Gothenburg patient study

rifampicin (all results)

D2.07 - Internal report

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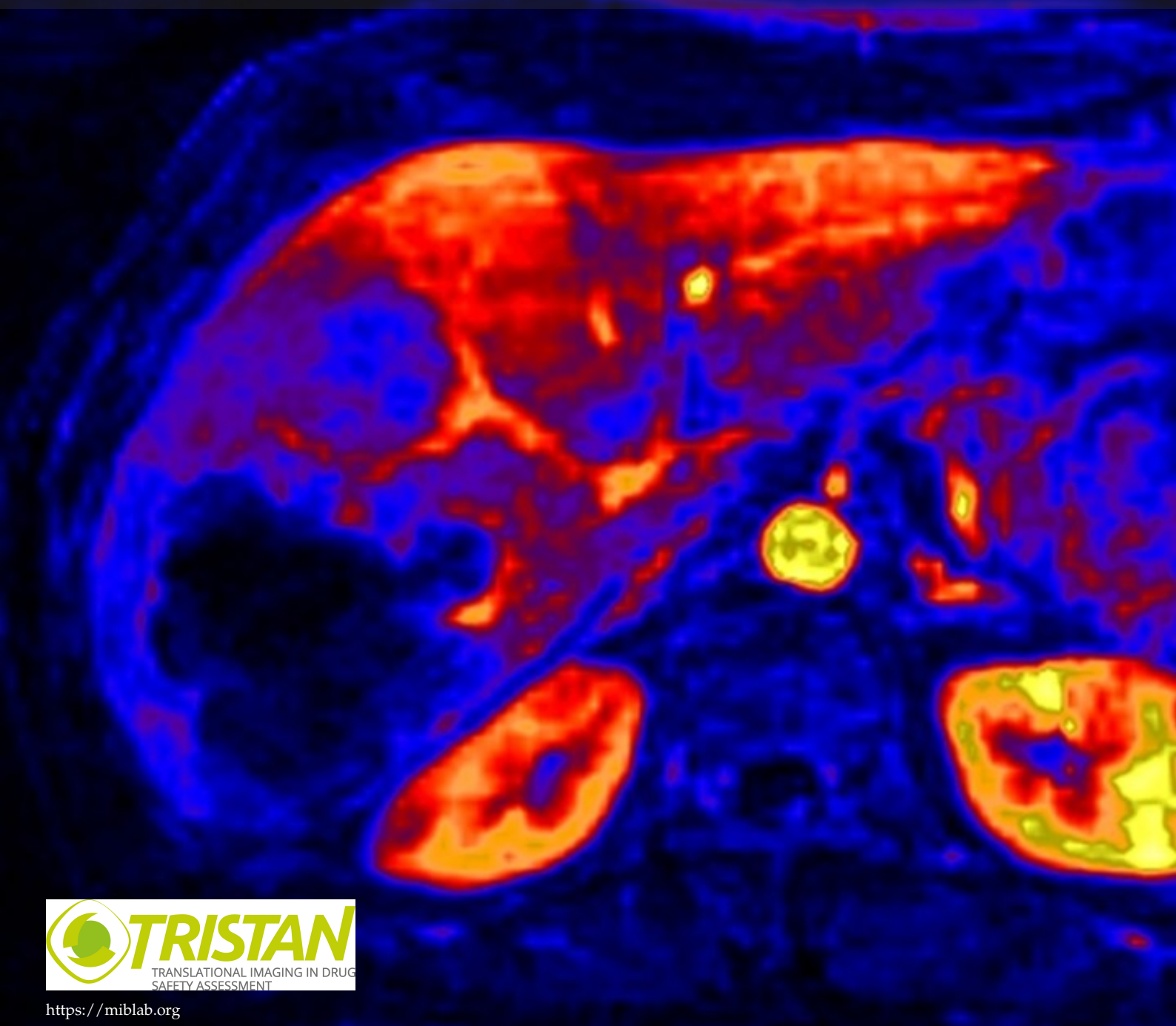

TRISTAN
TRANSLATIONAL IMAGING IN DRUG SAFETY ASSESSMENT

Gothenburg patient study

rifampicin (all results)

by

miblab.org

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TRISTAN
TRANSLATIONAL IMAGING IN DRUG SAFETY ASSESSMENT

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Two-scan results

1.1. Data summary

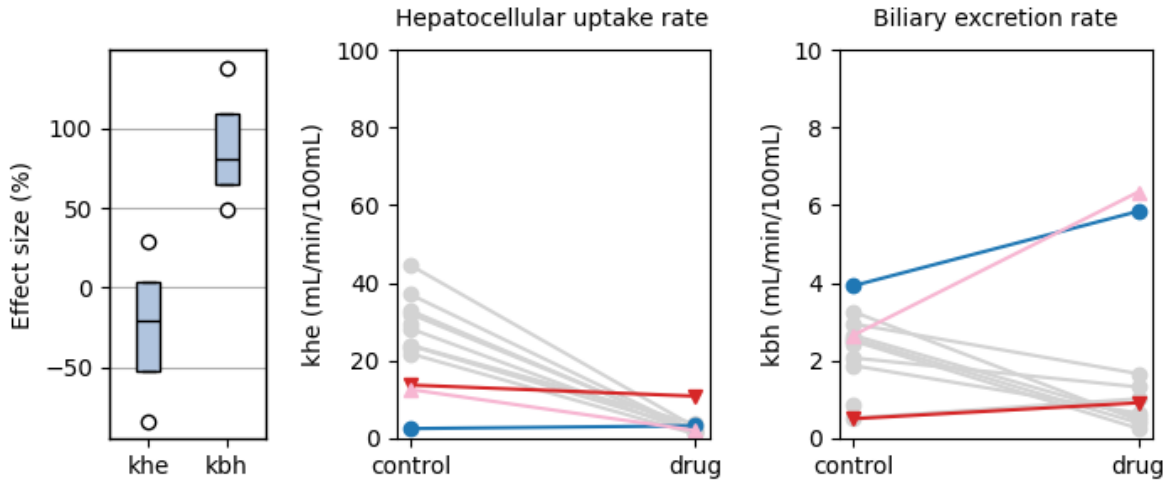

Figure 1.1: Effect size (%) on hepatocellular uptake (k_he, left) and biliary excretion (k_bh, right) of gadoxetate. The boxplot shows median, interquartile range and 95 percent range. The line plots show individual values for hepatocellular uptake (k_he, middle) and biliary excretion (k_bh, right) of gadoxetate of the control (left of plot) and treatment (right of plot). Grey lines are healthy controls with rifampicin injection.

parameter	count	mean	std	min	25%	50%	75%	max
khe effect size (%)	3.0	-25.2	56.3	-83.6	-52.2	-20.8	4.0	28.7
khe control (mL/min/100cm3)	3.0	9.62	6.17	2.53	7.57	12.6	13.17	13.74
khe drug (mL/min/100cm3)	3.0	5.4	4.78	2.07	2.67	3.26	7.07	10.88
kbh effect size (%)	3.0	89.1	45.4	48.7	64.6	80.5	109.4	138.3
kbh control (mL/min/100cm3)	3.0	2.37	1.73	0.51	1.58	2.66	3.29	3.93
kbh drug (mL/min/100cm3)	3.0	4.36	3.0	0.92	3.38	5.84	6.09	6.34

Table 1.1: Effect size and absolute values of hepatocellular uptake (k_he) and biliary excretion (k_bh) of gadoxetate

1.2. Liver biomarkers

Biomarker	p-value	Bayes Factor	Odds Ratio
AUC for Cl (0-35min)	0.25099	0.92	4.79
AUC for Cl (0-inf)	0.3815	0.7	3.97
Biliary excretion rate	0.16853	1.19	0.23
Biliary tissue excretion rate	0.21172	1.03	0.27
Extracellular dispersion	0.09444	1.73	4.09
Extracellular mean transit time	0.99189	0.47	0.99
Final biliary excretion rate	0.2935	0.83	0.2
Final hepatocellular uptake rate	0.58834	0.55	2.52
Hematocrit			
Hepatocellular mean transit time	0.1663	1.2	1.89
Hepatocellular tissue uptake rate	0.9649	0.47	1.07
Hepatocellular uptake rate	0.33144	0.77	4.0
Initial biliary excretion rate	0.96252	0.47	0.9
Initial hepatocellular uptake rate	0.24237	0.94	5.81
Liver T1-MOLLI at 45min	0.98716	0.47	1.01
Liver T1-MOLLI at baseline	0.07944	1.93	3.61
Liver T1-MOLLI at scan 2	0.54424	0.57	0.74
Liver blood clearance	0.35827	0.73	2.55
Liver extracellular volume fraction	0.13135	1.4	10.13
RE for R1l at 20min	0.22432	0.99	8.14
RE for Sl at 20min	0.2206	1.0	7.44

Table 1.2: Results of a pairwise comparison testing for differences in liver biomarkers between control and treatment. The results are ranked by their p-value, with most significant differences at the top of the list.

