Towards an early diagnostic of insulinoma

PET/CTM using Carbidopa + ^18F-FDOPA

Sporadic Insulinoma, 8mm, Ki67: 1% (G1)
Imperiale et al. EJNMMI 2015
Towards an early diagnostic of insulinoma

PROBLEMATIC & OBJECTIVE

Premedication With Carbidopa Masks Positive Finding of Insulinoma and β-Cell Hyperplasia in \[^{18}\text{F}\]-Dihydroxy-Phenyl-Alanine Positron Emission Tomography

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**To evaluate in vitro and in vivo the effect of carbidopa on the uptake of 18F-DOPA**
Towards an early diagnostic of insulinoma

**in vitro**
- beta cells RIN-m5F
- insulin secretion +++
- AA Decarboxylation +++

**in vivo**
- Xenograft developed on athymic nude mice after subcutaneous injection of RIN-m5F cells
Towards an early diagnostic of insulinoma

Effect of Carbidopa on $^{18}$F-FDOPA Uptake in Insulinoma: From Cell Culture to Small-Animal PET Imaging

Julien Detour$^{1,2}$, Alice Pierre$^{1,2}$, Frédéric Boisson$^3$, Guillaume Kreutter$^{4,5}$, Thomas Lavaux$^6$, Izzie Jacques Namez$^{2,5,7}$, Laurence Kessler$^{4,5}$, David Brasse$^1$, Patrice Marchand$^1$, and Alessio Imperiale$^{2,3,7}$

The Journal of Nuclear Medicine • Vol. 58 • No. 1 • January 2017
Towards an early diagnostic of insulinoma

Basal capillary blood glucose
Towards an early diagnostic of insulinoma

20 days after cells injection

30 days after cells injection
Towards an early diagnostic of insulinoma
Towards an early diagnostic of insulinoma

Without Carbidopa

![Image of 38 mm³ tumor](A)
- Early phase (0-5 min) SUV : 0.94
- Delayed phase (15-20 min) SUV : 0.46

Carbidopa

![Image of 52 mm³ tumor](B)
- Early phase (0-5 min) SUV : 1.46
- Delayed phase (15-20 min) SUV : 1.03
Towards an early diagnostic of insulinoma

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Julien Detour$^{1,2}$, Alice Pierre$^{1,2}$, Frédéric Boisson$^3$, Guillaume Kreutter$^{4,5}$, Thomas Lavaux$^6$, Izzie Jacques Namer$^{2,5,7}$, Laurence Kessler$^{4,5,9}$, David Brusse$^1$, Patrice Marchand$^1$, and Alessio Imperiale$^{2,3,5,7}$

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✓ Tumor detectable in all mice
✓ Similar dynamic profile uptake between treated and untreated
✓ Early increase and progressive decay of uptake
✓ SUV tumor carbopoda > SUV control (p <0.05)
First conclusion

✓ First preclinical investigation of the effect of carbidopa on the 18F-FDOPA uptake in insulinoma

✓ Carbidopa does not significantly influence the *in vitro* accumulation of 18F-FDOPA in RIN-m5F cells

✓ Carbidopa improves the visualization of insulinoma *in vivo*

✓ In humans, in the absence of radiolabeled GLP-1 analogues, we recommend 18F-FDOPA PET/CT with carbidopa and early pancreatic acquisition
Translational Approach

**O-(2-[^{18}F]-fluoroéthyl)-L-tyrosine (**^{18}F-FET**)**:

- is a tyrosine / phenylalanine analogue
- its cellular uptake depends on LATs as for **^{18}F-DOPA**
- is clinically available (lower price than **^{18}F-DOPA**)
- No pancreatic physiological uptake in humans

1. To evaluate the uptake of 18F-FET in comparison with 18F-DOPA in insulinoma from a murine xenograft model

2. Perform clinical proof of concept in a patient with endogenous hyperinsulinemic hypoglycemia
Translational Approach

- Similar kinetic uptake in the VOI
- Early detection of the tumor

Translational approach:
- $^{18}$F-FET: FDA in human
- No physiological pancreatic uptake
Translational Approach

**A**

$^{18}$F-FDOPA PET/CT

- 0-5 min p.i.
- 5-20 min p.i.
- Whole body (30 min p.i.)

**B**

$^{18}$F-FET PET/CT

- 0-5 min p.i.
- 5-20 min p.i.
- Whole body (30 min p.i.)

$^{111}$In-DTPA-exendin-4 (GLP-1)
In our preclinical model of insulinoma as well as in one patient, the binding patterns of $^{18}$F-FET and $^{18}$F-FDOPA were comparable.

The role of $^{18}$F-FET in the clinical detection of insulinoma seems interesting and should be explored in the patient in prospective studies.

Radiolabeled analogues of GLP-1 will be preferred when available in clinical routine.

Many preclinical developments found outcomes in clinic.
(Radio-) pharmaceutical development

Chemistry
- chemical product selection
- high-throughput screening
- compound optimisation

Biology
- target selection
- tests developments
- selective screening

Preclinical studies
- target specificity
- biodistribution
- pharmacokinetic
- toxicology

Clinical studies
- phase 0
- phase I
- phase II
- phase III

Product approbation for clinical use

✓ Animal models: in vivo studies
✓ Technical developments
✓ Imaging protocols
Acknowledgments

Virgile Bekaert
Nicolas Chevillon
Christian Fuchs
Jacky Sahr
Rachid Séfri
Xiaochao Fang
Marc Rousseau
Michel Pellicioli
Patrice Marchand
Lionel Thomas
Ali Ouadi
Patrice Laquerriere
Laurent Daeffler
Bruno Jessel
Jacky Schuler
Alessio Imperiale
David Brasse

... for your attention!!