Antithrombotic effects of Ir-CPI in an arterio-venous shunt model in the rabbit

Michel Guyaux[1], Pierre Gueret[2], François Becher[3], Jean Amiral[4], Stéphanie Simon[3], Edmond Godfroid[1]

[1]Bioxodes, Marche-en-Famenne, Belgium,[2]Hemostasis Unit, University Hospital Rennes and GETBO EA3878 Brest, France, [3]CEA Saclay, Gif sur Yvette, France, [4]Hyphen BioMed, Neuville sur Oise, France

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I. INTRODUCTION

Ir-CPI, a protein of 67 amino acids, has been isolated from the salivary glands of the tick *Ixodes ricinus.* It has demonstrated protective effects in arterial and venous thrombosis models in mice and rats[1]. As a contact phase inhibitor, Ir-CPI is susceptible to prevent thrombosis associated with blood exposure to non-physiological surfaces[2].

Similar inhibitions of FXI and FXII coagulant activities by Ir-CPI were observed in human and rabbit using *in vitro* coagulation assays, indicating this last species could be relevant for investigating pharmacodynamic effects of Ir-CPI *in vivo*.

The aims of this study were:

- to determine the efficient antithrombotic dose of Ir-CPI in an arterio-venous (AV) shunt model in rabbits.
- to evaluate the pharmacokinetic and pharmacodynamic (PK/PD) relationships.

II. METHODS

Study was carried out on New-Zealand white male rabbits (2.5 – 4.5 kg, n = 30). The experiment was performed under xylazine-ketamine anesthesia. An AV shunt device was connected between the femoral artery and vein. A silk thread was used as thrombogenic material in the AV shunt compartment.

- Ir-CPI was administrated at variable doses, either as a bolus or as a bolus followed by an infusion (Figure 2).
- Unfractionated heparin (UFH) was given as a bolus.
- Phosphate buffered saline (PBS) was used as control.

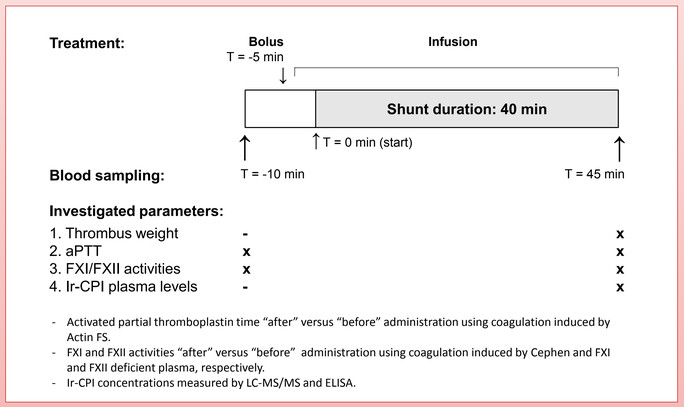


Figure 1 – Experimental design.

III. RESULTS

- Dose-dependent reduction of thrombus weight.

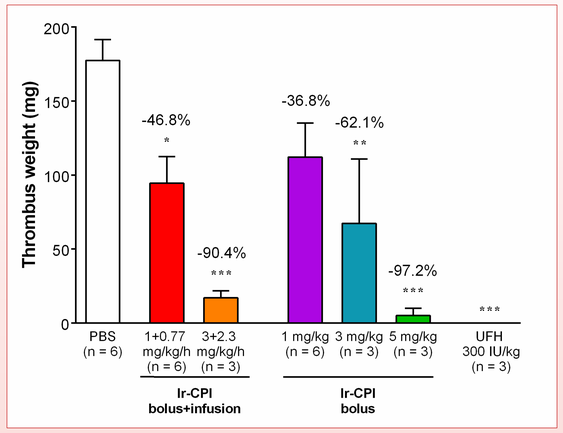


Figure 2 – Effect of Ir-CPI on thrombus weight.

