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Recirculatory Moment Analysis of Drugs in Man: Estimation of Extraction Ratio and Mean Cycle Time for Single Systemic and Pulmonary Circulation

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The extraction ratio (E_c) and the mean cycle times ($\bar{t}_c$) for single systemic and pulmonary circulation were evaluated for 115 drugs in man. Heparin and fluorohydrocortisone, which have the smallest $\bar{t}_c$ values (about 1 min) show the small E_c values (close to zero). This result suggests that these drugs circulate through the body restricted within the blood vessels. The theoretical considerations indicate that the clearances defined by $A_i(\infty)/AUC$ differ from E_iQ_i, where $A_i(\infty)$ is the amount eliminated by organ i, AUC is the area under the plasma concentration curve, E_i is the extraction ratio and Q_i is plasma flow rate through organ i. The hepatic extraction ratios (E_h) of alprenolol, metoprolol and propranolol calculated from intravenous data alone are large (above 80%). It is also shown that the steady-state volume of distribution (V_{ss}) is rather independent of hepatic and renal extraction ratios, while the mean residence time (MRT) is considerably affected by change of these ratios.

Keywords——mean transit time; mean cycle time; mean residence time; pharmacokinetics; moment analysis; first-pass effect

Introduction

Recently, a theory of drug disposition based on the anatomy of the blood circulation system has been developed from the viewpoint of stochastic pharmacokinetics and the network theory (recirculatory moment analysis).[1-4] The aim of this theory is to characterize the interaction between an organ and a drug in terms of organ extraction ratio and mean transit time and variance of transit time and to correlate these organ characteristics with total body clearance, steady-state volume of distribution and mean residence time of the drug in the body. The concept of mean transit time of a drug through an organ was previously proposed by Stewart[5] and Hamilton *et al.*[6]

Figure 1 shows a plot of total body clearance (CL) *versus* mean residence time (MRT) for 115 drugs in man. These values were calculated using reported data.[7,8] It is clear in Fig. 1 that there is a lower limit of CL which increases as MRT decreases. There also seems to be an upper limit of CL which is independent of MRT. Figure 2 shows the steady-state volume of distribution (V_{ss}) *versus* MRT, which indicates that there is an upper limit of CL which decreases as MRT decreases. There seems to be a lower limit of V_{ss} which is independent of MRT. It is expected that these lower and upper limits are related to total blood volume, total blood flow rate and the local blood flow rates through organs, which are almost constant in man. The classical compartment model offers no explanation for these limits.

The purpose of the present article is to explain these limits of CL and V_{ss} *versus* MRT from the viewpoint of recirculatory moment analysis. The main theoretical foundation is found in the work of Weiss[1] who applied the network theory to pharmacokinetics. His discussion is restricted to the blood concentration of a drug. Since the plasma concentration is

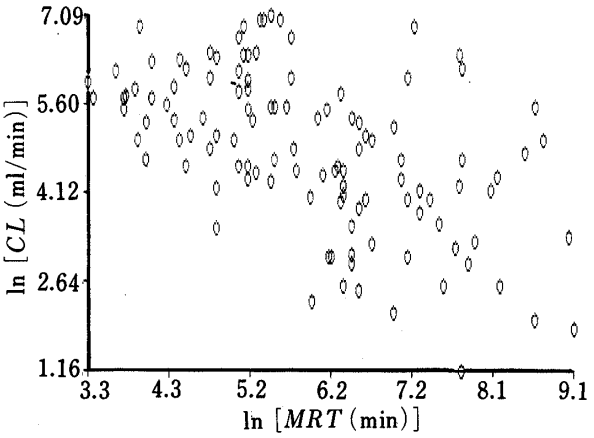

Fig. 1. Logarithmic Plots of *CL versus* Logarithm of *MRT* in Man (Body Weight is Assumed to be 70 kg)

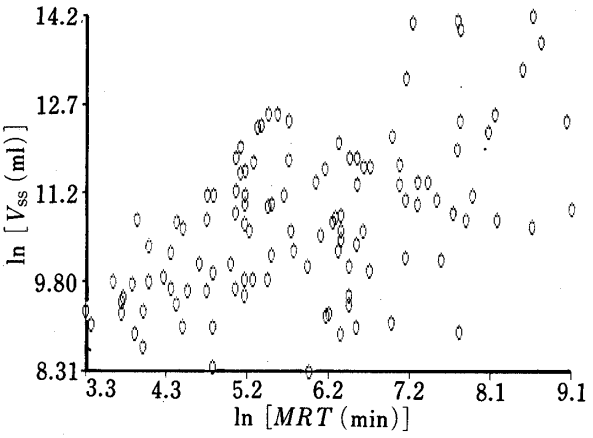

Fig. 2. Logarithmic Plots of V_{ss} *versus* Logarithm of *MRT* in Man (Body Weight is Assumed to be 70 kg)

usually given in the literature, the theory based on the plasma concentration is developed here. The present article gives equations which differ from those given by Weiss. It is shown that V_{ss} decreases as the hepatic and renal extraction ratios decrease. In addition, the first-pass effect of 115 drugs are evaluated using the intravenous data.