Biomarker	Units	control	drug	change (%)
AUC for Cl (0-35min)	mM*sec	54.3 (33.0)	34.8 (15.0)	-25.7 (44.0)
AUC for Cl (0-inf)	mM*sec	289.0 (420.0)	86.7 (67.0)	-36.7 (64.0)
Biliary excretion rate	mL/min/100cm3	2.37 (2.0)	4.36 (3.4)	89.1 (51.0)
Biliary tissue excretion rate	mL/min/100cm3	3.23 (2.4)	5.52 (4.4)	64.8 (51.0)
Extracellular dispersion	%	84.6 (5.6)	79.7 (8.3)	-5.85 (3.9)
Extracellular mean transit time	sec	52.4 (9.4)	52.5 (7.4)	1.02 (15.0)
Final biliary excretion rate	mL/min/100cm3	3.38 (3.7)	5.46 (0.78)	593.0 (1100.0)
Final hepatocellular uptake rate	mL/min/100cm3	11.1 (9.4)	7.04 (8.8)	-1.57 (90.0)
Hematocrit	%	45.0 (0.0)	45.0 (0.0)	0.0 (0.0)
Hepatocellular mean transit time	min	55.3 (64.0)	37.7 (48.0)	-36.5 (17.0)
Hepatocellular tissue uptake rate	mL/min/100cm3	28.8 (16.0)	28.1 (26.0)	17.6 (97.0)
Hepatocellular uptake rate	mL/min/100cm3	9.62 (7.0)	5.4 (5.4)	-25.2 (64.0)
Initial biliary excretion rate	mL/min/100cm3	4.3 (2.6)	4.47 (3.9)	74.5 (220.0)
Initial hepatocellular uptake rate	mL/min/100cm3	8.1 (6.9)	3.77 (2.0)	-39.5 (43.0)
Liver T1-MOLLI at 45min	sec	0.793 (0.14)	0.793 (0.13)	0.33 (10.0)
Liver T1-MOLLI at baseline	sec	0.983 (0.12)	0.916 (0.089)	-6.57 (3.5)
Liver T1-MOLLI at scan 2	sec	0.807 (0.16)	0.827 (0.11)	3.25 (8.1)
Liver blood clearance	L/min	0.107 (0.089)	0.0677 (0.084)	-20.0 (68.0)
Liver extracellular volume fraction	mL/100cm3	30.6 (11.0)	20.3 (6.8)	-32.1 (16.0)
RE for R1l at 20min	%	22.2 (10.0)	14.0 (4.4)	-28.8 (37.0)
RE for Sl at 20min	%	18.9 (9.1)	12.4 (2.0)	-26.7 (30.0)

Table 1.3: Mean values along with their 95 percent confidence intervals for all liver biomarkers of the control and treatment visit. The last column shows the relative change at the treatment visit. The results are ranked by their p-value, with most significant differences at the top of the list.

1.3. Systemic biomarkers

Biomarker	p-value	Bayes Factor	Odds Ratio
AUC for Cb (0-35min)	0.23873	0.95	0.29
AUC for Cb (0-inf)	0.99702	0.47	1.01
Body extraction fraction	0.85592	0.48	0.66
Cardiac output	0.93019	0.47	0.82
Heart-lung dispersion	0.9169	0.47	0.87
Heart-lung mean transit time	0.94174	0.47	1.12
Organs blood mean transit time	0.07746	1.96	259.84
Organs extraction fraction	0.6145	0.54	2.05
Organs extravascular mean transit time	0.44094	0.64	4.86
RE for R1b at 20min	0.29105	0.84	0.29
RE for Sb at 20min	0.35362	0.74	0.13

Table 1.4: Results of a pairwise comparison testing for differences in systemic biomarkers between control and treatment visit. The results are ranked by their p-value, with most significant differences at the top of the list.

Biomarker	Units	control	drug	change (%)
AUC for Cb (0-35min)	mM*sec	29.9 (7.8)	37.6 (16.0)	23.2 (26.0)
AUC for Cb (0-inf)	mM*sec	58.4 (29.0)	58.3 (38.0)	19.9 (86.0)
Body extraction fraction	%	4.24 (3.4)	4.97 (3.8)	183.0 (450.0)
Cardiac output	L/min	9.93 (1.0)	10.1 (1.6)	2.65 (27.0)
Heart-lung dispersion	%	42.4 (14.0)	43.2 (8.9)	7.01 (33.0)
Heart-lung mean transit time	sec	15.0 (2.5)	14.7 (7.5)	-1.44 (46.0)
Organs blood mean transit time	sec	31.2 (0.58)	23.5 (4.0)	-24.5 (14.0)
Organs extraction fraction	%	17.8 (0.85)	16.5 (4.8)	-7.38 (23.0)
Organs extravascular mean transit time	min	6.38 (4.4)	3.86 (1.5)	-23.5 (51.0)
RE for R1b at 20min	%	20.4 (6.4)	27.1 (15.0)	29.8 (44.0)
RE for Sb at 20min	%	14.9 (3.9)	26.1 (16.0)	93.8 (160.0)

Table 1.5: Mean values along with their 95 percent confidence intervals for all systemic biomarkers at the control and and treatment visit. The last column shows the relative change at the treatment visit. The results are ranked by their p-value, with most significant differences at the top of the list.

1.4. Comparison to reference values

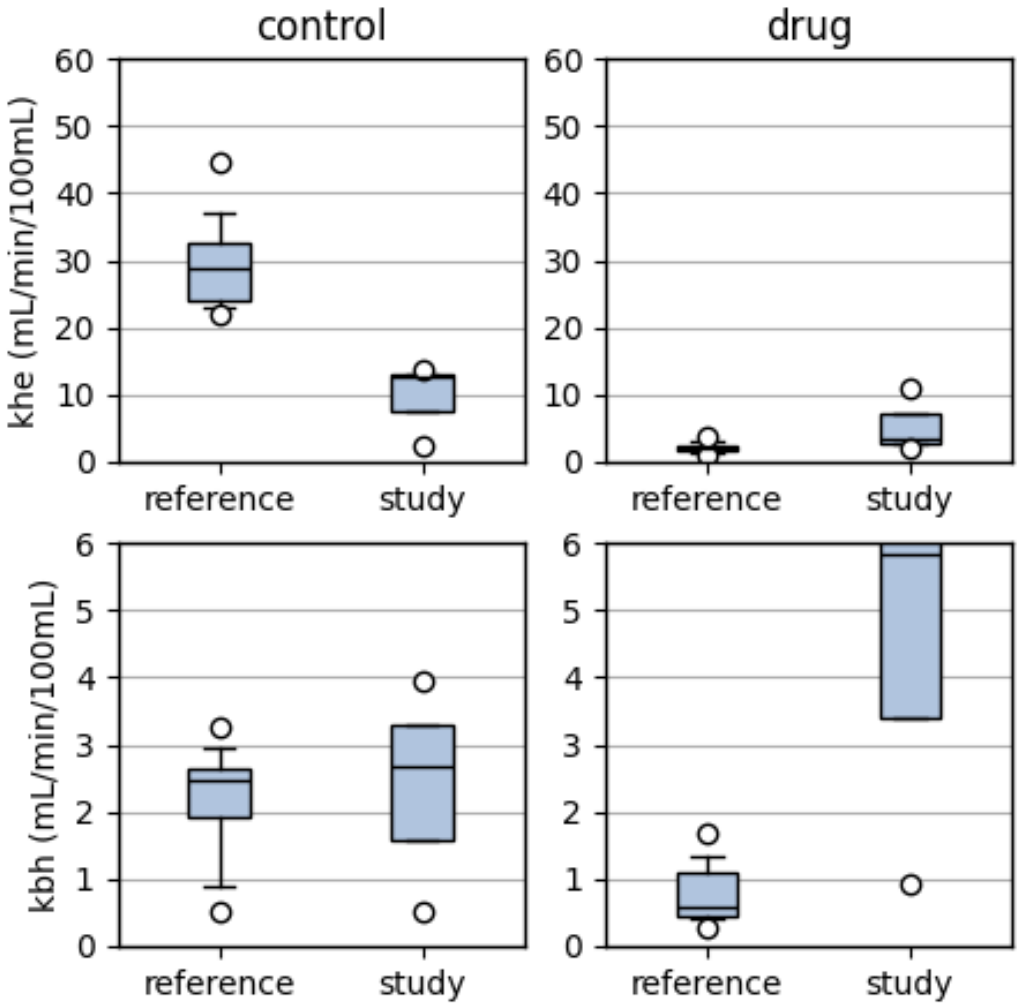

Figure 1.2: Comparison to reference values in healthy volunteers treated with the drug and under control conditions.

