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References.

1. Vázquez H, Chávez-Haro A, García-Ubbelohde W, Mancilla-Nava R, Paniagua-Solís J, Alagón A, Sevcik C. 2005. Pharmacokinetics of a F(ab')₂ scorpion antivenom in healthy human volunteers. *Toxicol.* 46(7):797-805.
2. Vázquez, H., Olvera, F., Paniagua-Solís, J., Alagón, A., Sevcik, C., 2010. Pharmacokinetics in rabbits and anti-sphingomyelinase D neutralizing power of Fab, F(ab')₂, IgG and IgG(T) fragments from hyper immune equine plasma. *Internat. Immunopharm.* 10, 447-454.