

Predicting liver-mediated drug-drug interactions with MRI: A first-in-human study

Results

Internal report
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by

miblab.org

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Figures

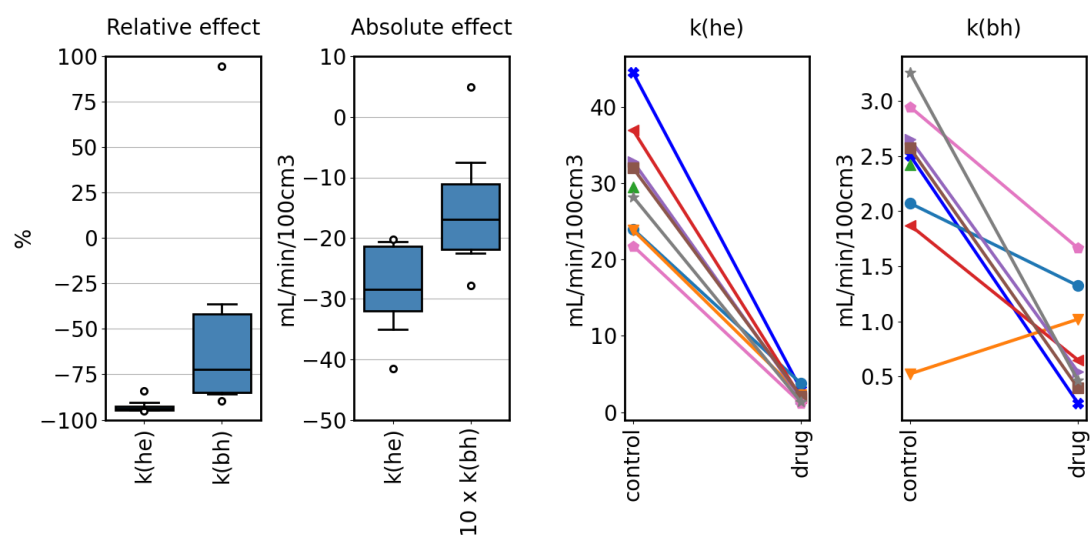


Figure 1.1: Visualisation of the primary endpoints k_{he} and k_{bh} across the population, showing a significant response to drug: (a) the relative and absolute effect size across the population as box plots; and (b) the individual values at control (left of plots) and after single dose of drug (right of plot). Colored lines in (b) represent individual volunteers. Note: absolute effect sizes for k_{bh} have been scaled with a factor 10 to improve visualisation.

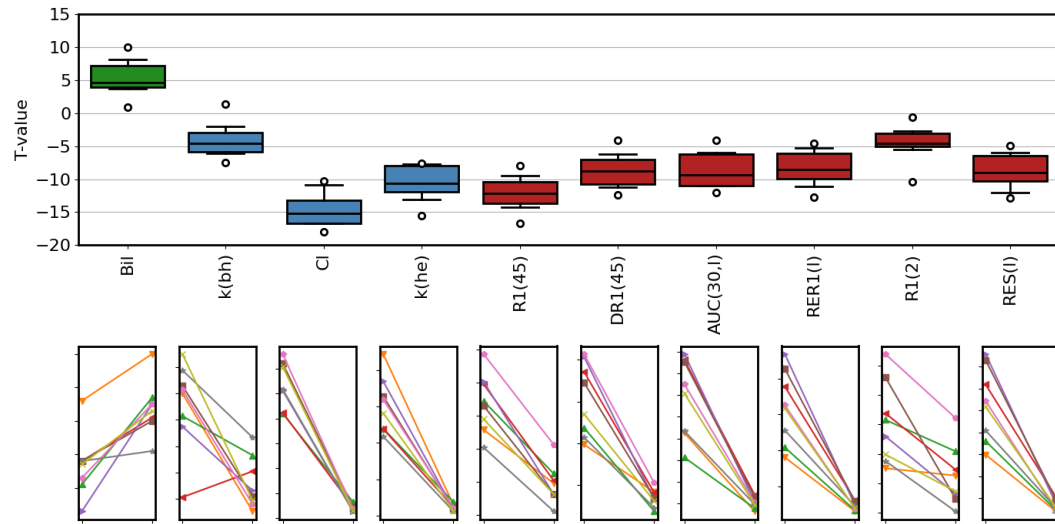


Figure 1.2: drug effect for all parameters that show a significant reduction in the mean value ($p < 0.01$). The top row shows the difference relative to the standard error of the difference, and the bottom row shows the individual effects for the corresponding biomarkers.