Theoretical

The organs and tissues in man and animals are connected in a parallel and/or serial manner mainly by blood vessels. A drug molecule which is injected into the venous system circulates through the heart, the pulmonary circulation, the heart and the artery system and returns to the venous system (Fig. 3).

The molecule takes various times to pass through various organs or tissues (transit times), a particular time to return to the venous system where it was injected (cycle time), and a particular time to leave the body after several circulations through the blood vessels (residence time). Since a dose of drug consists of numerous molecules, the mean times (*i.e.* mean transit times, mean cycle time and mean residence time) represent the overall behavior of the drug molecules in the body. Weiss[1] shows that the transfer function for infinite cycles is given by the transfer function for the single-pass system as follows[9]

$$\tilde{f}_R(s)=\tilde{f}_c(s)/(1-\tilde{f}_c(s)) \tag{1}$$

where $\tilde{f}_R(s)$ and $\tilde{f}_c(s)$ are the transfer functions for the closed loop system and for the single-pass system, respectively.

If a drug is injected into the vein or the artery in the heart and the blood concentration in the same region is measured, the time course of the blood concentration is given by

$$\tilde{C}_b(s)=D\tilde{f}_i(s)/Q_b\tilde{f}_c(s)/(1-f_c(s)) \tag{2}$$

where $\tilde{C}_b(s)$ is the Laplace transform of the time course curve of venous or arterial blood concentration, D is the dosed amount, Q_b is the blood flow rate through the heart and $\tilde{f}_i(s)$ is the input transfer functions. When the drug is rapidly administered into the blood, Eq. 2 is reduced to Eq. 3.

$$\tilde{C}_b(s)=D/Q_b\tilde{f}_c(s)/(1-\tilde{f}_c(s)) \tag{3}$$

The time course data available in the literature are given as plasma concentrations rather than

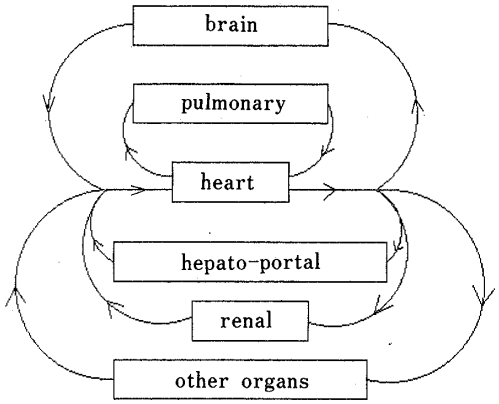

Fig. 3. Blood Circulation System

blood concentrations. The plasma concentration (C_p) is correlated to blood concentration by the following equation.

$$C_b/C_p=(A_p+A_{bc})/(V_p+V_{bc})/(A_p/V_p)=f_p(1+k_b) \tag{4}$$

where A_p and A_{bc} are the amounts in plasma and blood cells, respectively, and V_p and V_{bc} are the volumes of plasma and blood cells, respectively. f_p is the ratio of plasma volume to the volume of blood cells and k_b is the ratio of amount in blood cells to that in plasma.

$$f_p=V_p/(V_p+V_{bc}) \tag{5}$$

$$k_b=A_{bc}/A_p \tag{6}$$

Substituting Eq. 4 into Eq. 3,

$$\tilde{C}_p(s)=D/((1+k_b)Q)\tilde{f}_c(s)/(1-\tilde{f}_c(s)) \tag{7}$$

where Q is plasma flow rate through the heart, given by

$$Q=f_pQ_b \tag{8}$$

We define the effective plasma flow rate $\bar{Q}$ by

$$\bar{Q}=(1+k_b)Q \tag{9}$$

Equation 7 becomes the simple expression (10).

$$\tilde{C}_p(s)=D/\bar{Q}\tilde{f}_c(s)/(1-\tilde{f}_c(s)) \tag{10}$$

Equation 10 is the basic equation in this article. It should be noted that Eq. 10 is independent of a specific physiological or compartment model. The area under the curve (AUC) and the mean residence time (MRT) of $C_p(t)$ are given as

$$AUC=\lim_{s\to 0}\tilde{C}_p(s)=D/\bar{Q}F_c/(1-F_c)=D/\bar{Q}(1-E_c)/E_c \tag{11}$$

$$MRT=\lim_{s\to 0}-\mathrm{d}/\mathrm{d}s\ln\tilde{C}_p(s)=\bar{t}_c/(1-F_c)=\bar{t}_c/E_c \tag{12}$$

where F_c, E_c and $\bar{t}_c$ are the recovery ratio, extraction ratio and mean cycle time for single passage, and they are given by

$$F_c=1-E_c=\int_0^\infty f_c(t)\,\mathrm{d}t=\lim_{s\to 0}\tilde{f}_c(s) \tag{13}$$

$$\bar{t}_c=\int_0^\infty tf_c(t)\,\mathrm{d}t\Big/\int_0^\infty f_c(t)\,\mathrm{d}t=\lim_{s\to 0}-\mathrm{d}/\mathrm{d}s\ln\tilde{f}_c(s) \tag{14}$$

