Characterization of in vitro glucuronidation clearance of a range of drugs in human kidney microsomes: Comparison to liver and intestinal glucuronidation and impact of albumin - Drug Metabolism and Disposition

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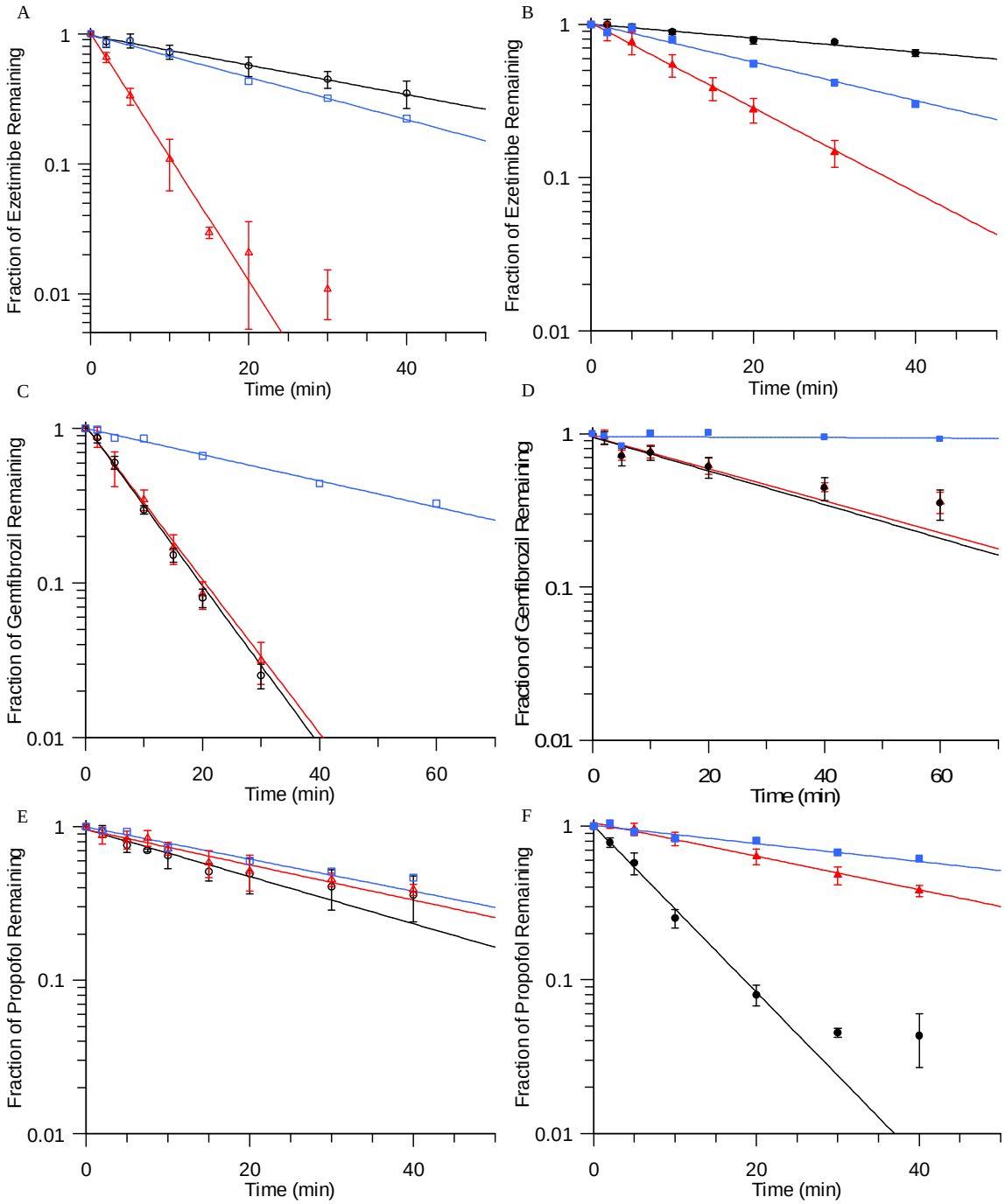

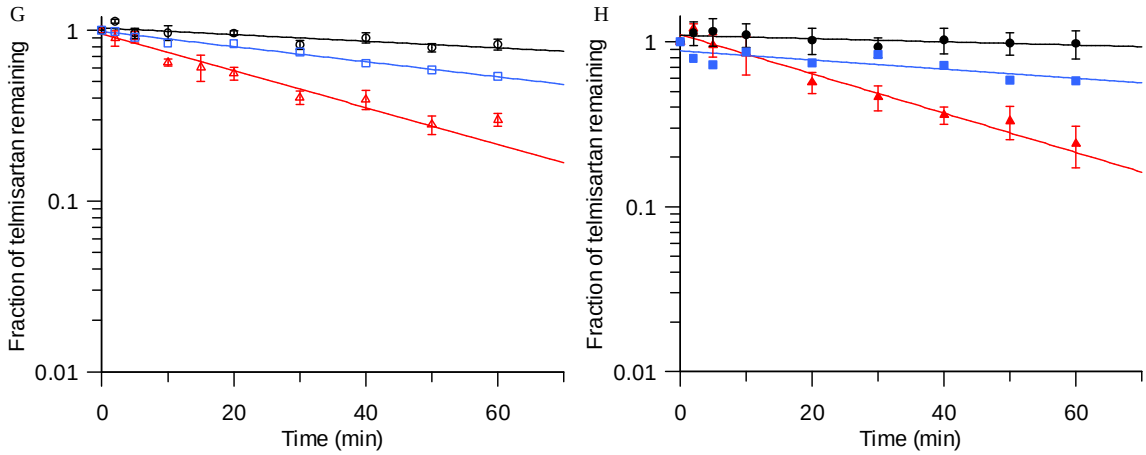

Figure S1. Mean fraction of drug remaining (+/- SD) over time in human kidney, liver and intestinal microsomes in the presence (B, D, F and H) and absence (A, C, E and H) of bovine serum albumin: ○, Δ and □ represent depletion in human kidney, liver and intestinal microsomes without BSA, respectively. ●, ▲ and ■ represent depletion in human kidney, liver and intestinal microsomes with BSA, respectively. A and B represent ezetimibe. C and D represent gemfibrozil. E and F represent propofol. G and H represent telmisartan.

