

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

Results

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

Results

by

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Figures

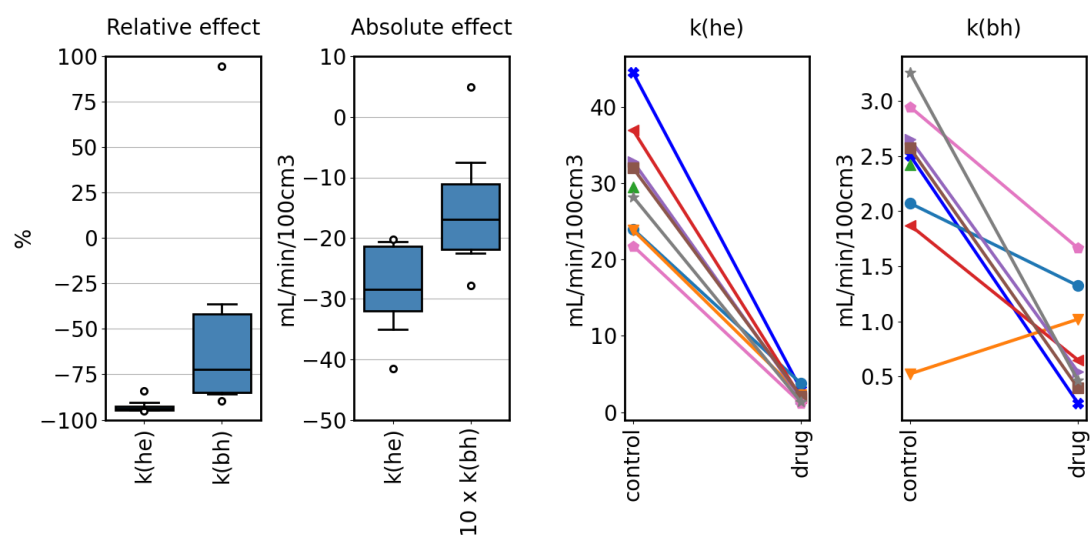


Figure 1.1: Visualisation of the primary endpoints khe and kbh across the population, showing a significant response to drug: (a) the relative and absolute effect size across the population as box plots; and (b) the individual values at control (left of plots) and after single dose of drug (right of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

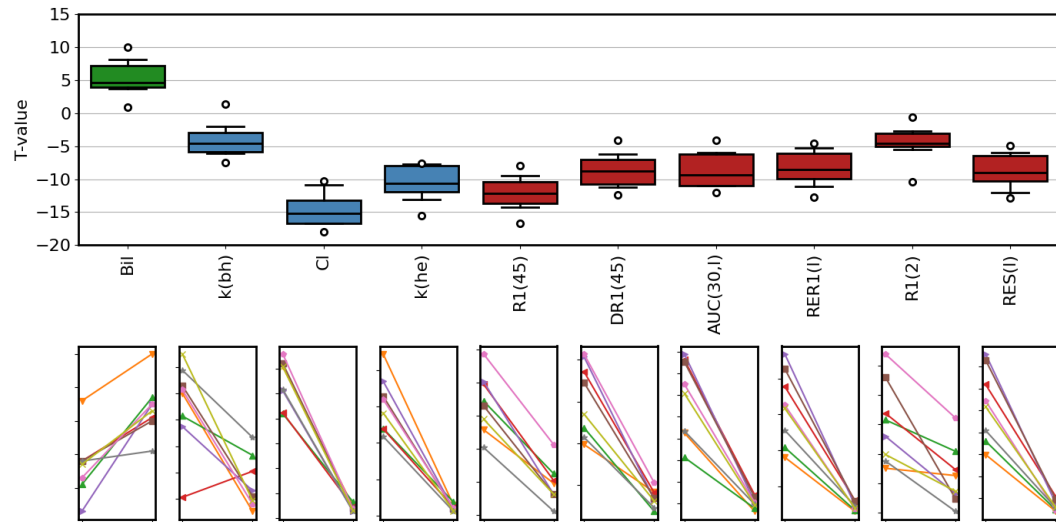


Figure 1.2: drug effect for all parameters that show a significant reduction in the mean value ($p < 0.01$). The top row shows the difference relative to the standard error of the difference, and the bottom row shows the individual effects for the corresponding biomarkers.

