A systems approach to predicting differences in pharmacological response to a CYP1A2 substrate, resulting from pharmacokinetic differences in non-smokers, passive smokers and heavy smokers.

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Background

The Induction of CYP1A2 by polycyclic aromatic hydrocarbons in cigarette smoke is well established. Altered plasma concentrations due to increased hepatic clearance by CYP1A2 in smokers has been reported for substrates metabolised primarily by CYP1A2 such as clozapine, theophylline and olanzapine [1-3]. Passive smoking has also been shown to increase the clearance of theophylline significantly [4]. Differences in the clearance of the CYP1A2 substrates in smokers and passive smokers may require higher doses of the drug to produce a pharmacological effect similar to that in non-smokers. Additionally, smoking cessation may lead to significantly increased plasma concentrations and toxicity. This could be a serious therapeutic concern with substrates that have a narrow margin of safety.

A recent report suggests the possibility of predicting consequential pharmacokinetic (PK) differences in CYP1A2 substrates due to smoking by using *in vitro – in vivo* extrapolation (IVIVE) combined with physiologically–based PK (PBPK) [5]. Using quantitative assumptions of CYP1A2 abundance relative to daily cigarette usage, these authors demonstrated the possibility of predicting changes in the clearance of CYP1A2 substrates. Although reports on PK differences between non-smokers and smokers are abundant in the literature, studies on the associated pharmacodynamic (PD) responses are infrequent.

Objectives

To predict differences in pharmacological response resulting from PK differences in passive smokers and heavy smokers, using theophylline as an example of a CYP1A2 substrate, with forced expiratory volume (FEV_1) as a marker of response.

Methods

The Simcyp PBPK simulator (V11.1) was used to simulate a population of heavy smokers (>20 cigarettes/day), passive smokers and non-smokers. The Simcyp default CYP1A2 abundance of 52 pmol P450/mg protein (CV 67%) was used for non-smokers. An increased CYP1A2 abundance of 94 pmol P450/mg protein (CV 43%) [5] was used to model heavy smokers and a CYP1A2 abundance of 75 pmol P450/mg protein (CV 43%) [4] was used to model a population of passive smokers (exposed to cigarette smoke for >4 hours/day). PK/PD profiles were simulated for 10 trials with 30 subjects each, using the study design and PD model from a PK/PD study of Caucasian non-smokers with moderate respiratory dysfunction [2]. A sigmoid Emax model with an effect compartment and additive baseline was used. Parameters are shown in Table1 and CV was assumed to be 20% since these values were not published.

Table1: Parameters used in the PD model

Parameter	Value
Keo	1.19 1/h
Emax	25.1%
EC50	55 µM
Sigmoidicity	5
Baseline	60%

The simulated PK profiles of theophylline in heavy and passive smokers were then compared with clinically observed data [2,4]. Based on the PD model in non-smokers and PK differences in the three groups, PD responses in heavy smokers and passive were simulated. It was assumed that PD model parameters did not change in the three groups. Models did not consider the direct effect of cigarette smoke on FEV_1.

