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Age-dependent pulmonary first-pass elimination of propranolol in rats

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Abstract—Plasma levels of propranolol after 2·5 mg kg^{-1} given i.v. and i.a. have been compared in 3- to 4-week-old rats to evaluate the effect of age on pulmonary first-pass elimination of the drug. In 5- to 52-week-old rats, the area under the plasma concentration-time curve (AUC) after an intra-arterial dose was always larger than that after the i.v. dose. The plasma elimination half-lives after both routes of administration were almost identical, but tended to increase with age between weeks 7 and 104. First-pass pulmonary clearance and extraction ratio tended to decrease with age between weeks 7 and 52.

Organs other than the liver possess some ability to eliminate drugs, though their metabolic capacity is less. Lung tissue contains enzymes capable of metabolizing therapeutic agents (particularly some basic and volatile drugs), environmental toxicants and endogenous substances (Roth 1985). Some compounds are metabolized in the lungs, whereas others are removed from the circulation and accumulated in lung tissue. Extensive first-pass pulmonary elimination (or uptake with high capacity) of propranolol after intravenous administration at 1 to 10 mg kg^{-1} in rats has been described by Iwamoto et al (1987a). Other workers have reported first-pass pulmonary clearance of phenol in rats (Cassidy & Houston 1980) and the contribution of pulmonary clearance to the total body clearance of meperidine in dogs (Kramer et al 1985). However, the mechanism of pulmonary first-pass elimination of drugs and the effects of age or disease states on it have received little attention. Because the lungs mature relatively late in body development and also tend to decrease in physiological function in senescence, age-related differences in pulmonary drug clearance may be also expected.

In the present study, plasma levels of propranolol after 2·5 mg kg^{-1} given intravenously or intra-arterially have been compared in 3- to 104-week-old rats to evaluate the effect of age on the pulmonary first-pass clearance and extraction ratio of the drug. In addition, effect of age-related changes in lung blood flow on the pulmonary clearance of propranolol has also been discussed.

Methods

Male Wistar rats, 3 (60–75 g), 5 (110–135 g), 7 (210–220 g), 11 (350–385 g), 15 (375–405 g), 24 (450–520 g), 52 (625–720 g) and 104 (790–865 g) weeks old were chronically cannulated into the jugular vein and artery in the manner reported by Iwamoto et al (1982; 1987a) and fasted overnight before the experiments. Propranolol (ICI-Pharma, Ltd.), 2·5 mg kg^{-1}, was given intravenously or intra-arterially to the cannulated rat. Periodic collection of blood samples and preparation of the plasma samples were as described by Iwamoto et al (1985a) except that the sample volume was reduced to 0·06 or 0·12 mL of blood (i.e. 0·025 or 0·05 mL of plasma). Propranolol concentration in the plasma samples was determined by the method of Iwamoto & Watanabe (1984).

Pharmacokinetic parameters, area under the plasma concentration-time curve (AUC), total body clearance (CL_{tot}), pulmonary clearance (CL_p) and extraction ratio (E_p), were estimated according to Iwamoto et al (1987a).

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An abdominal midline incision (1 to 3 cm) was made in 3- to 104-week-old rats lightly anaesthetized with urethane (800 mg kg^{-1} i.p.), which were chronically cannulated into the jugular vein and artery as described above. After placing an Ag-AgCl reference electrode of hydrogen monitor (PHG-300, M.T.-Giken, Co.) into the peritoneal space and a tip of the needle Pt-Pt black H_2-electrode into the lung tissue through diaphragm, a trace amount of hydrogen gas was given to the rat by inhalation. The apparent lung blood flow was estimated in the same way as reported by Iwamoto et al (1985a, b; 1987b).

Results and discussion

Plasma propranolol concentration (C)-time curves after i.v. and i.a. administration were analysed according to the least-squares regression analysis program MULTI (Yamaoka et al 1981) for bi-exponential decline expressed as $C = Ae^{-\alpha t} + Be^{-\beta t}$, where A, B, α and β are hybrid parameters. Table 1 summarizes pharmacokinetic parameters including elimination half-life ($t_{\frac{1}{2}\beta}$) and CL_{tot}. After the intravenous administration, CL_{tot} was found to decrease with age between weeks 7 and 24. Almost the same age-dependence in that parameter after an i.v. dose of 1·0 mg kg^{-1} has been reported (Iwamoto et al 1985a). The $t_{\frac{1}{2}\beta}$ showed no difference between both routes of administration to the same age-group but it tended to increase with age from 7 to 104 weeks. The identical elimination half-life after the distribution equilibrium of the drug given to the rat both intravenously and intra-arterially was thought to be due to the overall elimination (i.e. hepatic and pulmonary elimination) rate, which might be independent of route of administration.