- Reduction of thrombus weight by > 90%:
  - Plasma Ir-CPI concentration ≥ 2.0 - 2.5 µg/mL
  - aPTT increases ≥ 50%
  - FXI and FXII inhibition ≥ 35 - 40%

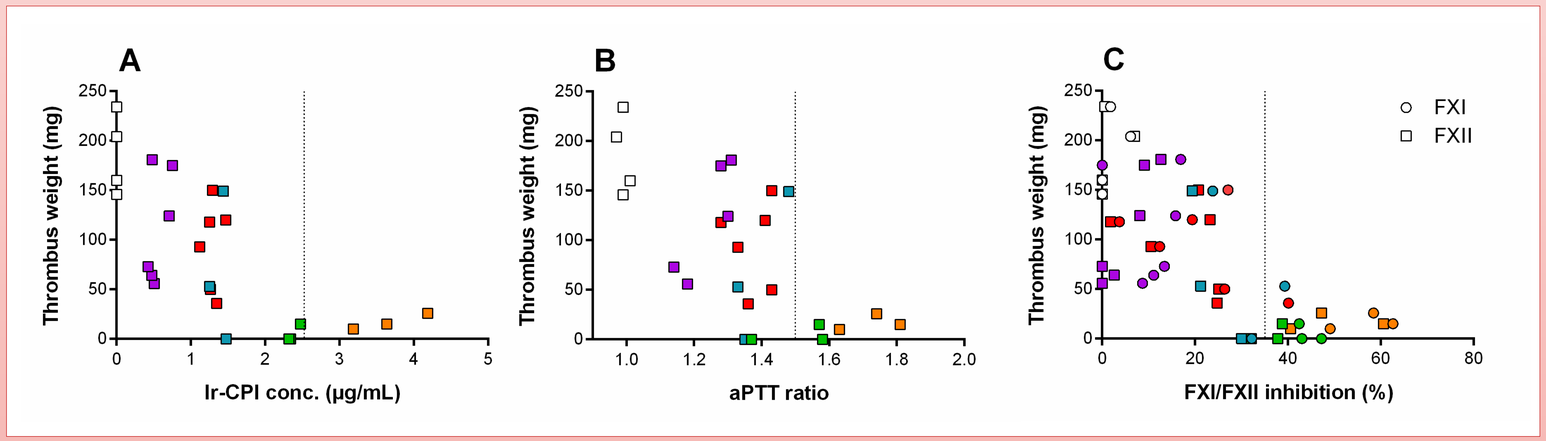
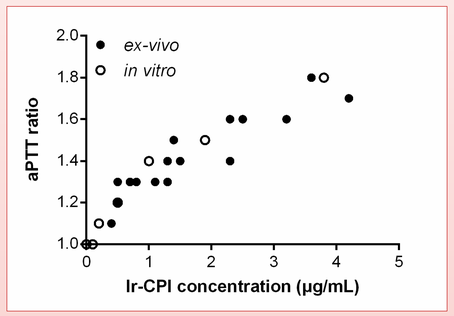


Figure 3 – Relation of PK/PD parameters.
Each point corresponds to individual data and colors to treatment groups as indicated in Figure 2.

IV. CONCLUSIONS

- Confirmed antithrombotic activity of Ir-CPI in a model of AV shunt in the rabbit.
- Established pharmacodynamics and pharmacokinetic relationships with an effective circulating concentration of the active principle of 2.5 µg/mL.
- Partial inhibition of factors XI and XII may be sufficient to prevent thrombosis.

- Similar effects on aPTT *ex-vivo* and *in vitro*.
- Ir-CPI plasma concentrations measured *in vivo* thus correspond to the active compound.



Ex-vivo: plasma of animals treated with Ir-CPI (AV shunt model)

In vitro: plasma from naive animals spiked with Ir-CPI (rabbit plasma pool)

Figure 4 – Effects of Ir-CPI on aPTT measured *ex-vivo* versus *in vitro*.

V. References

1. Ir-CPI, a coagulation contact phase inhibitor from the tick *Ixodes ricinus*, inhibits thrombus formation without impairing hemostasis. Decrem et al. J Exp Med. 2009; 206(11):2381-95
2. Efficacy of a novel contact pathway inhibitor, Ir-CPI, in an extracorporeal membrane oxygenator model. Combe et al. (ISTH 2015, Poster PO166-TUE)