**Title page**

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

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**Abbreviated title page**

Title of the manuscript: Predicting liver-mediated drug-drug interactions with MRI: A first-in-human study

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A summary statement:

MRI measurements of gadoxetate liver uptake and biliary excretion rates robustly detect drug-induced inhibition of hepatocellular transporter function.

Key Results

* A single clinical dose of rifampicin caused a strong reduction in hepatocellular uptake (-93%) and biliary excretion (-50%) of gadoxetate, demonstrating potential of these biomarkers for predicting of drug-drug interactions in humans.
* The effect of rifampicin on uptake and excretion were uncorrelated, showing the importance of separately measuring both effects.
* The effect of LFT’s was substantially weaker and uncorrelated to effects on uptake and excreting, showing the added value of the MRI assay.

List of all abbreviations

DILI: Drug-induced liver injury

DDI: Drug-drug interaction

DCE-MRI: Dynamic Contrast-Enhanced MRI

CI: Confidence interval

MOLLI: modified Look-Locker sequence

khe: Hepatocellular uptake rate

kbh: Biliary excretion rate

**Abstract (<300) words**

Background

Effective management of liver-mediated drug-drug interactions in drug development and clinical practice requires biomarkers to assess drug effects on hepatic transporters OATP1B and MRP2. Preclinical evidence in rats has shown that dynamic gadoxetate-enhanced MRI (DGE-MRI) is suitable for this purpose, but it is not known whether these findings translate to humans

Purpose

To investigate the effects of rifampicin, a known inhibitor of hepatocyte uptake and biliary excretion transporters, on gadoxetate uptake and excretion rates in the liver of healthy volunteers.

Materials and Methods

This prospective study (2022-2023) recruited 10 healthy volunteers, who were assessed on two separate visits. DGE-MRI was performed over two separate scans, one hour apart, due to the slow hepatic excretion of gadoxetate. DGE was acquired with a fast (2.5 sec) 3D free-breathing protocol collecting data continuously for 50 minutes. Gadoxetate was injected at 1/8th of a clinical dose, escalated to 1/4th after the first 3 volunteers. On the second visit, rifampicin (600mg) was administered orally one hour before the start of the scan. Liver uptake and excretion rates were derived from signal-time curves in aorta and liver. The effect of rifampicin was determined with a paired t-test with significance level at p<0.01.

Results

Eight of the 10 participants (3 female/7 male, mean age 32) completed both visits. Rifampicin reduced hepatocellular uptake rate by 93% (95%CI 91-95%, p<0.001). Biliary excretion rate reduced by 50% (p=0.004) but the effect was more variable (95%CI 8-92%). Both rate constants were reduced by rifampicin in every subject, except for the excretion rate of one participant who had low baseline levels.

Conclusion

MRI measurements of gadoxetate liver uptake and biliary excretion can robustly detect drug-induced inhibition of hepatocellular function mediated via OATP1B and MRP2 transporters.

**Introduction**

Numerous clinically relevant drug-drug interactions (DDIs) arise via inhibition of hepatic uptake or excretion of victim drugs, which may affect their efficacy and toxicity. These interactions are often associated with organic anion transporting polypeptide (OATP) 1B1 and 1B3 expressed on basolateral membrane of hepatocytes [Galetin 2024]. Transporter-mediated DDIs are assessed during drug development by a combination of in vitro and in silico methods. Unfortunately, predictions are difficult to verify clinically – especially when inhibition of excretion by the perpetrator drug causes a change in liver exposure to the victim drug [Guo 2018]. Consequently, clinical trials risk either underestimating DDIs, and so potentially harming study subjects, or overestimating DDIs and consequently failing to show efficacy.

Reducing the risk of DDIs in clinical trials therefore requires a more accurate measurement of inhibition of liver uptake and excretion by perpetrator drugs in humans.

