Performance Verification of V17 updates to Sim-Japanese Population: a focus on CYP abundance

Oliver Hatley, Kate Gill, Karen Rowland Yeo and Iain Gardner

Abstract

The Sim-Japanese population is important for bridging clinical data from Caucasian studies. An update of the Sim-Japanese population was undertaken as part of the Version 17 wishlist project. Differences in hepatic CYP abundance between Caucasian and Japanese subjects were analysed using two approaches: 1) meta-analysis of reported absolute abundance in Japanese livers; and 2) using matched studies where Caucasian and Japanese CYP liver abundances were measured in the same study. Key differences were seen in CYP2C19 and CYP2D6 abundance from approach 1 and 2. Simulations were run using the meta-analysis and matched study based abundances. In general, for most CYP isozymes the data from the matched studies predicted well the pharmacokinetics in Japanese subjects. However for CYP2D6, the abundance from the meta-analysis best described *in vivo* data. This was confirmed using further verification with additional CYP2D6 clinical probes.

Background

The Sim-Japanese population was updated in Simcyp V17 as part of the population wishlist (Item #4). Latest data on demographics were updated, including the a user defined age distribution function to better describe the age distribution in the population. CYP abundances were updated since these values are key for describing CYP mediated differences in pharmacokinetics between populations. Two approaches were taken: 1) a meta-analysis of Japanese hepatic CYP abundance; 2) the correction of Sim-NEurCaucasian abundance based on the ratio of Japanese to Caucasian abundance from studies where samples from both populations were analysed by the same technique.

Methods

The available literature for hepatic CYP abundance from both matched studies (6 studies, n=269 livers) as well as from independent Japanese studies (17 studies, n=397 livers) were analysed. Data was excluded where donors were known to be duplicated (7 studies, n=184), or data was mean including paediatric samples (1 study, n=10). One study (n=23) was excluded on the basis that the data was not peer reviewed. For matched studies, Japanese hepatic CYP abundance was obtained by correcting the Sim-NEurCaucasian abundance by the observed Japanese:Caucasian ratio. To assess the consequence of the differences observed between the two scenarios simulations were conducted using probe CYP substrates for enzyme abundance scenarios and compared to clinical observations. Simulations were conducted in V17 build 50.

Results

Japanese hepatic CYP abundances were similar using both analysis approaches except for CYP2C19, CYP2D6 and CYP3A7 (Fig. 1). The paired approach for CYP3A7 was discounted however as the Caucasian reference value was 10 fold lower than observed in our meta-analysis. Simulations were run for both abundance scenarios for CYP2C19 using the in vivo probe substrate omeprazole in EM and PM individuals[1]. Improved predictions were observed using the paired analysis approach (Table 1).

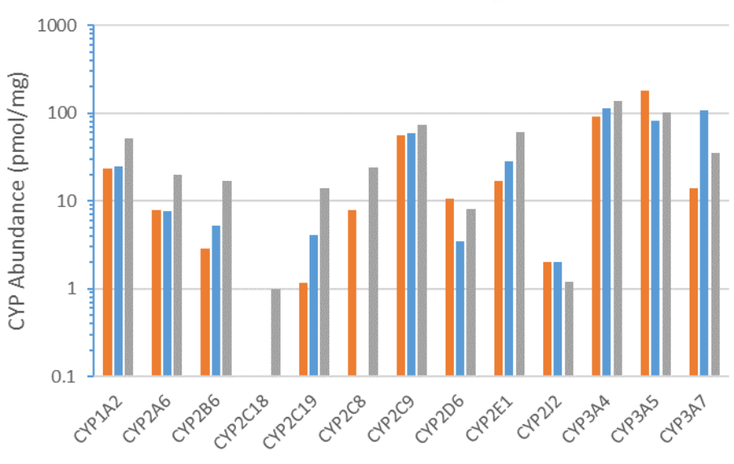

Figure 1: Comparison of hepatic CYP abundance based on Meta-analysis (orange) and paired (blue) Japanese and Caucasian sample analysis. Sim-NEurCaucasian values are shown in grey.

	CYP2C19 Meta-analysis (EM 1.2, PM 0 pmol/mg)			CYP2C19 Paired (EM 4.1, PM 0 pmol/mg)			Observed		
	C_{max} (ng/ml)	AUC_{inf} (ng/ml.h)	CL (L/h)	C_{max} (ng/ml)	AUC_{inf} (ng/ml.h)	CL (L/h)	C_{max} (ng/ml)	AUC_{inf} (ng/ml.h)	CL (L/h)
EM	889.6	3071.4	8.6	666	1835	17.8	495	1092	18.3
PM	1074	4552	6	1168	5702	5.7	1177	4240	4.7

Table 1: Comparison of simulated omeprazole simulations for the two CYP2C19 abundance scenarios compared to clinically observed data[1]. Simulations based on 10 trials of 27 (non-PM) and 7 (PM) individuals ages 22-47 (22% female).

