The use of the IV microtracer technique to drive formulation optimisation

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Strategy – Use IV microtracer technique to de risk compounds with PK issues and drive formulation development

For compounds where exposure/pharmacokinetics (PK) is thought to be a risk, determine intravenous PK parameters and confirm absolute bioavailability (% F) in man as soon as possible using the IV microtracer technique, 3 examples are discussed.

1. Drug X – Exposure assumed to be limited by solubility and therefore an enhanced formulation will be required - is a product viable?
2. Drug Y – Exposure thought to be low and $t_{1/2}$ predictions uncertain – is a once a day (UID) product viable?
3. Drug Z – Lead compound carries significant PK risk, will PK be a significant risk for drug Z (back up compound) progressing?

Metholodogy - IV Microtracer Technique

The IV microtracer technique involves giving a IV ^{14}C-microtracer concurrently with an oral therapeutic dose in a single period study, avoiding the concerns of dose dependant kinetic issues. Accelerator mass spectrometry (AMS) is used to analyse the low concentrations of ^{14}C parent drug in plasma arising from the IV microtracer dose. AMS is an extremely sensitive quantitative analytical method for the detection of ^{14}C. Coupled with a chromatographic separation step it can be used to quantify levels of 14C-labelled analytes in biological samples. The IV microtracer technique offers the ability to generate absolute bioavailability (% F) data without developing a conventional IV formulation and without an intravenous toxicity safety package (Lappin and Stevens 2008). The development and manufacture of the IV formulations and the clinical studies for drugs X, Y and Z were conducted at Quotient Clinical Ltd (Nottingham, UK). HPLC AMS analysis of samples for all studies was conducted by Xceleron Ltd (York, UK). Ethics approval for the study for drug X was from Capenhurst independent ethics committee (Manchester, UK) and for drugs Y and Z was from Yorkshire independent ethics committee (Leeds, UK). Informed consent was given by all subjects prior to study initiation.

Drug X

- Tentative BCS Class IV compound, amorphous free base.
- Apparent permeability (P_{app}) in Caco-2 cells was moderate (P_{app} 1.7 x 10^{-6} cm/s at 10 µM).
- Solubility in human intestinal fluid (HIF) was very low (~ 2 µg/ml), however there was evidence of increased solubility in the fed state, and other biorelevant media (e.g. Mullertz media = 37 µg/ml).
- Predicted human fraction absorbed (Fabs) using an AZ in silico CAT model was 2 % for a 250 mg dose UID, , with exposure predicted to be strongly solubility limited, maximum absorbable dose (MAD) = 7 mg.
- Phase I formulation was a suspension of amorphous free base in HPMC and orange juice. Exposure in man was poor and it was estimated that a 5-10 fold increase is needed for a successful product.
- Proposed lipid based formulation for future development.

Methodology

1. Determine % F in man using IV microtracer technique.
2. Assess enhanced formulation options in dog.
3. Using modelling tools (PBPK and CAT modelling software) assess if a 5-10 fold increase in exposure is achievable.

References

1. Lappin and Stevens, Expert Opinion on Drug Metabolism and Toxicology, 2008 4(8): 1021-1033

1. IV microtracer study

An open-label study was conducted in 6 healthy male volunteers. Each subject received a single oral dose of 250 mg drug X (suspension in orange juice), then at t_{max} (after 1 hour and 45 mins) received a single IV infusion over 15 mins of 20 µg (< 270 nCi) ^{14}C drug X . Blood samples were taken at various time points following oral and IV administration (see Figure 1 for plasma profiles). The non-radiolabelled drug was analysed by liquid chromatography/mass spectrometry (LC/MS), with the ^{14}C drug X analysed by HPLC AMS.

Results

- Average % F was 12.7 ± 2.17 (n = 5), clearance (Cl) calculated from the IV dose was low at 1.8 ml min^{-1} kg^{-1} (8 % LBF) indicating that the poor % F was low due to poor absorption and not high Cl. Fabs was calculated to be approx 15 %.
- Potential to increase exposure by up to 8 fold through solubility enhancement.
- Variability in C_{max} and AUC was low, and $t_{1/2}$ similar, following both IV and oral administration.

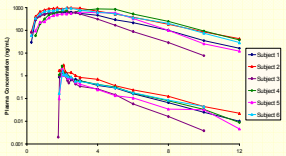


Figure 1. Individual plasma profiles of drug X in man

2. Optimised formulation in dog

Formulation work produced three optimised formulations which were assessed in dog (Figure 2). Exposure of 2 semi solid lipidic capsule formulations and a pH 3.5 citrate buffer suspension were compared to that of the Phase I suspension formulation.

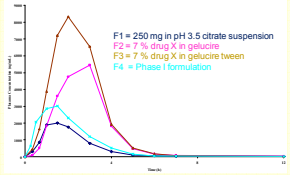


Figure 2. Geomean plasma profiles of drug X in dog from various formulation

Results

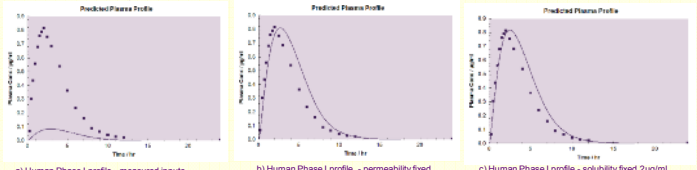
- Both lipidic capsule formulations had higher exposure in dog compared to that of the Phase I suspension formulation.
- Fabs was doubled with the gelucire tween formulation compared to that of the Phase I formulation, 44% compared to 21 % respectively.
- Exposure of the gelucire tween formulation (F3) in man was then predicted using modelling approaches.

