Efficacy of a novel contact pathway inhibitor, Ir-CPI, in an extracorporeal membrane oxygenator (ECMO) model

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I. INTRODUCTION

ECMO involves blood exposure to non-physiological surfaces, inducing contact phase activation. Anticoagulation treatment is required to prevent thrombus formation during extra-corporeal circulation. Heparins whereas efficient anticoagulant are suboptimal in managing bleeding complications during these procedures.

Ir-CPI is a 67 aa protein from the tick salivary glands that is a dual inhibitor of human FXIIa and FXIa with demonstrated antithrombotic activity in animal models[1,2].

Inhibition of FXI/FXII is thought to provide antithrombotic potential with reduced bleeding complications (ref. review).

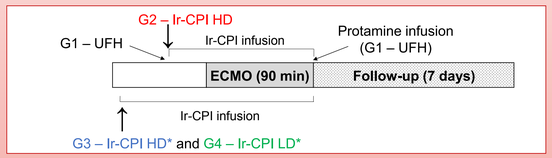
The aim of this study was:

- to evaluate whether Ir-CPI might confer antithrombotic activity during an ECMO procedure in dog, close to a clinical situation.
- to assess the efficacious dose, the safety and tolerability during and post-procedure, the pharmacokinetics and pharmacodynamics relationships.

II. METHODS

Study was carried out on adult male Beagle dogs (11.05 ± 0.79 kg, n = 12) using a pediatric ECMO system, connected between the carotid artery and the jugular vein. The cardiopulmonary bypass was maintained for 90 min.

Experimental design:



	TREATMENT		
Group (n = 3)	**Bolus (i.v.)**	**Infusion (i.v.)**	**ECC circuit priming**
G1 - UFH	300 IU UFH/kg	Protamine (1:1 UFH)	-
G2 – Ir-CPI HD	10.79 mg Ir-CPI/kg	7.46 mg Ir-CPI/kg.h	-
G3 – Ir-CPI HD*	10.79 mg Ir-CPI/kg	7.46 mg Ir-CPI/kg.h	5 mg Ir-CPI
G4 – Ir-CPI LD*	2.16 mg Ir-CPI/kg	1.49 mg Ir-CPI/kg.h	1 mg Ir-CPI

Investigated parameters:

A. Hemodynamics (ECG, blood pressure and flow, pressure gradient in circuit)
B. Gas exchanges (e.g. SpO_2, PaO_2)
C. ECMO materials: pump and oxygenator examination (clot and fibrin deposits)
D. Clinical signs and outcome during procedure and recovery (e.g. behaviour, wound bleeding and healing)
E. Hemostasis (aPTT, D-dimers, soluble fibrin monomers, TAT complexes, fibrinogen, plasmin anti plasmin complex, antithrombin, PT,)
F. Hematology, biochemistry, inflammation
G. Necropsy and histology (heart, lung, kidney, liver, brain)
H. PK-PD (Ir-CPI plasma levels, aPTT, FXI/FXII activities)

III. RESULTS

(A) Hemodynamics

No significant effect on:

- pump flow/CO (Figure 1)
- mean arterial pressure
- arterial line pressure and gradient

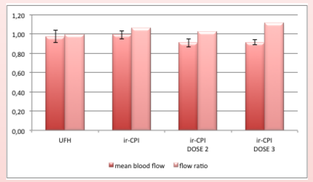


Figure 1 – Pump flow and ratio compared to cardiac output (CO).

(B) Gas exchanges, (C) ECMO materials

- Decreased gas exchange capacity during ECMO
- Fibrin deposits in oxygenator & pump and significant improvement with priming & earlier administration

Figure 2 – Illustration of effects on a dog of group G2 – Ir-CPI HD versus a dog of group G3 – Ir-CPI HD* on PaO2 and on fibrin deposits (hematoxylin staining) in the oxygenator.

G2 – Ir-CPI HD

G3 – Ir-CPI HD*

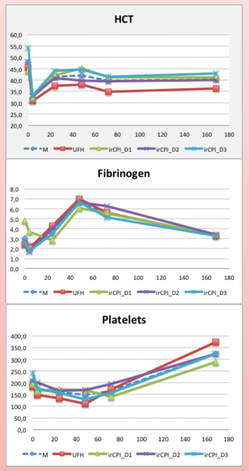
(D) Clinical signs and outcome

- No bleeding complications
- No thrombotic events
- No seepage at surgical wounds
- Normal recovery after procedure

(E) Hemostasis, (F) Hematology

- Decreased HCT, fibrinogen and platelets during ECMO (hemodilution)
- Normal recovery post surgery
- No difference compared to UFH
- No toxicity (biochemistry)

Figure 3 – HCT, fibrinogen, platelets.



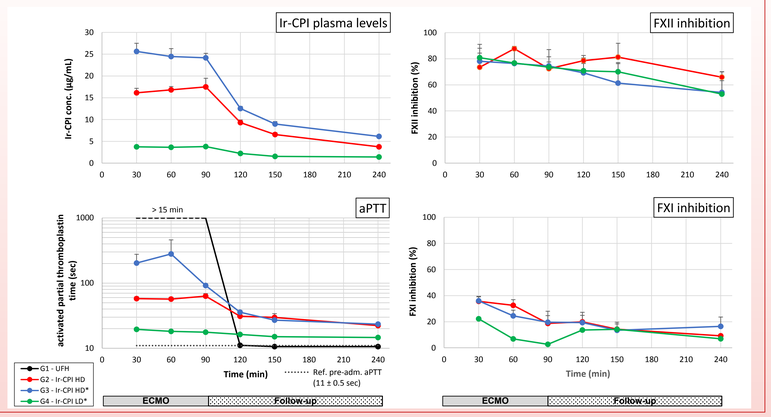
(G) Necropsy and histology

- No treatment-related lesions

(H) PK – PD

- Anticoagulant activity during ECMO at LD* (efficacious dose) corresponds to:
  - Ir-CPI plasma conc. of 3.7 µg/mL
  - aPTT increase of 68%
  - FXII inhibition of 77.0%
  - FXII inhibition of 10.6%

Figure 4 – Pharmacokinetics - pharmacodynamics.



IV. CONCLUSIONS

- Ir-CPI can be used to achieve anticoagulation during an ECMO procedure in dogs using material in the setting of a pediatric clinical instrumentation.
- No bleeding, no thrombotic events and no toxicity were observed during and after ECMO.
- Optimization remains to be performed in order to improve gas exchanges.
- Limitation of this dog model: Similar inhibition of FXI and FXII by Ir-CPI was not observed due to species differences compared to human.

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. Antithrombotic effects of Ir-CPI in an arterio-venous shunt model in the rabbit. Guyaux et al. (poster)
3. Ref. Review paper