ERRATUM

Quantitative Relationships Between Structure and Pharmacokinetics of Beta-Adrenoceptor Blocking Agents in Man¹

Peter H. Hinderling,² Olga Schmidlin,^{2,4} and Jochen K. Seydel³

A review of the steady state volume of distribution (V_{SS}) data of the beta-adrenoceptor blocking agents (BA) in the report (Vol. 12, No. 3, p. 272, Table II) showed that an erroneous value of 37 l had been calculated and employed for timolol. As this value of V_{SS} was used in calculating the steady state volume of distribution referenced to the unbound drug in plasma, Vu_{SS} , the ratio of the fraction of drug bound and unbound to tissue, r_T , and the mean residence time, MRT , the values of these three parameters were also erroneous for timolol. Consequently, the regressions (linear or parabolic) of Vu_{SS} , r_T , and MRT against the apparent octanol/buffer (pH 7.4) partition coefficient determined by the shake flask method, $K_{SF}^{7.4}$, and against the partition coefficient of drug between plasma and plasma water, K_p , had to be repeated for the whole series of BA tested. On the basis of the new regression equations obtained, the predictions of the Vu_{SS} - and MRT -values of the BA considered were then revised.

The correct values for V_{SS} (100 l), Vu_{SS} (270 l), r_T (0.840), and MRT (168 min) for timolol are given in the revised Tables II and III. The correct coefficients of the log-log regressions of Vu_{SS} , r_T , and MRT on $K_{SF}^{7.4}$ and K_p for the BA tested are presented in Tables IV and V, respectively. The log-log fits of the recalculated Vu_{SS} - and MRT -values against $K_{SF}^{7.4}$ are shown in Figs. 4 and 8, and the correctly predicted values for Vu_{SS} and

¹J. Pharmacokin. Biopharm. 12: 263-287 (1984).

²Department of Pharmacology, Biocenter, University of Basle, Klingelbergstr. 70, 4056 Basle, Switzerland.

³Department of Medicinal and Pharmaceutical Chemistry, Research Institute Borstel, Parkallee 1-40, 2061 Borstel, Federal Republic of Germany.

⁴Present Address: Department of Internal Medicine, University of Basle, Petersgraben 6, 4059 Basle, Switzerland.

Table II. Mean Primary Pharmacokinetic Parameters of β -Adrenoceptor Antagonists^a