The total body clearance (CL) and steady-state volume of distribution (V_{ss}) are given from Eqs. 5 and 6 as

$$CL = D/AUC = \bar{Q}E_c/(1-E_c) \tag{15}$$

$$V_{ss} = CL\ MRT = \bar{Q}\bar{t}_c/(1-E_c) \tag{16}$$

Weiss[1] gave the following equations based on the network theory in case where a drug is eliminated exclusively by liver and kidney.

$$E_c = (\bar{Q}_h E_h + \bar{Q}_r E_r)/\bar{Q} \tag{17}$$

$$\bar{t}_c = \bar{t}_p + (\bar{Q}_h \bar{t}_h F_h + \bar{Q}_r \bar{t}_r F_r + \bar{Q}_o \bar{t}_o)/(\bar{Q}_h F_h + \bar{Q}_r F_r + \bar{Q}_o) \tag{18}$$

where the subscripts h, r, p and o specify hepato-portal, renal, pulmonary and other organs and tissues, respectively, $\bar{Q}_i$ is the effective plasma flow rate through organ i, E_i ($=1-F_i$) is the organ extraction ratio, and $\bar{t}_i$ is the mean transit time through organ i.

The urinary recovery of drug (F_e) is given by

$$F_e = \bar{Q}_r E_r/(\bar{Q}_h E_h + \bar{Q}_r E_r) \tag{19}$$

The following equations are obtained by rearranging Eqs. 12 and 15.

$$E_c = CL/(\bar{Q} + CL) \tag{20}$$

$$\bar{t}_c = MRT\ E_c \tag{21}$$

By combining Eq. 15 with Eq. 16, E_c and $\bar{t}_c$ can also be calculated. E_r and E_h are obtained from Eqs. 17 and 19 as

$$E_r = \bar{Q}E_c F_e/\bar{Q}_r \tag{22}$$

$$E_h = (\bar{Q}E_c - \bar{Q}_r E_r)/\bar{Q}_h \tag{23}$$

Using Eqs. 20 and 23, E_c, $\bar{t}_c$, E_r and E_h can be estimated from the macroscopic quantities CL, MRT (or V_{ss}) and F_e.

Numerical Procedures

A personal computer system (PC9801, NEC) with a graphic printer (MK3618-22, NEC) and an XY-plotter (MYPLOT, Watanabe) were used. The XY-plotter was controlled by a program written in BASIC. The arithmetic calculations were also carried out by BASIC program. CL, MRT and V_{ss} were calculated from pharmacokinetic constants.[7,8]

Results

Table I presents the values of CL, MRT, V_{ss} and F_e of 115 drugs (the averages obtained from several human subjects). Prodrugs for oral use and drugs which show apparent capacity-limited disposition are not included in Table I. E_c, $\bar{t}_c$, E_r and E_h calculated using Eqs. 20—23 are also shown in Table I. Strictly speaking, Eqs. 20—23 are valid for the time course of plasma concentration in the heart. It is assumed here that the venous plasma concentration in the heart can be approximated by that in the arm. E_c, $\bar{t}_c$, E_r and E_h in Table I are calculated on the assumption that the effective flow rate $\bar{Q}$ is equal to plasma flow rate Q (*i.e.* the distribution of drugs into blood cells is negligible). The plasma flow rates ($Q=3100$ ml/min, $Q_h=840$ ml/min and $Q_r=690$ ml/min) were obtained by multiplying the blood flow rates by the plasma volume ratio ($f_p=0.56$).[10] A 70 kg body weight was supposed. E_c' in the last column is the extraction ratio calculated on the assumption that $\bar{Q}$ is equal to blood flow rate Q_b (*i.e.* drugs distribute into the blood cells at the same concentration as in plasma). The