Pulmonary clearance (CL_p) and extraction ratio (E_p) are summarized in Table 2. Both CL_p and E_p in 3-week-old rats were far smaller than those from other age-groups. This may be due to the immaturity of the lung of 3-week-old rats affecting the disposal of the drug. Both parameters increased with maturation to 7 weeks and then tended to decrease with ageing to 52 weeks.

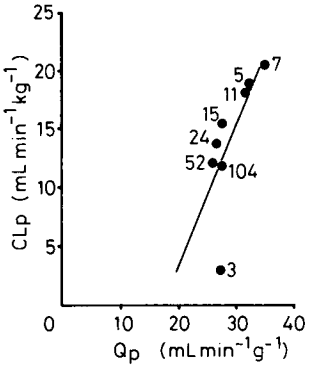

FIG. 1. Correlation between pulmonary clearance (CL_p) of propranolol and apparent pulmonary blood flow (Q_p) in 3- to 104-week-old rats. Q_p is expressed as mL min^{-1} g^{-1} for the unit tissue wet weight. The solid line indicates the regression line for this correlation between both mean values as $Y = 1{\cdot}19X - 20{\cdot}4$ (where $r = 0{\cdot}719$, $P < 0{\cdot}05$), where Y and X represent CL_p and Q_p respectively. The numbers indicate the age (weeks) of the rats.

Among age-dependent changes, those directly sensitive to age included hepatic metabolic rate (and/or activity), the renal function. The effect of age on the hepatic clearance of propranolol has been reported in rats (Iwamoto et al 1985a), indicating that the age-dependent decrease in the clearance is largely due to a reduction in elimination rate which might be accompanied by an age-dependent decrease in liver blood flow. In the present study, the apparent lung blood flow (Q_p, mL min^{-1} g^{-1}) was measured by the hydrogen gas clearance method and the CL_p value plotted against Q_p as shown in Fig. 1. These blood flow data may not represent the real blood flow in the lung tissue because of the lack of a real partition coefficient value for the indicator gas (hydrogen gas) between tissue and the blood space and due to the urethane anaesthesia (Iwamoto et al 1987b). Only a weak age-dependence in Q_p was obtained and there was not a highly significant correlation between CL_p and Q_p ($r=0.719$, $P<0.05$) as observed with the hepatic clearance (Iwamoto et al 1985a). Furthermore, when the lung blood flow was normalized

Table 1. Pharmacokinetic parameters for propranolol after intravenous adminstration of 2·5 mg kg^{-1} to rats (n = 4) 3 to 104 weeks old.

	Mean ± s.d.[a] in age (weeks):							
Parameter	3	5	7	11	15	24	52	104
A (μg mL^{-1})								
i.v.	4·63	2·32	3·07	3·15	2·96	2·14	1·04	0·896
	(0·62)	(0·38)	(0·29)	(0·42)	(0·36)	(0·26)	(0·21)	(0·13)
i.a.	4·86	4·94	2·57	5·17	5·48	3·54	1·95	2·29
	(0·51)	(0·51)	(0·78)	(0·81)	(0·41)	(0·33)	(0·24)	(0·21)
B (μg mL^{-1})								
i.v.	0·96	0·66	0·52	0·60	0·64	0·61	0·64	0·65
	(0·14)	(0·11)	(0·10)	(0·11)	(0·09)	(0·09)	(0·09)	(0·08)
i.a.	0·94	0·78	1·98	0·97	0·99	1·12	0·98	0·82
	(0·18)	(0·13)	(0·44)	(0·27)	(0·15)	(0·18)	(0·13)	(0·11)
α (10^{-1} min^{-1})								
i.v.	1·01	1·12	1·14	1·08	0·96	0·81	0·70	0·69
	(0·21)	(0·18)	(0·15)	(0·23)	(0·23)	(0·17)	(0·15)	(0·11)
i.a.	0·85	0·98	1·01	1·02	1·01	0·91	0·67	0·71
	(0·10)	(0·12)	(0·61)	(0·33)	(0·30)	(0·19)	(0·10)	(0·15)
β (10^{-2} min^{-1})								
i.a.	1·88	2·11	2·22	2·06	1·81	1·39	1·22	1·13
	(0·24)	(0·24)	(0·22)	(0·31)	(0·36)	(0·31)	(0·28)	(0·22)
i.a.	1·81	2·34	3·26	1·97	1·77	1·47	1·36	1·11
	(0·22)	(0·31)	(0·98)	(0·33)	(0·29)	(0·33)	(0·29)	(0·24)
$t_{\frac{1}{2}}\beta$ (min)								
i.v.	36·8	32·8	31·2	33·6	38·2	49·8	56·9	61·1
	(4·3)	(4·2)	(4·0)	(4·8)	(7·0)	(7·7)	(8·2)	(8·4)
i.a.	38·2	29·6	21·3	35·2	39·1	47·2	50·8	62·4
	(4·2)	(4·1)	(7·6)	(5·6)	(4·9)	(7·8)	(8·0)	(8·6)
AUC (μg min mL^{-1})								
i.v.	96·9	52·0	50·5	58·1	66·3	70·2	67·5	70·6
	(10·2)	(10·1)	(8·9)	(10·1)	(8·7)	(9·2)	(8·7)	(14·9)
i.a.	109	83·9	86·2	100	113	115	101	106
	(13·1)	(14·6)	(17·1)	(17·2)	(12·1)	(16·1)	(11·5)	(22·1)
CL_{tot} (mL min^{-1} kg^{-1})								
i.v.	25·8	48·1	49·5	43·0	37·7	35·6	37·0	35·4
	(4·5)	(5·8)	(7·8)	(6·3)	(4·8)	(5·1)	(6·9)	(5·6)
i.a.	22·9	29·8	29·0	24·9	22·1	21·8	25·0	23·5
	(3·9)	(4·1)	(6·1)	(4·1)	(3·9)	(4·2)	(4·4)	(4·1)