1.4.1. Control

Biomarker	Units	p-value	Bayes Factor	Power
Initial hepatocellular uptake rate	mL/min/100cm3	0.0033	109.82	0.99
RE for Sl at 20min	%	0.00351	10.25	0.49
Hepatocellular uptake rate	mL/min/100cm3	0.01003	37.58	0.98
RE for R1l at 20min	%	0.01166	4.71	0.34
AUC for Cl (0-35min)	mM*sec	0.02077	3.13	0.28
Liver T1-MOLLI at 45min	sec	0.02492	11.26	0.92
Extracellular dispersion	%	0.05792	1.65	0.19
Final hepatocellular uptake rate	mL/min/100cm3	0.06083	1.84	0.31
Extracellular mean transit time	sec	0.06117	1.77	0.28
Liver blood clearance	L/min	0.06271	6.11	0.98
Liver T1-MOLLI at baseline	sec	0.08246	4.3	0.99
Liver extracellular volume fraction	mL/100cm3	0.12674	1.45	0.42
Liver T1-MOLLI at scan 2	sec	0.13938	1.39	0.44
AUC for Cl (0-inf)	mM*sec	0.20518	0.88	0.15
Hepatocellular tissue uptake rate	mL/min/100cm3	0.20952	0.84	0.1
Initial biliary excretion rate	mL/min/100cm3	0.31052	0.81	0.44
Biliary tissue excretion rate	mL/min/100cm3	0.69064	0.54	0.09
Final biliary excretion rate	mL/min/100cm3	0.70083	0.53	0.09
Biliary excretion rate	mL/min/100cm3	0.8651	0.51	0.06
Hepatocellular mean transit time	min	0.94183	0.5	0.05
Hematocrit	%			

Table 1.6: Results of a pairwise comparison testing for differences in liver biomarkers between this study and healthy reference data, under control conditions.

Biomarker	Units	p-value	Bayes Factor	Power
Cardiac output	L/min	0.08831	1.3	0.17
Organs blood mean transit time	sec	0.23847	0.79	0.09
Body extraction fraction	%	0.29053	0.78	0.19
AUC for Cb (0-35min)	mM*sec	0.45341	0.6	0.07
Heart-lung dispersion	%	0.60745	0.55	0.08
Organs extraction fraction	%	0.71562	0.52	0.05
Heart-lung mean transit time	sec	0.81435	0.51	0.05
AUC for Cb (0-inf)	mM*sec	0.84708	0.51	0.05
Organs extravascular mean transit time	min	0.85213	0.51	0.06
RE for Sb at 20min	%	0.935	0.5	0.05
RE for R1b at 20min	%	0.96006	0.5	0.05

Table 1.7: Results of a pairwise comparison testing for differences in aorta biomarkers between this study and healthy reference data, under control conditions.

1.4.2. Treatment

Biomarker	Units	p-value	Bayes Factor	Power
Final biliary excretion rate	mL/min/100cm3	0.00061	772.87	1.0
RE for Sl at 20min	%	0.00571	18.01	0.91
Hepatocellular mean transit time	min	0.03335	2.46	0.39
Liver T1-MOLLI at baseline	sec	0.11494	1.76	0.63
Extracellular mean transit time	sec	0.12781	1.14	0.23
RE for R1l at 20min	%	0.13782	1.65	0.72
Extracellular dispersion	%	0.14179	1.31	0.42
Biliary excretion rate	mL/min/100cm3	0.17366	1.5	0.89
Initial hepatocellular uptake rate	mL/min/100cm3	0.1792	1.3	0.66
Biliary tissue excretion rate	mL/min/100cm3	0.18129	1.43	0.87
Initial biliary excretion rate	mL/min/100cm3	0.30182	0.79	0.25
Hepatocellular tissue uptake rate	mL/min/100cm3	0.32239	0.81	0.49
Liver T1-MOLLI at scan 2	sec	0.34862	0.74	0.27
Hepatocellular uptake rate	mL/min/100cm3	0.36141	0.75	0.44
AUC for Cl (0-35min)	mM*sec	0.37139	0.72	0.29
Liver blood clearance	L/min	0.38271	0.72	0.43
Liver T1-MOLLI at 45min	sec	0.42268	0.67	0.21
Final hepatocellular uptake rate	mL/min/100cm3	0.42512	0.68	0.35
AUC for Cl (0-inf)	mM*sec	0.5571	0.58	0.13
Liver extracellular volume fraction	mL/100cm3	0.76794	0.53	0.06
Hematocrit	%			

Table 1.8: Results of a pairwise comparison testing for differences in liver biomarkers between this study and healthy reference data, under treatment conditions.

Biomarker	Units	p-value	Bayes Factor	Power
Organs extravascular mean transit time	min	0.03168	3.39	0.58
Cardiac output	L/min	0.07676	1.9	0.47
Organs blood mean transit time	sec	0.10947	1.18	0.19
Organs extraction fraction	%	0.45093	0.63	0.11
Heart-lung dispersion	%	0.51351	0.59	0.08
Body extraction fraction	%	0.51984	0.61	0.19
RE for Sb at 20min	%	0.55072	0.58	0.11
RE for R1b at 20min	%	0.63761	0.56	0.09
AUC for Cb (0-inf)	mM*sec	0.68467	0.54	0.07
AUC for Cb (0-35min)	mM*sec	0.81335	0.52	0.06
Heart-lung mean transit time	sec	0.95915	0.51	0.05

Table 1.9: Results of a pairwise comparison testing for differences in aorta biomarkers between this study and healthy reference data, under treatment conditions.

1.5. Case notes

1.5.1. Subject GOT-001

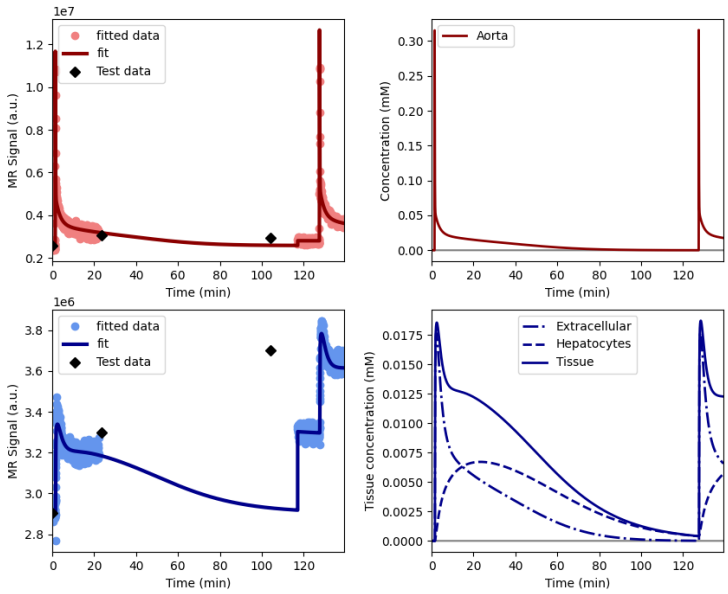

Figure 1.3: Signal-time curves for subject GOT-001 at the control visit.

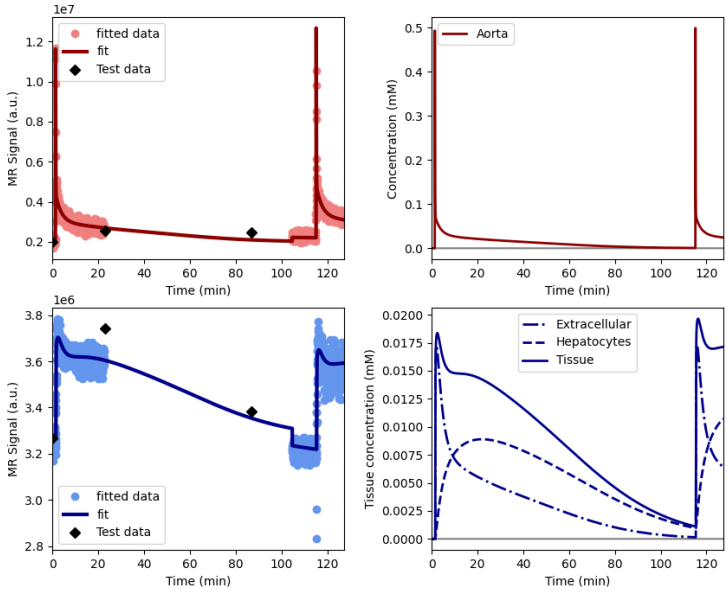

Figure 1.4: Signal-time curves for subject GOT-001 at the treatment visit.

