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

J. Fred Pritchard, Ph.D.
Vice President
Drug Development

DIA 2011
Chicago, Illinois
DIA®
www.diahome.org

Disclaimer

- The views and opinions expressed in the following PowerPoint slides are those of the individual presenter and should not be attributed to Drug Information Association, Inc. (“DIA”), its directors, officers, employees, volunteers, members, chapters, councils, Special Interest Area Communities or affiliates, or any organization with which the presenter is employed or affiliated.
-

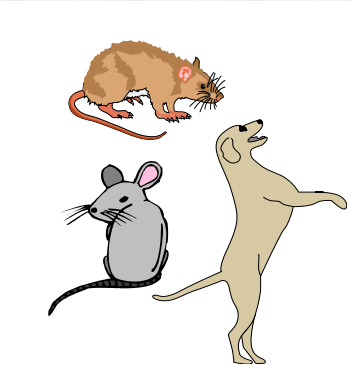
Questions

- 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

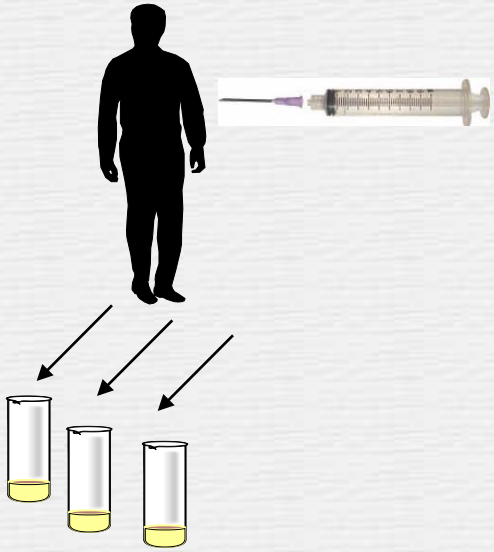
IND for IV form for human use

Cost > $1M

Significant intravenous formulation development

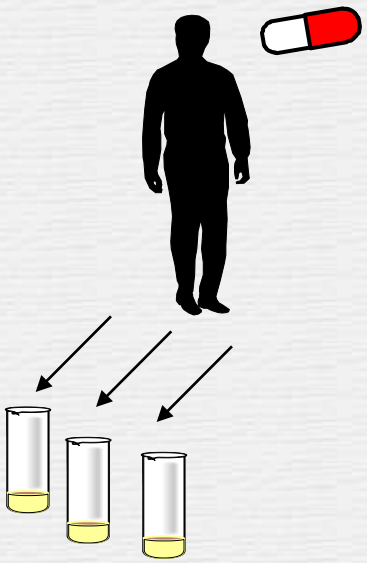