A potential solution is provided by dynamic gadoxetate-enhanced MRI (DGE-MRI). Gadoxetate is a substrate of the liver uptake and biliary efflux transporters OATP1B1, OATP1B3, NTCP, MRP2 and MRP3 [Tsuboyama 2010, Nassif 2012, Scotcher 2021], and is approved as a radiographic contrast agent to detect and characterize liver lesions [Poetter-Lang 2020]. With appropriate modelling and analysis, the data can be used to quantify gadoxetate liver uptake- and excretion rates in humans [Sourbron 2012, Georgiou 2017]. In a context of DDI prediction, these data can then be combined with preclinical- and in vitro data to predict the effect of perpetrator drugs on the distribution of victim drugs more accurately [Melillo 2023].

Studies in rats have shown that drug-induced inhibition of liver uptake and excretion can be measured reproducibly with DGE-MRI, can distinguish inhibitors from non-inhibitors, and inhibition of uptake from inhibition of excretion [Ulloa 2013, Karageorgis 2018, Melillo 2023]. Based on this evidence the Food and Drug Administration (FDA) has indicated an interest in the gadoxetate-MRI assay by accepting it into their biomarker qualification program [FDA 2021], but evidence of efficacy in humans is critically needed to evidence utility in drug development.

The aim of this study was to test whether findings in rats translate to humans, by measuring the change in liver gadoxetate uptake and excretion after administration of a known potent and selective inhibitor drug in healthy volunteers. Rifampicin was selected as a test drug since the preclinical studies revealed a strong inhibition of biliary efflux in addition to the expected inhibition in OATP1B activity.

**Materials and Methods**

Study design

The study was approved by the local research ethics committee and prospectively recruited 10 healthy volunteers, who gave informed consent. Exclusion criteria beyond standard MRI exclusions were previous history of liver or kidney disease and regular prescribed medication, including oral contraceptives.

After screening and consenting, each subject underwent two study visits on different days, 2-4 weeks apart (Fig 1). The visits were identical except for an extra blood sample and oral administration of 600 mg rifampicin on day 2, one hour before the start of MRI scanning. Timing of administration was based on simulations aiming for maximum inhibition at the start of DGE-MRI [Scotcher 2021, Melillo 2023].

Since biliary excretion of gadoxetate after inhibition is slow, the measurement on each day was split over two different scans, separated by an hour where the subject left the scanner and could rest. In each of the two scans, DGE-MRI was performed continuously for 50 minutes. Participants were allowed to eat and drink before the study in moderation. Blood samples were taken before and after each scan for standard liver function tests (LFT’s).

The study design included a gadoxetate dose escalation strategy to ensure that no higher gadoxetate dose was used than strictly necessary. Initial dosage was one eighth of a standard clinical dose in each of the four scans. The data were reviewed after two participants completed both visits and investigators were allowed to increment the dose at this stage if this was deemed necessary to improve the data integrity.

MRI protocol

MRI was performed in a single site on a 3T Siemens Prisma. The protocol included localizers, high-resolution T2-weighted axial and coronal scans, transverse T2\* mapping, transverse T1-mapping with a modified Look-Locker sequence (MOLLI), B1-mapping, coronal variable flip angle T1-mapping (VFA) and coronal free-breathing DGE-MRI. The first MRI of each day concluded with a post-contrast transverse MOLLI T1 measurement. T2\*, B1 and VFA T1 were acquired for secondary objectives and are not reported in this paper.

MOLLI was acquired with 5 slices, 5 mm thick, FA=12 deg, TR/TE = 423/2.75 ms, 7(2)4 scheme with simulated ECG trace set at 80 bpm. The DGE sequence was a 3D FLASH with a time resolution of 2.3 sec, 36 slices, FOV 450 mm, TR 4.93 ms, TE 1.23 ms, flip angle 15 deg, voxel size 4.7x4.7x5 mm3, base resolution 96x96 and 3D GRAPPA factor 2. Gadoxetate was injected at 1 mL/sec and followed by a 20 mL saline flush at the same rate. Injection was performed 5 mins after the start of the DGE-MRI sequence on the first scan, and after 10 mins on the second.