Biomarker	Units	control	drug	change (%)
AUC for Cl (0-35min)	mM*sec	25.84	30.64	18.59
AUC for Cl (0-inf)	mM*sec	51.46	65.42	27.12
Biliary excretion rate	mL/min/100cm3	3.93	5.84	48.67
Biliary tissue excretion rate	mL/min/100cm3	4.91	6.81	38.66
Extracellular dispersion	%	83.13	75.77	-8.85
Extracellular mean transit time	sec	54.08	47.83	-11.56
Final biliary excretion rate	mL/min/100cm3	3.16	5.37	69.83
Final hepatocellular uptake rate	mL/min/100cm3	2.17	3.49	60.75
Hematocrit	%	45.0	45.0	0.0
Hepatocellular mean transit time	min	20.36	14.69	-27.88
Hepatocellular tissue uptake rate	mL/min/100cm3	12.67	22.94	81.01
Hepatocellular uptake rate	mL/min/100cm3	2.53	3.26	28.72
Initial biliary excretion rate	mL/min/100cm3	5.18	6.4	23.48
Initial hepatocellular uptake rate	mL/min/100cm3	2.89	3.03	4.65
Liver T1-MOLLI at 45min	sec	0.85	0.77	-10.15
Liver T1-MOLLI at baseline	sec	0.99	0.9	-8.95
Liver T1-MOLLI at scan 2	sec	0.86	0.84	-2.09
Liver blood clearance	L/min	0.02	0.03	35.71
Liver extracellular volume fraction	mL/100cm3	19.99	14.21	-28.89
RE for R1l at 20min	%	11.73	12.59	7.29
RE for Sl at 20min	%	10.28	10.69	3.98

Table 1.10: Values for liver of subject GOT-001

Biomarker	Units	control	drug	change (%)
AUC for Cb (0-35min)	mM*sec	37.82	52.95	39.99
AUC for Cb (0-inf)	mM*sec	59.75	93.55	56.57
Body extraction fraction	%	4.38	2.79	-36.24
Cardiac output	L/min	10.35	10.33	-0.27
Heart-lung dispersion	%	47.28	52.19	10.37
Heart-lung mean transit time	sec	15.82	8.26	-47.75
Organs blood mean transit time	sec	30.69	27.53	-10.3
Organs extraction fraction	%	17.16	12.23	-28.75
Organs extravascular mean transit time	min	4.52	5.35	18.44
RE for R1b at 20min	%	26.89	40.07	49.0
RE for Sb at 20min	%	11.54	41.54	260.15

Table 1.11: Values for aorta of subject GOT-001

1.5.2. Subject GOT-002

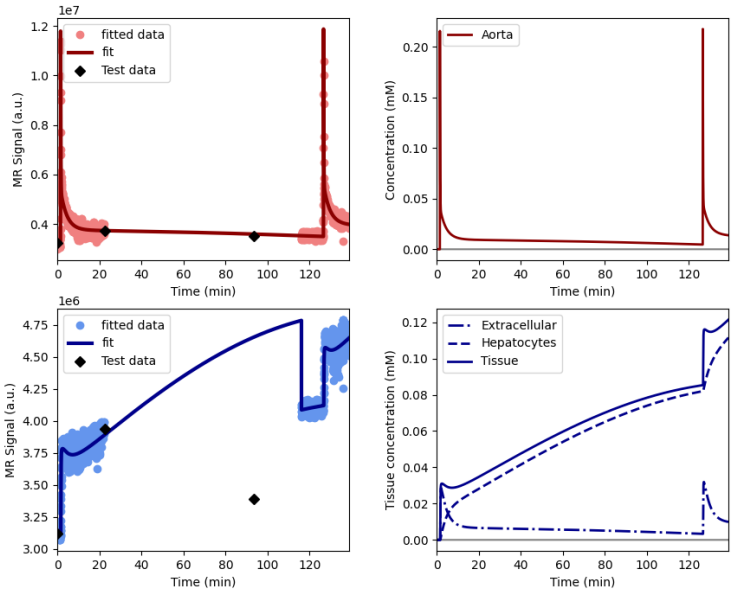

Figure 1.5: Signal-time curves for subject GOT-002 at the control visit.

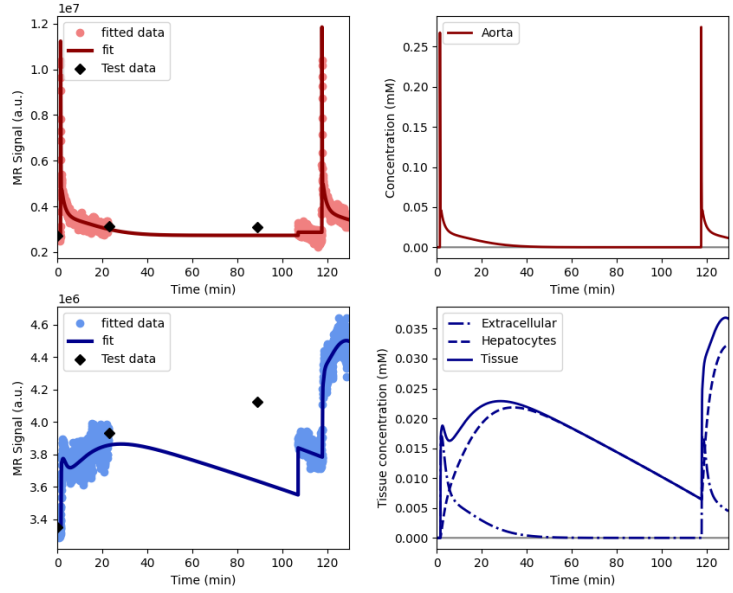

Figure 1.6: Signal-time curves for subject GOT-002 at the treatment visit.

Biomarker	Units	control	drug	change (%)
AUC for Cl (0-35min)	mM*sec	83.56	50.06	-40.1
AUC for Cl (0-inf)	mM*sec	717.83	154.03	-78.54
Biliary excretion rate	mL/min/100cm3	0.51	0.92	80.47
Biliary tissue excretion rate	mL/min/100cm3	0.83	1.15	38.38
Extracellular dispersion	%	80.59	75.25	-6.63
Extracellular mean transit time	sec	43.38	49.63	14.41
Final biliary excretion rate	mL/min/100cm3	0.26	4.81	1717.44
Final hepatocellular uptake rate	mL/min/100cm3	12.72	16.0	25.76
Hematocrit	%	45.0	45.0	0.0
Hepatocellular mean transit time	min	120.28	86.92	-27.73
Hepatocellular tissue uptake rate	mL/min/100cm3	35.26	53.33	51.24
Hepatocellular uptake rate	mL/min/100cm3	13.74	10.88	-20.82
Initial biliary excretion rate	mL/min/100cm3	6.07	0.51	-91.67
Initial hepatocellular uptake rate	mL/min/100cm3	14.76	5.76	-60.96
Liver T1-MOLLI at 45min	sec	0.66	0.69	5.95
Liver T1-MOLLI at baseline	sec	0.87	0.84	-3.06
Liver T1-MOLLI at scan 2	sec	0.65	0.72	11.38
Liver blood clearance	L/min	0.18	0.15	-12.51
Liver extracellular volume fraction	mL/100cm3	38.97	20.4	-47.65
RE for R1l at 20min	%	28.91	18.5	-36.02
RE for Sl at 20min	%	26.27	14.14	-46.16

Table 1.12: Values for liver of subject GOT-002

Biomarker	Units	control	drug	change (%)
AUC for Cb (0-35min)	mM*sec	25.05	24.22	-3.32
AUC for Cb (0-inf)	mM*sec	83.62	26.98	-67.74
Body extraction fraction	%	1.19	8.82	638.65
Cardiac output	L/min	10.55	8.52	-19.25
Heart-lung dispersion	%	51.47	39.13	-23.97
Heart-lung mean transit time	sec	16.66	21.47	28.83
Organs blood mean transit time	sec	31.72	22.14	-30.18
Organs extraction fraction	%	18.6	20.77	11.69
Organs extravascular mean transit time	min	10.85	3.1	-71.42
RE for R1b at 20min	%	16.9	14.38	-14.92
RE for Sb at 20min	%	14.55	15.14	4.09