Results

Simulations of the *in vivo* clinical interaction for the CYP2D6 substrate Aripiprazole following single and multiple dose exposure[2]. Predicted AUC_{inf} following 6mg single dose PO was 2091 ng/ml.h (meta) and 2995 ng/ml.h (paired, obs 1473 ng/ml.h). Predicted C_{max} was similar for both scenarios and close to observed values (Meta: 27.6, Paired: 28.9, Obs: 31.7 ng/ml) (Fig. 2A,B).

Multiple dose exposure of daily administration of 3 mg PO to a population of CYP2D6 EM and IMs further demonstrated improved predictions using paired meta-analysis abundance data, however there was an over prediction of exposure in both cases. ($AUClast_{0-24}$ Meta: 1102, Paired: 1475, Obs: 678 ng/ml.h) (Fig. 2C,D).

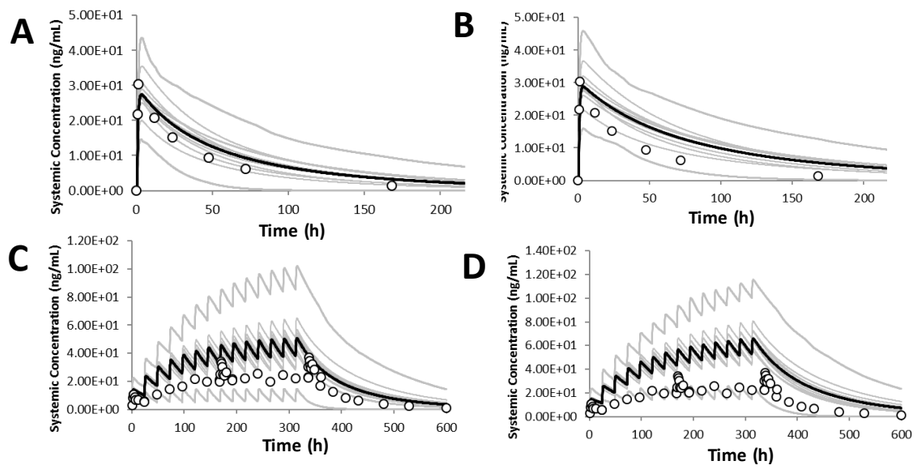

Figure 2: Comparison of aripiprazole pharmacokinetics using meta-analysis (A, C) and paired (B, D) CYP 2D6 abundance scenarios compared to clinically observed data[3] following single dose (6 mg) or multiple dose (3 mg). Simulations based on 10 trials of 9 (EM (A, B) or 12 EM and 3 IM (C,D)) individuals ages 20-25 (0% female)[3]. Fixed trial design was used for C,D.

Further verification of the suitability of meta-analysis abundance values for CYP2D6. The interaction following time dependant inhibition of CYP2D6 after multiple dose administration of paroxetine in Japanese CP2D6 EM and IM subjects. Both abundance scenarios the AUR_{inf} ratio for EMs was under predicted (meta-analysis: 1.57, paired :1.45, observed 2.4[3]).

	CYP2D6 Meta-analysis (EM 10.5 PM 3.9 pmol/mg)			CYP2D6 Paired (EM 3.4, IM 1.3 pmol/mg)			Observed		
	C_{max} Ratio	AUC_{inf} Ratio	CL Ratio	C_{max} Ratio	AUC_{inf} Ratio	CL Ratio	C_{max} Ratio	AUC_{inf} Ratio	CL Ratio
EM	1.08	1.58	0.75	1.08	1.45	0.75	1.39	2.40	0.42
IM	1.07	1.57	0.71	1.06	1.30	0.81	1.27	1.30	0.77

Table 2: Comparison of aripiprazole SV-paroxetine DDI simulation for meta-analysis and paired CYP2D6 abundance scenarios compared to clinically observed data[2]. Simulations based on 10 trials of 7 CYP2D6 EM or 7 IM individuals (ages 20-40 (0% female) following multiple dose 20 mg paroxetine and a single 3mg dose aripiprazole co-administered on day 7.

Conclusions

- Paired analysis was similar to meta-analysis for the majority of enzymes studied.
- Omeprazole (CYP2C19 substrate) was improved using updated paired analysis abundance *vs.* meta-analysis values.
- Aripiprazole (CYP2D6) exposure and DDI simulations were improved using meta-analysis *vs.* paired analysis abundance values. Fraction metabolised by CYP2D6 of aripiprazole may need to be further refined to reflect DDI in Japanese population.

References

1. Ieiri, I., et al. (1996). Clin Pharmacol Ther **59**(6): 647-653.
2. Kubo, M., et al. (2007). Drug Metab Pharmacokinet **22**(5): 358-366.
3. Azuma, J., et al. (2012). Eur J Clin Pharmacol **68**(1): 29-37.