TABLE I. *CL*, *MRT*, V_{ss} and F_e Values of 115 Drugs in Man

Drug name	*CL* (ml/min)	*MRT* (min)	V_{ss} (ml)	F_e (%)	E_c (%)	$\bar{t}_c$ (min)	E_r (%)	E_h (%)	E_c'/E_c
Acebutolor	480	170	81600	40	13.4078	22.7933	24.0952	29.6887	0.588816
Acetaminophen	350	190	66500	3	10.1449	19.2754	1.36736	36.3164	0.579832
N-Acetylprocainamide	220	440	96800	81	6.62651	29.1566	24.1147	4.64644	0.570447
Alprenolol	1100	230	253000	0.5	26.1905	60.2381	0.588337	96.1721	0.626866
Amikacin	77	190	14630	98	2.42367	4.60497	10.6712	0.17889	0.559627
Amitriptyline	430	1300	559000	—	12.1813	158.357	—	—	0.585406
Amobarbital	37	1900	70300	—	1.17947	22.4099	—	—	0.556502
Amoxicillin	370	78	28860	52	10.6628	8.317	24.9108	18.8884	0.58124
Amphotericin B	30	9000	270000	3	0.958466	86.262	0.129185	3.43108	0.55595
Ampicillin	270	72	19440	90	8.01187	5.76855	32.3958	2.95677	0.574106
Atenolol	91	540	49140	85	2.85177	15.3996	10.8905	1.57866	0.56071
Bishydroxycoumarin	12	720	8640	—	0.385604	2.77635	—	—	0.554526
Carbamazepin	65	1500	97500	1	2.05371	30.8057	9.22682×10^{-2}	7.50339	0.558694
Carbenicillin	150	84	12600	82	4.61538	3.87692	17.0033	3.06593	0.565217
Cefamandole	200	56	11200	96	6.06061	3.39394	26.1397	0.894661	0.568966
Cefazolin	67	130	8710	80	2.11557	2.75024	7.60378	1.56149	0.558849
Cefoxitin	400	28	11200	78	11.4286	3.2	40.0497	9.27891	0.583333
Cephalexin	300	60	18000	96	8.82353	5.29412	38.0563	1.30252	0.576271
Cephaloridine	160	96	15360	85	4.90798	4.71166	18.7428	2.71692	0.565972
Cephalothin	470	39	18330	52	13.1653	5.13445	30.7571	23.3213	0.588138
Cephapirin	300	30	9000	49	8.82353	2.64706	19.4246	16.6071	0.576271
Cephradine	360	49	17640	86	10.4046	5.09827	40.2011	5.37572	0.580537
Chloramphenicol	260	250	65000	5	7.7381	19.3452	1.73827	27.1294	0.573379
Chlordiazepoxide	26	840	21840	1	0.831734	6.98656	3.73678×10^{-2}	3.0388	0.555635
Chlorthiazide	320	44	14080	92	9.35673	4.11696	38.6745	2.76246	0.577703
Chlorpromazine	610	2400	1.464×10^{6}	1	16.442	394.609	0.738701	60.0722	0.597424
Chlortetracycline	250	490	122500	18	7.46269	36.5672	6.03504	22.5835	0.57265
Chlorthalidone	110	2500	275000	65	3.42679	85.6698	10.0072	4.42627	0.562172
Cimetidine	840	170	142800	77	21.3198	36.2437	73.7541	18.0964	0.611801
Clindamycin	250	190	47500	14	7.46269	14.1791	4.69392	23.6851	0.57265
Clofibrate	13	600	7800	32	0.417604	2.50562	0.600381	1.04799	0.554605
Clonazepam	64	3500	224000	1	2.02276	70.7965	9.08774×10^{-2}	7.39028	0.558616
Clonidine	220	660	145200	62	6.62651	43.7349	18.4582	9.29289	0.570447
Cloxacillin	250	43	10750	30	7.46269	3.20896	10.0584	19.2786	0.57265
Cyclophosphamide	96	560	53760	14	3.00375	16.821	1.88932	9.53335	0.561096
Demeclocycline	110	1200	132000	42	3.42679	41.1215	6.46621	7.33497	0.562172
Deslanoside	81	3800	307800	62	2.54637	96.762	7.09293	3.57098	0.559937
Diazepam	27	2900	78300	1	0.863447	25.04	3.87926×10^{-2}	3.15467	0.555714
Dicloxacillin	110	56	6160	60	3.42679	1.919	9.23744	5.0586	0.562172
Digitoxin	60	600	36000	33	1.89873	11.3924	2.81508	4.69485	0.558304
Digoxicin	120	5300	636000	72	3.72671	197.516	12.0551	3.85094	0.562937
Disopiramide	91	600	54600	55	2.85177	17.1106	7.04677	4.73598	0.56071
Doxepin	980	1400	1.372×10^{6}	—	24.0196	336.275	—	—	0.620061
Doxycycline	56	1700	95200	40	1.7744	30.1648	3.18877	3.92902	0.557992
Erythromycin	420	120	50400	15	11.9318	14.3182	8.04101	37.429	0.584718
Ethambutol	610	190	115900	79	16.442	31.2399	58.3574	12.7426	0.597424
Ethosuximide	19	2700	51300	19	0.60917	16.4476	0.520001	1.82098	0.555081
Flucytosine	84	470	39480	84	2.63819	12.3995	9.9563	1.55779	0.560169
Flunitrazepam	190	1100	209000	1	5.77508	63.5258	0.25946	21.0997	0.568221
Fluorohydrocortisone	10	410	4100	84	0.321543	1.31833	1.21348	0.189864	0.554367

TABLE I. (continued).