BA	f_b	f_A	f_G	$K_{BC/PW}$	$V_{SS}(l)$	CL_{NR} (ml/min)	CL_R (ml/min)	$Ae(oo)/D$
Penbutolol	0.98 ⁽²¹⁾				130 ⁽²²⁾	535 ^(22,60)	4 ⁽⁶⁰⁾	0.02 ⁽⁶⁰⁾
Bufuralol	0.91 ⁽²²⁾				148 ⁽⁴⁰⁾	718 ^(23,40)	37 ^(23,40)	0.05 ⁽²³⁾
Tolamolol	0.91 ⁽⁴⁰⁾			5.11 ⁽⁴⁰⁾	137 ⁽⁵²⁾	676 ^(52,61)	27 ⁽⁶¹⁾	0.04 ⁽⁶¹⁾
Propranolol	0.93 ⁽⁴¹⁾	0.55 ⁽⁴¹⁾	0.69 ⁽⁴¹⁾	5.5 ⁽⁴⁶⁾	75 ^(53,54)	435 ^(23,62)	18 ⁽⁶⁵⁾	0.02 ⁽⁶²⁾
Alprenolol	0.76 ⁽⁴¹⁾	0.40 ⁽⁴¹⁾	0.55 ⁽⁴¹⁾	4.00 ⁽⁴⁷⁾		174 ^(63,48)	22 ⁽⁴⁸⁾	0.11 ^(48,63)
Oxprenolol	0.92 ⁽⁴¹⁾	0.23 ⁽⁴¹⁾	0.72 ⁽⁴¹⁾	1.39 ⁽⁴⁸⁾		475 ⁽⁴²⁾	295 ⁽⁴²⁾	0.41 ⁽⁴²⁾
Acebutolol	0.26 ⁽⁴²⁾			2.88 ⁽⁴²⁾	93 ⁽⁴²⁾	524 ⁽⁶⁴⁾	70 ⁽⁶⁴⁾	0.12 ⁽⁶⁴⁾
Timolol	0.60 ⁽⁴¹⁾	0.07 ⁽⁴¹⁾	0.27 ⁽⁴¹⁾	1.27 ⁽²⁸⁾	100 ^(55,56)	701 ⁽⁵⁷⁾	93 ⁽⁵⁷⁾	0.15 ⁽⁵⁷⁾
Metoprolol	0.08 ⁽⁴¹⁾	0.16 ⁽⁴¹⁾	0.06 ⁽⁴¹⁾	1.40 ⁽²⁹⁾	223 ⁽⁶⁷⁾	266 ⁽⁵⁸⁾	272 ⁽⁵⁸⁾	0.50 ⁽⁵⁸⁾
Pindolol	0.59 ⁽⁴¹⁾	0.18 ⁽⁴¹⁾	0.31 ⁽⁴¹⁾	1.86 ⁽⁴⁹⁾	81 ⁽⁵⁸⁾			
Practolol	0.07 ⁽⁴³⁾			1.10 ⁽⁵⁰⁾				
Atenolol	0.03 ⁽⁴¹⁾			1.21 ⁽⁵¹⁾	78 ⁽⁵⁹⁾	10 ⁽⁵⁹⁾	168 ⁽⁵⁹⁾	0.94 ⁽⁵⁹⁾
Nadolol	0.28 ⁽⁴⁴⁾				133 ⁽⁴⁴⁾	49 ⁽⁴⁴⁾	153 ⁽⁴⁴⁾	0.76 ⁽⁴⁴⁾
Sotalol	0 ⁽⁴⁵⁾			1.16 ⁽²⁸⁾	95 ⁽⁴⁵⁾	0 ⁽⁴⁵⁾	159 ⁽⁴⁵⁾	1.00 ⁽⁴⁵⁾

^aNumber in parentheses are references.

Table III. Mean Secondary Pharmacokinetic Parameters of β -Adrenoceptor Antagonists in Humans

BA	K_p	r_A	r_G	K_{BC}	V_{dSS} (l)	r_T	r	MRT (min)	CL_{TUB} (ml/min)
Pentbutolol	931				1440	34.7	61.5	241	-8
Bufuralol	192				1640	36.9	19.4	195	25
Tolamolol	192			6.30	1960	41.0	25.3	195	18
Propranolol	253	1.23	2.21	6.86	313	8.09	65.7	170	13
Alprenolol	60.2	0.658	1.20	4.71					
Oxprenolol	219	0.294	2.58	0.990			8.09		12
Acebutolol	6.67			3.11	126	4.56	1.44	121	199
Timolol	28.5	0.0753	0.362	0.810	250	0.840	7.33	168	18
Metoprolol	13.2	0.155	0.0661	1.00	242	7.55	5.67	281	-27
Pindolol	27.5	0.225	0.443	1.66	198	2.88	1.00	151	219
Practolol	1.43			0.570					
Atenolol	0.587			0.730	80	1.59	0.0638	517	42
Nadolol	7.39				185	3.65	0.316	658	59
Sotalol				0.660	95	0.0718		597	29

Table IV. Regressions of the Pharmacokinetic Parameters on the Apparent Octanol/Buffer (pH 7.4) Partition Coefficient

