

Intravenous Pharmacokinetics in Humans Using Low Dose ^{14}C - Labeled Drug and Accelerator Mass Spectrometry

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Questions

- What are the advantages of using ^{14}C -labelled drug and Accelerator Mass Spectrometry (AMS) for measurement of intravenous pharmacokinetics?
- How are these studies done?
- What are some examples of successful application of this technique?
 - Absolute Bioavailability
 - First Pass Metabolism
 - Prodrug Conversion

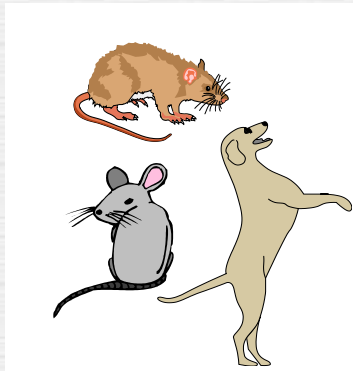


Why IV-PK in Humans

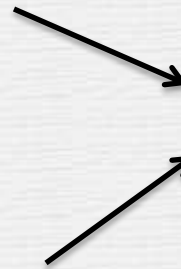
- IV-PK provides the complete description of the systemic distribution and elimination of the drug.
- From IV data one calculates the fundamental PK parameters of clearance (CL), volume of distribution (V) and absolute bioavailability (along with PK data from the extravascular route)
- In the past, only been conducted when absolute oral bioavailability data has been required - need an intravenous formulation that can be given at similar doses as extravascular dose.