Table 1.13: Values for aorta of subject GOT-002

1.5.3. Subject GOT-003

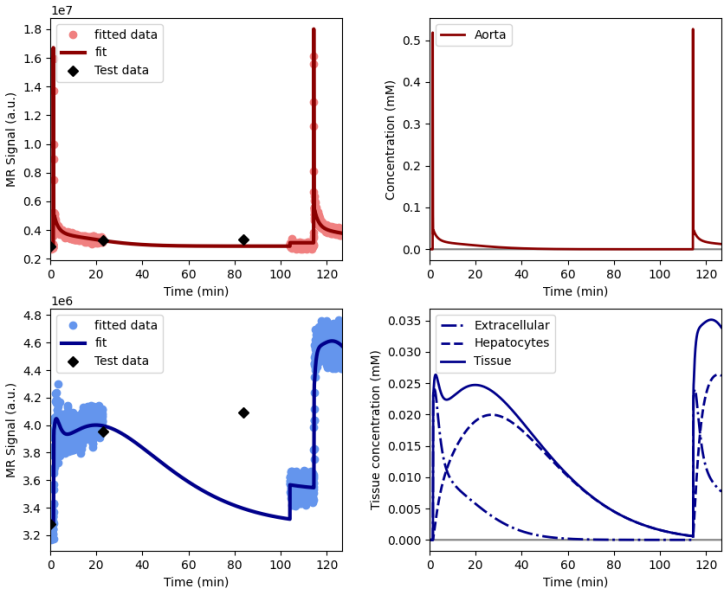

Figure 1.7: Signal-time curves for subject GOT-003 at the control visit.

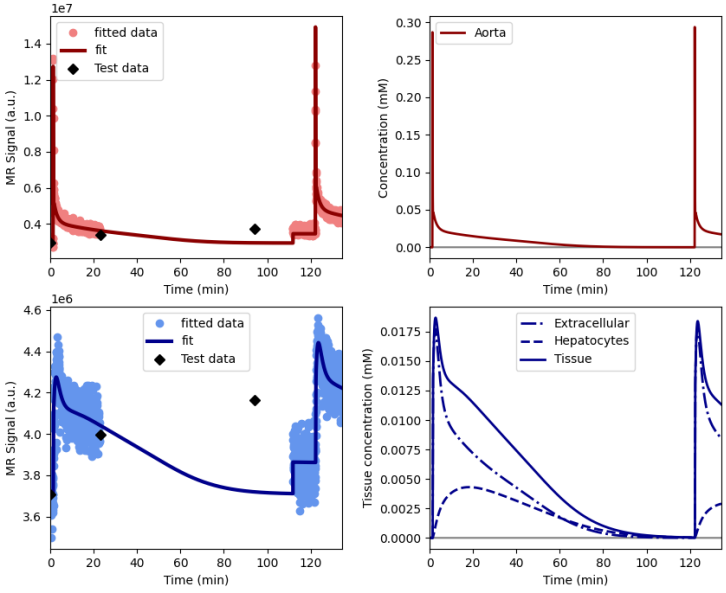

Figure 1.8: Signal-time curves for subject GOT-003 at the treatment visit.

Biomarker	Units	control	drug	change (%)
AUC for Cl (0-35min)	mM*sec	53.51	23.68	-55.74
AUC for Cl (0-inf)	mM*sec	98.09	40.63	-58.57
Biliary excretion rate	mL/min/100cm3	2.66	6.34	138.28
Biliary tissue excretion rate	mL/min/100cm3	3.95	8.59	117.26
Extracellular dispersion	%	90.08	88.23	-2.06
Extracellular mean transit time	sec	59.79	59.92	0.21
Final biliary excretion rate	mL/min/100cm3	6.72	6.19	-7.97
Final hepatocellular uptake rate	mL/min/100cm3	18.55	1.63	-91.23
Hematocrit	%	45.0	45.0	0.0
Hepatocellular mean transit time	min	25.29	11.64	-53.97
Hepatocellular tissue uptake rate	mL/min/100cm3	38.48	7.89	-79.49
Hepatocellular uptake rate	mL/min/100cm3	12.6	2.07	-83.57
Initial biliary excretion rate	mL/min/100cm3	1.66	6.49	291.8
Initial hepatocellular uptake rate	mL/min/100cm3	6.64	2.51	-62.16
Liver T1-MOLLI at 45min	sec	0.87	0.92	5.19
Liver T1-MOLLI at baseline	sec	1.08	1.0	-7.71
Liver T1-MOLLI at scan 2	sec	0.91	0.92	0.46
Liver blood clearance	L/min	0.13	0.02	-83.3
Liver extracellular volume fraction	mL/100cm3	32.74	26.23	-19.88
RE for R1l at 20min	%	26.04	11.05	-57.55
RE for Sl at 20min	%	20.11	12.47	-37.98

Table 1.14: Values for liver of subject GOT-003

Biomarker	Units	control	drug	change (%)
AUC for Cb (0-35min)	mM*sec	26.83	35.65	32.87
AUC for Cb (0-inf)	mM*sec	31.79	54.28	70.75
Body extraction fraction	%	7.16	3.29	-54.01
Cardiac output	L/min	8.9	11.34	27.45
Heart-lung dispersion	%	28.33	38.14	34.62
Heart-lung mean transit time	sec	12.51	14.34	14.61
Organs blood mean transit time	sec	31.27	20.93	-33.05
Organs extraction fraction	%	17.5	16.61	-5.09
Organs extravascular mean transit time	min	3.78	3.12	-17.41
RE for R1b at 20min	%	17.36	26.96	55.34
RE for Sb at 20min	%	18.48	21.67	17.26

Table 1.15: Values for aorta of subject GOT-003

2

One-scan results

2.1. Data summary

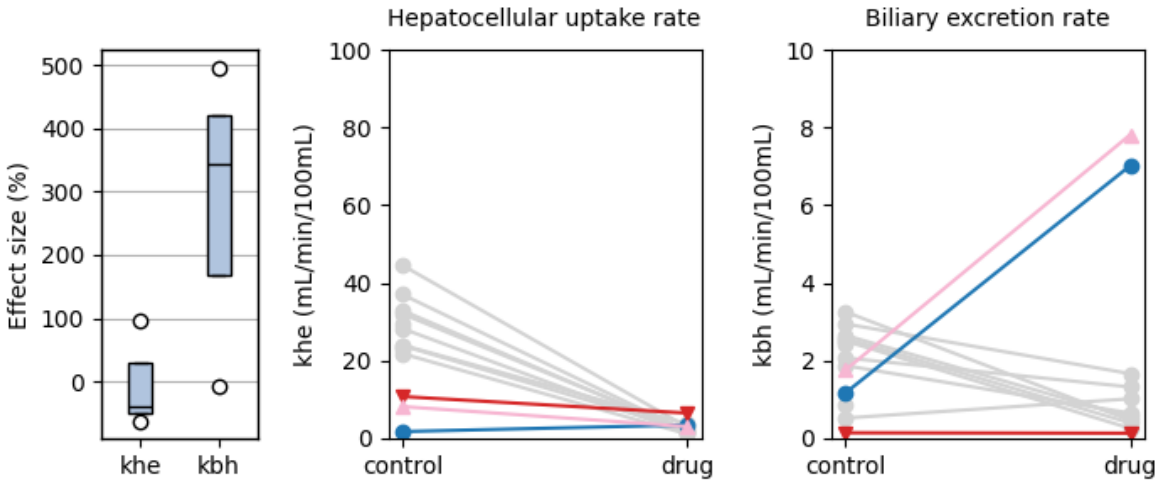

Figure 2.1: Effect size (%) on hepatocellular uptake (k_he, left) and biliary excretion (k_bh, right) of gadoxetate. The boxplot shows median, interquartile range and 95 percent range. The line plots show individual values for hepatocellular uptake (k_he, middle) and biliary excretion (k_bh, right) of gadoxetate of the control (left of plot) and treatment (right of plot). Grey lines are healthy controls with rifampicin injection.