Linear Regressions					
Eq. I	$\log K_P$	$= 1.41(\pm 0.12) + 0.65(\pm 0.10) \cdot \log K_{SF}^{I,4}$	$r = 0.895$	$n = 13$	$p < 0.0001^a$
Eq. II	$\log r_A$	$= -0.65(\pm 0.10) + 0.57(\pm 0.15) \cdot \log K_{SF}^{I,4}$	$r = 0.890$	$n = 6$	$p < 0.02^a$
Eq. III	$\log r_G$	$= -0.34(\pm 0.21) + 0.63(\pm 0.32) \cdot \log K_{SF}^{I,4}$	$r = 0.703$	$n = 6$	$p < 0.2$
Eq. IV	$\log K_{BC}$	$= 0.28(\pm 0.07) + 0.31(\pm 0.06) \cdot \log K_{SF}^{I,4}$	$r = 0.867$	$n = 11$	$p < 0.001^a$
Eq. V	$\log V_{dSS}$	$= 2.52(\pm 0.08) + 0.34(\pm 0.71) \cdot \log K_{SF}^{I,4}$	$r = 0.865$	$n = 11$	$p < 0.002^a$
Eq. VI	$\log r_T$	$= 0.70(\pm 0.12) + 0.51(\pm 0.15) \cdot \log K_{SF}^{I,4}$	$r = 0.827$	$n = 11$	$p < 0.002^a$
Eq. VII	$\log r$	$= 0.59(\pm 0.12) + 0.75(\pm 0.10) \cdot \log K_{SF}^{I,4}$	$r = 0.926$	$n = 11$	$p < 0.0001^a$
Eq. VIII	CL_{TUB}	$= 63.00(\pm 25.50) - 1.28(\pm 1.21) \cdot K_{SF}^{I,4}$	$r = 0.316$	$n = 11$	$p < 0.5$
Parabolic Regressions					
Eq. IX	$\log CL_R$	$= 1.96(\pm 0.14) - 0.38(\pm 0.08) \cdot \log K_{SF}^{I,4} - 0.13(\pm 0.07) \cdot \log K_{SF}^{I,4,2}$	$r = 0.846$	$n = 12$	$p < 0.002^a$
Eq. X	$\log CL_{NR}$	$= 2.65(\pm 0.13) + 0.39(\pm 0.08) \cdot \log K_{SF}^{I,4} - 0.21(\pm 0.07) \cdot \log K_{SF}^{I,4,2}$	$r = 0.896$	$n = 11$	$p < 0.001^a$
Eq. XI	$\log MRT$	$= 2.21(\pm 0.05) - 0.10(\pm 0.03) \cdot \log K_{SF}^{I,4} + 0.11(\pm 0.02) \cdot \log K_{SF}^{I,4,2}$	$r = 0.925$	$n = 11$	$p < 0.001^a$

^aLevels of $p < 0.05$ were considered to be significant.

Table V. Regressions of Pharmacokinetic Parameters on the Protein/Plasma Water Partition Coefficient

