Supplemental Data

Assessing the risk of drug-induced cholestasis using unbound intrahepatic concentrations

Julia Riede, Birk Poller, Jörg Huwyler, Gian Camenisch

Drug Metabolism and Disposition

Calculation of pharmacokinetic parameters:

The absorption rate constant (k_a) was calculated based on eq. 1 and 2 [1]:

$$T_{max} = \frac{ln(\frac{k_a}{k_e})}{k_a - k_e} \quad (1)$$

$$k_e = \frac{ln(2)}{T_{1/2}} \quad (2)$$

where T_{max} is the time to reach the maximum plasma concentration, k_e is the elimination rate constant and $T_{1/2}$ is the elimination half-life.

The fraction absorbed and escaping gut metabolism (F_a x F_g) was calculated based on eq. 3 and 4 [1]:

$$F_a \times F_g = \frac{F}{F_h} \quad (3)$$

$$F_h = 1 - \frac{CL_h}{Q_h} \quad (4)$$

where F represents the oral bioavailabilty, F_h is the fraction escaping hepatic clearance, CL_h is the hepatic blood clearance and Q_h is the hepatic blood flow (1.45 l/min).

Pharmacokinetic parameters required for the calculations and literature references for all 18 compounds are summarized in Supplemental Table 2.

Human *in vitro* BSEP inhibition:

K_i values from Hirano et al., 2005 [2] were converted to IC_{50} values according to eq. 5, assuming competitive inhibition [3]:

$$IC_{50} = K_i \times (1 + \frac{[S]}{K_m}) \quad (5)$$

where the substrate concentration of taurocholate [S] = 3 µM and Michealis-Menten constant (K_m) for BSEP-mediated taurocholate transport = 4.64 µM [2].

SUPPLEMENTAL TABLE 1: Hepatic *in vivo* and *in vitro* Kp_{uu} in rat

Drug compound	ECM class	*in vitro*						*in vivo*									
		Hepatic process clearances [4]				Kp_{uu}		Kp_{uu}		Kp		fu_{liver}		fu_p		fu_b	
		$PS_{inf,act}$	$PS_{inf,pas}$	$CL_{int.met}$	$CL_{int.sec}$												
		[ml/min/kg]															
Atorvastatin	4	2935.3	212.8	158.3	1.2	8.46		7.76		8.2[c]	[5]	0.0284[e]		0.03	[4]	0.025	[4]
						63.2[a]	[6]										
						494[a]	[7]										
Cyclosporine A	4	191.3	83.5	37.4	13.1	2.05		1.80		11.0[d]	[8]	0.0077[f]	[9]	0.06	[4]	0.047	[4]
Furamidine						53[b]	[10]	23	[10]								
Ketoconazole	1	0.0	1939.1	4674.6	3.3	0.29		0.72		4.36[d]	[11]	0.0035[e]		0.01	[4]	0.014	[4]
Pravastatin	4	185.4	57.3	3.37	3.5	3.78		4.30		16.3[c]	[12]	0.1689[e]		0.64	[4]	0.84	[4]
						16.5[a]	[6]										
						22.9[a]	[7]										
Ritonavir						1.1[b]	[10]	1.1	[10]								
Rosuvastatin		-				6.1[b]	[10]	7.9	[10]								
						30.2[a]	[6]										
						58.2[a]	[7]										
Verapamil	1	0.0	340.6	2636.6	8.8	0.11		0.28		7.67[d]	[11]	0.0024[e]		0.06	[4]	0.066	[4]

$PS_{inf,act}$ = active hepatic uptake, $PS_{inf,pas}$ = passive hepatic uptake, PS_{eff} = sinusoidal efflux, $CL_{int,met}$ = intrinsic metabolic clearance, $CL_{int,sec}$ = intrinsic biliary clearance, Kp_{uu} = liver-to-blood partition coefficient for unbound drug, Kp = liver-to-blood partition coefficient, fu_{liver} = fraction unbound in liver, fu_p = fraction unbound in plasma, fu_b = fraction unbound in blood. If not stated otherwise, *in vitro* Kp_{uu} values were calculated according to ECM ($Kp_{uu} = PS_{inf} / (PS_{eff} + CL_{int})$, assuming $PS_{eff} = PS_{inf,pas}$). [a] $Kp_{uu} = (CL_{active} + P_{diff}) / P_{diff}$, where CL_{active} and P_{diff} are active and passive hepatic uptake clearances, respectively. [b] Kp_{uu} values were derived from Kp and fu in sandwich-cultured rat hepatocytes. [c] rat liver-to-plasma Kp, *in vivo* Kp_{uu} values were derived from $Kp_{uu} = Kp \times fu_{liver} / fu_p$. [d] rat liver-to-blood Kp, *in vivo* Kp_{uu} values were derived from $Kp_{uu} = Kp \times fu_{liver} / fu_b$. [e] In-house data for the fraction unbound in suspended human hepatocytes determined from steady-state incubations at 4°C [6]. [f] Fraction unbound in homogenized rat liver. Literature references are shown in brackets. DataThief III (http://www.datathief.org) was partially used for extraction of literature data.