Table S1: Protein concentration, incubation length and BSA concentration for use in human kidney, liver and intestine microsomes glucuronidation depletion assays for 7 drugs

Drug	Acid / Base	BSA Concentration (%)	Without BSA						With BSA					
			Protein Concentration (mg/mL)			Incubation Length (mins)			Protein Concentration (mg/mL)			Incubation Length (mins)		
			HLM	HKM	HIM	HLM	HKM	HIM	HLM	HKM	HIM	HLM	HKM	HIM
Diclofenac	Acid	1	0.50	0.25	0.50	60.0	60.0	60.0	1.00	1.00	1.00	60.0	60.0	60.0
Ezetimibe	Neutral	2	0.25	0.50	0.50	30.0	40.0	40.0	0.25	0.50	0.50	30.0	40.0	40.0
Gemfibrozil	Acid	1	0.50	0.50	1.00	30.0	30.0	60.0	1.00	1.00	1.00	60.0	60.0	60.0
Mycophenolic Acid	Acid	1	0.50	0.25	1.00	60.0	60.0	60.0	0.50	0.25	1.00	60.0	60.0	60.0
Naloxone	Base	2	1.00	1.00	1.00	60.0	60.0	60.0	1.00	1.00	1.00	60.0	60.0	60.0
Propofol	Base	2	0.50	0.50	0.50	40.0	40.0	40.0	0.50	0.50	0.50	40.0	40.0	40.0
Telmisartan	Acid	1	0.50	1.00	1.00	40.0	60.0	60.0	1.00	1.00	1.00	60.0	60.0	60.0

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Table S2: Summary of plasma CL_{IV} data used for IVIVE

Drug	Weighted mean CL_{IV} ($mL.min^{-1}.kg^{-1}$)	Minimum CL_{IV} ($mL.min^{-1}.kg^{-1}$)	Maximum CL_{IV} ($mL.min^{-1}.kg^{-1}$)	Total number subjects	Total number of studies	References
Diclofenac	4.84	3.97	5.81	23	3	(Willis et al., 1979; Willis et al., 1980; Hinz et al., 2005)
Gemfibrozil	1.7	-	-	ND	1	(Goodman and Gilman, 2006)
Mycophenolic Acid	2.49	-	-	12	1	(Bullingham et al., 1996)
Naloxone	21.7	19.0	30.0	18	4	(Fishman et al., 1973; Albeck et al., 1989; Harris et al., 2000; Dowling et al., 2008)
Propofol[#]	27.7	21.8	34.9	121	12	(Cockshott et al., 1987; Gepts et al., 1987; Campbell et al., 1988; Servin et al., 1988a; Servin et al., 1988b; Simons et al., 1988; Gill et al., 1990; Servin et al., 1990; Doenicke et al., 1997; Mertens et al., 2004; Vuyk et al., 2009)
Telmisartan	12.3	7.74	14.1	53	3	(Wallenstein et al., 1999; Stangier et al., 2000a; Stangier et al., 2000b)

ND = no data.
[#] blood clearance data.

Table S3: Summary of CL_R data used for IVIVE

Drug	Weighted mean CL_R ($mL.min^{-1}.kg^{-1}$)	Minimum CL_R ($mL.min^{-1}.kg^{-1}$)	Maximum CL_R ($mL.min^{-1}.kg^{-1}$)	Total number subjects	Total number of studies	References
Diclofenac	0.06	-	-	8	1	(Willis and Kendall, 1978)
Gemfibrozil	0.02[#]	-	-	-	1	(Goodman and Gilman, 2006)
Mycophenolic Acid	0.01	-	-	12	1	(Bullingham et al., 1996)
Naloxone	0.00	-	-	-	2	(Vozeh et al., 1988; Goodman and Gilman, 2006)
Propofol	0.00	0.00	< 2.8	20	3	(Vree et al., 1987; Simons et al., 1988; Veroli et al., 1992)
Telmisartan	0.00[+]	-	-	-	1	(Moffat et al., 2004)

[#] Data in similar range to CL_R calculated from weighted mean CL_{IV} and urinary fraction excreted data presented in 4 other studies (http://www.pfizer.com/files/products/uspi_lopid.pdf; Okerholm et al., 1976; Knauf et al., 1990; Reyderman et al., 2004).
[+] minute amounts excreted in urine (Moffat et al., 2004).

Table S4: Summary of $f_{u,p}$ data used for IVIVE

Drug	Weighted mean $f_{u,p}$	Minimum $f_{u,p}$	Maximum $f_{u,p}$	Total number subjects	Total number of studies	References
Diclofenac	0.004	-	-	ND	3	(Brenner et al., 2003; Obach et al., 2008; Deguchi et al., 2011)
Gemfibrozil	0.005*	-	-	ND	1	(Deguchi et al., 2011)
Mycophenolic Acid	0.010	0.010	0.020	59	2	(Nowak and Shaw, 1995; Lévesque et al., 2008)
Naloxone	0.570	0.540	0.600	ND	2	(Moffat et al., 2004; Obach et al., 2008)
Propofol	0.015	0.0106	0.022	50	4	(Kirkpatrick et al., 1988; Servin et al., 1988b; Dawidowicz and Kalityński, 2003; Dawidowicz et al., 2004)
Telmisartan	0.005	0.005	0.005	9	2	(Stangier et al., 2000a; Stangier et al., 2000b)

ND = no data.
* measurement made in vitro.

Table S5: Summary of R_B data used for IVIVE

Drug	Weighted mean R_B	Minimum R_B	Maximum R_B	Total number subjects	Total number of studies	References
Diclofenac	0.71*	-	-	ND	1	(Deguchi et al., 2011)
Gemfibrozil	0.75*	-	-	ND	1	(Deguchi et al., 2011)
Mycophenolic Acid	0.60	0.50	0.69	ND	4	(Langman et al., 1994; Nowak and Shaw, 1995; Bullingham et al., 1998; Deguchi et al., 2011)
Naloxone	1.00 [$]	-	-	-	-	
Propofol	0.88	0.78	0.97	22	2	(Kirkpatrick et al., 1988; Servin et al., 1988b)
Telmisartan	1.24*	-	-	ND	1	(Deguchi et al., 2011)

[$] no data available;1 assumed for basic drugs.
* measurement made in vitro.