Absolute Bioavailability

2 period crossover study



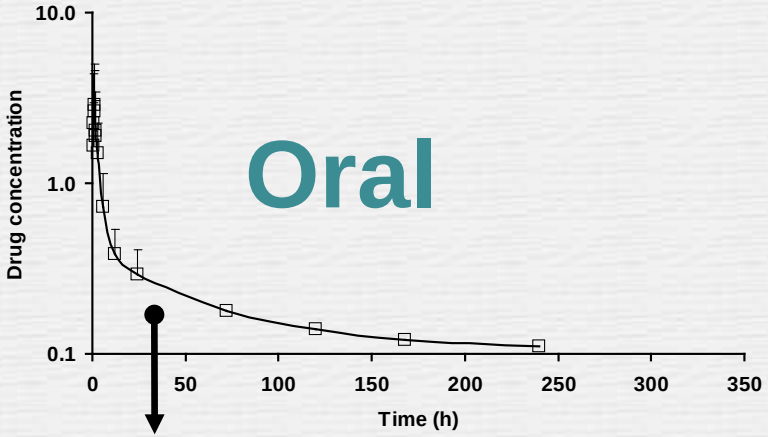
Treatment A

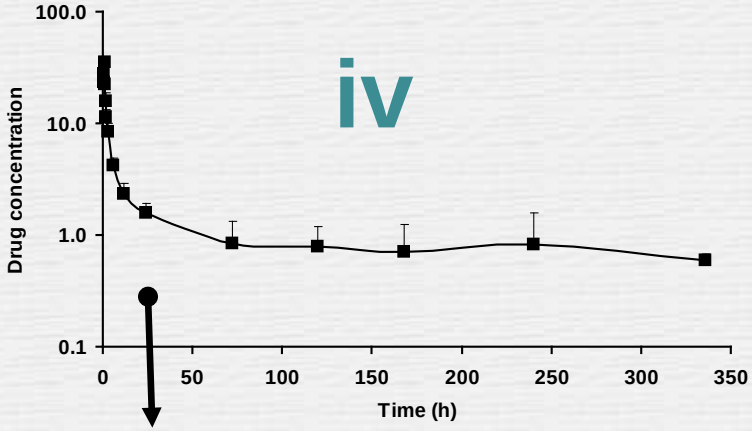
X



Treatment B

Calculation of Absolute Bioavailability





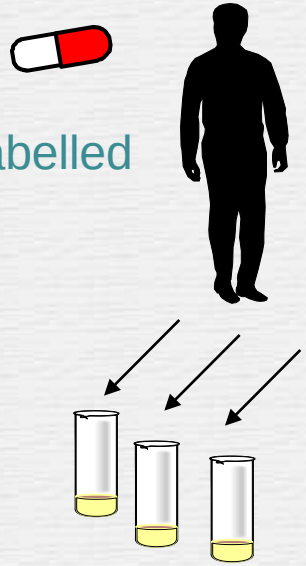
AUC_{ex}

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



Unlabelled drug

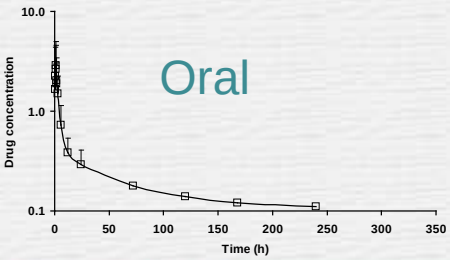
^{14}C-drug

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

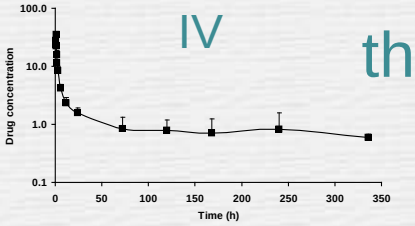
$$F \times dose = Cl \times AUC$$

Plasma drug concentration the same (for elimination phase)

Oral



IV



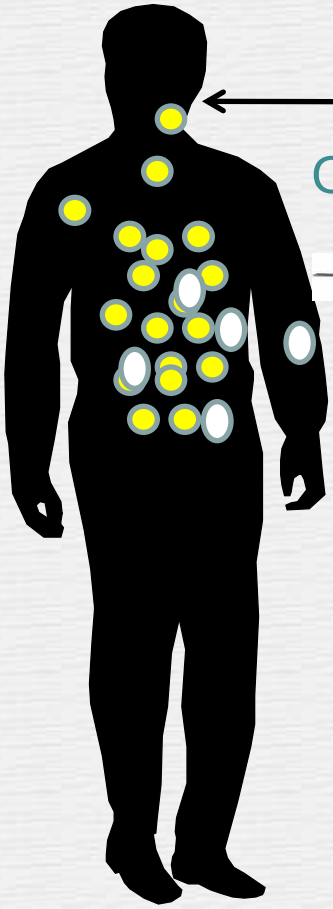
14C Isotopic Labelling and AMS

- 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

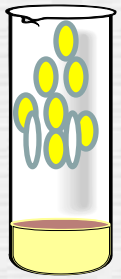
Isotopic Tracer Principle



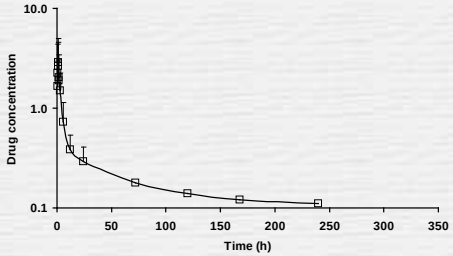
Oral dose

IV dose (labelled)

