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

IND for IV form for human use

Cost > $1M

Significant intravenous formulation development
Absolute Bioavailability

2 period crossover study

Treatment A

×

Treatment B
Calculation of Absolute Bioavailability

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

$$F \times \text{dose} = Cl \times AUC$$
Isotopic Labelling Method

Isotopic tracer method developed in 1970s

\[ F \times \text{dose} = Cl \times AUC \]

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 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

**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
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
6 healthy male volunteers

Plasma collected over 24 h

Single oral dose
120 mg non-labelled fexofenadine

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

Plasma analysis
- Total fexofenadine determined by HPLC-fluorescence
- Total $^{14}$C determined by AMS
- $^{14}$C-fexofenadine determined by HPLC and AMS

Acknowledgement:
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Total $^{14}$C vs Parent IV Dose

Mean data (errors bars are Std Dev)

Confirm fexofenadine undergoes very limited metabolism
Absolute Oral Bioavailability of Fexofenadine

Mean data (errors bars are Std Dev)

Results are dose normalized to 1mg

IV $^{14}$C-tracer dose

Oral therapeutic dose (120 mg)

Mean oral absolute bioavailability 28%
## PK Parameters for Fexofenadine

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

* 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

Total $^{14}$C (AMS)

Unchanged drug IV (HPLC-AMS)

Unchanged drug oral (HPLC-UV)
# Propafenone Pharmacokinetics

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

* - dose dependent
Propafenone First Pass Metabolism

First pass metabolism

IV

Oral

Total $^{14}$C

Parent

Total $^{14}$C

Parent
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 minimizing 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