SUPPLEMENTAL TABLE 2: Human dose and systemic exposure

Drug compound	maximum daily dose		C_{max} [µM]		C_{max} study conditions
Atazanavir	400 mg qd	[13]	8.3239	[14]	400 mg qd (6 days), healthy subjects
Atorvastatin	80 mg qd	[13]	0.4511	[15]	80 mg qd (14 days), healthy subjects
Bosentan (125 mg bid)	125 mg bid	[13]	3.3193	[16]	125 mg bid (6 days), healthy subjects
Bosentan (1000 mg bid)	1000 mg bid	[17]	23.2209	[18]	1000 mg (extrapolated from C_{max} values after administration of 3 - 1200 mg), healthy subjects
Cerivastatin	0.8 mg qd	[19]	0.0300	[15]	0.8 mg qd (4 weeks), healthy subjects
Cyclosporine A	7.5 mg/kg bid	[20]	0.7317	[21]	5 mg/kg (single dose), healthy subjects, [a)]
Erythromycin	1000 mg bid	[20]	20.1655	[22]	1000 mg bid (4 days), healthy elderly subjects
Fluvastatin	80 mg qd	[13]	0.2605	[23]	80 mg qd (repeated), healthy subjects
Glibenclamide	10 mg bid	[13]	0.9372	[24]	7 mg (single dose), diabetic patients
Ibuprofen	800 mg tid	[20]	392.8916	[25]	800 mg (single dose), healthy subjects
Imatinib	400 mg bid	[13]	9.5623	[26]	400 mg qd (4 days), chronic myeloid leukemia patients
Ketoconazole	400 mg qd	[13]	16.6061	[27]	400 mg qd (11 days), healthy subjects
Lovastatin acid	80 mg qd	[13]	0.1006	[15]	80 mg qd (17 days), hypercholesterolemic patients
Pitavastatin	4 mg qd	[13]	0.2769	[28]	4 mg (single dose), healthy subjects
Pravastatin	40 mg qd	[20]	0.1376	[29]	40 mg qd (4 days), healthy subjects
Rosiglitazone	8 mg qd	[13]	1.8241	[30]	8 mg qd (14 days), healthy subjects
Rosuvastatin	40 mg qd	[13]	0.0768	[31]	40 mg qd (11 days), healthy subjects
Simvastatin acid	80 mg qd	[13]	0.0133	[32]	80 mg qd (7 days), healthy subjects
Verapamil	480 mg qd	[20]	0.5521	[33]	180 mg bid (3 days), healthy subjects

C_{max} = maximum available drug plasma concentration in human. qd = once daily; bid = twice daily; tid = three times daily. [a)] C_{max} in plasma was converted from C_{max} in blood ($C_{max,plasma} = C_{max,blood} / R_b$, where R_b is the blood-to-plasma partition coefficient). The literature references are shown in brackets.