MRI processing

DICOM images were anonymised, exported and uploaded on a central server and further analysed using 21CFR11-compliant software, Voxelflow (Bioxydyn, Manchester UK). The axial MOLLI T1 maps calculated by the scanner software (syngo MR E11) were manually segmented to extract median whole liver and aorta T1 values. Whole liver regions were drawn in parenchyma avoiding major blood vessels. Breathing motion and patient positioning between scans was corrected using 3D rigid and deformable motion correction [Avants2011]. The whole liver and aorta were segmented manually on a peak enhancement map. Signal-time curves for both scans were exported as csv files for quantification in separate python scripts.

DGE-MRI modelling

DGE-MRI was performed with the open-source python package dcmri.org [Sourbron2025] using the function AortaLiver2scan. Source data have been published for independent replication [TRISTAN2025] and the analysis is replicated in the examples section of dcmri.org.

AortaLiver2scan models gadoxetate concentrations in aorta using a simplified whole-body model of the circulation. Aorta concentrations are subsequently used as input to a 2-site liver model with uptake into hepatocytes from an extracellular space, and excretion into bile. Uptake and excretion rates khe and kbh were varied linearly over time to allow for changes in liver function during the day. Concentrations were converted to longitudinal relaxation rates using the precontrast MOLLI T1 and literature values for the gadoxetate relaxivities in liver and in blood at 3T [Ziemian 2021]. Relaxation rates were converted to signals using the standard model for a spoiled gradient echo sequence in the steady state [Buxton 1987]. The model was fitted to the signals using least-squares methods, with default initial values and constraints for all parameters.

Data analysis

Effect sizes were calculated for each participant and each parameter as the relative difference with baseline value. Mean values over all participants and 95% confidence intervals on the mean (95%CI) were calculated for all parameters at baseline and after rifampicin, and for their effect sizes. A two-sided paired t-test was used to evaluate differences between baseline and rifampicin values. p<0.01 was considered significant. Effect sizes between parameters were compared using the t-statistic.

The primary outcome markers were the hepatocellular uptake rate khe and biliary excretion rate kbh, averaged over the duration of the acquisition. Other DGE-MRI markers were also tested for rifampicin effect as exploratory aims. For comparison with non-imaging pharmacokinetic studies, MRI-measured liver volumes were used to derive whole liver clearance (mL/min). For comparison between MRI and LFT’s, the pre-scan and post-scan LFT values were averaged.

**Results**

Ten volunteers (3 female, 7 male) were recruited and underwent the baseline scan (Table 1). LFT’s before the first scan verified that all participants had normal liver function, and that liver function had not changed between visits (table 2). No incidental imaging findings were noted for any of the 10 participants.

Eight volunteers completed all visits. In one volunteer, the gadoxetate at baseline was mistakenly administered at 1.25 times a standard clinical dose instead of 0.125 as prescribed. The volunteer was withdrawn from the study and followed up clinically, but no adverse events were reported. Another subject could not complete the second visit because of difficulties in accessing a vein.

Following the staged design, data from the first two complete baseline/rifampicin studies were reviewed before continuing. At this point it was decided to escalate the gadoxetate dose per scan from 1/8th to 1/4th of a clinical dose to boost the enhancement-to-noise level. Data for both doses were combined for analysis.

Visual inspection of signals (Fig 2) show that the model fits the data well and reveals clear differences after rifampicin, consistent with reduced uptake and delayed excretion. At baseline the extracellular phase of the signal is masked by a rapid uptake which peaks after approximately 25 minutes (Fig 2a). After rifampicin, uptake is much reduced with no obvious hepatobiliary peak concentration, revealing the extracellular phase (Fig 2b). The second injection shows a similar pattern as the first. No qualitative differences between baseline and rifampicin data were observed in the aorta signal (Fig 2 c, d).