3. Modelling - Is a 5-10 fold increase in exposure feasible with the lipid based formulation in man?

AZ *in silico* CAT (GI-Sim) software was used to develop a compound specific/tuned model to predict if the required increase in exposure was viable. The human phase I data was fitted using this model and then applied pre-clinically. *In vitro* measured HIF solubility was used for the initial modelling. PK profiles for the Phase I formulation were modelled to give best fit by fixing one measured parameter (e.g. permeability or solubility) and then optimising the none fixed parameter. The IV microtracer study provided the IV parameters which were essential to the successful *in silico* modelling.

AZ In house CAT model (GI-Sim) profiles - squares represent mean plasma conc following oral dose 250 mg, solid line predicted plasma concentrations.

Human Phase I PK profiles

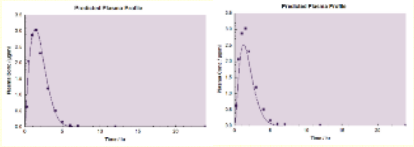


a) Human Phase I profile - measured inputs, solubility 2µg/ml, Caco-2 Papp 1.7 x 10^{-6}cm/s

b) Human Phase I profile - permeability fixed (Caco-2 Papp = 1.7 x 10^{-6} cm/s), solubility varied to give best fit 19.5 µg/ml

c) Human Phase I profile - solubility fixed 2µg/ml, Caco-2 Papp varied to give best fit (Papp = 40 x 10^{-6} cm/s, Peff = 10.6 x 10^{-4})

Dog Phase I PK profiles

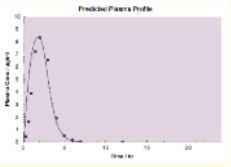


d) Dog Phase I profile –permeability fixed (Caco-2 Papp = 1.7 x 10^{-6} cm/s), solubility varied to give best fit 55 µg/ml

e) Dog Phase I profile – solubility fixed 2 µg/ml, dog Peff 200 x 10^{-4} cm/s (max value allowable)

Results

Modelling suggests that solubility is increased *in vivo* compared to measured values in HIF, (supported by evidence in biorelevant media), Peff value used to fit human data is very high and Peff to fit dog data is completely unrealistic. *For predictions to man assume solubility higher than measured in HIF.*



f) Dog gelucire tween formulation (F3) profile – permeability fixed (Caco-2 Papp 1.7 x 10^{-6} cm/s) solubility 140 µg/ml, gastric emptying increased to 45 min to predict tmax

Results – Lipidic formulation in dog

- To get a good fit (regardless of permeability used) solubility needs to be increased ~ 3x, possible explanations for this are;
  - Natural solubility of X in lipid/intestinal fluid mix.
  - Lipid excipients induces gall bladder emptying and increases bile acid/phospholipid conc in small intestine that increases solubilisation.
  - Digestion of lipid excipients creates a environment capable of solubilisation.
  - Combination of the above.
- Could not fix t_{max} (faster input required), gastric emptying time extended to 45 min to give best fit – would lipid content increase gastric emptying in dogs? Will this occur in humans?

Simulation of Lipidic formulation exposure in man

- Caco-2 permeability value of 1.7 x 10^{-6} cm/s used.
- Modelling was performed at either 3 x the solubility (60 µg/ml) determined to give best fit in humans for the phase 1 formulation, or the absolute *in vivo* lipidic solubility determined via modelling from dog - 140 µg/ml.
- Gastric emptying time was kept standard (15 min) or increased to 45 min.

Table 1. Predicted % human Fabs for 250 mg lipidic formulation

	Standard Gastric emptying time (15 min)	Increased Gastric emptying time (45 min)
60 µg/ml	38	45
140 µg/ml	64	70

- PBPK simulations were used to predict the PK profiles in man using the lipidic formulation. % Fabs was predicted to be 55 % using this model, which is within the range predicted using the CAT model.

Conclusion

- IV microtracer technique confirmed that % F of drug X was low due to poor absorption (Fabs 15 %)
- A 5-10 fold increase in exposure from the Phase I formulation (% 15 Fabs) was required in man, modelling (using increased intestinal solubility parameters and gastric emptying) has predicted < 5 fold increase
- Modelling indicated that a commercial formulation to provide the required exposure using an acceptable capsule load was not viable
- Drug X progression STOPPED

Other examples of the use of the IV microtracer technique

Drug Y – back up candidate drug (CD), UID required, risk of short $t_{1/2}$ due to discrepancies in *in vitro* Cl predictions, can formulation be used to achieve a UID if required. Low exposure also a risk.

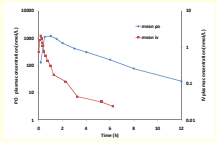


Figure 3. Mean plasma profiles following oral and IV microtracer dose of drug Y

- Outcome – limited duration of exposure due to short $t_{1/2}$ (1.55 hours), UID (conventional or modified release) not possible, therefore drug Y stopped.

Drug Z – back up CD, lead compound carried significant PK risk, however drug Z was predicted to have better PK. Absolute bioavailability (% F) data was required early in clinical development to support this.

Outcome - % F 92 (geomean), $t_{1/2}$ 11.1 hours, PK superior to lead compound, de risked drug Z for development.

Summary

The IV microtracer technique can be used in early clinical development to provide absolute bioavailability data and robust intravenous PK parameters), to indentify if absorption is responsible for poor exposure and thus indicate if formulation options can be used to increase exposure, and to de risk compounds which carry a PK liability.