parameter	count	mean	std	min	25%	50%	75%	max
khe effect size (%)	3.0	-1.9	85.8	-62.5	-51.0	-39.4	28.4	96.2
khe control (mL/min/100cm3)	3.0	6.92	4.64	1.77	4.98	8.2	9.49	10.78
khe drug (mL/min/100cm3)	3.0	4.36	1.89	3.07	3.27	3.47	5.0	6.53
kbh effect size (%)	3.0	277.6	258.4	-7.1	167.9	342.9	420.0	497.1
kbh control (mL/min/100cm3)	3.0	1.03	0.82	0.14	0.66	1.17	1.47	1.76
kbh drug (mL/min/100cm3)	3.0	4.99	4.22	0.13	3.57	7.01	7.41	7.81

Table 2.1: Effect size and absolute values of hepatocellular uptake (k_he) and biliary excretion (k_bh) of gadoxetate

2.2. Liver biomarkers

Biomarker	p-value	Bayes Factor	Odds Ratio
AUC for Cl (0-35min)	0.21906	1.0	5.23
AUC for Cl (0-inf)	0.30851	0.8	2.57
Biliary excretion rate	0.18434	1.12	0.09
Biliary tissue excretion rate	0.18973	1.1	0.11
Extracellular dispersion	0.10973	1.57	10.6
Extracellular mean transit time	0.24133	0.94	4.76
Hematocrit			
Hepatocellular mean transit time	0.69364	0.51	0.8
Hepatocellular tissue uptake rate	0.60454	0.54	0.37
Hepatocellular uptake rate	0.3553	0.74	3.7
Liver T1-MOLLI at 45min	0.98716	0.47	1.01
Liver T1-MOLLI at baseline	0.07944	1.93	3.61
Liver blood clearance	0.33491	0.76	2.63
Liver extracellular volume fraction	0.05011	2.55	35.26
RE for R1l at 20min	0.19081	1.1	8.69
RE for Sl at 20min	0.16114	1.23	15.25

Table 2.2: Results of a pairwise comparison testing for differences in liver biomarkers between control and treatment. The results are ranked by their p-value, with most significant differences at the top of the list.

Biomarker	Units	control	drug	change (%)
AUC for Cl (0-35min)	mM*sec	52.2 (27.0)	34.8 (14.0)	-26.7 (35.0)
AUC for Cl (0-inf)	mM*sec	387.0 (490.0)	209.0 (240.0)	-39.9 (37.0)
Biliary excretion rate	mL/min/100cm3	1.03 (0.93)	4.99 (4.8)	278.0 (290.0)
Biliary tissue excretion rate	mL/min/100cm3	1.46 (1.3)	6.04 (5.9)	225.0 (260.0)
Extracellular dispersion	%	84.8 (5.4)	76.4 (8.8)	-9.96 (7.1)
Extracellular mean transit time	sec	58.8 (2.4)	54.9 (6.9)	-6.83 (8.3)
Hematocrit	%	45.0 (0.0)	45.0 (0.0)	0.0 (0.0)
Hepatocellular mean transit time	min	173.0 (240.0)	208.0 (380.0)	-36.8 (80.0)
Hepatocellular tissue uptake rate	mL/min/100cm3	20.0 (12.0)	25.7 (12.0)	84.3 (190.0)
Hepatocellular uptake rate	mL/min/100cm3	6.92 (5.3)	4.36 (2.1)	-1.9 (97.0)
Liver T1-MOLLI at 45min	sec	0.793 (0.14)	0.793 (0.13)	0.33 (10.0)
Liver T1-MOLLI at baseline	sec	0.983 (0.12)	0.916 (0.089)	-6.57 (3.5)
Liver blood clearance	L/min	0.0781 (0.07)	0.0512 (0.04)	3.97 (100.0)
Liver extracellular volume fraction	mL/100cm3	31.7 (9.8)	17.7 (5.9)	-44.0 (11.0)
RE for R1l at 20min	%	24.7 (12.0)	15.2 (5.4)	-31.9 (34.0)
RE for Sl at 20min	%	19.8 (9.4)	10.5 (3.2)	-40.0 (33.0)

Table 2.3: Mean values along with their 95 percent confidence intervals for all liver biomarkers of the control and treatment visit. The last column shows the relative change at the treatment visit. The results are ranked by their p-value, with most significant differences at the top of the list.

2.3. Systemic biomarkers

Biomarker	p-value	Bayes Factor	Odds Ratio
AUC for Cb (0-35min)	0.17259	1.17	0.22
AUC for Cb (0-inf)	0.45331	0.63	0.36
Body extraction fraction	0.79023	0.49	1.39
Cardiac output	0.39029	0.69	9.38
Heart-lung dispersion	0.6102	0.54	0.49
Heart-lung mean transit time	0.89335	0.47	1.35
Organs blood mean transit time	0.65412	0.52	2.61
Organs extraction fraction	0.9023	0.47	0.78
Organs extravascular mean transit time	0.95093	0.47	0.96
RE for R1b at 20min	0.19551	1.08	0.24
RE for Sb at 20min	0.42448	0.66	0.65

Table 2.4: Results of a pairwise comparison testing for differences in systemic biomarkers between control and treatment visit. The results are ranked by their p-value, with most significant differences at the top of the list.

Biomarker	Units	control	drug	change (%)
AUC for Cb (0-35min)	mM*sec	31.4 (9.3)	42.0 (18.0)	31.6 (27.0)
AUC for Cb (0-inf)	mM*sec	73.3 (36.0)	108.0 (94.0)	47.8 (81.0)
Body extraction fraction	%	3.26 (2.3)	2.93 (1.7)	6.71 (92.0)
Cardiac output	L/min	9.6 (1.2)	7.92 (1.8)	-15.5 (30.0)
Heart-lung dispersion	%	39.8 (11.0)	44.3 (14.0)	13.5 (36.0)
Heart-lung mean transit time	sec	16.0 (7.5)	15.1 (3.9)	12.0 (76.0)
Organs blood mean transit time	sec	31.1 (3.4)	28.1 (8.3)	-7.85 (34.0)
Organs extraction fraction	%	21.2 (2.7)	21.7 (4.7)	3.77 (30.0)
Organs extravascular mean transit time	min	6.05 (3.0)	6.11 (3.4)	-0.186 (35.0)
RE for R1b at 20min	%	22.4 (7.9)	31.2 (16.0)	36.1 (36.0)
RE for Sb at 20min	%	19.0 (7.9)	21.0 (11.0)	8.21 (21.0)

Table 2.5: Mean values along with their 95 percent confidence intervals for all systemic biomarkers at the control and and treatment visit. The last column shows the relative change at the treatment visit. The results are ranked by their p-value, with most significant differences at the top of the list.

2.4. Case notes

2.4.1. Subject GOT-001

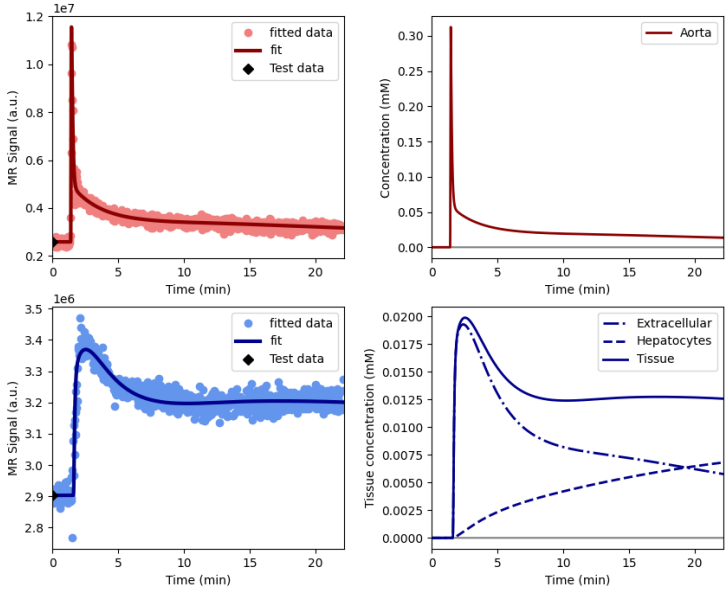

Figure 2.2: Signal-time curves for subject GOT-001 at the control visit.

