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^{14}C Microtracer approaches to inform formulation development strategies in early clinical drug development

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PURPOSE

Administration of ^{14}C labelled drug product in clinical drug development is usually associated with regulatory ADME studies. However, the increase in sensitivity of bioanalytical detection techniques such as accelerator mass spectrometry (AMS) to measure microtracer amounts of ^{14}C from clinical samples, opens up the opportunity for more innovative study designs in early clinical development to increase the understanding of the absorption and bioavailability of drugs. This information can then be used to inform and guide formulation development strategies and influence go/no go program decisions.

The following poster describes how combining an intravenous (IV) microtracer regimen with an oral tracer regimen, can generate key pharmacokinetic (PK) parameters including, IV clearance (Cl_{IV}) and absolute bioavailability (F) and information to enable estimation of hepatic extraction ratio (E_H), fraction absorbed into enterocytes (F_{abs}) and fraction of drug surviving gut metabolism (F_g).

Data from an anonymised (Drug X) example case study is presented to illustrate this approach. Drug X was investigated in a 2 part study design, where subjects received an IV microtracer regimen in Part 1 and an oral tracer regimen in Part 2.

BACKGROUND

An oral tracer regimen involves administering a single drug product containing an oral therapeutic dose, labelled with microtracer (≤ 37 kBq) amounts of ^{14}C.

An IV microtracer regimen involves administering an oral therapeutic dose concomitantly with a 15 min IV infusion of a microdose (≤ 100µg and usually 1/1000th oral dose) of drug containing microtracer (≤ 37 kBq) amounts ^{14}C, in a single period. The IV infusion is timed to end at the T_{max} of the oral dose. This avoids the concerns of dose dependent kinetics when extrapolating IV PK from a microdose, as the systemic exposure is at therapeutic concentrations. This enables generation of absolute bioavailability (% F) without the need of a conventional IV formulation or an IV toxicity safety package, or local tolerability studies as long as pharmacopoeial excipients are used.

Dosimetry data and approval for administration of radiolabelled drug products are not required for microtracers, given the low levels of activity administered (≤ 37 kBq).

STUDY DESIGN

The study was an open-labelled, non-randomised, 2-part study in 12 healthy male subjects; 6 in Part 1 and 6 in Part 2.

In Part 1 the volunteers received an IV microtracer regimen. Plasma samples were collected to analyse parent drug via HPLC MS/MS (oral dose) and for total radioactivity (TRA) and parent via HPLC AMS (IV dose). Standard IV and oral PK parameters were estimated.

In Part 2 the volunteers received an oral tracer regimen. Plasma samples were collected for analysis of parent drug via HPLC MS/MS and for TRA via HPLC AMS. Standard oral PK parameters were estimated. Samples for haematology and clinical chemistry safety assessments, were also taken.

METHODS

Data from Part 1 enables estimation of F, metabolite load following IV dosing (ML_{IV}) and (F_{abs} x F_g) i.e. the amount of drug appearing in the hepatic portal vein following oral dosing:

$$F = (AUC_{oral}/AUC_{IV}) \times (Dose_{IV}/Dose_{oral}) \times 100\ \%$$ - **Equation 1**;

AUC_{oral} and AUC_{IV} are the area under the plasma curve following oral and IV dosing, respectively.

$$ML_{IV} = (AUC_{TRA,IV} - AUC_{IV})/AUC_{TRA,IV}$$ – **Equation 2**;

$AUC_{TRA,IV}$ is the area under the plasma curve of TRA following IV dosing.

$$F_{abs} \times F_g = F/(1 - E_H)$$ **– Equation 3**;

$E_H = Cl_{IV}$/hepatic blood flow, Cl_{IV} is IV clearance, assuming Cl_{IV} is hepatic, metabolic.
Hepatic blood flow is 1450 ml/min[1].

Data from Part 2 enables estimation of metabolite load following oral dosing (ML_{oral}):

$$ML_{oral} = (AUC_{TRA,oral} - AUC_{oral})/AUC_{TRA,oral}$$ – **Equation 4**;

$AUC_{TRA,oral}$ is the area under the plasma curve of TRA.

F_{abs} i.e. fraction of drug crossing into gastrointestinal epithelial cells (enterocytes), and F_g i.e. the fraction of drug surviving gut metabolism, can be estimated:

$$F_g = 1 - (ML_{oral} - ML_{IV})$$ – **Equation 5**

Re-arrangement of Equation 3 enables assessment of F_{abs}.

RESULTS

Table 1: Parameter Estimates for Drug X

Regimen Route Analyte No. of Subjects	A Oral Drug X N = 6	B IV ^{14}C-Drug X N = 6	C Oral Drug X N = 6
F (%)	12.2	NA	12.6
ML	NA	0.17	0.98
E_H	NA	0.21	NA
F_{abs} x F_g	NC	NA	0.16
F_g	NC	NA	0.19
F_{abs}	NC	NA	0.84

NA: not applicable; NC: not calculated

Table 1 presents the parameter estimates for Drug X, calculated from the data generated in the study. Cl_{IV} of Drug X was low (21% liver blood flow), and F was approximately 12%. The ML following oral and IV administration of ^{14}C-Drug X was 98% and 17%, respectively. For Drug X the low F was attributed to high gut metabolism, rather than poor absorption (F_g = 19%; F_{abs} = 84%). This information enables consideration of a modified release formulation to deliver the drug further down the gastrointestinal tract where CYP3A4 metabolism is reduced, due to lower enzyme expression.

CONCLUSION

- The study design successfully enables calculation of definitive IV PK parameters and F.
- It is possible to estimate the parameters that influence systemic exposure e.g. F_{abs}, F_g, E_H, and investigate the cause of poor bioavailability.
- This information can be utilised to inform and guide formulation development, support PBPK modelling approaches and influence strategy in clinical development.

REFERENCES

1. Davis, B and Morris, T. Physiological Parameters in Laboratory Animals and Humans. Pharmaceutical Research Vol 10. No. 7. 1093-1095. 1993.

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