Drug name	CL (ml/min)	MRT (min)	V_{ss} (ml)	F_e (%)	E_c (%)	$\bar{t}_c$ (min)	E_r (%)	E_h (%)	E'_c/E_c
Furosemide	150	51	7650	74	4.61538	2.35385	15.3445	4.42857	0.565217
Heparin	34	130	4420	—	1.08488	1.41034	—	—	0.556266
Hexobarbital	260	300	78000	1	7.7381	23.2143	0.347654	28.2717	0.573379
Hydrochlorothiazide	340	170	57800	95	9.88372	16.8023	42.1849	1.82378	0.579125
Indomethacin	130	330	42900	15	4.02477	13.2817	2.71234	12.6253	0.5637
Isoniazid	490	90	44100	29	13.649	12.2841	17.7833	35.7637	0.589491
Kanamycin	98	190	18620	90	3.06442	5.82239	12.3909	1.13091	0.56125
Lidocatine	640	120	76800	2	17.1123	20.5348	1.53763	61.8895	0.599359
Lincomycin	58	400	23200	72	1.83661	7.34642	5.94102	1.89783	0.558148
Lithium	25	2300	57500	95	0.8	18.4	3.41449	0.147619	0.555556
Lorazepam	77	1200	92400	1	2.42367	29.084	0.10889	8.85505	0.559627
Meperidine	1200	250	300000	22	27.907	69.7674	27.5834	80.3322	0.632353
Methacycline	55	1300	71500	79	1.74326	22.6624	6.18733	1.35103	0.557913
Methadone	150	6600	990000	10	4.61538	304.615	2.07358	15.3297	0.565217
Methotrexate	110	260	28600	94	3.42679	8.90966	14.472	0.758789	0.562172
Methyldopa	220	110	24200	63	6.62651	7.28916	18.7559	9.04834	0.570447
Metoprolol	1100	280	308000	10	26.1905	73.3333	11.7667	86.9898	0.626866
Minocycline	21	1300	27300	11	0.672861	8.7472	0.33253	2.21003	0.555239
Morphine	1100	220	242000	10	26.1905	57.619	11.7667	86.9898	0.626866
Nadolol	200	720	144000	73	6.06061	43.6364	19.877	6.03896	0.568966
Nafcillin	410	190	77900	27	11.6809	22.1937	14.1695	31.4689	0.584027
Neostigmine	580	84	48720	67	15.7609	13.2391	47.4425	19.1945	0.595469
Nitrazepam	70	2400	168000	1	2.2082	52.9968	9.92091×10^{-2}	8.06782	0.559083
Nitroglycerin	150	160	24000	1	4.61538	7.38462	0.207358	16.8626	0.565217
Nortriptyline	500	2500	1.25×10^{6}	2	13.8889	347.222	1.24799	50.2315	0.590164
Oxacillin	300	43	12900	55	8.82353	3.79412	21.8031	14.6534	0.576271
Oxytetracycline	160	780	124800	70	4.90798	38.2822	15.4352	5.43383	0.565972
PAS	210	78	16380	10	6.34441	4.94864	2.85039	21.0725	0.569707
Penicillin G	550	60	33000	79	15.0685	9.0411	53.4822	11.6781	0.593496
Penicillin V	980	52	50960	26	24.0196	12.4902	28.0577	65.5964	0.620061
Pentobarbital	13	3900	50700	—	0.417604	16.2865	—	—	0.554605
Phenobarbital	6.5	9600	62400	24	0.209239	20.0869	0.225614	0.586865	0.554089
Pindolol	430	320	137600	41	12.1813	38.9802	22.4383	26.5233	0.585406
Prazosin	210	200	42000	1	6.34441	12.6888	0.285039	23.1798	0.569707
Prednisolone	90	340	30600	—	2.82132	9.59248	—	—	0.560633
Prednisone	260	260	67600	—	7.7381	20.119	—	—	0.573379
Primidone	55	780	42900	42	1.74326	13.5975	3.28946	3.73142	0.557913
Procainamide	640	210	134400	67	17.1123	35.9358	51.5105	20.8403	0.599359
Propranolol	840	320	268800	0.5	21.3198	68.2234	0.478923	78.2868	0.611801
Protriptyline	260	6000	1.56×10^{6}	—	7.7381	464.286	—	—	0.573379
Pyridostigmine	600	130	78000	90	16.2162	21.0811	65.5699	5.98456	0.596774
Quinidine	330	580	191400	18	9.62099	55.8017	7.78045	29.115	0.578415
Rifampin	620	180	111600	16	16.6667	30	11.9807	51.6667	0.598071
Spectinomycin	95	90	8550	74	2.9734	2.67606	9.88546	2.85304	0.561018
Streptomycin	88	210	18480	30	2.76035	5.79674	3.72047	7.13091	0.560478
Sulfadiazine	44	1500	66000	38	1.39949	20.9924	2.38928	3.20217	0.557052
Sulfadimethoxine	7.6	6000	45600	58	0.244562	14.6737	0.637278	0.379071	0.554176
Sulfaethidole	19	660	12540	—	0.60917	4.02052	—	—	0.555081
Sulfamerazine	13	2000	26000	—	0.417604	8.35207	—	—	0.554605
Sulfamethazine	70	600	42000	20	2.2082	13.2492	1.98418	6.51945	0.559083

TABLE I. (continued).

Drug name	CL (ml/min)	MRT (min)	V_{ss} (ml)	F_e (%)	E_c (%)	$\bar{t}_c$ (min)	E_r (%)	E_h (%)	E'_c/E_c
Sulfisoxazole	21	520	10920	53	0.672861	3.49888	1.60219	1.16709	0.555239
Sulfisomidine	35	660	23100	9	1.11643	7.36842	0.451425	3.74934	0.556344
Sulfamethoxazole	22	660	14520	30	0.704676	4.65086	0.949781	1.82041	0.555318
Tetracycline	130	720	93600	48	4.02477	28.9783	8.6795	7.72372	0.5637
Theophylline	48	720	34560	8	1.52478	10.9784	0.548036	5.17698	0.557365
Ticarcillin	130	120	15600	86	4.02477	4.82972	15.5508	2.07946	0.5637
Tobramycin	74	250	18500	90	2.33144	5.82861	9.42714	0.860414	0.559394
Tolbutamide	21	500	10500	—	0.672861	3.36431	—	—	0.555239
Triamterene	980	180	176400	3.9	24.0196	43.2353	4.20865	85.1867	0.620061
Trimethoprim	150	840	126000	53	4.61538	38.7692	10.99	8.00549	0.565217
Tubocurarine	160	130	20800	43	4.90798	6.38037	9.48164	10.3243	0.565972
Valproic acid	8.4	1100	9240	1.8	0.270235	2.97259	2.18538×10^{-2}	0.979346	0.55424
Vancomycin	53	580	30740	90	1.68094	9.74944	6.79684	0.620346	0.557757
Viomycin	97	170	16490	80	3.03409	5.15796	10.9052	2.23945	0.561173
Warfarin	3.2	2500	8000	—	0.103119	2.57798	—	—	0.553826