Table 3 shows numerical results for all liver biomarkers. On average, rifampicin reduces the hepatocellular uptake rate of khe by 93% (95%CI 91-95%, p<0.001). The biliary excretion rate kbh reduces by only 50% and the effect is more variable (95%CI 8-92%, p=0.004). The liver blood clearance shows the strongest response (t = 15); most semi-quantitative measures also show a clear effect (4.5 < t < 12).

Table 4 shows results for all LFT’s. Bilirubin shows a significant change of 82% (95%CI 30-134, p=0.001), but the effect is substantially weaker than most MRI biomarkers (t = -5.4). The other LFT’s show no systematic effect.

Figure 3 shows the individual results for the primary outcomes. Both rate constants reduce in each subject with the exception of one kbh value which is low at baseline (Fig3 c, red line). Visual assessment confirms atypical kinetics in that subject showing no peak enhancement within the acquisition window (not shown).

Figure 4 shows the individual results for all biomarkers that respond to rifampicin, confirming consistent response in all individuals except for the aforementioned k(bh) value. The figure also shows the strong systematic response of simple semi-quantitative measures such as R1 at 45 min.

Correlation analysis at baseline (Fig 5) show 3 distinct clusters in the MRI liver biomarkers. The hepatocellular markers k(he), k(bh) and Cl are a distinct group but are not correlated; the semi-quantitative markers and the extracellular markers are all strongly correlated within the cluster. Some of the LFT’s correlate with extracellular volume but only conjugated bilirubin is correlated with k(he).

The same clusters remain visible when comparing the changes in the biomarkers after rifampicin (Fig 6). Changes in uptake and excretion rates are not significantly correlated. LFT changes show some correlations with semi-quantitative markers but not with hepatocellular markers.

**Discussion**

Effective management of liver-mediated DDI risk in drug development and in clinical practice requires non-invasive methods to assess the effects of drugs on hepatocellular transport function. This is particularly important if modulation of transporters causes different drug exposure in the blood/plasma and liver. The aim of this study was to investigate if liver uptake and excretion rates of gadoxetate, as measured with MRI in healthy volunteers, can detect changes caused by rifampicin, a known inhibitor of OATP1B1/MRP2 transporters. Results showed a strong and consistent reduction in liver uptake and biliary excretion of gadoxetate after rifampicin single dose administration, indicating a potential role of these imaging biomarkers in drug safety assessment.

The result is consistent with findings using similar imaging biomarkers in rats [Melillo 2023] where rifampicin caused a 90% reduction in liver uptake and 43% in biliary excretion, in close agreement with our observations in healthy volunteers. Preclinical study also found a similar effect of cyclosporin (OATP1B1/MRP2 inhibitor) on gadoxetate), whereas other test drugs showed marginal effect on excretion (pioglitazone, asunaprevir). Such experiments with multiple test drugs have not yet been done in humans, but the current proof of concept using rifampicin provides a strong rationale for more in-depth validation in human subjects.

Our results provide insights in the use of MRI for evaluation of transporter DDIs where changes in liver exposure differ relative to blood. Inhibition of intracellular uptake via OATP1B1 is stronger than the inhibition of biliary clearance via MRP2, a distinction that cannot be made with assays based on blood clearance. Inhibition of biliary clearance is also more variable compared to uptake – indicating the need for a personalised approach to DDI prediction. Finally, inhibition of uptake and excretion are uncorrelated, confirming the importance of accessing both.

The effect of rifampicin can also be detected from bilirubin levels using routine LFTs. The effect is substantially more variable than with the MRI assay and uncorrelated to the effect on uptake and excretion – reducing the utility of LFTs for DDI assessment.

An important property of the gadoxetate-MRI assay is that it specifically probes potential inhibitors of OATP1B1 and MRP2, allowing it to positively confirm inhibition of these transporters. In contrast, this also means it cannot detect specific inhibition of other transporters, such as the bile salt export pump (BSEP). Inhibition of BSEP is important because genetically inherited defects in BSEP expression have been found to cause severe cholestatic liver injury and because many drugs that cause human idiosyncratic drug-induced liver injury inhibit BSEP activity [Wagner 2009]. The latest ICH M12 guidance recommends testing of BSEP inhibition on a case-by-case basis.