Blood samples over time

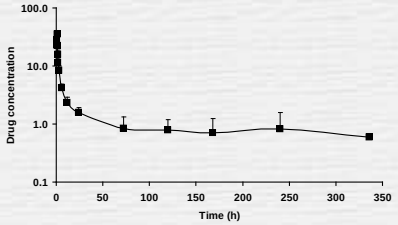


LC-MS measures total drug



Providing the ^{14}C-drug concentration is very small this = oral dose

HPLC-AMS measures ^{14}C-drug



This = IV dose

F = AUC*po*/AUC*iv* X Dose*iv*/Dose*po*

CASE STUDIES

FEXOFENADINE and PROPOFENONE

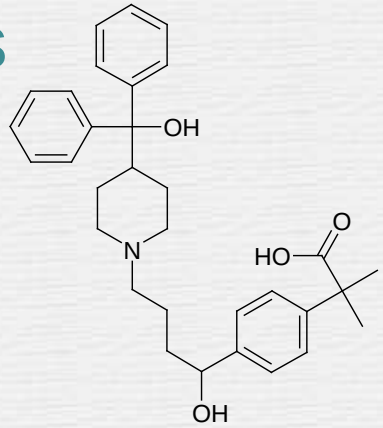
DIA 2011
Chicago, Illinois

DIA®

www.diahome.org

Fexofenadine

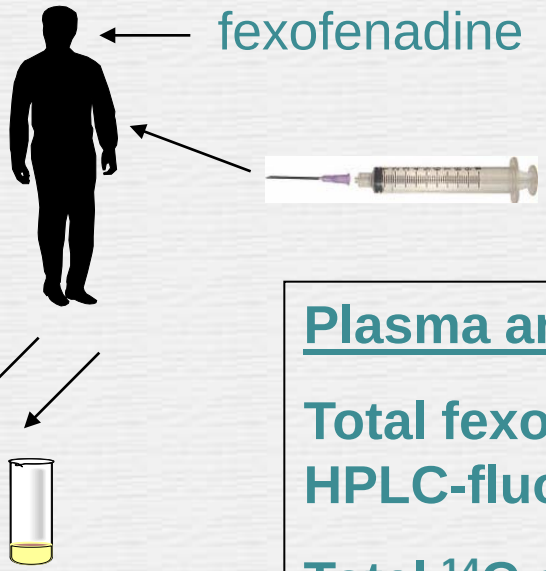
- Fexofenadine HCl is a histamine H1-receptor antagonist used to treat allergies
- It is a PgP and an OATP substrate
- Fexofenadine is not substantially metabolized
- It has been on the market for over 12 years
- Although fexofenadine is a well established drug, it has never previously been administered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

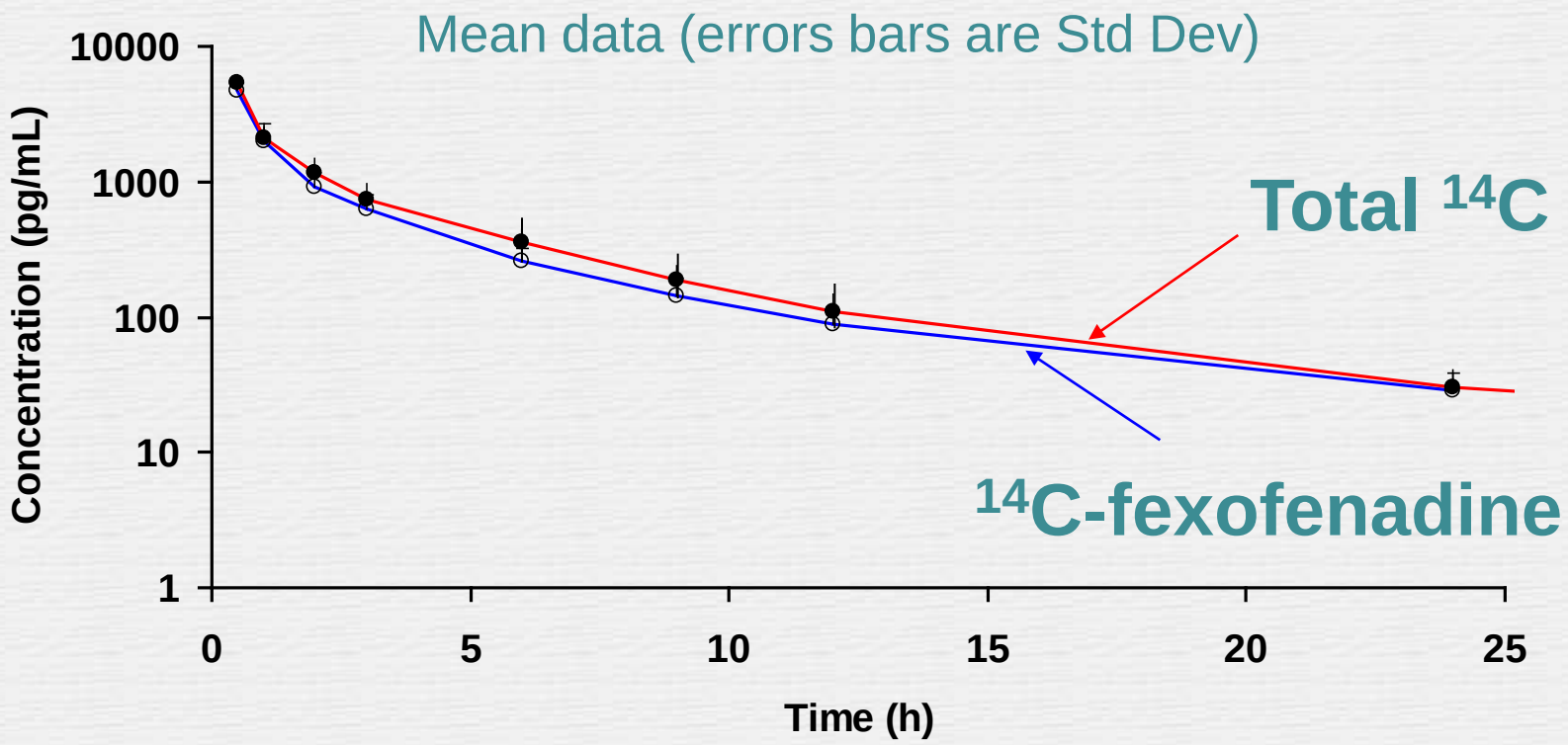
Total fexofenadine determined by HPLC-fluorescence