Dosing of Extravascular Drugs IV



Significant pre-clinical toxicology testing



Significant intravenous formulation development



IND for IV form for human use

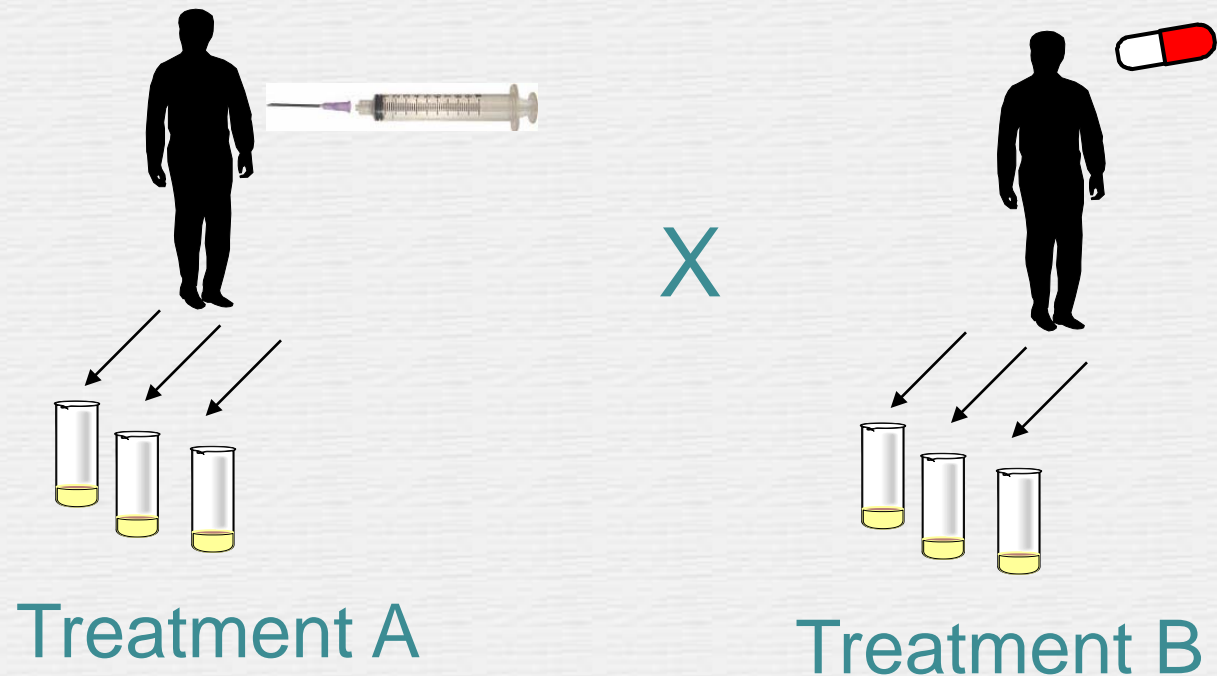


Cost > \$1M

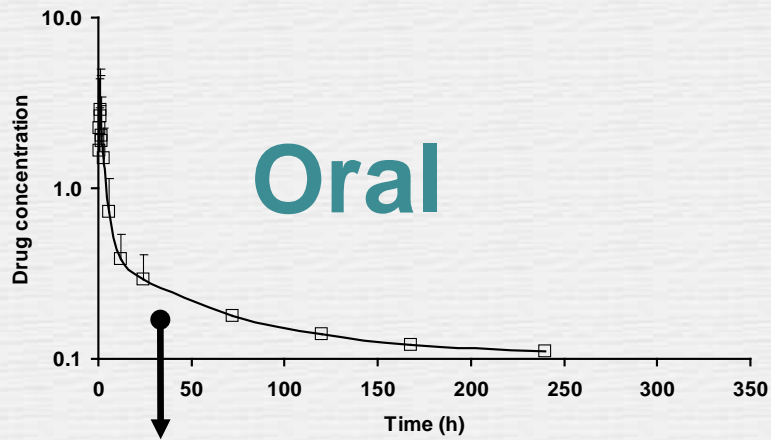


Absolute Bioavailability

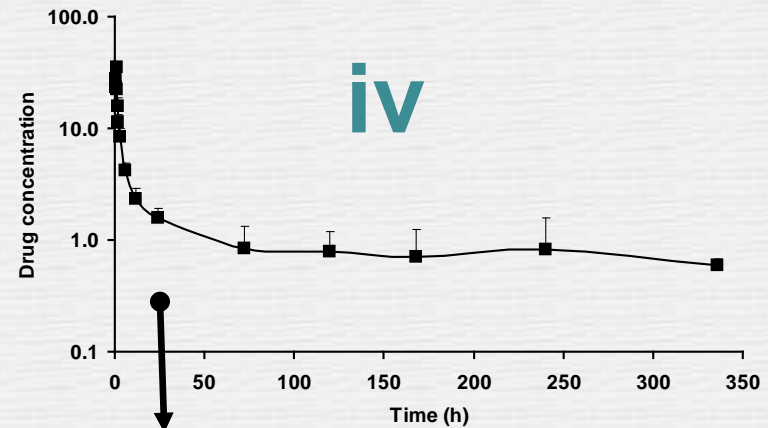
2 period crossover study



Calculation of Absolute Bioavailability



AUC_{ex}



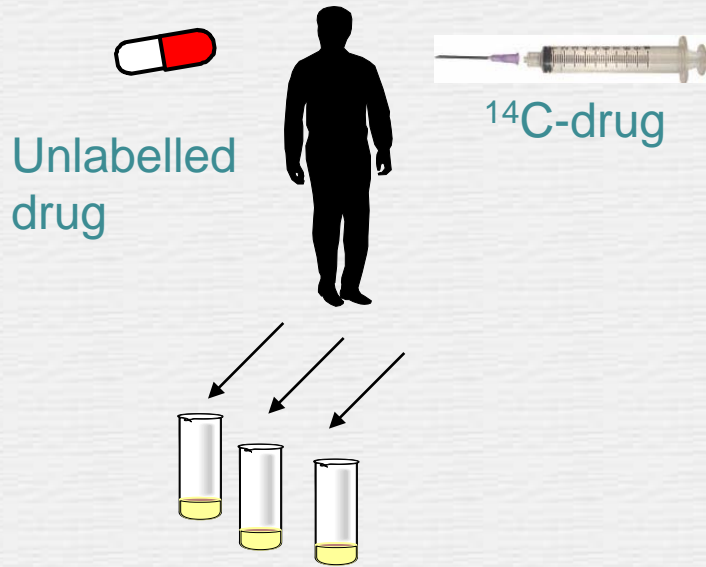
AUC_{iv}

$$F_{ev} = \left(\frac{AUC_{ev}}{AUC_{iv}} \right) \left(\frac{Dose_{iv}}{Dose_{ev}} \right)$$

$$F \times dose = Cl \times AUC$$



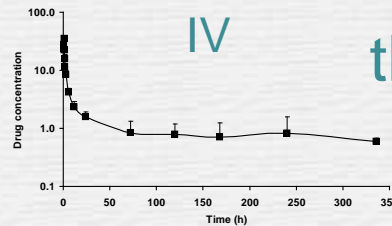
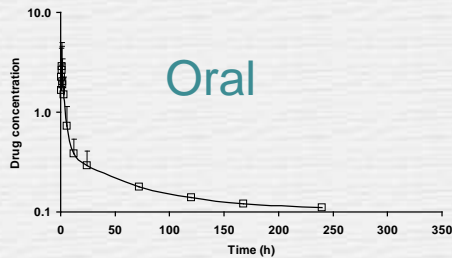
Isotopic Labelling Method



Isotopic tracer method developed in 1970s
Strong *et al* (1975) Clin Pharmacol Ther 18
613-622

$$F \times \text{dose} = Cl \times AUC$$

↑
Plasma drug concentration
the same (for elimination phase)