Table S6: Summary of $f_{m,UGT}$ data used for IVIVE

Drug	$f_{m,UGT}$ without BSA	$f_{m,UGT}$ with BSA	Minimum $f_{m,UGT}$	Maximum $f_{m,UGT}$	Total number subjects	Total number of studies	References
Diclofenac	0.62*	0.65*	-	-	-	1	(Kilford, 2008)
Gemfibrozil	0.79*	0.86*			-	1	(Kilford, 2008)
Mycophenolic Acid[#]	0.95	0.95	0.90	1.00	ND	3	(Bullingham et al., 1998; Morissette et al., 2001; Miles et al., 2005)
Naloxone	0.65*	0.89*	-	-	-	1	(Kilford, 2008)
Propofol	0.14*	0.53*	-	-	-	1	(Kilford, 2008)
Telmisartan[#]	1.00	1.00	-	-	ND	1	(Moffat et al., 2004)

ND = no data.

* data taken from in vitro measurements.

[#] no suitable in vitro data available so in vivo data used instead, $f_{m,UGT}$ assumed to be the same with and without BSA.

Table S7. Summary of kidney weight estimates

Population / Country	N	Age Range (yrs)	Mean Body Weight (kg)	Kidney Weight (g/kg body weight)	Reference
Caucasian	M: 355	Mainly <50	68	4.7	(de la Grandmaison et al., 2001)
	F: 329		58	4.7	
NP	M: 2414	20-40	70	4.4	(ICRP, 1975)
	F: 1014		58	4.7	
Denmark	M: 19	16-83	70*	4.1	(Nyengaard and Bendtsen, 1992)
	F: 8	20-87	58*	4.1	
NP	NP	NP	70	5.0	(Rowland and Tozer, 2011)
Total[#] =	4149		Weighted mean[#] =	4.5	
Total M[#] =	2708		Weighted mean M[#] =	4.5	
Total F[#] =	1361		Weighted mean F[#] =	4.7	

F = Females; M = Males; NP = Not presented.

* Mean body weight of 70 kg for males and 58 kg for females assumed as actual value not presented (ICRP, 1975).

Totals and means do not include values presented by Rowland and Tozer (2011).

Table S8. Summary of kidney blood flow estimates

Population / Country	Method	N	Age Range (yrs)	Mean Body Weight (kg)	Kidney Blood Flow (mL/min/kg body weight)	Reference
NP	PAH	M: 3	22-46	70*	21.9~	(Aas and Blegen, 1949)
		F: 6	Mean = 36	58*	18.2~	
NP	PAH	M: 13	24-43	70*	18.1~	(Aurell et al., 1966)
NP	US	5	Mean = 28	70*	17.7~	(Avasthi et al., 1987)
NP	Diodone	M: 13	20-24	70*	18.2~	(Barclay et al., 1947a)
NP	Diodone	10	NP	70*	17.2~	(Barclay et al., 1947b)
NP	PAH	M: 13	29-62	70*	17.2~	(Bolomey et al., 1949)
		F: 5	NP	58*	15.9~	
NP	PAH	5	NP	70*	16.9~	(Bradley and Halperin, 1947)
NP	Diodrast	M: 10	21-25	70*	16.8~	(Brun et al., 1947a)
		F: 10	19-27	58*	16.8~	
NP	PAH	M: 8	23-37	70*	18.1~	(Brun et al., 1947b)
NP	PAH	F: 3	29-51	58*	19.0~	(Bucht, 1949)
NP	PAH	M: 27	18-44	70*	15.2~	(Bucht, 1951)
		F: 20	17-45	58*	14.9~	
NP	PAH	6	22-30	70*	13.6~	(Bucht et al., 1953)
NP	PAH	10	NP	70*	18.9~	(Cargill, 1949)
NP	PAH	M: 9	21-32	70*	16.2~	(Chapman et al., 1948)
NP	PAH	M: 11	NP	70*	19.0~	(Chasis et al., 1945)
		F: 8	NP	58*	17.2~	
NP	Microsphere	M: 6	27-67	70*	11.7~	(Crean et al., 1986)
NP	N_2O	M: 5	21-37	70*	18.2~	(Crosley et al., 1956)
NP	PAH	M: 9	15-44	70*	16.0~	(Culbertson et al., 1957)
NP	Diodrast	M: 28	20-50	70*	18.1~	(Davies and Shock, 1950)
NP	NP	NP	NP	70	17.7	(Davies and Morris, 1993)
NP	PAH	M: 3	NP	70*	19.2~	(De Wardener and McSwiney, 1951)
NP	PAH	M: 8	Mean = 34	70*	20.4~	(Edelman et al., 1950)
		F: 4	Mean = 39	58*	19.2~	
NP	PAH	M: 2	21/52	70*	18.0~	(Fishman et al., 1951)
NP	Diodrast	M: 6	26-62	70*	15.6~	(Foa. P and Foa, 1942)
		F: 5	23-58	58*	17.2~	

Table 8 continued. Summary of kidney blood flow estimates

Population / Country	Method	N	Age Range (yrs)	Mean Body Weight (kg)	Kidney Blood Flow (mL/min/kg body weight)	Reference
NP	PAH	15	NP	70*	15.6~	(Freeman et al., 1955)
NP	Diodrast	M: 6	22-50	70*	21.7~	(Friedman et al., 1941)
		F: 5	25-40	58*	16.9~	
NP	Diodrast	M: 43	NP	70*	20.1~	(Goldring et al., 1940)
		F: 11	Mean = 32	58*	17.1~	
NP	Doppler	16	Mean = 28	70*	11.7~	(Greene et al., 1981)
NP	PAH	M: 15	21-44	70*	16.2~	(Grimby, 1965)
NP	PAH	M: 8	20-45	70*	18.9~	(Heller and Jacobson, 1950)
NP	Xe	36	23-69	70*	16.3~	(Hollenberg et al., 1969)
NP	Diodrast	M: 36	20-50	70*	14.4~	Hogeman, 1948 – reported in (Smith, 1958)
		F: 20		58*	13.3~	
NP	PAH	M: 11	21-56	70*	17.3~	(Ikkos et al., 1956)
		F: 10	23-52	58*	14.0~	
NP	PAH	25	Mean = 31	70*	20.1~	(Kirkendall et al., 1959)
NP	PAH	M: 2	36/45	70*	17.5~	(Kolberg, 1959)
		F: 4	26-46	58*	17.0~	
NP	Xe	M: 6	23-27	70*	19.7~	(Ladefoged and Pedersen, 1967)
NP	Video Dilution	26	NP	70*	15.0~	(Lantz et al., 1981)
NP	PAH	M: 4	42-62	70*	17.7~	(Lauson et al., 1944)
		F: 2	21/48	58*	17.2~	
NP	PAH	M: 7	Mean = 24	70*	20.2~	(Lee et al., 1966)
NP	NP	NP	NP	70*	16.6	(Lentner and Pharmaceuticals, 1981)
		M: NP		70*	17.2	
		F: NP		58*	16.9	
Caucasian	EBCT	8	22-55	90	7.8	(Lerman et al., 1996)
NP	PAH	M: 7	24-42	70*	18.2~	(Lewis et al., 1952)
NP	PAH	M: 18	20-66	70*	16.6~	(Maxwell and Breed, 1951)
NP	PAH	M: 9	Mean = 38	70*	20.1~	(Miles et al., 1952)
NP	PAH	M: 10	22-40	70*	17.3~	(Mokotoff et al., 1948)
		F: 4	23-45	58*	19.1~	
NP	PAH & Diodrast	M: 8	17-48	70*	17.1~	(Nickel et al., 1954)
		F: 10	24-55	58*	15.6~	