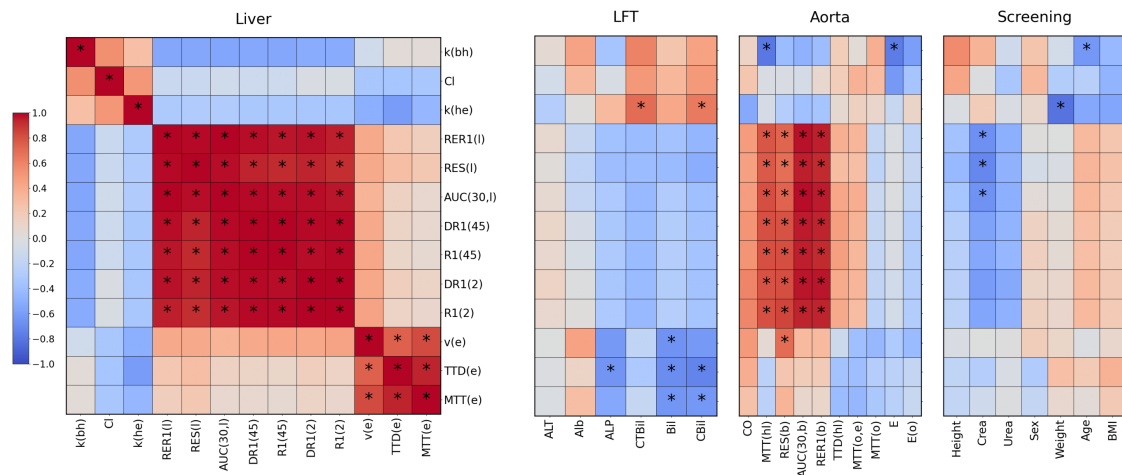


Figure 1.3: Correlations between parameters at control.

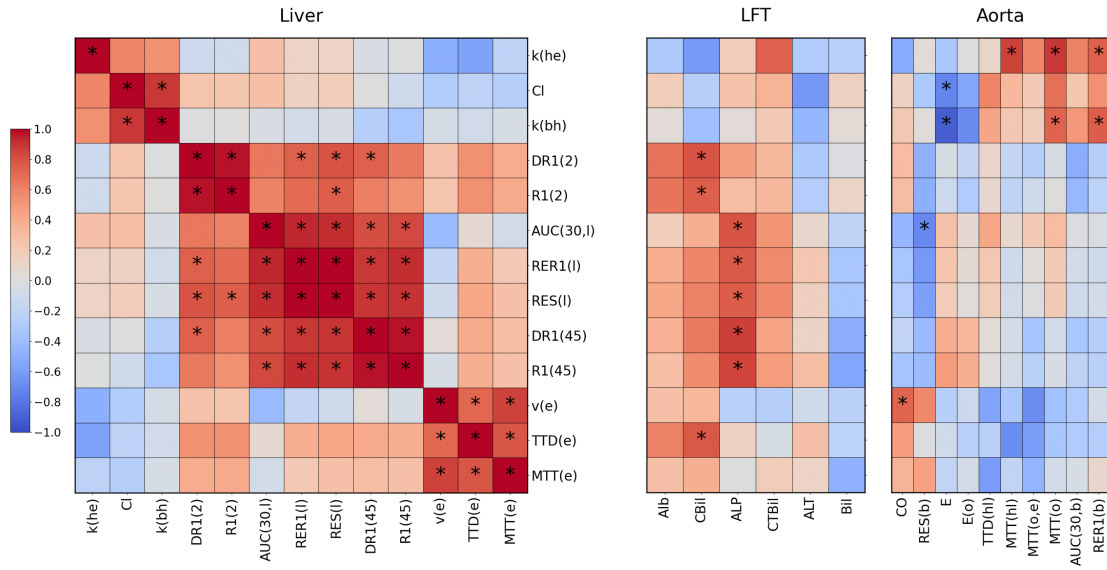


Figure 1.4: Correlations between parameter changes.