14C Isotopic Labelling and AMS

- Using ^{14}C isotopic labelling and AMS, enables:
 - The IV dose to be kept very low (a few μg)
 - The radioactive dose is low ~ 200 nCi
 - The parent drug plasma assay to be very sensitive (fg – ag/mL plasma range)

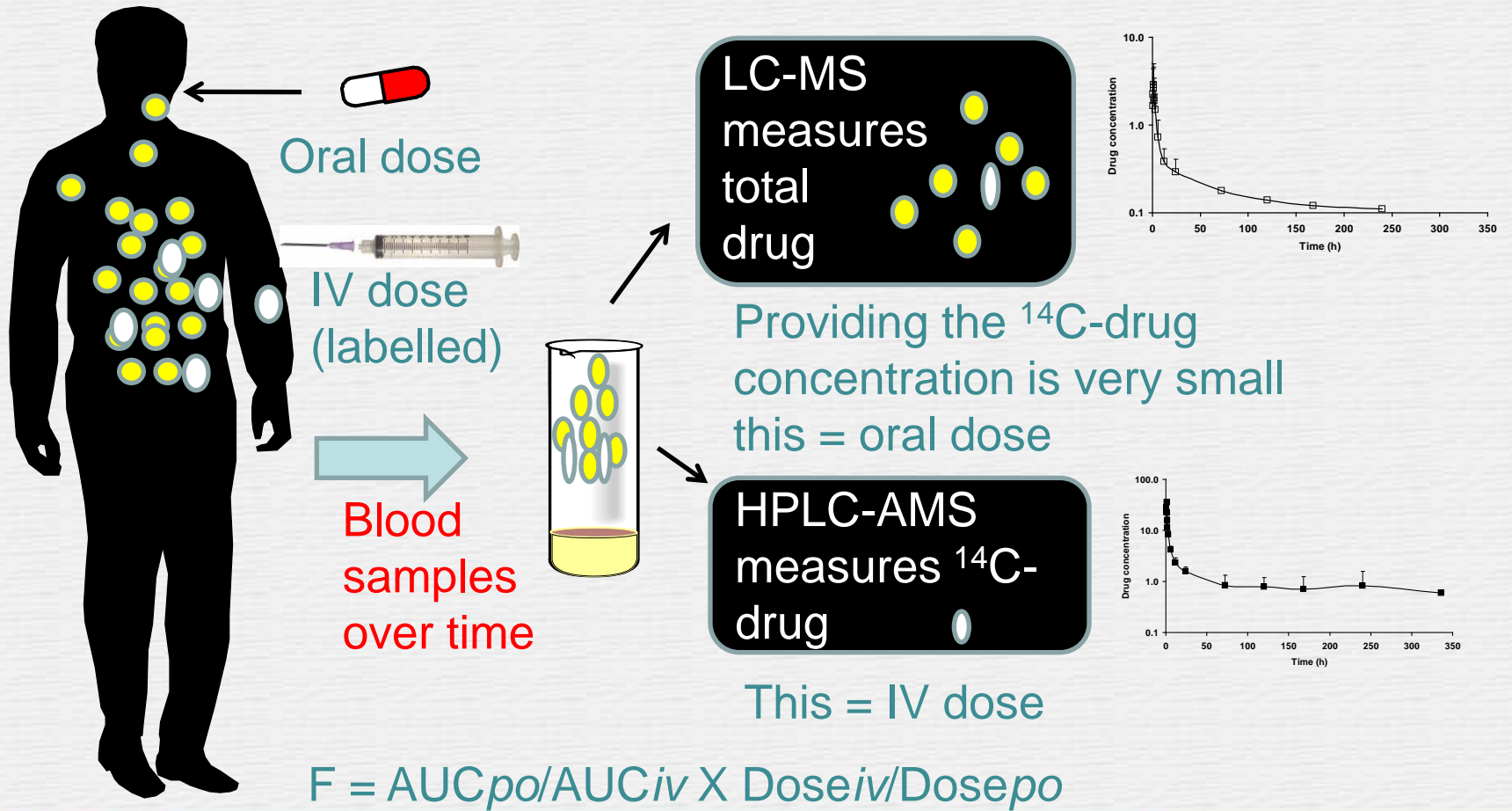


Low is Good

- Low levels of radioactivity: < 500 nCi does not require formal regulatory approval for administration of radioactivity (e.g. Nebraska NRC)
- The IV dose is very low which typically negates the need for IV toxicology (ICH M3 Guideline)
 - Covered by oral toxicology data
- The concentration of the IV dose is very low thereby significantly reducing the effort for formulation