Table 8 continued. Summary of kidney blood flow estimates

Population / Country	Method	N	Age Range (yrs)	Mean Body Weight (kg)	Kidney Blood Flow (mL/min/kg body weight)	Reference
NP	PAH	M: 4	NP	70*	16.1~	(Pfeiffer et al., 1950)
		F: 11	23-57	58*	15.5~	
NP	PAH	M: 5	NP	70*	20.7~	(Radigan and Robinson, 1949)
NP	Individual Dilution	8	NP	70*	16.7~	(Reubi et al., 1973)
NP	PAH	M: 10	20-49	70*	19.3~	(Sirota et al., 1950)
NP	PAH	M: 6	NP	70*	14.5~	(Smith et al., 1952)
NP	Diodrast	M: 67	16-60	70*	20.4~	(Smith, 1958)
		F: 17	16-55	58*	17.1~	
NP	PAH	M: 8	30-52	70*	15.9~	(Smythe et al., 1952)
		F: 10	18-37	58*	17.0~	
USA	MRIf	9	26-68	70*	19.6	(Sommer et al., 1992)
	MRIm				11.6	
	PAH				15.0	
NP	TI	M: 6	33-49	70*	12.0~	(Svensson et al., 1982)
NP	Diodrast	M: 3	18-54	70*	20.5~	(Talbott et al., 1942)
		F: 2	23/32	58*	18.3~	
NP	PAH	M: 11	19-40	70*	17.8~	(Thomasson, 1957)
		F: 6	21-40	58*	16.2~	
NP	PAH	50	NP	70*	16.6~	(Werko et al., 1952)
NP	PAH	13	NP	70*	13.6~	(Werko et al., 1952)
NP	PAH	M: 8	27-43	70*	16.6~	(Wesson, 1964)
		F: 4	19-33	58*	14.8~	
NP	PAH	M: 8	20-30	70*	15.6~	(White and Rolf, 1948)
NP	PAH	M: 2	36/43	70*	19.0~	(Wiggins et al., 1951)
		F: 2	32/49	58*	15.2~	
USA	PAH	10	24-56	70*	15.7	(Wolf et al., 1993)
	MR				15.8	

Table 8 continued. Summary of kidney blood flow estimates

Population / Country	Method	N	Age Range (yrs)	Mean Body Weight (kg)	Kidney Blood Flow (mL/min/kg body weight)	Reference
	Total # =	977		Weighted mean # =	16.4	
	M Total # =	520		Weighted mean M # =	16.7	
	F Total # =	177		Weighted mean F # =	16.2	
	PAH Total =	514		Weighted mean PAH =	16.6	

EBCT = Electron beam computer tomography; F = female; M = males; MR = Magnetic resonance imaging; MRIf = Magnetic resonance imaging, flow images; MRIm = Magnetic resonance imaging, magnitude images; NP = Not presented; PAH = Clearance of para-aminohippuric acid.

* Mean body weight of 70 kg for males or mixed populations and 58 kg for females assumed as actual value not presented (ICRP, 1975).

Totals do not include values presented by Giegy Sci Tables (Lentner and Pharmaceuticals, 1981) or Davies and Morris (1993).

~ Percentage of cardiac output data (Williams and Leggett, 1989) converted to blood flow using cardiac output of 6700 mL/min for males and 5800 mL/min for females.

Table 9: Prediction accuracy for IVIVE for intravenous clearance data using the well stirred model to scale up in vitro human liver and kidney microsomal $CL_{int,u,UGT}$ in the presence and absence of BSA and comparison to in vivo CL_{UGT} (% predicted / observed)

Drug	Predicted / Observed CL_{UGT} (% of observed)			
	In vitro HLM data only		In vitro HLM + HKM data	
	- BSA	+ BSA	- BSA	+ BSA
Diclofenac[#]	74.4	102	75.8	106
Gemfibrozil[#]	77.6	360	83.3	396
Mycophenolic Acid	26.5	71.7	33.4	102
Naloxone[#]	28.1	60.8	30.6	68.9
Propofol[#]	24.7	17.8	27.0	24.3
Telmisartan	2.64	12.9	2.66	13.0
N within 2-fold	2	3	2	3
Range (% of observed)	3-78	13-360	3-83	13-396
Mean	39.0	104	42.1	118
Prediction Bias	0.0678	0.337	0.0801	0.458
Prediction Precision	5.54	6.60	5.42	6.60

[#] in vitro $f_{m,UGT}$ in the presence and absence of BSA taken from Kilford (2008).
For mycophenolic acid and telmisartan $f_{m,UGT}$ from in vivo data used.