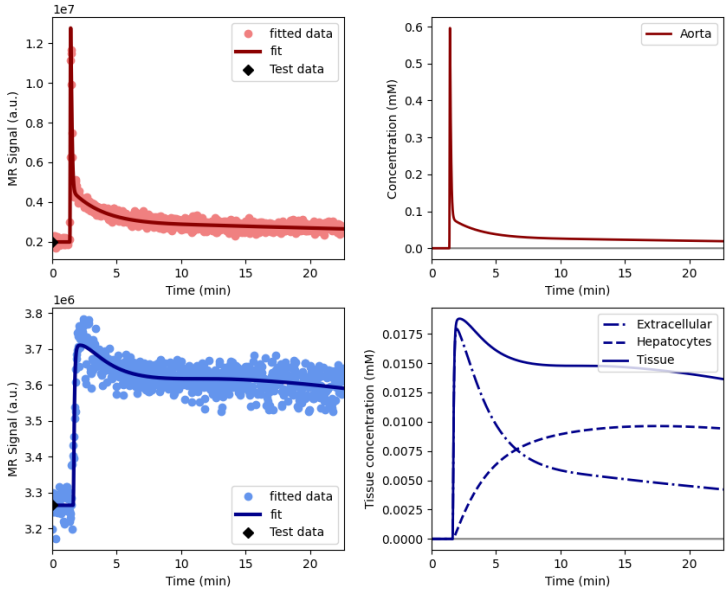

Figure 2.3: Signal-time curves for subject GOT-001 at the treatment visit.

Biomarker	Units	control	drug	change (%)
AUC for Cl (0-35min)	mM*sec	28.67	30.9	7.79
AUC for Cl (0-inf)	mM*sec	134.02	129.06	-3.7
Biliary excretion rate	mL/min/100cm3	1.17	7.01	497.05
Biliary tissue excretion rate	mL/min/100cm3	1.52	7.96	424.77
Extracellular dispersion	%	80.2	73.98	-7.76
Extracellular mean transit time	sec	60.0	56.46	-5.9
Hematocrit	%	45.0	45.0	0.0
Hepatocellular mean transit time	min	65.9	12.56	-80.94
Hepatocellular tissue uptake rate	mL/min/100cm3	7.83	29.11	271.82
Hepatocellular uptake rate	mL/min/100cm3	1.77	3.47	96.21
Liver T1-MOLLI at 45min	sec	0.85	0.77	-10.15
Liver T1-MOLLI at baseline	sec	0.99	0.9	-8.95
Liver blood clearance	L/min	0.01	0.03	106.87
Liver extracellular volume fraction	mL/100cm3	22.58	11.92	-47.23
RE for R1l at 20min	%	13.26	13.29	0.22
RE for Sl at 20min	%	10.45	9.61	-7.97

Table 2.6: Values for liver of subject GOT-001

Biomarker	Units	control	drug	change (%)
AUC for Cb (0-35min)	mM*sec	40.87	59.13	44.66
AUC for Cb (0-inf)	mM*sec	99.85	204.19	104.49
Body extraction fraction	%	2.33	1.16	-50.4
Cardiac output	L/min	10.75	6.38	-40.6
Heart-lung dispersion	%	50.22	43.21	-13.95
Heart-lung mean transit time	sec	14.48	14.44	-0.27
Organs blood mean transit time	sec	29.4	35.99	22.43
Organs extraction fraction	%	18.91	21.69	14.68
Organs extravascular mean transit time	min	5.31	7.04	32.62
RE for R1b at 20min	%	30.43	45.6	49.83
RE for Sb at 20min	%	27.02	31.64	17.09

Table 2.7: Values for aorta of subject GOT-001

2.4.2. Subject GOT-002

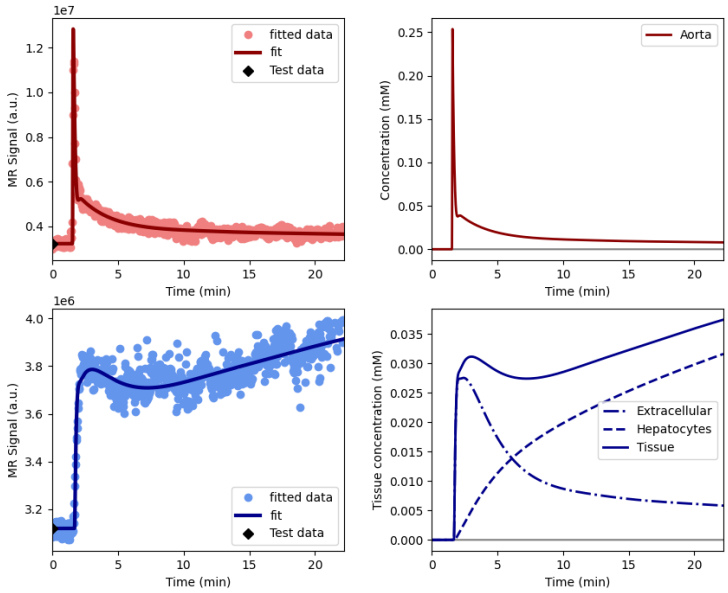

Figure 2.4: Signal-time curves for subject GOT-002 at the control visit.

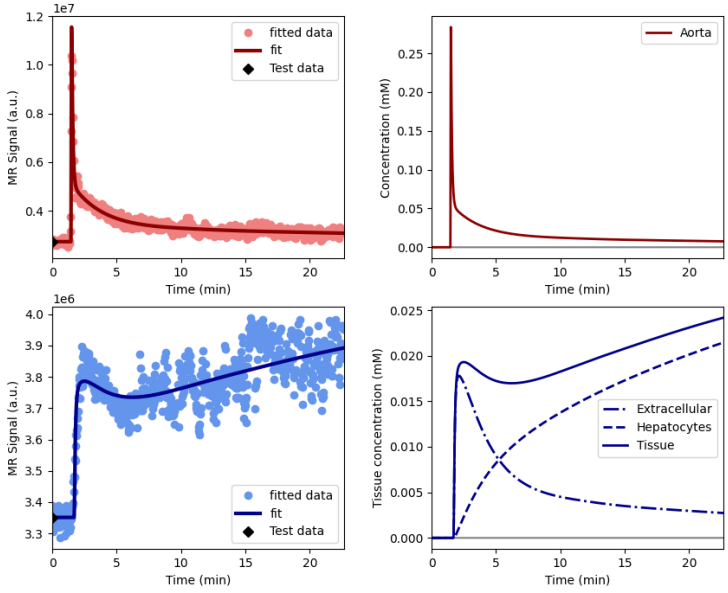

Figure 2.5: Signal-time curves for subject GOT-002 at the treatment visit.

Biomarker	Units	control	drug	change (%)
AUC for Cl (0-35min)	mM*sec	76.72	48.41	-36.9
AUC for Cl (0-inf)	mM*sec	889.04	452.61	-49.09
Biliary excretion rate	mL/min/100cm3	0.14	0.13	-7.13
Biliary tissue excretion rate	mL/min/100cm3	0.24	0.17	-30.75
Extracellular dispersion	%	84.49	70.11	-17.02
Extracellular mean transit time	sec	56.36	48.14	-14.58
Hematocrit	%	45.0	45.0	0.0
Hepatocellular mean transit time	min	415.51	599.99	44.4
Hepatocellular tissue uptake rate	mL/min/100cm3	27.07	33.88	25.16
Hepatocellular uptake rate	mL/min/100cm3	10.78	6.53	-39.39
Liver T1-MOLLI at 45min	sec	0.66	0.69	5.95
Liver T1-MOLLI at baseline	sec	0.87	0.84	-3.06
Liver blood clearance	L/min	0.14	0.09	-33.03
Liver extracellular volume fraction	mL/100cm3	39.81	19.28	-51.57
RE for R1l at 20min	%	33.14	20.6	-37.83
RE for Sl at 20min	%	26.31	13.65	-48.1

Table 2.8: Values for liver of subject GOT-002

Biomarker	Units	control	drug	change (%)
AUC for Cb (0-35min)	mM*sec	26.31	27.28	3.72
AUC for Cb (0-inf)	mM*sec	82.01	55.71	-32.08
Body extraction fraction	%	1.84	3.67	99.78
Cardiac output	L/min	8.56	9.53	11.45
Heart-lung dispersion	%	38.7	57.34	48.19
Heart-lung mean transit time	sec	23.26	12.05	-48.19
Organs blood mean transit time	sec	29.23	26.79	-8.36
Organs extraction fraction	%	23.65	17.51	-26.0
Organs extravascular mean transit time	min	9.0	8.52	-5.42
RE for R1b at 20min	%	17.87	17.77	-0.54
RE for Sb at 20min	%	14.38	12.44	-13.45

Table 2.9: Values for aorta of subject GOT-002

2.4.3. Subject GOT-003

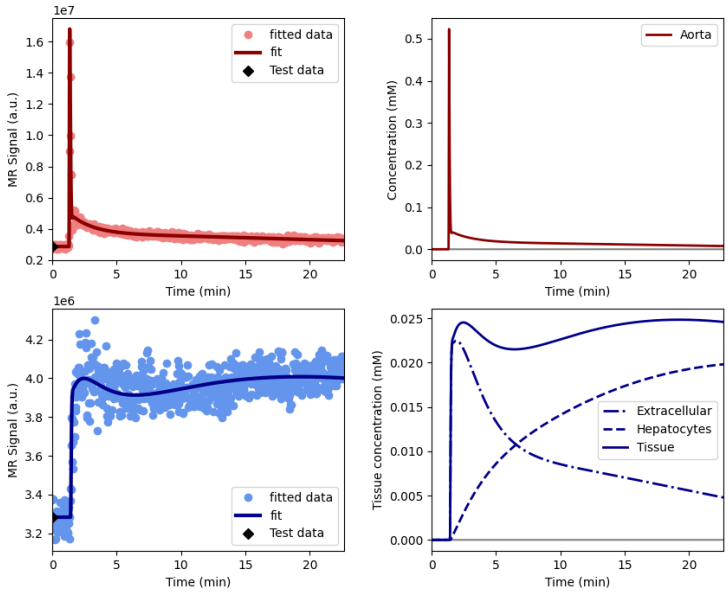

Figure 2.6: Signal-time curves for subject GOT-003 at the control visit.