Isotopic Tracer Principle



CASE STUDIES

FEXOFENADINE
and
PROPOFENONE



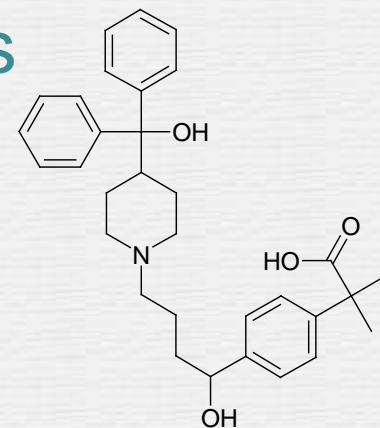
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Fexofenadine

- Fexofenadine HCl is a histamine H1-receptor antagonist used to treat allergies
- It is a P-gP and an OATP substrate
- Fexofenadine is not substantially metabolized
- It has been on the market for over 12 years
- Although fexofenadine is a well established drug, it has never previously been administered intravenously



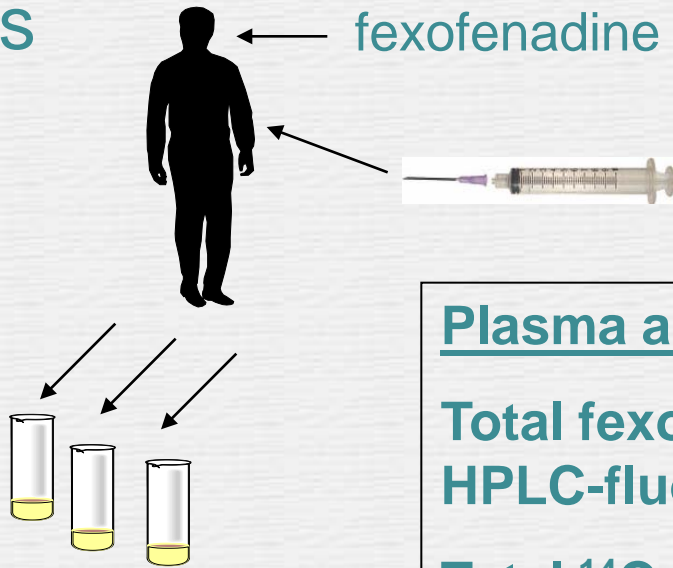
Study Design

6 healthy male
volunteers

Single oral dose
120 mg non-labelled