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

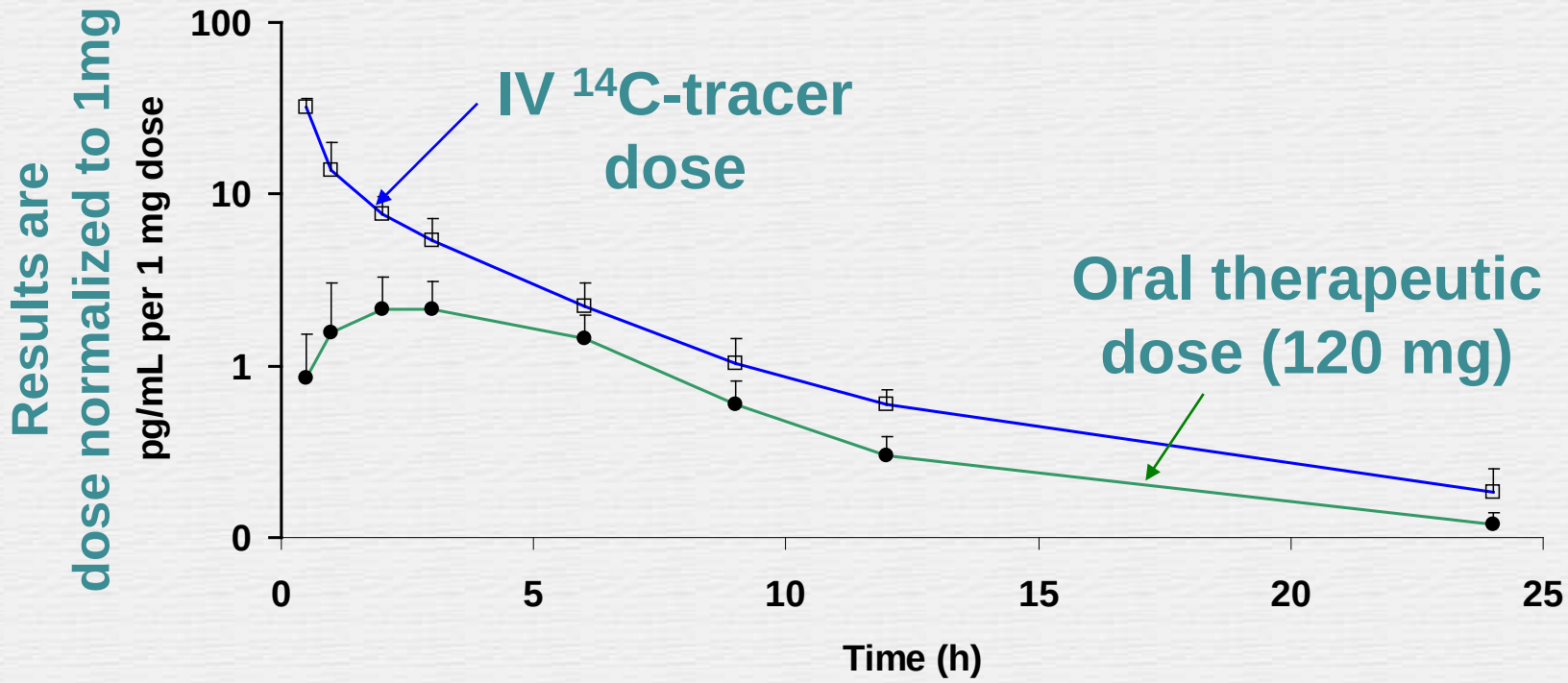
Total ^{14}C vs Parent IV Dose



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

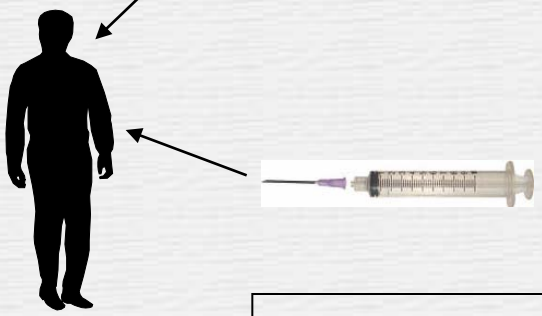
Parameter	Microtracer data (%CV, n= 6)	Literature data
$t_{1/2}$ (h)	10 (27)	14
CL (L/h)	17 (23)	4.2*
V (L)	245 (17)	85
F(%)	28 (26)	? 10*