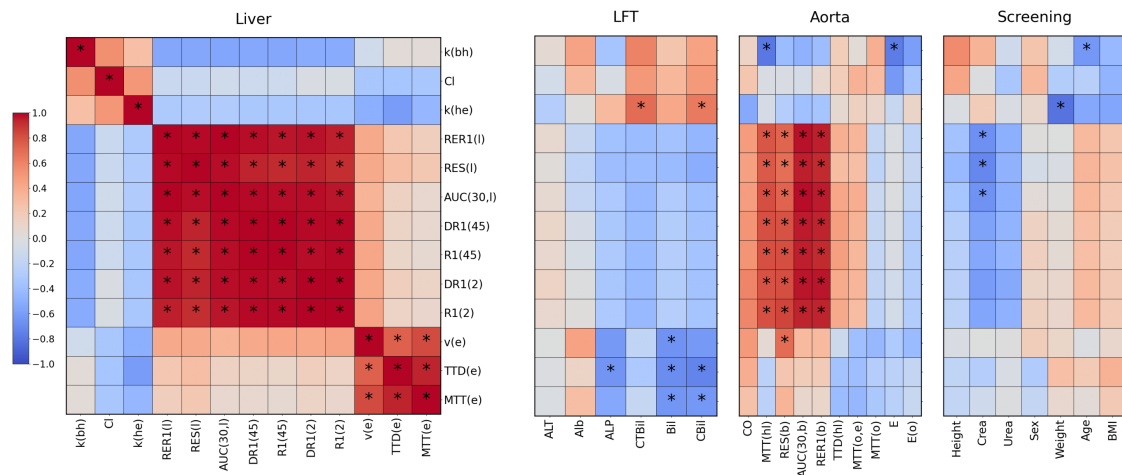


Figure 1.3: Correlations between parameters at control.

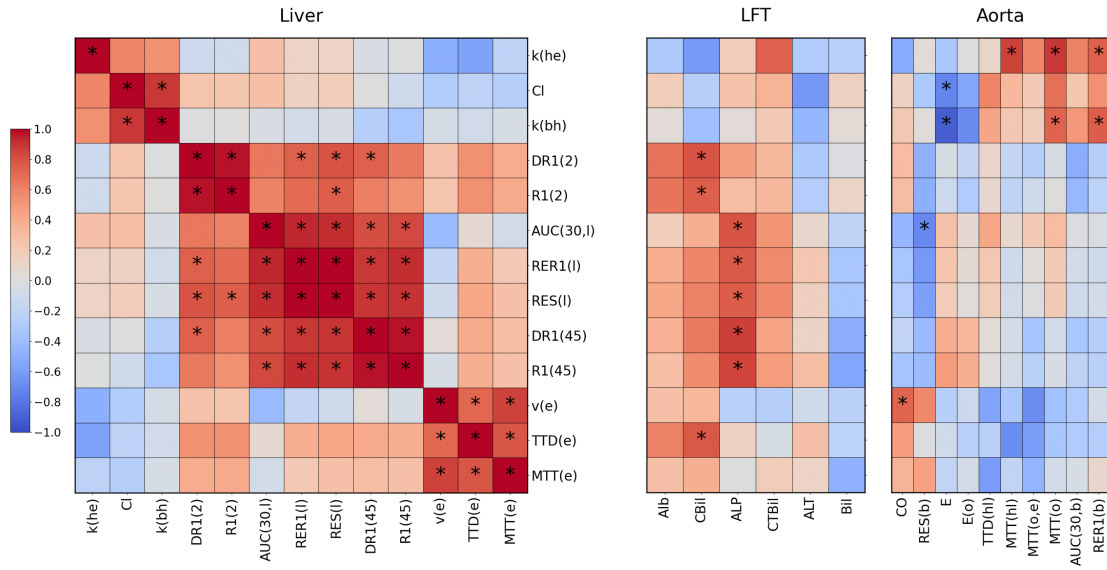


Figure 1.4: Correlations between parameter changes.

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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

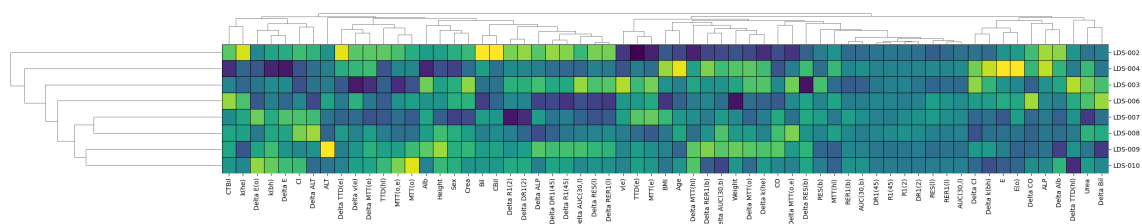


Figure 3.1: Clustering of parameters and subjects.