SUPPLEMENTAL TABLE 3: Human pharmacokinetic parameters

Drug compound	T_{max} [h]	$T_{1/2}$ [h]	k_a [h^{-1}]	k_e [h^{-1}]	CL_{tot} [ml/min/kg]		CL_h [ml/min/kg]		fn_h		F		F_h	F_a x F_g
Atazanavir	2.5	5.9	0.96	0.12	9.59	[34]	8.92	[-]	0.93	[35]	0.60	[36]	0.60	1.00
Atorvastatin	1.6	10.3	2.27	0.07	5.96	[-]	5.90	[37]	0.99	[37]	0.14	[37]	0.71	0.20
Bosentan (125 mg bid)	3.6	5.8	0.54	0.12	3.43	[18]	3.40	[-]	0.99	[38]	0.50	[39]	0.84	0.60
Bosentan (1000 mg bid)	3.0	16.2	1.14	0.04	2.38	[18]	2.36	[-]	0.99	[38]	0.50	[39]	0.89	0.56
Cerivastatin	2.2	2.9	0.77	0.24	3.40	[37]	3.40	[-]	1.00	[37]	0.60	[37]	0.84	0.71
Cyclosporine A	1.7	11.9	2.19	0.06	3.13	[-]	3.10	[40]	0.99	[41]	0.22	[41]	0.85	0.26
Erythromycin	3.6	2.0	0.22	0.35	5.39	[42]	5.12	[-]	0.95	[35]	0.40	[43]	0.75	0.53
Fluvastatin	5.5	5.7	0.26	0.12	7.46	[37]	7.01	[-]	0.94	[37]	0.24	[37]	0.66	0.36
Glibenclamide	2.8	7.9	0.93	0.09	2.21	[44]	2.21	[-]	1.00	[35]	0.93	[45]	0.93	1.00
Ibuprofen	1.3	2.4	1.61	0.29	1.33	[46]	1.33	[-]	1.00	[35]	1.00	[47]	1.00	1.00
Imatinib	3.0	17.3	1.16	0.04	4.17	[48]	3.96	[-]	0.95	[35]	0.98	[49]	0.98	1.00
Ketoconazole	2.2	2.7	0.74	0.26	4.02	[-]	3.90	[40]	0.97	[41]	0.81	[41]	0.81	1.00
Lovastatin acid	4.1	3.4	0.29	0.20	12.60	[37]	11.34	[-]	0.90	[37]	0.05	[37]	0.45	0.11
Pitavastatin	0.8	11.4	6.13	0.06	3.48	[37]	3.48	[-]	1.00	[37]	0.51	[37]	0.83	0.61
Pravastatin	1.2	2.7	1.94	0.26	19.64	[-]	10.41	[37]	0.53	[37]	0.18	[37]	0.50	0.36
Rosiglitazone	1.9	3.8	1.20	0.18	1.20	[50]	1.20	[-]	1.00	[35]	0.99	[51]	0.99	1.00
Rosuvastatin	4.5	20.7	0.71	0.03	16.87	[37]	12.15	[-]	0.72	[37]	0.20	[37]	0.41	0.49
Simvastatin acid	4.3	6.1	0.41	0.11	29.00	[37]	25.23	[-]	0.87	[37]	0.05	[37]	0.05	1.00
Verapamil	9.2	8.9	0.15	0.08	14.10	[-]	13.68	[40]	0.97	[41]	0.26	[41]	0.34	0.76

T_{max} = time to reach the maximum plasma concentration, $T_{1/2}$ = elimination half-life, T_{max} and $T_{1/2}$ values were obtained from Pharmapendium (Elsevier Properties, New York, SA) and represent the average of all reported values after administration of the maximum available recommended single dose in healthy subjects. CL_{tot} = total blood clearance, fn_h = hepatic (non-renal) eliminated fraction, CL_h = hepatic blood clearance, CL_h was either taken from literature or calculated with CL_{tot} x fn_h, assuming a human body weight of 70 kg. F = absolute oral bioavailability, F_h = fraction escaping hepatic clearance, F_a x F_g = fraction absorbed and escaping gut metabolism. bid = twice daily. The literature references are shown in brackets. [-] = calculated parameter.

SUPPLEMENTAL TABLE 4: Binding and physicochemical properties

Drug compound	R_b		fu_p		fu_{mic}		$logD_{7.4}$	
Atazanavir	0.74	[a]	0.14	[36]	0.84	[a]	5.77	[52]
Atorvastatin	0.63	[37]	0.05	[37]	0.51	[37]	1.30	[37]
Bosentan	0.57	[a]	0.02	[53]	0.83	[a]	1.25	[7]
Cerivastatin	0.60	[37]	0.01	[37]	0.69	[37]	1.90	[37]
Cyclosporine A	2.33	[41]	0.07	[53]	0.73	[4]	2.92	[41]
Erythromycin	0.73	[a]	0.05	[53]	0.89	[a]	1.11	[7]
Fluvastatin	0.52	[37]	0.02	[37]	0.31	[37]	1.60	[37]
Glibenclamide	0.55	[a]	0.01	[53]	0.95	[a]	2.19	[54]
Ibuprofen	0.57	[a]	0.01	[53]	0.96	[a]	0.81	[35]
Imatinib	0.80	[a]	0.05	[55]	0.48	[a]	2.40	[56]
Ketoconazole	0.50	[41]	0.01	[53]	0.17	[4]	4.05	[41]
Lovastatin acid	0.57	[37]	0.05	[37]	0.10	[37]	1.51	[37]
Pitavastatin	0.58	[37]	0.04	[37]	0.43	[37]	1.50	[37]
Pravastatin	0.54	[37]	0.52	[37]	0.88	[37]	-0.40	[37]
Rosiglitazone	0.55	[a]	0.002	[53]	0.72	[a]	2.60	[57]
Rosuvastatin	0.69	[37]	0.12	[37]	0.98	[37]	-0.89	[37]
Simvastatin acid	0.57	[37]	0.06	[37]	0.05	[37]	1.88	[37]
Verapamil	0.85	[41]	0.11	[41]	0.50	[4]	1.75	[41]