* 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

Plasma analysis

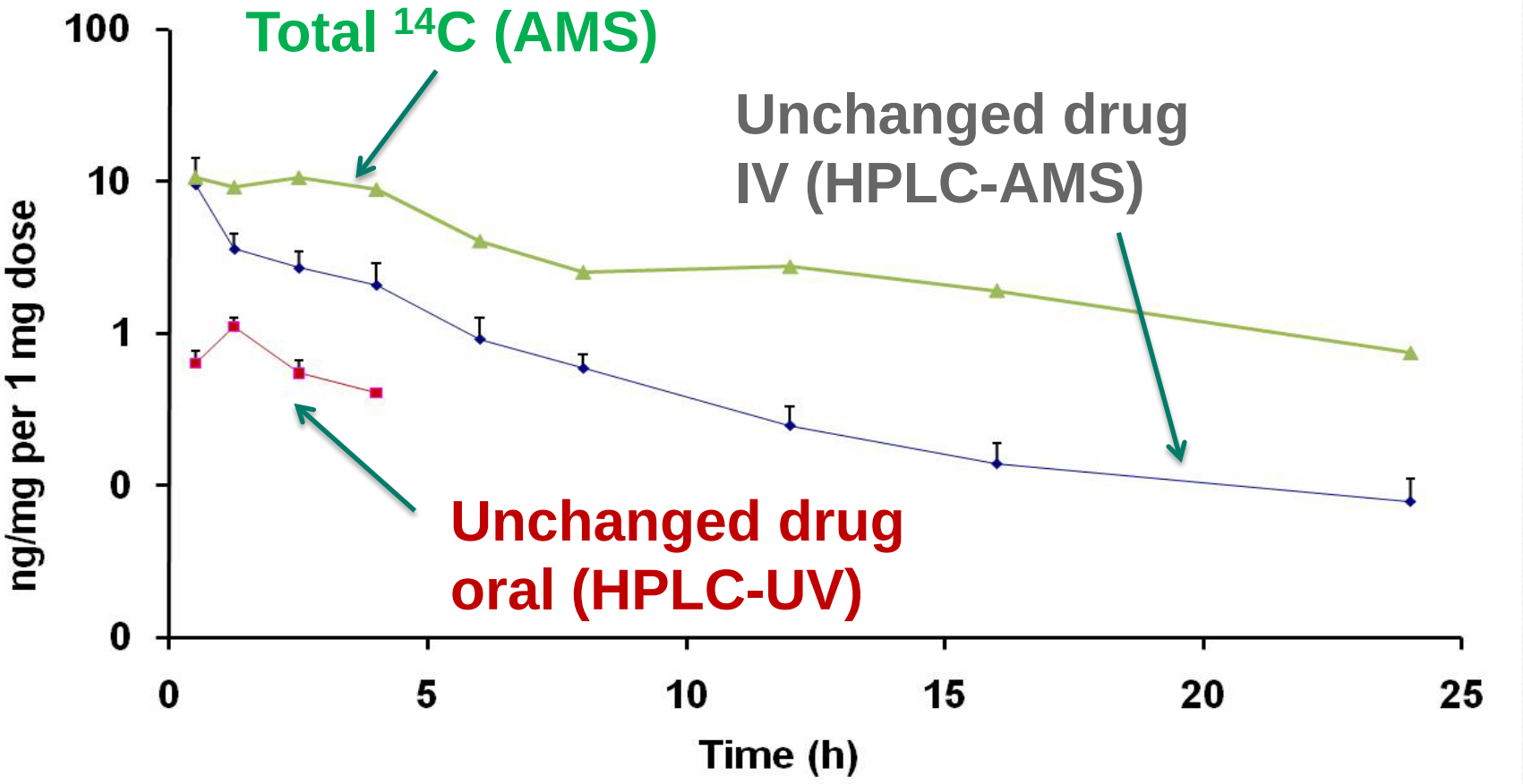
Total propafenone determined by HPLC-UV

Total ^{14}C determined by AMS

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

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