fexofenadine

Simultaneous IV dose of
100 μg , 200 nCi ^{14}C -
fexofenadine

Plasma
collected
over 24 h



Plasma analysis

Total fexofenadine determined by
HPLC-fluorescence

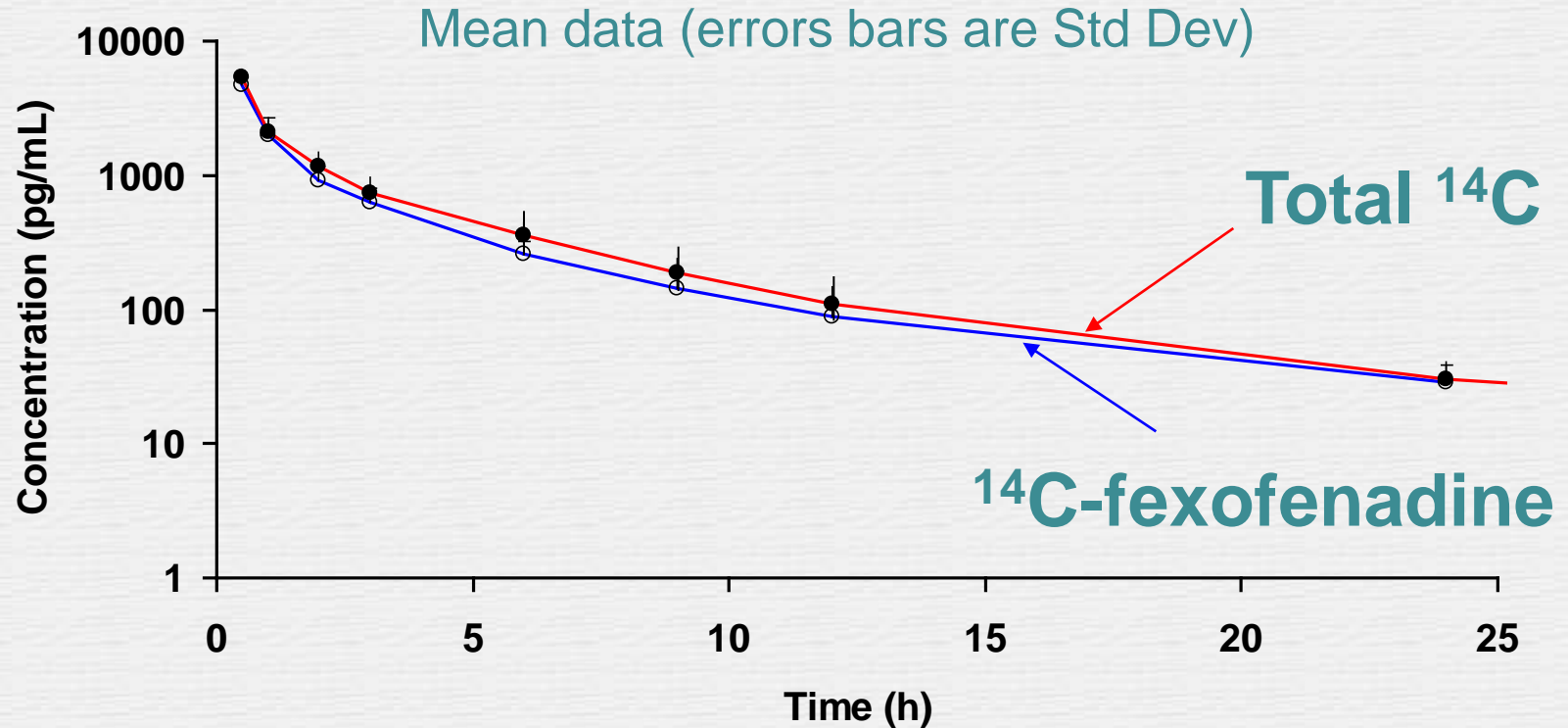
Total ^{14}C determined by AMS

^{14}C -fexofenadine determined by
HPLC and AMS

Acknowledgement:

This research study was funded by the European
Commission grant number LSHG-CT-2005-018672

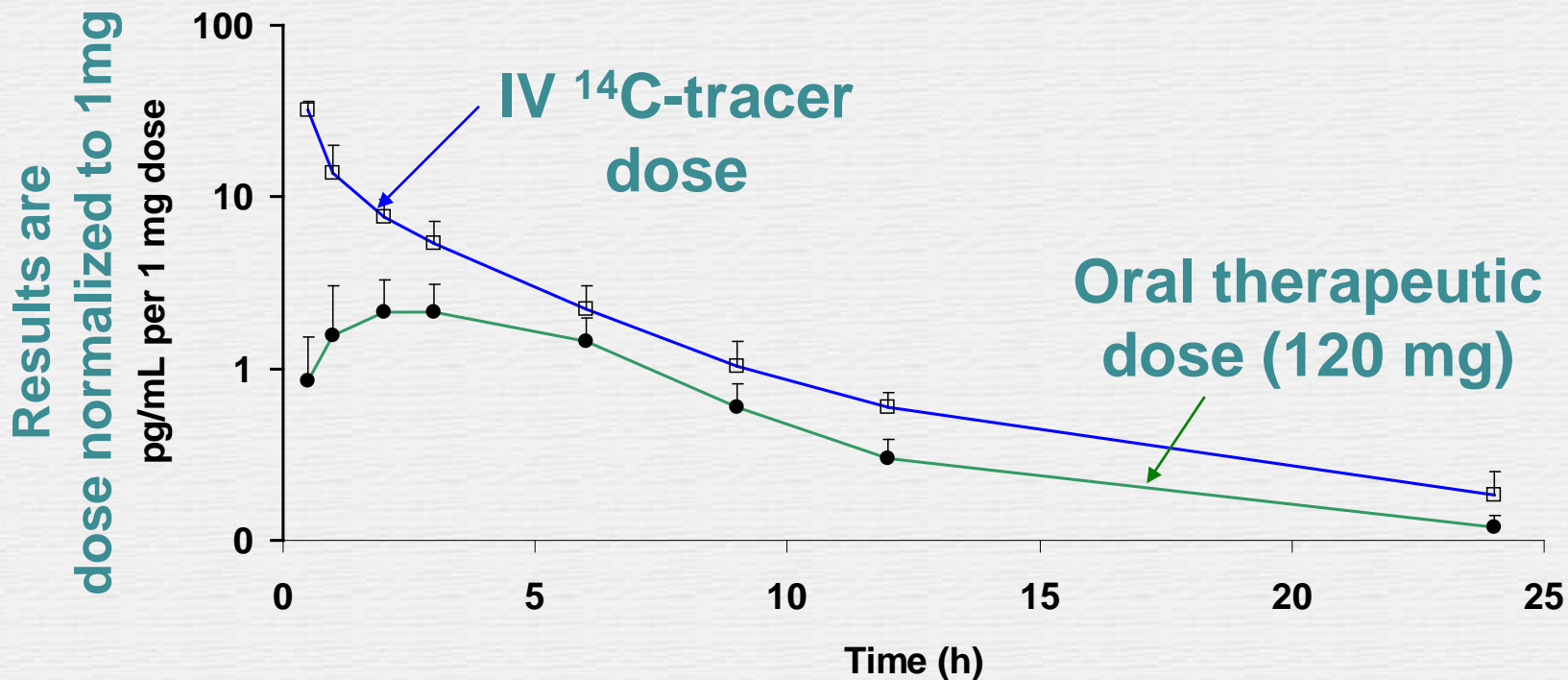
Total ^{14}C vs Parent IV Dose



Confirms fexofenadine undergoes very limited metabolism

Absolute Oral Bioavailability of Fexofenadine

Mean data (errors bars are Std Dev)