E_c, $\bar{t}_c$, E_h and E_r are calculated on the assumption that $\bar{Q}$ is approximated by Q. E'_c is the extraction ratio for one cycle through the body, when $\bar{Q}$ is equal to Q_b.
$Q=3100$ ml/min, $Q_h=840$ ml/min, $Q_r=690$ ml/min, $W_t=70$ kg.

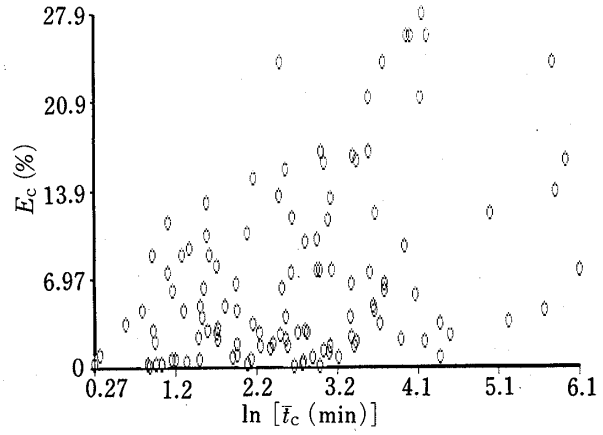

Fig. 4. Plots of E_c *versus* Logarithm of $\bar{t}_c$

The effective plasma flow rate is equal to plasma flow rate (*i.e.* $Q=3100$ ml/min, $Q_h=840$ ml/min and $Q_r=690$ ml/min).

ratios E'_c/E_c are from 0.55 to 0.63. By multiplying $\bar{t}_c$, E_r and E_h by this ratio, the mean cycle time and the renal and hepatic extraction ratios for the case where $\bar{Q}$ is equal to Q_b can be calculated.

Figure 4 shows the plots of E_c *versus* $\bar{t}_c$. The drugs which have a large mean cycle time ($\bar{t}_c$) give a wide range of E_c values. The drugs which have small $\bar{t}_c$ values give small E_c values. The smallest $\bar{t}_c$ values are those for heparin (1.4 min) and fluorohydrocortisone (1.3 min). Since the cycle time of blood in man is about 1 min (*i.e.* total blood volume is 5400 ml and total blood flow rate is 5600 ml/min),[10] these drugs are presumed to circulate through the body localized mainly within the blood vessels. Since a drug of small $\bar{t}_c$ value passes quickly through organs such as the kidney and liver without distribution into tissues, the decrease of the upper limit of E_c with decrease of $\bar{t}_c$ is qualitatively understandable. However, experimental evidences for the relationships between $\bar{t}_h$ and E_h and between $\bar{t}_r$ and E_r, are required for a quantitative explanation of the upper limit of E_c.

The drugs which have the large E_h values (above 50%) are alprenolol (96%), chlor-

promazine (60%), lidocaine (62%), meperidine (80%), metoprolol (87%), nortriptyline (50%), penicillin V (66%), propranolol (78%), rifampin (52%) and triamteren (85%). These drugs are expected to show low bioavailability, even if the absorption from the GI tract into the portal vein is complete. The β-adrenergic blockers (alprenolol, metaprenolol and propranolol) are known to suffer the first-pass effect.[11] Clinical studies in patients proved that 70% of lidocaine is eliminated during a single pass through the hepato-portal system.[12] The E_h value (62%) of lidocaline in Table I is very close to this experimental result.

Discussion

CL, V_{ss} and *MRT versus* E_h and E_r

Figure 5 shows the theoretical three-dimensional surface of *CL versus* E_h and E_r according to Eqs. 15 and 17, shown as a meshwork surface. In the calculation, the effective flow rate $\bar{Q}$ is supposed to be equal to the plasma flow rate Q. The three-dimensional surface of *CL* according to Eq. 24 is also shown in Fig. 5.

$$CL = QE_c \tag{24}$$

Equation 24 has been derived from physiological models.[13-15] The reason why Eq. 15 differs from Eq. 24 is discussed in the following section. As both E_h and E_r increase, the meshwork surface ($CL = Q\ E_c/(1-E_c)$) becomes removed from the surface ($CL = QE_c$). Figure 5 demonstrates that *CL* of a drug which is exclusively eliminated by the hepato-portal system does not exceed about 1200 ml/min and that *CL* of drug which is excreted by the kidney does not exceed about 900 ml/min. The *CL* of alprenolol (1100 ml/min) is close to the upper limit of the former type of drug. However, a drug which is considerably distributed into blood cells can show a *CL* value greater than these boundary clearance values, in accord with Eq. 15.