Propafenone

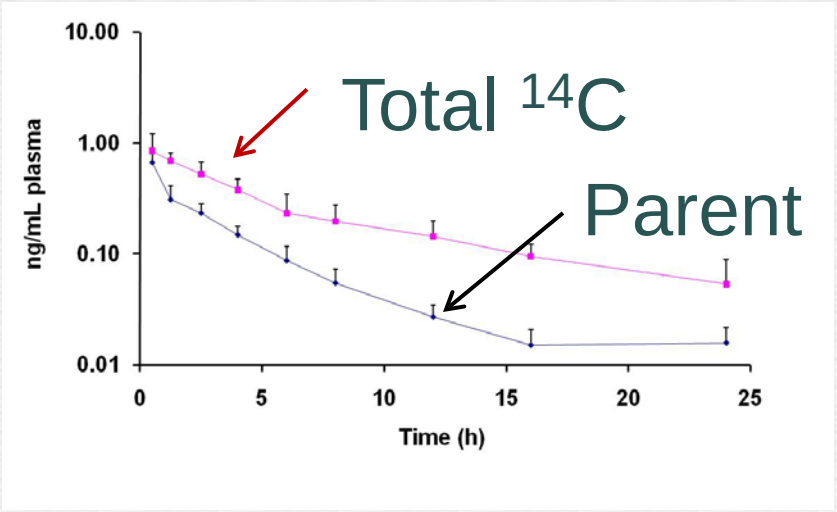


Propafenone Pharmacokinetics

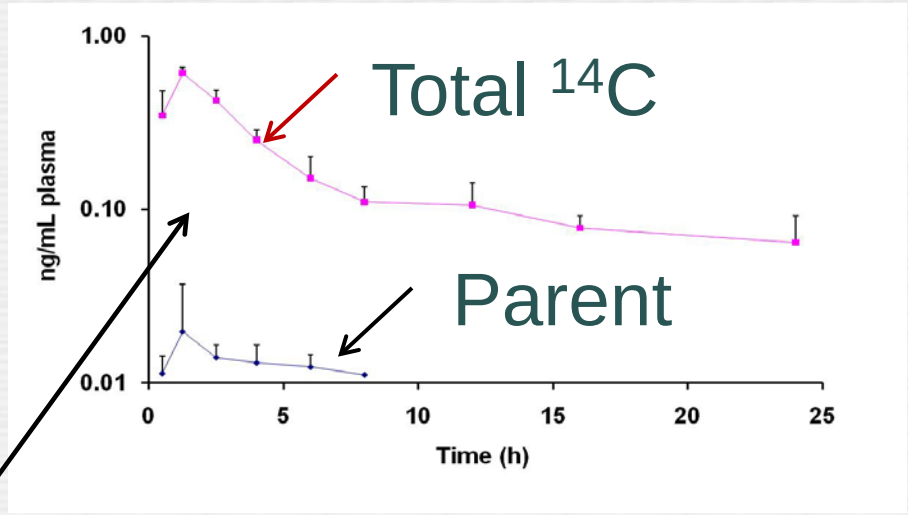
Parameter	Microtracer data (%CV, n= 6)	Literature data
$t_{1/2}$ (h)	5	6
CL (L/h)	44 (23)	60
V (L)	159 (12)	200
F(%)	13 (68)	10*