Mean oral absolute bioavailability 28%

PK Parameters for Fexofenadine

Parameter	Microtracer data (%CV, n= 6)	Literature data
$t_{1/2}$ (h)	10 (27)	14
CL (L/h)	17 (23)	4.2*
V (L)	245 (17)	85
F(%)	28 (26)	? 10*

* Minimum based on excretion of unchanged drug in urine



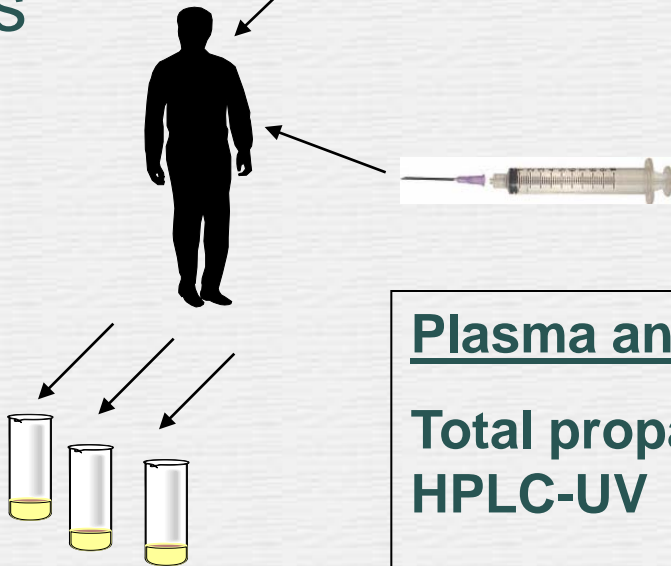
Propafenone

6 healthy male
volunteers

Single oral dose
150 mg non-labelled propafenone

Simultaneous IV dose of
100 μg , 200 nCi ^{14}C -
propafenone

Plasma
collected
over 24 h



Acknowledgement:

This research study was funded by
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number LSHG-CT-2005-018672