Linear Regressions					
Eq. I	$\log r_A$	$= -1.50 (\pm 0.55) + 0.56 (\pm 0.30) \cdot \log K_P$	$r = 0.677$	$n = 6$	$p < 0.2$
Eq. II	$\log r_G$	$= -2.09 (\pm 0.36) + 1.68 (\pm 0.19) \cdot \log K_P$	$r = 0.938$	$n = 6$	$p < 0.01^a$
Eq. III	$\log K_{BC}$	$= -0.14 (\pm 0.20) + 0.29 (\pm 0.12) \cdot \log K_P$	$r = 0.640$	$n = 10$	$p < 0.05^a$
Eq. IV	$\log V_{t_{SS}}$	$= 1.76 (\pm 0.08) + 0.55 (\pm 0.14) \cdot \log K_P$	$r = 0.919$	$n = 10$	$p < 0.002^a$
Eq. V	$\log r_T$	$= 0.06 (\pm 0.17) + 0.54 (\pm 0.27) \cdot \log K_P$	$r = 0.753$	$n = 10$	$p < 0.01^a$
Eq. VI	$\log r$	$= -0.85 (\pm 0.33) + 1.01 (\pm 0.19) \cdot \log K_P$	$r = 0.868$	$n = 11$	$p < 0.001^a$
Eq. VII	CL_{TUB}	$= 81.40 (\pm 32.6) - 0.33 (\pm 0.25) \cdot K_P$	$r = 0.402$	$n = 10$	$p < 0.5$
Parabolic Regressions					
Eq. VIII	$\log CL_R$	$= 2.32 (\pm 0.29) + 0.11 (\pm 0.44) \cdot \log K_P - 0.25 (\pm 0.17) \cdot \log K_P^2$	$r = 0.805$	$n = 10$	$p < 0.01^a$
Eq. IX	$\log CL_{NR}$	$= 1.35 (\pm 0.26) + 1.42 (\pm 0.41) \cdot \log K_P - 0.37 (\pm 0.15) \cdot \log K_P^2$	$r = 0.844$	$n = 11$	$p < 0.01^a$
Eq. X	$\log MRT$	$= 2.65 (\pm 0.16) - 0.38 (\pm 0.25) \cdot \log K_P + 0.10 (\pm 0.10) \cdot \log K_P^2$	$r = 0.584$	$n = 10$	$p < 0.2$

^aLevels of $p < 0.05$ were considered to be significant.

Table VI. Predicted and Experimentally Found Values of Pharmacokinetic Parameters of β -Adrenoceptor Antagonists

Drug	V_{tSS} (L)		CL_R (ml/min)		CL_{NR} (ml/min)		MRT (min)		Ave % error (range)
	Pred	Found	Pred	Found	Pred	Found	Pred	Found	
Bufuralol	1190	1440	14	4	468	535	222	241	29 (9-71)
Tolamolol	1064	1640	18	37	575	718	239	195	50 (18-106)
Propanolol	1014	1960	22	27	537	676	189	195	36 (3-93)
Alprenolol	635	313	43	18	589	435	180	170	36 (6-58)
Oxprenolol			43	22	490	174			
Acebutolol	228	126	140	295	263	475	213	121	70 (43-111)
Timolol	328	250	100	70	398	524	189	168	24 (11-32)
Metropolol	255	242	130	93	316	701	201	281	48 (5-122)
Pindolol	307	198	110	272	407	266	195	151	60 (23-147)
Practolol									
Atenolol	68	80	190	168	16	10	553	517	19 (7-37)
Nadolol	134	185	170	153	71	49	248	658	61 (10-165)
Ave % error (range)	38 (5-93)		59 (10-147)		45 (14-122)		24 (3-75)

Fig. 4. Correlation between the steady state volume of distribution referenced to the unbound drug in plasma and the octanol/buffer partition coefficient by the shake flask method.

MRT based on the regressions of these parameters on $K_{SF}^{7.4}$ and K_p are given in Table VI.

It can be seen that the recalculated parameters for timolol no longer deviated systematically from the best fitting line in the regressions (Figs. 4, 8) as they did previously. Consequently, the recalculated mean percent errors of the predicted values for $V_{u,ss}$ and *MRT* were smaller, and were 38 and 24% as against the previously obtained 51 and 48%, respectively (Table IV). The overall mean percent error for the predicted values of all the parameters considered also decreased from 60 to 42%.

In summary, all the conclusions drawn previously for the series of BA tested could be confirmed: there existed significant structure-pharmacokinetic relationships for beta-adrenoceptor antagonists.

Fig. 8. Correlation between the mean residence time and the octanol/buffer partition coefficient by the shake flask method.

The majority of the studied pharmacokinetic parameters depended on the apparent octanol/buffer (pH 7.4) partition coefficient. Significant correlations existed also among the pharmacokinetic parameters tested. Lipophilicity/hydrophilicity was the major determinant controlling the pharmacokinetic behavior of all the compounds studied, including timolol, which previously deviated systematically from the other BA. This result for timolol was new.