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Tables

parameter	count	mean	std	min	25%	50%	75%	max
Age (yr)	10.0	32.5	8.3	21.0	27.0	32.0	35.5	51.0
ALP (U/L)	10.0	67.8	26.5	39.5	53.4	60.0	67.5	118.0
ALT (U/L)	10.0	20.8	8.2	14.0	16.5	17.8	23.4	41.5
Albumin (g/L)	10.0	42.3	2.8	37.0	41.8	42.8	43.4	46.0
Bilirubin (umol/L)	10.0	13.0	4.2	6.5	10.8	12.8	14.0	23.0
Conjugated Bilirubin (umol/L)	10.0	4.7	2.1	3.0	3.5	4.2	5.0	10.0
Conjugated/total bilirubin (%)	10.0	36.2	6.4	25.0	33.4	36.2	39.0	46.5
BMI (kg/m2)	10.0	24.4	3.5	18.7	22.6	24.0	26.8	30.0
Creatinine (umol/L)	10.0	77.1	13.3	58.0	67.2	79.5	86.8	98.0
Height (cm)	10.0	174.3	8.1	163.1	167.6	175.7	179.9	187.8
Urea nitrogen (mmol/L)	10.0	5.8	1.5	3.4	5.0	5.8	7.0	7.8
Body weight (kg)	10.0	73.2	7.6	57.0	72.8	74.6	75.9	82.8

Table 2.1: Demographics of the study population.

parameter	V1	V2	Diff	p
ALP	67.6 (40.1)	69.4 (54.1)	1.8 (23.1)	0.687
ALT	21.8 (18.7)	25.4 (18.9)	3.6 (9.4)	0.069
Alb	44.5 (4.1)	43.9 (5.9)	-0.6 (6.3)	0.598
Bili	12.1 (8.5)	11.4 (9.3)	-0.8 (11.6)	0.731
ConBili	4.8 (3.7)	4.6 (4.2)	-0.1 (5.1)	0.89
ConTotBili	39.4 (11.3)	37.3 (9.1)	-3.0 (15.6)	0.358

Table 2.2: LFT changes between both visits.

parameter	Name	Group	control	drug	Effect size (%)	T	p-value
AvrBili	Bilirubin (umol/L)	LFT	13.0 (2.6)	22.0 (2.8)	81.9 (52.0)	-5.4	0.001
AvrConBili	Conjugated Bilirubin (umol/L)	LFT	4.7 (1.3)	12.6 (6.2)	146.0 (57.0)	-3.1	0.02
AvrAlb	Albumin (g/L)	LFT	42.3 (1.7)	40.9 (1.8)	-4.15 (2.9)	2.8	0.028
AvrConTotBili	Conjugated/total bilirubin (%)	LFT	36.2 (4.0)	44.6 (5.3)	23.1 (21.0)	-2.0	0.092
AvrALT	ALT (U/L)	LFT	20.8 (5.1)	24.1 (6.5)	17.4 (23.0)	-1.6	0.163
AvrALP	ALP (U/L)	LFT	67.8 (16.0)	73.9 (21.0)	-0.542 (11.0)	-0.0	0.986
CL	Liver blood clearance (L/min)	MRI	0.265 (0.028)	0.0199 (0.0044)	-92.3 (2.5)	14.6	0.0
R1_45min	R1 at 45mins (1/sec)	MRI	2.33 (0.82)	1.38 (0.083)	-26.1 (3.2)	12.1	0.0
khe	Hepatocellular uptake rate (mL/min/100cm3)	MRI	29.7 (4.5)	2.17 (0.59)	-92.6 (2.5)	10.6	0.0
RE_Sl	RE for Sl at 20min (%)	MRI	66.0 (23.0)	6.54 (1.7)	-87.5 (1.9)	8.8	0.0
DR1_45min	Delta R1 at 45mins (1/sec)	MRI	1.07 (0.81)	0.136 (0.03)	-77.1 (5.8)	8.7	0.0
AUC35_CI	AUC for CI (0-35min) (mM*sec)	MRI	205.0 (100.0)	25.8 (4.3)	-81.9 (2.7)	8.6	0.0
RE_R1l	RE for R1l at 20min (%)	MRI	86.9 (40.0)	8.86 (1.5)	-85.6 (1.9)	8.3	0.0
R1_scan2	R1 (scan 2) (1/sec)	MRI	1.73 (0.44)	1.32 (0.071)	-11.7 (4.6)	4.5	0.003
kbh	Biliary excretion rate (mL/min/100cm3)	MRI	2.17 (0.54)	0.791 (0.34)	-48.7 (42.0)	4.1	0.005
DR1_scan2	Delta R1 (scan 2) (1/sec)	MRI	0.459 (0.43)	0.0757 (0.018)	-31.4 (76.0)	3.1	0.017
ve	Liver extra-cellular volume fraction (mL/100cm3)	MRI	17.7 (6.5)	21.5 (3.3)	264.0 (420.0)	-1.4	0.199