Table 10: Primary UGT references for manuscript Tables 3 and 4

Drug	Reference
Diclofenac	King C, Tang W, Tephly T and Braun M (2001) Characterization of rat and human UDP-glucuronosyltransferases responsible for the in vitro glucuronidation of diclofenac. *Toxicol Sci* **61**: 49-53. Kuehl GE, Lampe JW, Potter JD and Bigler J (2005) Glucuronidation of nonsteroidal anti-inflammatory drugs: Identifying the enzymes responsible in human liver microsomes. *Drug Metab Dispos* **33**: 1027-1035.
Ezetimibe	Ghosal A, Hapangama N, Yuan Y, Achanfuo-Yeboah J, Iannucci R, Chowdhury S, Alton K, Patrick JE and Zbaida S (2004) Identification of human UDP-glucuronosyltransferase enzyme(s) responsible for the glucuronidation of ezetimibe (Zetia). *Drug Metab Dispos* **32**: 314-320.
Gemfibrozil	Sakaguchi K, Green M, Stock N, Reger TS, Zunic J and King C (2004) Glucuronidation of carboxylic acid containing compounds by UDP-glucuronosyltransferase isoforms. *Arch Biochem Biophys* **424**: 219-225. Mano Y, Usui T and Kamimura H (2007) The UDP-glucuronosyltransferase 2B7 isozyme is responsible for gemfibrozil glucuronidation in the human liver. *Drug Metab Dispos* **35**: 2040-2044.
Mycophenolic Acid	Cheng Z, Radominska-Pandya A and Tephly TR (1999) Studies on the substrate specificity of human intestinal UDP-glucuronosyltransferases 1A8 and 1A10. *Drug Metab Dispos* **27**: 1165-1170. Bernard O and Guillemette C (2004) The main role of UGT1A9 in the hepatic metabolism of mycophenolic acid and the effects of naturally occurring variants. *Drug Metab Dispos* **32**: 775-778. Miles KK, Stern ST, Smith PC, Kessler FK, Ali S and Ritter JK (2005) An investigation of human and rat liver microsomal mycophenolic acid glucuronidation: Evidence for a principal role of UGT1A enzymes and species differences in UGT1A specificity. *Drug Metab Dispos* **33**: 1513-1520. Picard N, Ratanasavanh D, Premaud A, Le Meur Y and Marquet P (2005) Identification of the UDP-glucuronosyltransferase isoforms involved in mycophenolic acid phase II metabolism. *Drug Metab Dispos* **33**: 139-146.
Naloxone	Cheng Z, Radominska-Pandya A and Tephly TR (1999) Studies on the substrate specificity of human intestinal UDP-glucuronosyltransferases 1A8 and 1A10. *Drug Metab Dispos* **27**: 1165-1170. Di Marco A, D'Antoni M, Attaccalite S, Carotenuto P and Laufer R (2005) Determination of drug glucuronidation and UDP-glucuronosyltransferase selectivity using a 96-well radiometric assay. *Drug Metab Dispos* **33**: 812-819.
Propofol	Court MH (2005) Isoform-selective probe substrates for in vitro studies of human UDP-glucuronosyltransferases. *Methods Enzymol* **400**: 104-116.
Telmisartan	Ebner T and Roth W (1999) In vitro glucuronidation of telmisartan, a novel angiotensin II receptor antagonist (abstract). *J Hum Hypertens* **13**: S12. Yamada A, Maeda K, Ishiguro N, Tsuda Y, Igarashi T, Ebner T, Roth W, Ikushiro S and Sugiyama Y (2011) The impact of pharmacogenetics of metabolic enzymes and transporters on the pharmacokinetics of telmisartan in healthy volunteers. *Pharmacogenet Genomics* **21**: 523-530.

References

Aas K and Blegen E (1949) The renal blood flow and the glomerular filtration rate in congestive heart failure and some other clinical conditions. *Scand J Clin Lab Invest* **1:**22-32.

Albeck H, Woodfield S, and Kreek MJ (1989) Quantitative and pharmacokinetic analysis of naloxone in plasma using high-performance liquid chromatography with electrochemical detection and solid-phase extraction. *J Chromatogr* **488:**435-445.

Aurell M, Fritjofsson A, and Grimby G (1966) Renal extraction of para-aminohippurate during variations in renal blood flow and tubular load in man. *Clin Sci* **31:**461-471.

Avasthi PS, Greene ER, and Voyles WF (1987) Noninvasive Doppler assessment of human postprandial renal blood flow and cardiac output. *Am J Physiol* **252:**F1167-1174.

Barclay JA, Cooke WT, and Kenney RA (1947a) Observations on the effects of adrenalin on renal function and circulation in man. *Am J Physiol* **151:**621-625.

Barclay JA, Cooke WT, Kenney RA, and Nutt ME (1947b) The effects of water diuresis and exercise on the volume and composition of the urine. *Am J Physiol* **148:**327-337.

Bolomey AA, Michie AJ, Michie C, Breed ES, Schreiner GE, and Lauson HD (1949) Simultaneous measurement of effective renal blood flow and cardiac output in resting normal subjects and patients with essential hypertension. *J Clin Invest* **28:**10-17.

Bradley SE and Halperin MH (1947) Renal oxygen consumption and sodium p-aminohippurate (PAH) extraction in normal man during abdominal compression. *Fed Proc* **6:**80.

Brenner SS, Herrlinger C., Dilger K., Murdter T.E., Hofmann U.; Marx C., and U. K (2003) Influence of Age and Cytochrome P450 2C9 Genotype on the Steady-State Disposition of Diclofenac and Celecoxib. *Clin Pharmacokinet* **42:**283-292.

Brun C, Hilden T, and Raaschou F (1947a) The maximum tubular excretion of diodrast in the normal human kidney. *Acta Med Scand* **127:**464-470.

Brun C, Hilden T, and Raaschou F (1947b) On the excretion of p-aminohippuric acid through the kidneys. *Acta Med Scand* **127:**471-479.

Bucht H (1949) Examination of the renal plasma flow by means of para-amino-hippuric acid (PAH) using one intramuscular injection. *Scand J Clin Lab Invest* **1:**126-130.

Bucht H (1951) Studies on renal function in man with special reference to glomerular filtration and renal plasma flow in pregnancy. *Scand J Clin Lab Invest* **3:**1-64.

Bucht H, Ek J, Eliasch H, Holmgren A, Josephson B, and Werko L (1953) The effect of exercise in the recumbent position on the renal circulation and sodium excretion in normal individuals. *Scand j Clin Lab Invest* **28:**95-100.

Bullingham R, Monroe S, Nicholls A, and Hale M (1996) Pharmacokinetics and bioavailability of mycophenolate mofetil in healthy subjects after single-dose oral and intravenous administration. *J Clin Pharmacol* **36:**315-324.

Bullingham RE, Nicholls AJ, and Kamm BR (1998) Clinical pharmacokinetics of mycophenolate mofetil. *Clin pharmacokinet* **34:**429-455.

Campbell GA, Morgan DJ, Kumar K, and Crankshaw DP (1988) Extended blood collection period required to define distribution and elimination kinetics of propofol. *Br J Clin Pharmacol* **26:**187-190.

Cargill WH (1949) The measurement of glomerular and tubular plasma flow in the normal and diseased human kidney. *J Clin Invest* **28:**533-538.

