Semi-Mechanistic Modelling Of The Tumour Growth Inhibitory Effects Of A New Anti-Angiogenic Drug.

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Introduction

A tumour is a swelling or lesion formed by an abnormal growth of cells. Tumour vascularization provides vital nutrients, growth factors, oxygen and clear toxic waste products of cellular metabolism.
Under conditions of nutrient deprivation tumour cells secrete stimulatory factors such as vascular endothelial growth factor (VEGF), which is a potent stimulator of endothelial cell proliferation and migration. Most of the new vessels differ from normal vasculature in that they are dilated, leaky, and made up of a disorganized array of peri-endothelial pericytes and smooth muscle cells.

Objective

To develop a mechanistic pharmacokinetic/pharmacodynamic (PK/PD) model for a new antiangiogenic drug using human xenografts

Methods

7 to 10 days → Two types of experiments

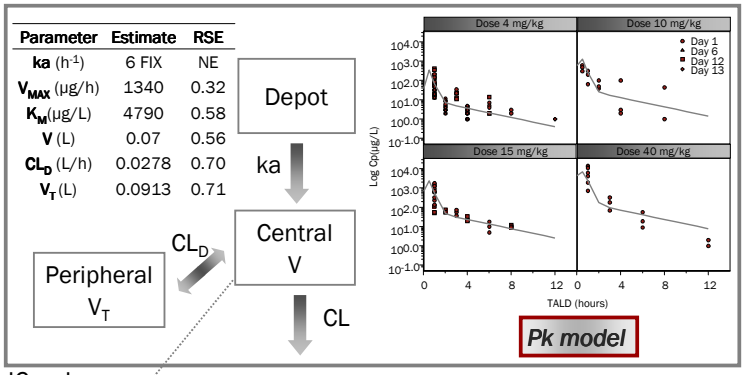
- PKPD: Plasma levels of the antiangiogenic drug
- PKPD: The percentage change (inhibition of a biomarker) with respect to baseline in tumour
- Tumour Growth → Kinetics of tumour growth was monitored during 20 to 41 days after the first day of drug administration.

Saline or Drug was administered orally as a single dose or in a multiple dosing design.

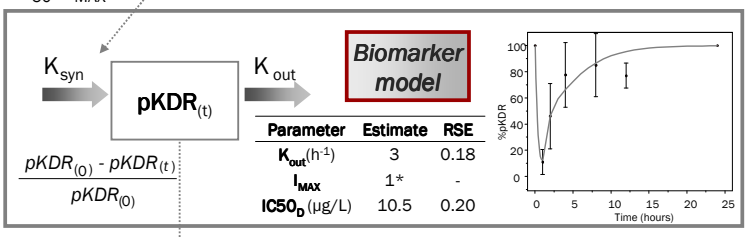
Data modeling. Plasma levels of the compound, percentage of pKDR in tumour, and tumour size were used to establish a semi-mechanistic, population PK/PD model that was used to predict tumour stabilisation using NONMEM [1].

Results

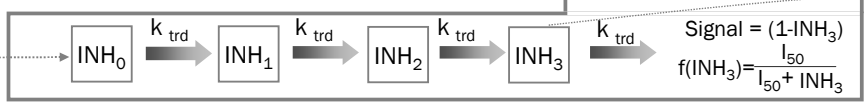
Parameter	Estimate	RSE
ka (h^{-1})	6 FIX	NE
V_{MAX} (µg/h)	1340	0.32
K_M(µg/L)	4790	0.58
V (L)	0.07	0.56
CL_D (L/h)	0.0278	0.70
V_T (L)	0.0913	0.71

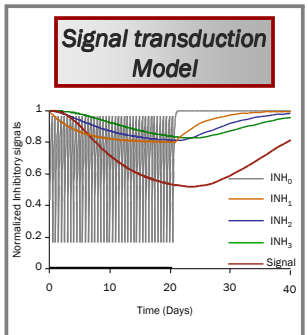


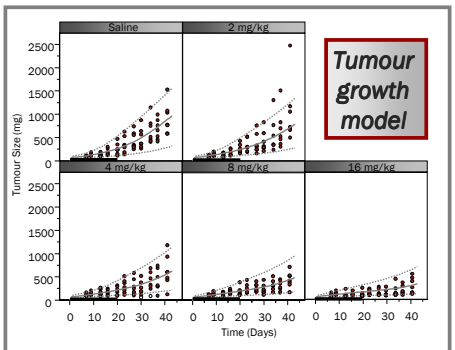
IC_{50}, I_{MAX}, n



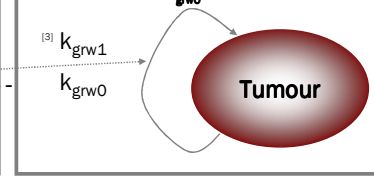
Parameter	Estimate	RSE
K_{out}(h^{-1})	3	0.18
I_{MAX}	1*	-
$IC50_D$ (µg/L)	10.5	0.20







Parameters	Estimate	RSE
K_{grw1} ($days^{-1}$)	0.079	0.144
K_{grw0} (mg $xdays^{-1}$)	64.7	0.038
TS_0 (mg)	49.9	0.206
MSPT (days)	24.5	0.207
Nut	0.00165	0.368
IAV in K_{grw1}	0.33	0.44
IAV in K_{grw0}	0.22	0.51



Conclusion

The integrated model was a useful tool to investigate different experimental scenarios, and provided valuable insights into the mechanisms of signal transduction and tumour growth. From a developmental perspective, these types of models provide a simulation platform to explore the relationship between drug exposure, efficacy, and toxicity *in silico*[2]

References [1] Beal S and Sheiner L. NONMEM users guide, 1992. [2] Bueno L et al., (2008) European Journal of Cancer 44, 142-150. [3] Simeoni M et al,. (2004) Cancer Research 64, 1094-11