Te	ExtracellularMRI mean transit time (sec)		36.5 (11.0)	43.0 (7.7)	148.0 (240.0)	-0.9	0.406
De	ExtracellularMRI disper- sion (%)		66.1 (16.0)	70.4 (4.8)	283.0 (550.0)	-0.7	0.531

Table 2.3: Univariate data analysis (liver).

parameter	Name	Group	control	drug	Effect size (%)	T	p-value
Eo	Organs extraction fraction (%)	MRI	18.4 (3.2)	14.1 (3.2)	-25.4 (12.0)	4.0	0.005
RE_R1b	RE for R1b at 20min (%)	MRI	20.6 (9.1)	22.9 (5.9)	45.2 (28.0)	-3.6	0.008
AUC35_Cb	AUC for Cb (0-35min) (mM*sec)	MRI	36.9 (16.0)	35.2 (8.1)	26.8 (16.0)	-3.5	0.011
Eb	Body extraction fraction (%)	MRI	6.73 (2.1)	3.46 (0.77)	-41.1 (16.0)	3.0	0.02
Dhl	Heart-lung dispersion (%)	MRI	47.3 (8.7)	47.4 (8.0)	10.7 (9.8)	-2.0	0.087
RE_Sb	RE for Sb at 20min (%)	MRI	15.3 (8.6)	20.2 (7.4)	136.0 (130.0)	-1.4	0.211
Toe	Organs extravascular mean transit time (min)	MRI	5.98 (1.3)	6.72 (1.3)	31.4 (48.0)	-1.0	0.336
To	Organs blood mean transit time (sec)	MRI	27.9 (5.5)	30.8 (7.0)	9.7 (20.0)	-0.8	0.464
Thl	Heart-lung mean transit time (sec)	MRI	14.5 (3.3)	14.5 (2.5)	11.9 (23.0)	-0.7	0.514
CO	Cardiac output (L/min)	MRI	7.75 (2.0)	7.7 (1.2)	17.8 (27.0)	-0.6	0.54

Table 2.4: Univariate data analysis (aorta).

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Supplements

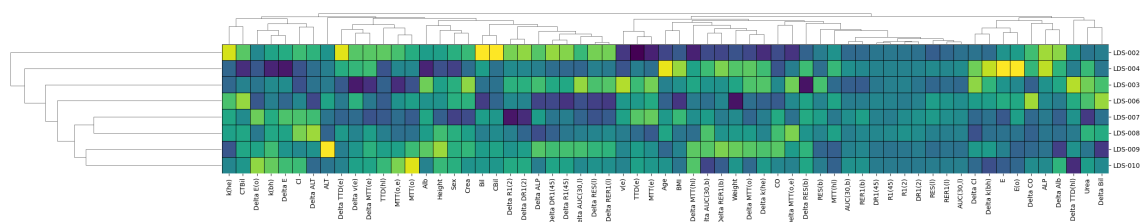


Figure 3.1: Clustering of parameters and subjects.