Chapman CB, Henschel A, Minckler J, Forsgren A, and Keys A (1948) The effect of exercise on renal plasma flow in normal male subjects. *J Clin Invest* **27:**639-644.

Chasis H, Redish J, Goldring W, Ranges HA, and Smith HW (1945) The use of sodium p-aminohippurate for the functional evaluation of the human kidney. *J Clin Invest* **24:**583-588.

Cockshott ID, Briggs LP, Douglas EJ, and White M (1987) Pharmacokinetics of propofol in female patients. Studies using single bolus injections. *Br J Anaesth* **59:**1103-1110.

Crean PA, Pratt T, Davies GJ, Myers M, Lavender P, and Maseri A (1986) The fractional distribution of the cardiac output in man using microspheres labelled with technetium-99m. *Br J Radiol* **59:**209-215.

Crosley APJ, Brown JF, Huston JH, Emanuel DA, Tuchman H, Castillo C, and Rowe GG (1956) The adaptation of the nitrous oxide method to the determination of renal blood flow and in vivo renal weight in man. *J Clin Invest* **35:**1340-1344.

Culbertson JW, Eckstein JW, Kirkendall WM, and Bedell GN (1957) General hemodynamics and splanchnic circulation in patients with coarctation of the aorta. *J Clin Invest* **36:**1537-1545.

Davies B and Morris T (1993) Physiological parameters in laboratory animals and humans. *Pharm Res* **10:**1093-1095.

Davies DF and Shock NW (1950) Age changes in glomerular filtration rate, effective renal plasma flow, and tubular excretory capacity in adult males. *J Clin Invest* **29:**496-507.

Dawidowicz AL and Kalityński R (2003) HPLC investigation of free and bound propofol in human plasma and cerebrospinal fluid. *Biomed Chromatogr* **17:**447-452.

Dawidowicz AL, Kalitynski R, and Fijalkowska A (2004) Relationships Between Total and Unbound Propofol in Plasma and CSF During Continuous Drug Infusion. *Clin Neurophamacol* **27:**129-132.

de la Grandmaison GL, Clairand I, and Durigon M (2001) Organ weight in 684 adult autopsies: new tables for a Caucasoid population. *Forensic Sci Int* **119:**149-154.

De Wardener HE and McSwiney RR (1951) Renal hemodynamics in vaso-vagal fainting due to hemorrhage. *Clin Sci* **10:**209-217.

Deguchi T, Watanabe N, Kurihara A, Igeta K, Ikenaga H, Fusegawa K, Suzuki N, Murata S, Hirouchi M, Furuta Y, Iwasaki M, Okazaki O, and Izumi T (2011) Human Pharmacokinetic Prediction of UDP-Glucuronosyltransferase Substrates with an Animal Scale-Up Approach. *Drug Metab Disp* **39:**820-829.

Doenicke AW, Roizen MF, Rau J, O'Connor M, Kugler J, Klotz U, and Babl J (1997) Pharmacokinetics and pharmacodynamics of propofol in a new solvent. *Anesth Analg* **85:**1399-1403.

Dowling J, Isbister GK, Kirkpatrick CM, Naidoo D, and Graudins A (2008) Population pharmacokinetics of intravenous, intramuscular, and intranasal naloxone in human volunteers. *Ther Drug Monit* **30:**490-496.

Edelman IS, Zweifach BW, Escher DJW, Grossman J, Mokotoff R, Weston RE, Leiter L, and Shorr E (1950) Studies on VEM and VDM in blood in relation to renal hemodynamics and renal oxygen extraction in chronic congestive heart failure. *J Clin Invest* **29:**925-934.

Fishman AP, Maxwell MH, Crowder CH, and Morales P (1951) Kidney function in cor pulmonale. Particular consideration of changes in renal hemodynamics and sodium excretion during variation in level of oxygenation. *Circulation* **3:**703-721.

Fishman J, Roffwarg H, and Hellman L (1973) Disposition of naloxone-7,8-3H in normal and narcotic-dependent men. *J Pharmacol Exp Ther* **187:**575-580.

Foa. P P and Foa NL (1942) A simple method for determining effective renal blood flow and tubular excretory mass in man. **51:**375-378.

Freeman OW, Mitchell GW, Wilson JS, Fitzhugh FW, Merrill AJ, Burns B, and Cavin E (1955) Renal hemodynamics, sodium and water excretion in supine exercising normal and cardiac patients. *J Clin Invest* **34:**1109-1113.

Friedman M, Selzer A, and Rosenblum H (1941) The renal blood flow in coarctation of the aorta. *J Clin Invest* **20:**107-111.

Gepts EM, Camu FM, Cockshott IDP, and Douglas EJH (1987) Disposition of Propofol Administered as Constant Rate Intravenous Infusions in Humans. *Anesth Analg* **66:**1256-1263.

Gill SS, Wright EM, and Reilly CS (1990) Pharmacokinetic interaction of propofol and fentanyl: Single bolus injection study. *Br J Anaesth* **65:**760-765.

Goldring W, Chasis H, Ranges HA, and Smith HW (1940) Relations of effective renal blood flow and glomerular filtration to tubular excretory mass in normal man. *J Clin Invest* **19:**739-750.

Goodman L and Gilman A (2006) *Goodman & Gilman's the pharmacological basis of therapeutics*. McGraw-Hill, New York

Greene ER, Venters MD, Avasthi PS, Conn RL, and Jahnke RW (1981) Noninvasive characterization of renal artery blood flow. *Kidney Int* **20:**523-529.

Grimby GJ (1965) Renal clearances during prolonged supine exercise at different loads. *J Appl Physiol* **20:**1294-1298.

Harris DS, Jones RT, Welm S, Upton RA, Lin E, and Mendelson J (2000) Buprenorphine and naloxone co-administration in opiate-dependent patients stabilized on sublingual buprenorphine. *Drug Alcohol Depend* **61:**85-94.

Heller BI and Jacobson WE (1950) Renal hemodynamics in heart disease. *Am Heart J* **39:**188-204.

Hinz B, Chevts J, Renner B, Wuttke H, Rau T, Schmidt A, Szelenyi I, Brune K, and Werner U (2005) Bioavailability of diclofenac potassium at low doses. *Br J Clin Pharmacol* **59:**80-84.