Plasma analysis

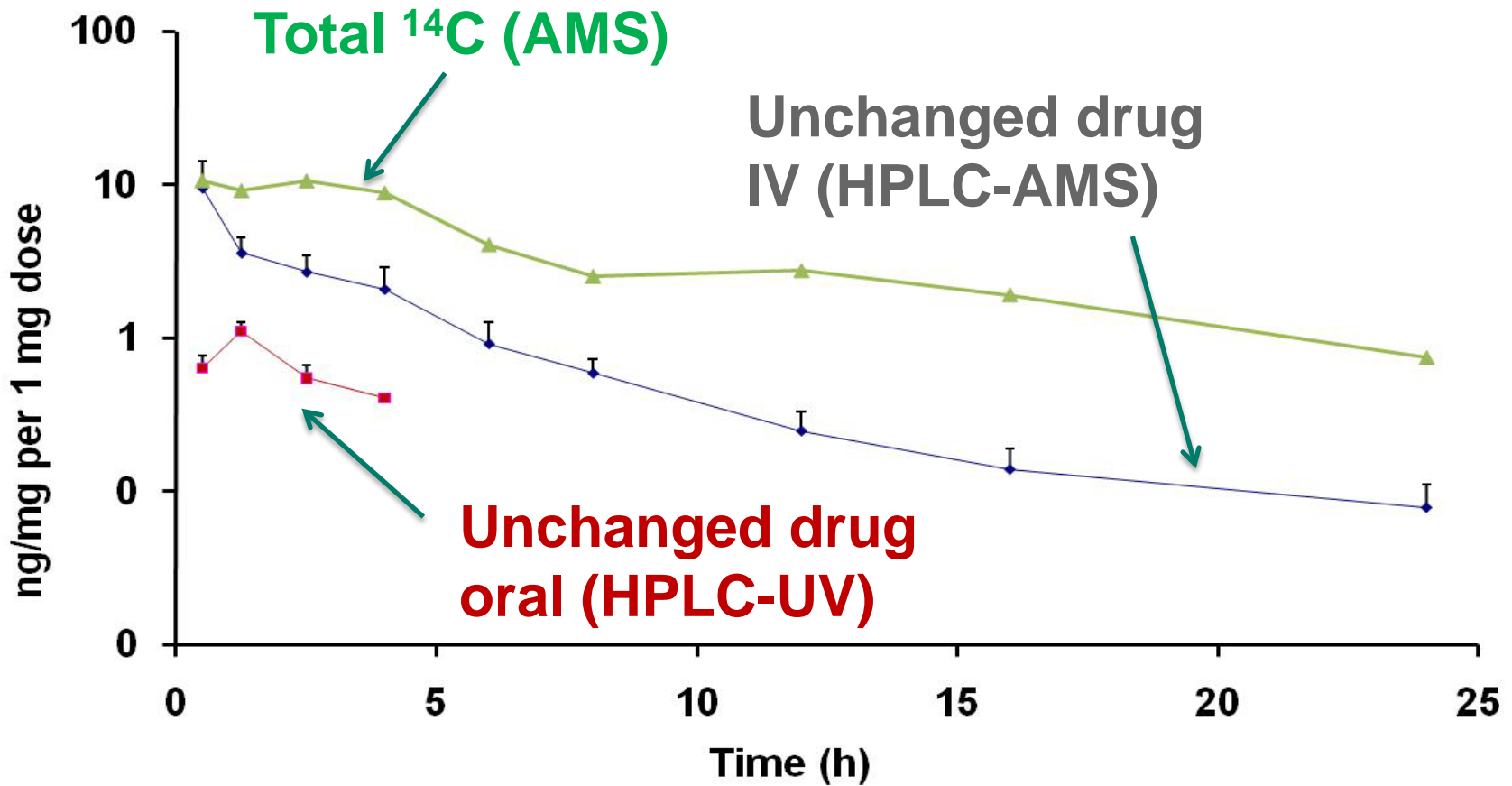
Total propafenone determined by
HPLC-UV

Total ^{14}C determined by AMS

^{14}C -propafenone determined by HPLC
and AMS



Propafenone



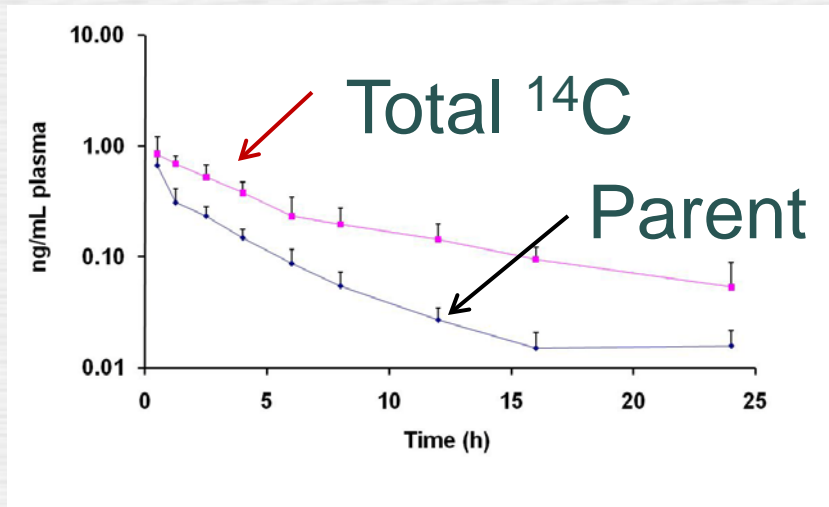
Propafenone Pharmacokinetics

Parameter	Microtracer data (%CV, n= 6)	Literature data
$t_{1/2}$ (h)	5	6
CL (L/h)	44 (23)	60
V (L)	159 (12)	200
F(%)	13 (68)	10*