The results have also demonstrated that the effect of rifampicin can be detected using much simpler MRI biomarkers, in particular R1 at 45 minutes after injection. These biomarkers do not require elaborate modelling or image analysis and they are available via in-line postprocessing of product sequences on most scanners. Similar approaches have been studied in chronic liver disease [Obmann 2022]. However, they do not distinguish between uptake and excretion, they cannot be compared to non-imaging assays, and their numerical values depend on experimental variables. This limits their utility for DDI assessment but for other diagnostic questions a semi-quantitative measure may well be sufficient.

The assay used in this study was designed for early-stage drug development, where it is intended to inform critical decisions on whether a novel drug is likely to cause a DDI risk and/or for dose selection/optimisation in later clinical trials. Elaborate designs such as the 2-scan protocol deployed in this study are realistic at this stage of drug development, but they are unlikely to be applicable to routine clinical practice. This precludes application of the method for diagnostic questions involving liver function in chronic liver disease [Poetter-Lang 2020]. However, the distinction between uptake and excretion is arguably less critical in a clinical setting, and uptake alone can be measured reliably with substantially shorter protocols [Sourbron2012].

Study limitations: analysis of the data revealed some variations in liver function during the course of the experiment, particularly between the first and second scan on the same day. The study design did not standardize preparation of the participants by controlled diet or fluid intake before the visit, and participants were not given any dietary instructions between the two scans. It is not clear whether differences in intake explain the variability observed, but it appears prudent for future validation studies to include some level of standardization in the diet and the timing of the scan.

In conclusion, this study showed that gadoxetate liver uptake and biliary excretion rates are promising biomarkers to investigate inhibition of OATP1B1/MRP2 transporters in humans, and predict liver exposure to victim drugs. Future studies should investigate whether these findings can be replicated with a wider range of test drugs and evaluate the effect of drug-mediated inhibition in patients with impaired liver function.

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**Figures**

A diagram of a patient's schedule

Description automatically generated with medium confidence

**Figure 1**: Flow diagram showing the study design and assessments performed at each visit. Visit 0 was a screening visit to assess eligibility for the study, take informed consent and collect key data. Visit 1 was the baseline visit, no more than 60 days after consent, and involved two MRI scans at least 2 hours apart, and blood tests before and after the scans. The post-treatment visit 2 took place between 2 and 4 weeks after the baseline visit, and involved blood sampling before oral rifampicin administration, and then after 1 hour a repeat of the same protocol performed at visit 1.

A group of graphs showing different types of data

Description automatically generated

**Figure 2**: Signal-time curves for the two scans performed on the same day for one volunteer at baseline (a, c) and after rifampicin single dose of 600 mg (b, d). The top row shows gadoxetate data in the liver (blue, a, b), the bottom row shows the data in the aorta (red c, d). In each case the model fit is superposed on the data as a smooth continuous line. The MOLLI T1-values are fed through the signal model and plotted as part of the quality control process but are not used in the actual model fit.

A diagram of a graph

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**Figure 3**. Rifampicin effect on the primary endpoints k(he) (hepatocellular uptake rate) and kbh (hepatocellular excretion rate) across the population. Box plots on the left show the relative and absolute effect size across the population (absolute effect sizes for k(bh) have been scaled with a factor 10 to improve visualisation). Line plots on the right show individual values at baseline and after single dose of rifampicin, with each line representing an individual volunteer.

A diagram of a graph

AI-generated content may be incorrect.

**Figure 4**. Subject-level rifampicin effect for all parameters that show a significant change in the mean value (p<0.01). The top row shows the difference between rifampicin and baseline relative to the standard error of the difference (T-value), with LFT markers in green, hepatocellular markers in blue, and semi-quantitative markers in red. The bottom row shows the individual changes for the corresponding biomarkers. Explicit names for the biomarkers can found in tables 3, 4.