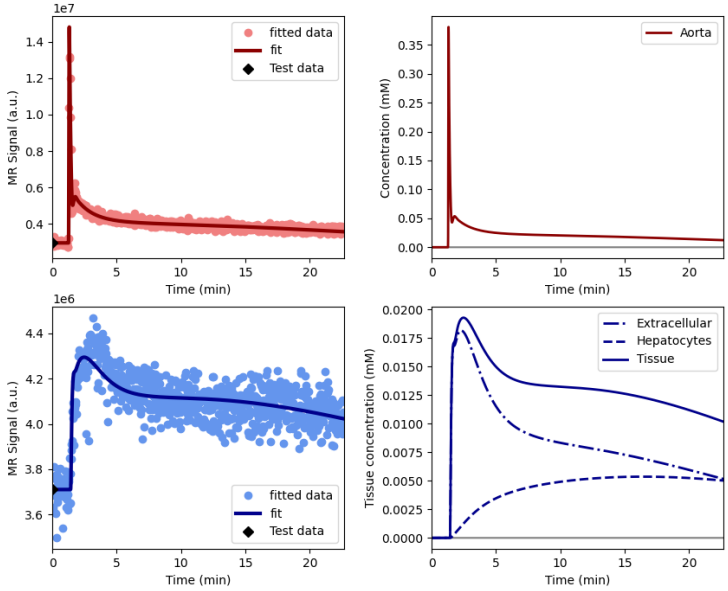

Figure 2.7: Signal-time curves for subject GOT-003 at the treatment visit.

Biomarker	Units	control	drug	change (%)
AUC for Cl (0-35min)	mM*sec	51.08	25.05	-50.97
AUC for Cl (0-inf)	mM*sec	138.99	45.86	-67.0
Biliary excretion rate	mL/min/100cm3	1.76	7.81	342.93
Biliary tissue excretion rate	mL/min/100cm3	2.62	10.0	281.48
Extracellular dispersion	%	89.67	85.11	-5.09
Extracellular mean transit time	sec	60.0	60.0	-0.0
Hematocrit	%	45.0	45.0	0.0
Hepatocellular mean transit time	min	38.16	10.0	-73.79
Hepatocellular tissue uptake rate	mL/min/100cm3	25.06	14.04	-43.98
Hepatocellular uptake rate	mL/min/100cm3	8.2	3.07	-62.53
Liver T1-MOLLI at 45min	sec	0.87	0.92	5.19
Liver T1-MOLLI at baseline	sec	1.08	1.0	-7.71
Liver blood clearance	L/min	0.08	0.03	-61.93
Liver extracellular volume fraction	mL/100cm3	32.73	21.89	-33.12
RE for R1l at 20min	%	27.78	11.61	-58.22
RE for Sl at 20min	%	22.72	8.23	-63.78

Table 2.10: Values for liver of subject GOT-003

Biomarker	Units	control	drug	change (%)
AUC for Cb (0-35min)	mM*sec	26.96	39.48	46.44
AUC for Cb (0-inf)	mM*sec	38.01	65.03	71.09
Body extraction fraction	%	5.62	3.98	-29.26
Cardiac output	L/min	9.49	7.84	-17.38
Heart-lung dispersion	%	30.51	32.37	6.11
Heart-lung mean transit time	sec	10.22	18.85	84.49
Organs blood mean transit time	sec	34.59	21.58	-37.62
Organs extraction fraction	%	21.08	25.85	22.63
Organs extravascular mean transit time	min	3.84	2.77	-27.76
RE for R1b at 20min	%	18.98	30.19	59.08
RE for Sb at 20min	%	15.64	18.92	21.01

Table 2.11: Values for aorta of subject GOT-003

3

Secondary results

3.1. Diurnal variation

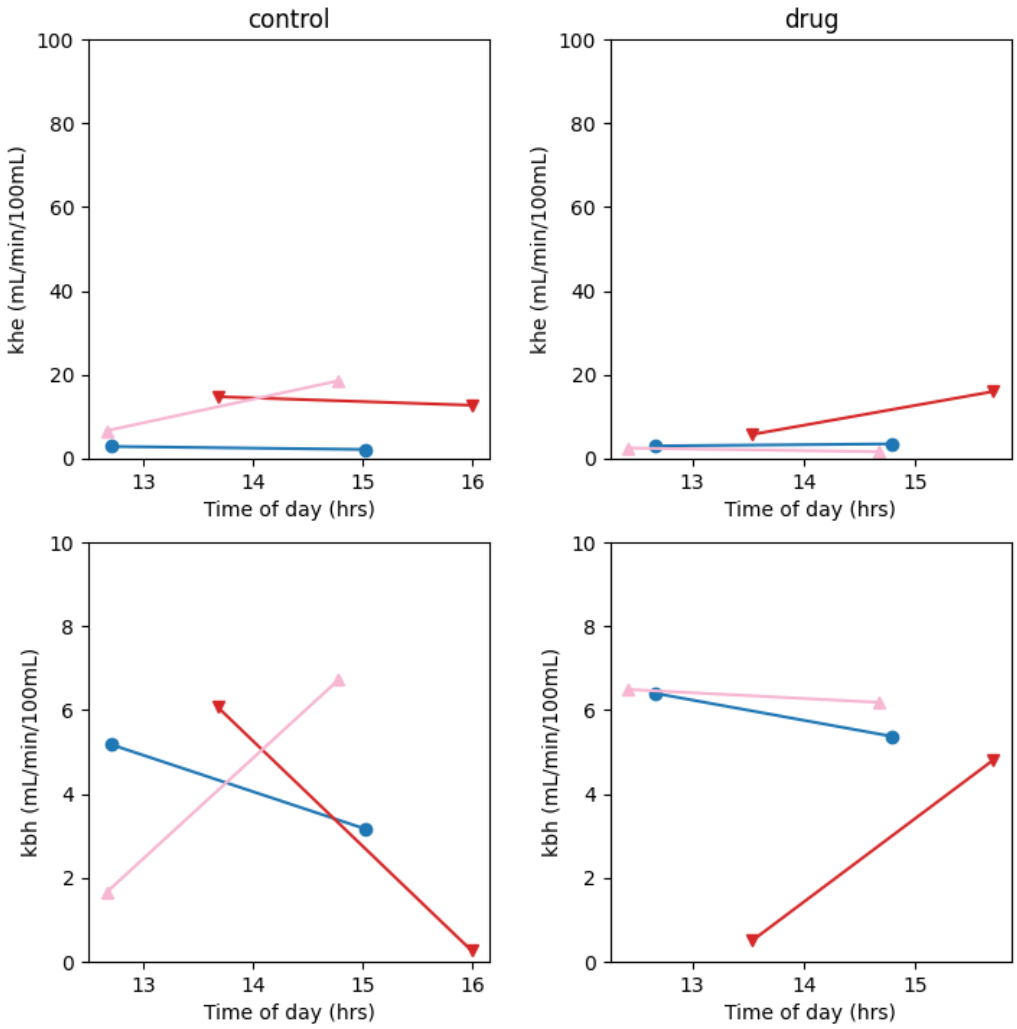

Figure 3.1: Intra-day changes in hepatocellular uptake (k_he, top row) and biliary excretion (k_bh, bottom row) of gadoxetate at for the control (left column) and treatment (right column). Full lines connect values taken in the same subject at the same day.