Weiss[3] and Pang *et al.*[16] showed that the organ extraction ratio E_i and the mean transit time $\bar{t}_i$ are given by the following equations, if the process in an organ approximates to the mammillary model.

$$E_i = CL_i(\text{int})/(\bar{Q}_i + CL_i(\text{int})) \tag{25}$$

$$\bar{t}_i = V_i/(\bar{Q}_i + CL_i(\text{int})) \tag{26}$$

where subscript i means the hepato-portal system or kidney, V_i is the organ volume of distribution and CL_i(int) is the intrinsic clearance of the organ. From Eqs. 25 and 26, CL_i(int) and V_i are given by

$$CL_i(\text{int}) = \bar{Q}_i E_i/(1-E_i) \tag{27}$$

$$V_i = \bar{Q}_i \bar{t}_i/(1-E_i) \tag{28}$$

It is interesting to note that Eqs. 27 and 28, which express microscopic relationships, take the

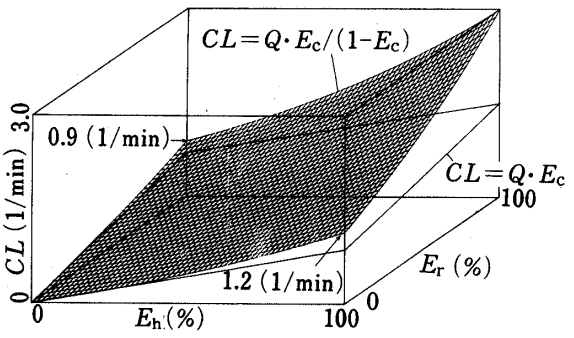

Fig. 5. Surface of *CL versus* E_h and E_r

The meshwork surface is calculated according to Eq. 15 and the flat surface according to Eq. 24.

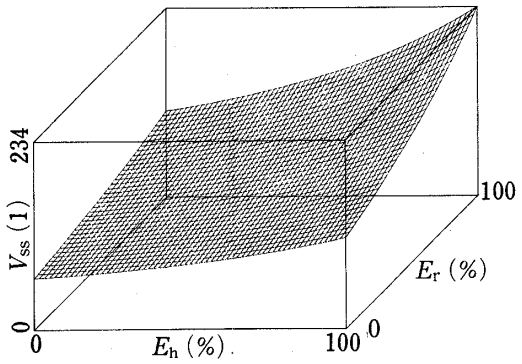

Fig. 6. Surface of V_{ss} *versus* E_h and E_r

Organ distribution volumes are supposed to be the same as the organ volumes (*i.e.* V_h (hepatoportal-system) = 3900 ml, V_p (pulmonary) = 600 ml, V_r (renal) = 300 ml and V_o (the others) = 59800 ml).

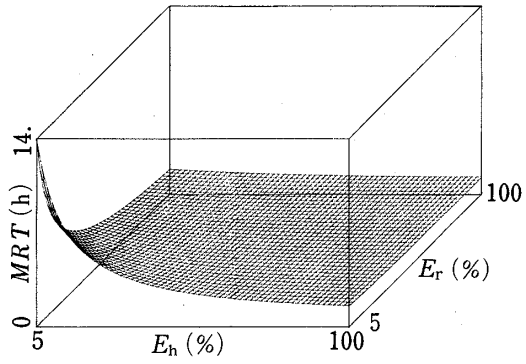

Fig. 7. Surface of *MRT versus* E_h and E_r

The organ volumes are the same as in Fig. 6.

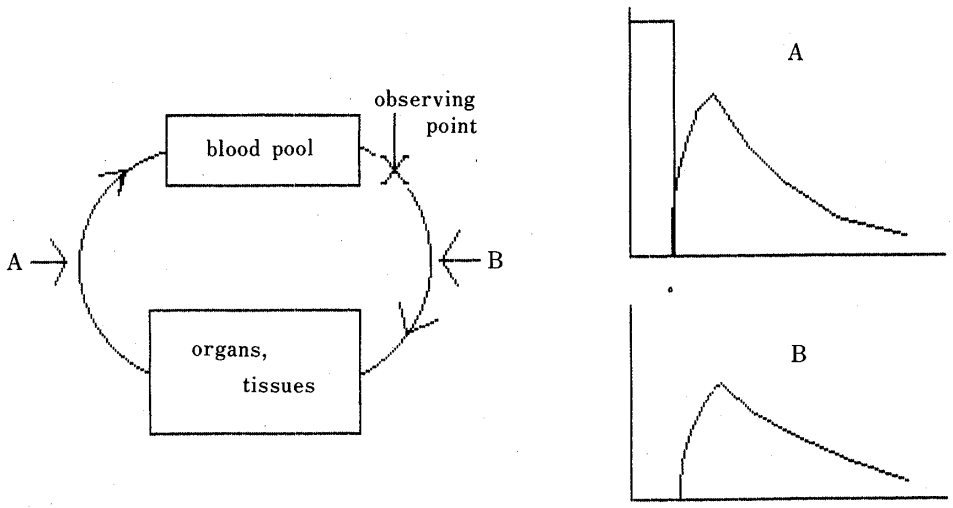

Fig. 8. A Physiological Model

In administration A, the drug injected into the body arrives first at the observing point without elimination. In administration B, the injected drug arrives first at the observing point after partial loss.

same mathematical forms as Eqs. 15 and 16 which represent macroscopic relationships.