A screenshot of a graph

AI-generated content may be incorrect.

**Figure 5**. Cluster plot of correlations between liver biomarkers at baseline. The vertical axis for each panel shows the MRI liver biomarkers. The horizontal axis shows the MRI liver biomarkers (left panel) and LFT’s (right panel). Negative correlations are shown in blue and positive correlations in red, and significant correlations (p<0.01) are marked with (\*). Explicit names for the biomarkers can found in tables 3, 4.

A screenshot of a graph

AI-generated content may be incorrect.

**Figure 6**. Cluster plot of correlation coefficients between changes (rifampicin – baseline) in liver biomarkers. The vertical axis in each panel shows the change in MRI liver biomarkers. The horizontal axis shows the change in MRI liver biomarkers (left panel) and change in LFT’s (right panel). Negative correlations are shown in blue and positive correlations in red, and significant correlations (p<0.01) are marked with (\*). Explicit names for the biomarkers can found in tables 3, 4.

**Tables**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| *Parameter* | *mean* | *std* | *min* | *25%* | *50%* | *75%* | *max* |
| Age (yr) | 32 | 8.3 | 21 | 27 | 32 | 35 | 51 |
| BMI (kg/m2) | 24 | 3.5 | 19 | 23 | 24 | 27 | 30 |
| Height (cm) | 174 | 8.1 | 163 | 168 | 176 | 180 | 188 |
| Weight (kg) | 73 | 7.6 | 57 | 73 | 75 | 76 | 83 |
| Creatinine (umol/L) | 77 | 13 | 58 | 67 | 80 | 87 | 98 |
| Blood urea nitrogen (mmol/L) | 5.8 | 1.5 | 3.4 | 5 | 5.8 | 7 | 7.8 |
| ALP (U/L) | 68 | 26 | 39 | 53 | 60 | 67 | 118 |
| ALT (U/L) | 21 | 8.2 | 14 | 16 | 18 | 23 | 42 |
| Albumin (g/L) | 42 | 2.8 | 37 | 42 | 43 | 43 | 46 |
| Bilirubin (umol/L) | 13 | 4.2 | 6.5 | 11 | 13 | 14 | 23 |
| Conjugated Bilirubin (umol/L) | 4.7 | 2.1 | 3 | 3.5 | 4.2 | 5 | 10 |
| Conjugated/total bilirubin (%) | 36 | 6.4 | 25 | 33 | 36 | 39 | 47 |

**Table 1**: Demographics and clinical characteristics of the 10 participants recruited into the study. 3 of the participants (30%) were female.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| *Parameter* | *Visit 1* | *Visit 2* | *Diff* | *p-value* |
| ALP (U/L) | 68 (40) | 69 (54) | 1.8 (23) | 0.69 |
| ALT (U/L) | 22 (19) | 25 (19) | 3.6 (9.4) | 0.07 |
| Albumin (g/L) | 44 (4.1) | 44 (5.9) | -0.6 (6.3) | 0.6 |
| Bilirubin (umol/L) | 12 (8.5) | 11 (9.3) | -0.8 (12) | 0.73 |
| Conjugated Bilirubin (umol/L) | 4.8 (3.7) | 4.6 (4.2) | -0.1 (5.1) | 0.89 |
| Conjugated/total bilirubin (%) | 39 (11) | 37 (9.1) | -3.0 (16) | 0.36 |