Hollenberg NK, Epstein M, Basch RI, Merrill JP, and Hickler RB (1969) Renin secretion in the patient with hypertension: Relationship to intrarenal blood flow distribution. *Circ Res* **24:**113-122.

http://www.pfizer.com/files/products/uspi_lopid.pdf.

ICRP (1975) *International Commission on Radiological Protection. Report of the Task Group on Reference Man. ICRP Publication 23*. Pergamon Press, Great Britain.

Ikkos D, Ljunggren H, and Luft R (1956) Glomerular filtration rate and renal plasma flow in acromegaly. *Acta Endocrinol (Copenh)* **21:**226-236.

Kilford PJ (2008) In vitro assessment and prediction of drug glucuronidation clearance, in: *Faculty of Medical and Human Sciences*, University of Manchester, Manchester.

Kirkendall WM, Culbertson JW, and Eckstein JW (1959) Renal hemodynamics in patients with coarctation of the aorta. *J Lab Clin Med* **53:**6-21.

Kirkpatrick T, Cockshott ID, Douglas EJ, and Nimmo WS (1988) Pharmacokinetics of propofol (Diprivan) in elderly patients. *Br J Anaesth* **60:**146-150.

Knauf H, Kölle EU, and Mutschler E (1990) Gemfibrozil absorption and elimination in kidney and liver disease. *Klin Wochenschr* **68:**692-698.

Kolberg A (1959) Relations of renal tubular and glomerular function as influenced by 75 per cent reduction of nephron number. *Scand J Clin Lab Invest* **11:**1-152.

Ladefoged J and Pedersen F (1967) Renal blood flow, circulation times and vascular volume in normal man measured by the intraarterial injection - external counting technique. *Acta Physiol Scand* **69:**220-229.

Langman LJ, LeGatt DF, and Yatscoff RW (1994) Blood Distribution of Mycophenolic Acid. *Ther Drug Monit* **16:**602-607.

Lantz BMT, Foerster JM, Link DP, and Holcroft JW (1981) Regional distribution of cardiac output: Normal values in man determined by video dilution technique. *Am J Roentgenol* **137:**903-907.

Lauson HD, Bradley SE, Cournand A, and Andrews VV (1944) The renal circulation in shock. *J Clin Invest* **23:**381-402.

Lee TD, Lindeman RD, Yiengst MJ, and Shock NW (1966) Influence of age on the cardiovascular and renal responses to tilting. *J Appl Physiol* **21:**55-61.

Lentner C and Pharmaceuticals G (1981) *Geigy Scientific Tables. Vol.1, Units of Measurement, Body Fluids, Composition of the Body, Nutrition* Ciba-Geigy, Basle.

Lerman LO, Flickinger AL, Sheedy PF, and Turner ST (1996) Reproducibility of human kidney perfusion and volume determinations with electron beam computed tomography. *Invest Radiol* **31:**204-210.

Lévesque E, Benoit-Biancamano M-O, Delage R, Couture Fl, and Guillemette C (2008) Pharmacokinetics of mycophenolate mofetil and its glucuronide metabolites in healthy volunteers. *Pharmacogenomics* **9:**869-879.

Lewis CS, Samuels AJ, Daines MC, and Hecht HH (1952) Cardiorespiratory, vascular and renal adjustments in cor pulmonale. *Circulation* **6:**874-887.

Maxwell M, H, and Breed ES (1951) The effect of the intravenous administration of pitressin on renal function in man. *J Pharmacol Exp Ther* **103:**190-195.

Mertens MJ, Olofsen E, Burm AG, Bovill JG, and Vuyk J (2004) Mixed-effects Modeling of the Influence of Alfentanil on Propofol Pharmacokinetics. *Anesthesiology* **100:**795-805.

Miles BE, De Wardener HE, Churchill-Davidson HC, and Wylie WD (1952) The effect on the renal circulation of pentamethonium bromide during anesthesia. *Clin Sci* **11:**73-79.

Miles KK, Stern ST, Smith PC, Kessler FK, Ali S, and Ritter JK (2005) An investigation of human and rat liver microsomal mycophenolic acid glucuronidation: Evidence for a principal role of UGT1A enzymes and species differences in UGT1A specificity. *Drug Metab Dispos* **33:**1513-1520.

Moffat AC, Osselton MD, and Widdop B (2004) *Clarke's Analysis of Drugs and Poisons*. Pharmaceutical Press, London.

Mokotoff R, Ross G, and Leiter L (1948) Renal plasma flow and sodium reabsorption and excretion in congestive heart failure. *J Clin Invest* **27:**1-9.

Morissette P, Albert C, Busque S, St-Louis G, and Vinet B (2001) In vivo higher glucuronidation of mycophenolic acid in male than in female recipients of a cadaveric kidney allograft and under immunosuppressive therapy with mycophenolate mofetil. *Ther Drug Monit* **23:**520-525.

Nickel JF, Smythe C, Papper EM, and Bradley SE (1954) A study of the mode of action of the adrenal medullary hormones on sodium, potassium, and water excretion in man. *J Clin Invest* **33:**1687-1699.

Nowak I and Shaw LM (1995) Mycophenolic acid binding to human serum albumin: characterization and relation to pharmacodynamics. *Clin Chem* **41:**1011-1017.

Nyengaard JR and Bendtsen TF (1992) Glomerular number and size in relation to age, kidney weight, and body surface in normal man. *The Anatomical record* **232:**194-201.

Obach RS, Lombardo F, and Waters NJ (2008) Trend Analysis of a Database of Intravenous Pharmacokinetic Parameters in Humans for 670 Drug Compounds. *Drug Metab Disp* **36:**1385-1405.

Okerholm RA, Keeley FJ, Peterson FE, and Glazko AJ (1976) The metabolism of gemfibrozil. *Proc R Soc Med* **69:**11-14.

Pfeiffer JBJ, Wolff HG, and Winter OS (1950) Studies in renal circulation during periods of life stress and accompanying emotional reactions in subjects with and without essential hypertension; observations on the role of neural activity in regulation of renal blood flow. *J Clin Invest* **29:**1227-1242.

Radigan LR and Robinson S (1949) Effects of environmental heat stress and exercise on renal blood flow and filtration rate. *J Appl Physiol* **2:**185-191.

Reubi FC, Vorburger C, and Tuckman J (1973) Renal distribution volumes of indocyanine green, [Cr-51-] EDTA, and Na-24 in man during acute renal failure after shock. *J Clin Invest* **52:**223-235.