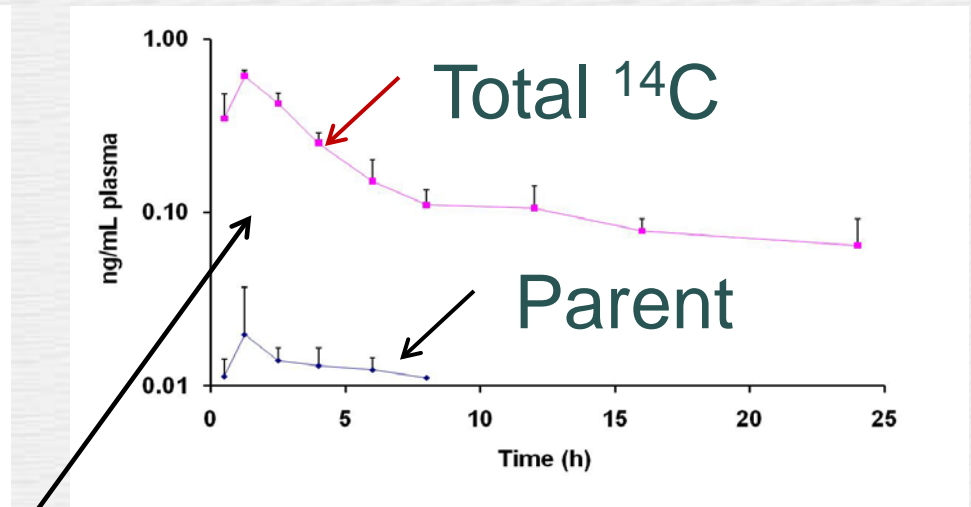
* - dose dependent



Propafenone First Pass Metabolism



IV

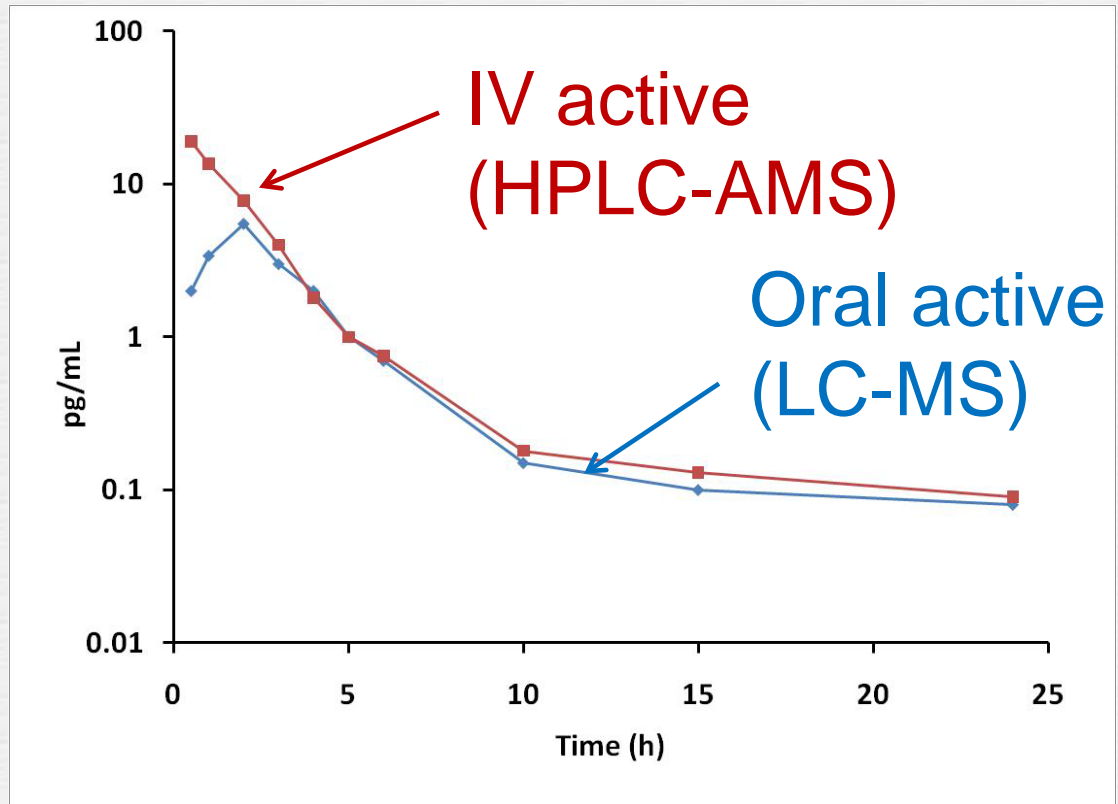
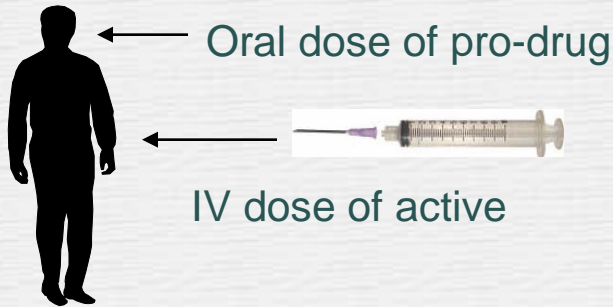


Oral

First pass metabolism



Prodrugs



As well as avoiding tox and formulation,
GMP-grade ^{14}C -active is not required

Conclusions

- Intravenous data can be generated in humans at therapeutic systemic concentrations
- IV safety toxicology can be avoided
- Minimal formulation issues
- Isotopic tracer design optimal for minimising effects due to differential clearance
- Applications with pro-drugs to determine exposure and rate of conversion
- Use of tracer also allows bioavailability to be determined after oral dosing to steady state