**Table 2**: Liver function tests (LFT) at the start of each visit showing no systematic difference in liver function between visits. For each parameter the table shows mean values (95% on the mean) at the start of visit 1 (Baseline) and visit 2 (Rifampicin), the difference between both and the p-value for the paired t-test.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| *Short name - parameter (units)* | *Type* | *Baseline* | *Rifampicin* | *Effect (%)* | *t* | *p* |
| **k(he) - Hepatocellular uptake rate (mL/min/100cm3)** | **HC** | **30 (5.3)** | **2.2 (0.6)** | **-93 (2.5)** | **11** | **<0.001** |
| **k(bh) - Biliary excretion rate (mL/min/100cm3)** | **HC** | **2.3 (0.6)** | **0.78 (0.34)** | **-50 (42)** | **4.2** | **0.004** |
| **Cl - Liver blood clearance (mL/min)** | **HC** | **272 (30)** | **20 (4)** | **-92 (2.5)** | **15** | **<0.001** |
| **RES - Relative signal enhancement at 20 min (%)** | **SQ** | **53 (12)** | **6.9 (1.8)** | **-87 (2.0)** | **8.6** | **<0.001** |
| **RER1 - Relative R1 enhancement at 20 min (%)** | **SQ** | **64 (14)** | **8.9 (1.5)** | **-86 (1.9)** | **8.2** | **<0.001** |
| **AUC(30) - Area under the curve at 30 min (mM\*sec)** | **SQ** | **148 (32)** | **26 (4.3)** | **-82 (2.8)** | **8.5** | **<0.001** |
| **R1(45) - R1 at 45 min (1/sec)** | **SQ** | **1.9 (0.1)** | **1.4 (0.08)** | **-26 (3.2)** | **12** | **<0.001** |
| **DR1(45) - R1 change at 45 min (1/sec)** | **SQ** | **0.61 (0.1)** | **0.14 (0.03)** | **-77 (5.8)** | **8.7** | **<0.001** |
| **R1(2) - R1 at scan 2 (1/sec)** | **SQ** | **1.5 (0.1)** | **1.3 (0.07)** | **-12 (4.6)** | **4.5** | **0.003** |
| DR1(2) - R1 change at scan 2 (1/sec) | SQ | 0.24 (0.11) | 0.08 (0.02) | -31 (76) | 3.1 | 0.02 |
| v(e) - Extracellular volume (mL/100cm3) | EC | 16 (7) | 22 (3.4) | 261 (410) | -1.5 | 0.17 |
| MTT(e) - Extracellular mean transit time (sec) | EC | 36 (13) | 43 (7.7) | 130 (210) | -0.9 | 0.42 |
| TTD(e) - Extracellular transit time dispersion (%) | EC | 64 (19) | 71 (4.8) | 90 (170) | -0.7 | 0.52 |

**Table 3**. Drug effect on the liver biomarkers including, in the top two rows, the primary outcome markers khe (hepatocellular uptake rate) and kbh (biliary excretion rate). The first column is the type of biomarker (HC = Hepatocellular, SQ = semi-quantitative, EC = extracellular). The other columns show mean (95% CI on the mean) values at baseline and after rifampicin administration, their relative effect size as well as the t-statistic and p-value for a paired t-test. Biomarkers that showed a significant change after rifampicin (p<0.01) are highlighted in bold.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| *Short name - parameter (units)* | *Baseline* | *Rifampicin* | *Effect (%)* | *t* | *p* |
| **Bil - Bilirubin (umol/L)** | **13 (3.2)** | **22 (2.8)** | **82 (52)** | **-5.4** | **0.001** |
| Cbil - Conjugated Bilirubin (umol/L) | 5.0 (1.5) | 13 (6.2) | 146 (57) | -3.1 | 0.02 |
| Alb - Albumin (g/L) | 43 (1.9) | 41 (1.8) | -4.1 (2.9) | 2.8 | 0.03 |
| CTBil - Conjugated/total bilirubin (%) | 37 (4.5) | 45 (5.3) | 23 (21) | -2 | 0.09 |
| ALT (U/L) | 21 (6.1) | 24 (6.5) | 17 (23) | -1.6 | 0.16 |
| ALP (U/L) | 74 (18) | 74 (21.0) | -0.54 (11) | 0 | 0.99 |

**Table 4**: Drug effect on LFT’s, showing mean (95% CI on the mean) values at baseline and after rifampicin administration, their relative effect size (%) as well as the t-statistic and p-value for a paired t-test. Biomarkers that showed a significant change after rifampicin (p<0.01) are highlighted in bold.