* - dose dependent

Propafenone First Pass Metabolism



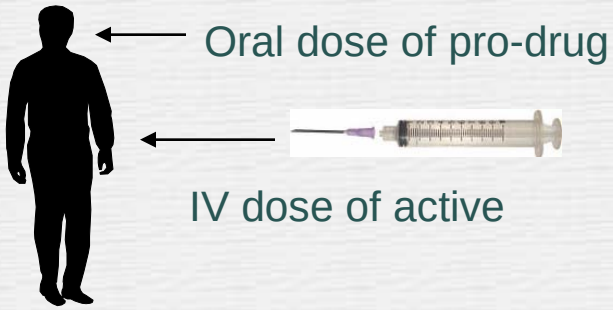
IV

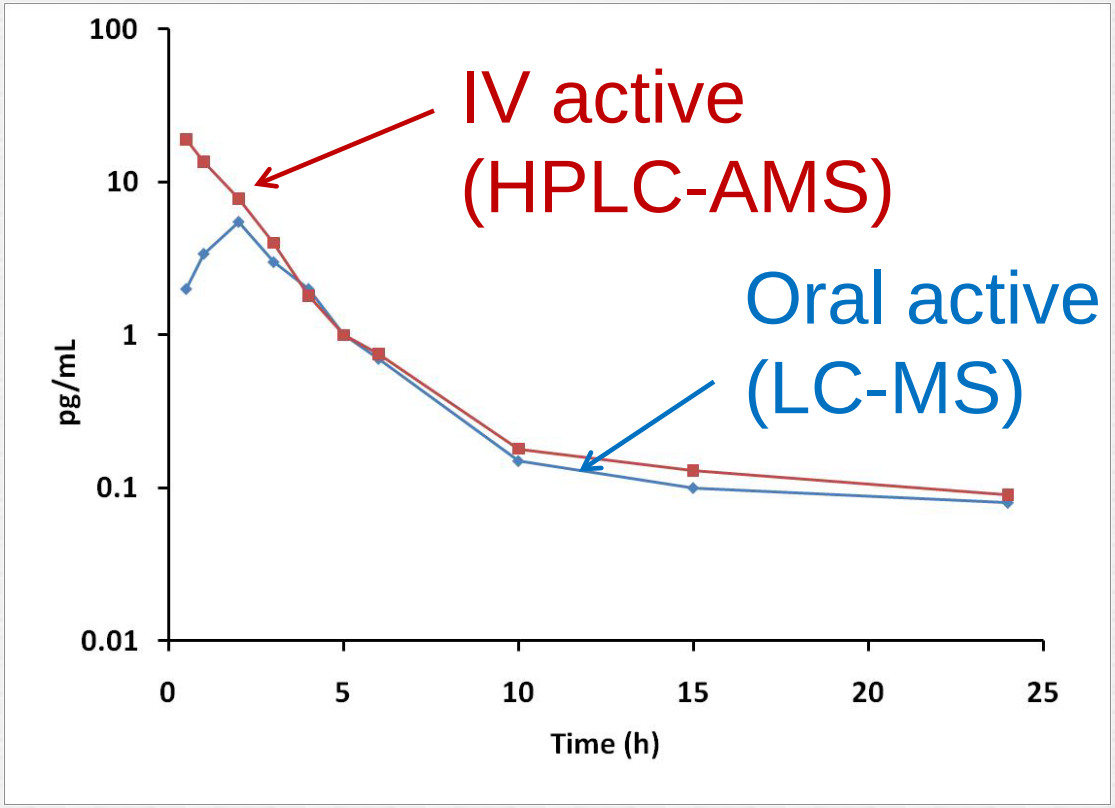


Oral

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