R_b = blood-to-plasma partition coefficient. fu_p = fraction unbound in plasma. fu_{mic} = fraction unbound in liver microsomes. [a] in house data. bid = twice daily. The literature references are shown in brackets.

SUPPLEMENTAL TABLE 5: Clinical cholestasis information and BSEP *in vitro* inhibition data

Drug compound	Cholestasis annotation		BSEP IC_{50} values [µM]	
common (cholestasis in > 2% of patients)				
Bosentan (1000 mg bid)	cholestasic/mixed liver injury (elevated AP and bile salts) in 8% of hypertensive patients (1000 mg bid)	[17]	22.0 − 38.1	[53, 58-60]
Cyclosporine A	cholestasis (elevated AP) in 27% of uveitis patients	[61]	0.4 − <10	[53, 58-60, 62]
Erythromycin	cholestasis in 2 - 4% of patients	[63]	4.1 − 13.0	[53, 59]
Imatinib	elevated AP (> 5x ULN) in up to 5% of chronic myeloid leukemia patients	[64]	<10 − 25.1	[59, 60]
rare (cholestasis in ≤ 2% of patients)				
Atazanavir	cholestasis is uncommon[a)]	[65]	3.1	[66]
Atorvastatin	cholestatic jaundice in < 2% of patients	[67]	15.0	[2]
Bosentan (125 mg bid)	cholestasic/mixed liver injury (elevated AP and bile salts) in 2% of hypertension (100 mg qd)	[17, 68]	22.0 − 38.1	[53, 59, 60]
Glibenclamide	cholestatic jaundice occurs rarely[a)]	[69]	1.5 − 11.3	[53, 58-60, 62]
Ibuprofen	liver injury with cholestatic/mixed pattern occurs very rarely[a)]	[70]	598.6 − >789	[53, 60]
Ketoconazole	cholestasis/mixed liver injury occurs very rarely[a)] / in 0.023% of patients	[71, 72]	2.9 – 4.1	[53, 59, 60]
Pitavastatin	elevated AP (> 2x ULN) in 0.2% of patients, cholestatic jaundice in 0.5% of patients	[14]	42.2	[2]
Pravastatin	cholestatic jaundice occurs rarely[a)]	[73]	268.4	[2]
Verapamil	elevated AP in 0.9% of patients, warning for elevated AP	[74, 75]	20.5	[60]
no cholestasis				
Cerivastatin	cholestasis or elevated AP (≥ 2x ULN) not reported in clinical studies		18.8	[2]
Fluvastatin	cholestasis or elevated AP (≥ 2x ULN) not reported in clinical studies		36.1 − 49.7	[2, 59]
Lovastatin acid	cholestasis or elevated AP (≥ 2x ULN) not reported in clinical studies		19.3	[59]
Rosiglitazone	cholestasis or elevated AP (≥ 2x ULN) not reported in clinical studies		1.9 − 6.4	[53, 59, 60, 66]
Rosuvastatin	cholestasis or elevated AP (≥ 2x ULN) not reported in clinical studies		197.6	[2]
Simvastatin acid	cholestasis or elevated AP (≥ 2x ULN) not reported in clinical studies		20.9	[2]

bid = twice daily. AP = serum alkaline phosphatase, ULN = upper limit of normal. [a)] uncommon = 1 – 0.1% of patients, rare = 0.01 – 0.1% of patients, very rare < 0.01% of patients [76]. BSEP IC_{50} data from Hirano et al., 2005 [2] were converted from reported K_i values according to eq. 5. The literature references are shown in brackets.

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