Figure 6 presents the three-dimensional surface of V_{ss} *versus* E_h and E_r based on Eqs. 16, 17, 18, 27 and 28. In Fig. 6, it is assumed that the effective flow rate is close to the plasma flow rate and the volumes of distribution are the same as the organ volumes (*i.e.* V_h (hepato-portal system) = 3900 ml, V_p (pulmonary) = 600 ml, V_r (renal) = 300 ml, V_o (others) = 59800 ml).[10] V_{ss} gradually increases, as E_h and E_r increase to 100%. There is no drug that has E_h and E_r values, which are both close to 100% (Table I). Therefore, the decreases of E_h and E_r due to liver and renal impairments do not greatly affect the V_{ss} values. However, it should be noted that decreases of E_r and E_h can make V_{ss} decrease, even if organ distribution volumes are constant. Gibaldi *et al.* reported that the co-administration of probenecid makes the distribution volumes of many β-lactam antibiotics decrease.[17] Figure 6 can explain these phenomena.

Figure 7 shows the three-dimensional surface of *MRT versus* E_h and E_r. The adopted distribution volumes are the same as in Fig. 6. *MRT* rapidly increases as E_h and E_r decrease to zero. There are many drugs that have E_h and E_r, which are both close to zero (Table I). In contrast with V_{ss}, *MRT* is greatly affected by decreases of E_h and E_r due to organ impairment.

Physiological Model and Recirculatory Moment Analysis

We will discuss here the reason why Eq. 15 differs from Eq. 24 which is derived from physiological models. Figure 8 shows a simplified physiological model. There are two ways to administer a drug, which are shown by A and B in Fig. 8. In case A, the drug which is injected arrives first at the observing point without elimination. In case B, the injected drug arrives first at the observing point after a partial loss (first-pass effect by the whole body). Since the input wave is also counted in case A, the AUC in case A is greater than that in case B (Fig. 8). While the physiological models have adopted the injection manner A,[18] the present work adopts the injection manner B, which we think to be closer to clinical conditions.

From Eq. 17, the following equation is valid.

$$\bar{Q}E_c=\bar{Q}_hE_h+\bar{Q}_rE_r \tag{27}$$

The following equation is also valid.

$$D/AUC=A_r(\infty)/AUC+A_h(\infty)/AUC \tag{28}$$

where $A_r(\infty)$ and $A_h(\infty)$ are the amounts eliminated from the renal and hepato-portal system, respectively. Equations 29 and 30 are obtained from Eqs. 11, 27 and 28.

$$A_r(\infty)/AUC=\bar{Q}_rE_r/(1-E_c) \tag{29}$$

$$A_h(\infty)/AUC=\bar{Q}_hE_r/(1-E_c) \tag{30}$$

It should be noted that the organ clearances defined by AUC ($A_r(\infty)/AUC$ and $A_h(\infty)/AUC$) differ from those defined by the extraction ratios ($\bar{Q}_rE_r$ and $\bar{Q}_hE_h$) in administration by method B. When E_c is small, Eq. 15 coincides with Eq. 24. However, there are drugs which show the quite large values of E_c (for example, alprenolol, cimetidine, meperidine *etc.*).

Injection Point and Sampling Point

Weiss[3] presented the following equation taking account of the difference of the injection point and the sampling point.

$$\tilde{C}_b(s)=\tilde{f}_p(s)\tilde{f}_{pv}(s)/\bar{Q}_b/(1-\tilde{f}_c(s)) \tag{31}$$

where $\tilde{f}_p(s)$ is the transfer function for pulmonary circulation and $\tilde{f}_{pv}(s)$ is the transfer function of the channel between arterial blood and the sampling vein. Equation 31 is superficially more reasonable than Eq. 3 which is the basic equation in this work. However, according to Eq. 31, the moments of time course of the drug in the arm vein are significantly different from those in the heart. We think that Eq. 3 is a reasonable approximation considering that the blood circulates very rapidly through the body (in about one minute).

The present discussion is based on the following assumptions:

(1) The disposition process in the body can be regarded as linear.

(2) The extraction ratios of organs or tissues other than the liver and kidney are small enough to be neglected.

(3) The time course of venous plasma concentration in the heart can be approximated by the time course in the vein of the arm.

In conclusion, the evaluation of k_b, E_r, E_h, $\bar{t}_p$, $\bar{t}_r$ and $\bar{t}_h$ of drugs is necessary in order to correlate the local organ pharmacokinetics to the macroscopic pharmacokinetics, which is of direct clinical significance. An understanding to these microscopic characteristics would make possible predictions of the changes of the macroscopic characteristics arising from renal and hepatic impairments or a decrease of blood flow rate.

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