Reyderman L, Kosoglou T, Statkevich P, Pember L, Boutros T, Maxwell SE, Affrime M, and Batra V (2004) Assessment of a multiple-dose drug interaction between ezetimibe, a novel selective cholesterol absorption inhibitor and gemfibrozil. *International journal of clinical pharmacology and therapeutics* **42:**512-518.

Rowland M and Tozer TN (2011) *Clinical Pharmacokinetics and Pharmacodynamics: Concepts and Applications*. Lippincott Williams and Wilkins, Philadelphia ; London.

Servin F, Cockshott ID, Farinotti R, Haberer JP, Winckler C, and Desmonts JM (1990) Pharmacokinetics of propofol infusions in patients With cirrhosis. *Br J Anaesth* **65:**177-183.

Servin F, Desmonts JM, Farinotti R, Haberer JP, and Wtnckler C (1988a) Pharmacokinetics of propofol administered by continuous infusion in patients with cirrhosis. *Anaesthesia* **43:**23-24.

Servin F, Desmonts JM, Haberer JP, Cockshott ID, Plummer GF, and Farinotti R (1988b) Pharmacokinetics and Protein Binding of Propofol in Patients with Cirrhosis. *Anesthesiology* **69:**887-891.

Simons PJ, Cockshott ID, Douglas EJ, Gordon EA, Hopkins K, and Rowland M (1988) Disposition in male volunteers of a subanaesthetic intravenous dose of an oil in water emulsion of 14C-propofol. *xenobiotica* **18:**429-440.

Sirota JH, Baldwin DS, and Villarreal (1950) Diurnal variations of renal function in man. *J Clin Invest* **29:**187-192.

Smith HW (1958) *The Kidney Structure and Function in Health and Disease*. Oxford University Press, New York

Smith JH, Robinson S, and Pearcy M (1952) Renal responses to exercise, heat and dehydration. *J Appl Physiol* **4:**659-665.

Smythe CM, Nickel JF, and Bradley SE (1952) The effect of epinephrine (USP), l-epinephrine, and l-norepinephrine on glomerular filtration rate, renal plasma flow, and the urinary excretion of sodium, potassium, and water in normal man. *J Clin Invest* **31:**499-506.

Sommer G, Noorbehesht B, Pelc N, Jamison R, Pinevich AJ, Newton L, and Myers B (1992) Normal renal blood flow measurement using phase-contrast cine magnetic resonance imaging. *Invest radiol* **27:**465-470.

Stangier J, Schmid J, Turck D, Switek H, Verhagen A, Peeters PA, van Marle SP, Tamminga WJ, Sollie FA, and Jonkman JH (2000a) Absorption, metabolism, and excretion of intravenously and orally administered [14C]telmisartan in healthy volunteers. *J Clin Pharmacol* **40:**1312-1322.

Stangier J, Su CAPF, and Roth W (2000b) Pharmacokinetics of Orally and Intravenously Administered Telmisartan in Healthy Young and Elderly Volunteers and in Hypertensive Patients. *J Int Med Res* **28:**149-167.

Svensson SE, Lomsky M, Olsson L, Persson S, Strauss HW, and Westling H (1982) Non-invasive determination of the distribution of cardiac output in man at rest and during exercise. *Clin Physiol* **2:**467-477.

Talbott JH, Pecora LJ, Melville RS, and Consolazio WV (1942) Renal function in patients with Addison's disease and in patients with adrenal insufficiency secondary to pituitary pan-hypofunction. *J Clin Invest* **21:**107-119.

Thomasson B (1957) Cardiac output in normal subjects under standard basal conditions: The repeatability of measurements by the Fick method. *Scand J Clin Lab Invest* **9:**365-376.

Veroli P, O'Kelly B, Bertrand F, Trouvin JH, Farinotti R, and Ecoffey C (1992) Extrahepatic metabolism of propofol in man during the anhepatic phase of orthotopic liver transplantation. *Br J Anaesth* **68:**183-186.

Vozeh S, Schmidlin O, and Taeschner W (1988) Pharmacokinetic drug data. *Clin Pharmacokinet* **15:**254-282.

Vree TB, Baars AM, and De Grood PMRM (1987) High-performance liquid chromatographic determination and preliminary pharmacokinetics of propofol and its metabolites in human plasma and urine. *J Chromatogr* **417:**458-464.

Vuyk J, Lichtenbelt BJ, Olofsen E, van Kleef JW, and Dahan A (2009) Mixed-effects modeling of the influence of midazolam on propofol pharmacokinetics. *Anesth Analg* **108:**1522-1530.

Wallenstein GC, Stangier J, and Ludden TM (1999) Analyzing Rich Data Using Different Methods Provided by NONMEM: Pharmacokinetics of Telmisartan Following Intravenous Infusion to Healthy Volunteers. *Pharm Res* **16:**772-776-776.

Werko L, Ek J, Bucht H, and Eliasch H (1952) Correlation between renal dynamics, cardiac output and right heart pressures in mitral valvular disease. *Scand J Clin Lab Invest* **4:**15-23.

Wesson LG (1964) Electrolyte excretion in relation to diurnal cycles of renal function. *Medicine* **43:**547-592.

White HL and Rolf D (1948) Effects of exercise and of some other influences on the renal circulation in man. *Am J Physiol* **152:**505-516.

Wiggins WS, Manry CH, Lyons RH, and Pitts RF (1951) The effect of salt loading and salt depletion on renal function and electrolyte excretion in man. *Circulation* **3:**275-281.

Williams LR and Leggett RW (1989) Reference values for resting blood flow to organs of man *Clin Phys Physiol Meas* **10:**187-217.

Willis JV and Kendall MJ (1978) Pharmacokinetic Studies on Diclofenac Sodium in Young and Old Volunteers. *Scand J Rheumatol* **7:**36-41.

Willis JV, Kendall MJ, Flinn RM, Thornhill DP, and Welling PG (1979) The pharmacokinetics of diclofenac sodium following intravenous and oral administration. *Eur J Clin Pharmacol* **16:**405-410.

Willis JV, Kendall MJ, and Jack DB (1980) A study of the effect of aspirin on the pharmacokinetics of oral and intravenous diclofenac sodium. *Eur J Clin Pharmacol* **18:**415-418-418.

Wolf RL, King BF, Torres VE, Wilson DM, and Ehman RL (1993) Measurement of normal renal artery blood flow: cine phase-contrast MR imaging vs clearance of p-aminohippurate. *Am J Roentgenol* **161:**995-1002.