Results

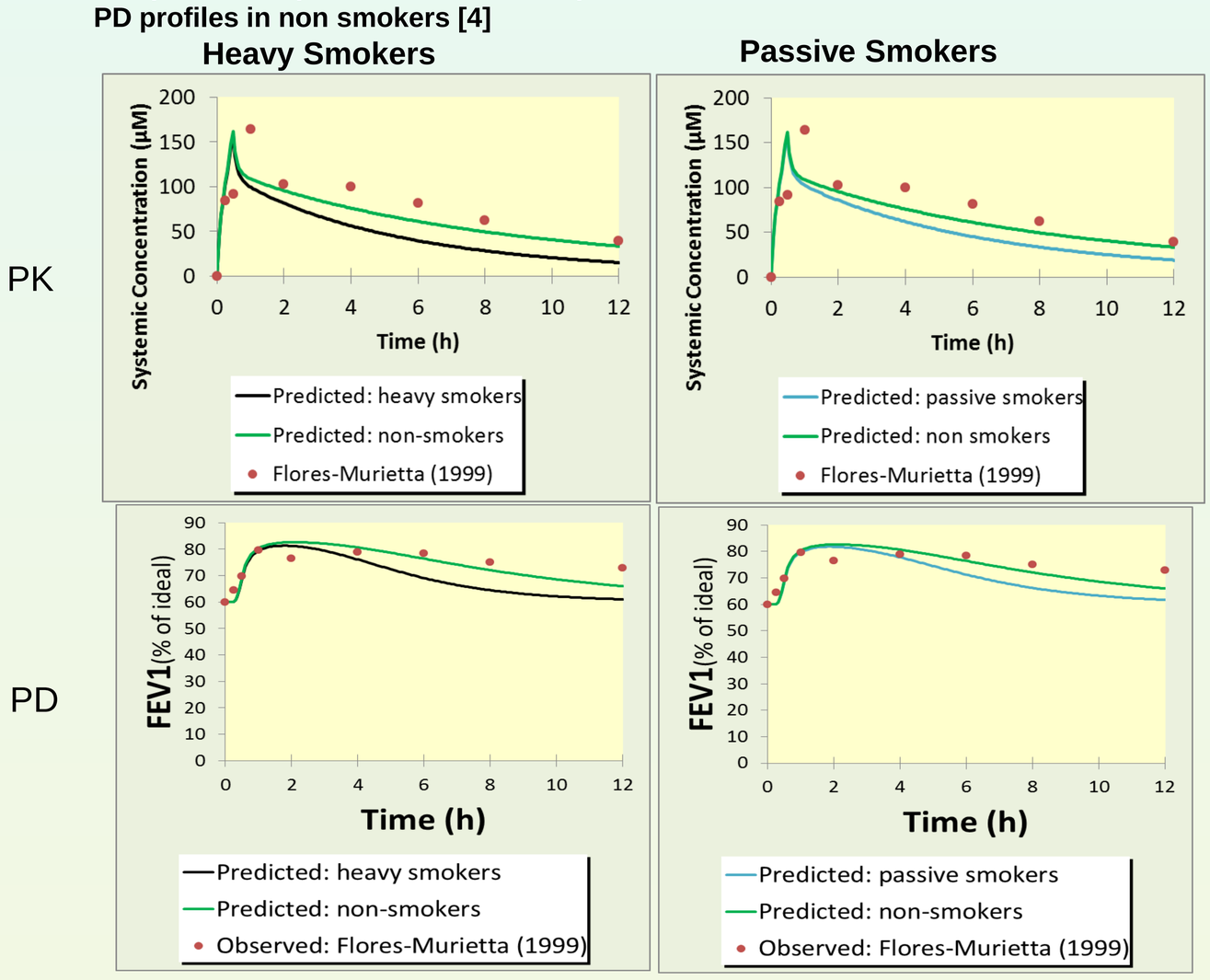
The simulated PK and PD profiles in non-smokers, heavy smokers and passive smokers are presented in Figure 1. Mean predicted PK and PD parameters and the clinically observed mean CL are presented for the three groups in Table 2. Predicted mean clearance in all three groups compare favourably with the observed values. Clearance (CL) in heavy smokers and passive smokers were on average 1.72 fold and 1.49 fold higher than in non-smokers, respectively. A paired t-test was used to compare differences in CL, Cmax, AUC, and AUCRcorr (area under the response curve corrected for baseline) for both heavy smokers and passive smokers with non smokers. The differences were shown to be statistically significant in all comparisons. The ratio of the mean AUCRcorr in heavy smokers and passive smokers compared with that in non smokers was 0.66 and 0.74 respectively, suggesting that a dosage adjustment may be required in smokers to achieve an equivalent response to that in non smokers.

Table2: Predicted PK and PD parameters in the 3 groups

	Non Smokers	Passive Smokers	Heavy Smokers
CL (L/h)-predicted	2.99(CV%=55)	4.25 (CV%=44)*	4.89 (CV%=44)*
CL (L/h)- observed	2.83(CV%=11) [4]	4.06 (CV%=44)[4] *	4.2(CV%=26) [6] *
Cmax (µM)	163.7	160.0*	158.1*
Tmax (h)	0.5	0.5	0.5
AUC (µM.h)	791.4	632.5*	575.6*
Rmax	82.81	81.9	81.6
T(Rmax)	2.23	1.95*	1.86*
AUCRcorr	175.6	130.7*	115.3*

* Significantly different from non smokers ($p < 0.0001$; paired t-test).

Figure 1. Predicted PK and PD profiles in heavy smokers and passive smokers compared with predicted PK and PD profiles in non smokers and observed PK and PD profiles in non smokers [4]



Conclusions

The Simcyp PBPK/PD model was able to differentiate the responses due to PK differences in passive smokers, heavy smokers and non-smokers. Significant changes in the CL and response of the CYP1A2 substrate in both passive and heavy smokers may have therapeutic implications. The PD Model does not consider the direct effect of cigarette smoke on FEV_1 so would be adequate for individuals who have recently started smoking; the baseline would require correction after prolonged smoking, due to direct effects of smoking on lung function. However, similar models using alternate PD markers can be developed and used to predict dosage adjustments in candidate drug molecules that are metabolised predominantly by CYP1A2, with a known PD profile in non smokers.

References

[1] Van der Weide et al (2003); [2] Flores-Murrieta et al (1999); [3] Bigos et al (2008); [4] Matsunga et al (1989); [5] Plowchalk and Rowland-Yeo (2012); [6] Gardner et al (1983).