[a] Shown in parentheses.
[b] With weight, $W(i)=1/(C)^2$.
[c] Estimated by the equation, $AUC=A/\alpha+B/\beta$.
[d] Estimated by the equation, $CL_{tot}=Dose/AUC$.

Table 2. Pulmonary clearance (CL_p) and extraction ratio (E_p) for propranolol when administered at 2·5 mg kg^{-1} to rats (n = 4) 3 to 104 weeks old.

	Mean ± s.d.[a] in age (weeks):							
Parameter	3	5	7	11	15	24	52	104
CL_p[b] (mL min^{-1} kg^{-1})	2·86	18·9	20·5	18·1	15·6	13·8	12·0	11·9
	(0·88)	(3·9)	(4·6)	(3·4)	(3·2)	(2·8)	(2·3)	(2·6)
E_p[c]	0·111	0·388	0·424	0·421	0·414	0·388	0·324	0·336
	(0·038)	(0·092)	(0·120)	(0·086)	(0·102)	(0·079)	(0·069)	(0·58)

[a] Shown in parentheses.
[b] Estimated by the equation, $CL_p=(CL_{tot})_{i.v.}-(CL_{tot})_{i.a.}$.
[c] Estimated by the equation, $E_p=1-(AUC)_{i.v.}/(AUC)_{i.a.}$.

to relate to body weight of the animal, it did not yield any significant correlation with CL_p. Therefore, the present results suggest that the age-dependence in the first-pass pulmonary clearance of propranolol may not be largely related to the age-dependent lung blood flow, but predominantly to the immaturity and senescence in pulmonary uptake capacity which has been proposed to be relatively high by Iwamoto et al (1987a).

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References

Cassidy, M. K, Houston, J. B. (1980) J. Pharm. Pharmacol. 32: 57–59

Iwamoto, K., Watanabe, J. (1984) Pharm. Res. 2: 53–54

Iwamoto, K., Takei, M., Watanabe, J. (1982) J. Pharm. Pharmacol. 34: 176–180

Iwamoto, K., Watanabe, J., Araki, K., Deguchi, N., Sugiyama, H. (1985a) Ibid. 37: 466–470

Iwamoto, K., Watanabe, K., Watanabe, J., Araki, K., Satoh, M., Deguchi, N. (1985b) J. Pharmacol. Exp. Ther. 234: 470–475

Iwamoto, K., Watanabe, J., Ayoama, Y. (1987a) J. Pharm. Pharmacol. 39: 1049–1051

Iwamoto, K., Watanabe, J., Atsumi, F. (1987b) J. Pharm. Dyn. 10: 280–284

Kramer, W. G., Gross, D. R., Medlock, C. (1985) J. Pharm. Sci. 74: 569–571

Roth, R. A. (1985) in: Benet, L. A., Massoud, N., Gambertoglio, J. G. (eds) Pharmacokinetic Basis for Drug Treatment. Raven Press, New York, pp 105–117

Yamaoka, K., Tanigawara, Y., Nakagawa, T., Uno, T. (1981) J. Pharm. Dyn. 4: 879–885

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Agonist profile of ergometrine (ergonovine) on a population of postsynaptic α-adrenoceptors

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Abstract—Ergometrine (0·02–5 μM) produced concentration-related contractions of the mouse anococcygeus muscle, which were unaffected by cocaine (2 μM) or by pretreatment of mice with 6-hydroxydopamine. Contractions were reduced by α-adrenoceptor antagonists; the rank order of potency was prazosin > phentolamine > yohimbine. With phenoxybenzamine as antagonist, the estimated dissociation constant (K_D) for ergometrine was 0·41 μM. It is concluded that ergometrine causes direct activation of postsynaptic α_1-adrenoceptors, and it is suggested that it acts on the same subtype of the receptor as imidazoline agonists.

Ergometrine (ergonovine) is used therapeutically in the management of postpartum haemorrhage and, more controversially, as a diagnostic agent for the detection of variant forms of angina (Editorial 1982). In both cases, the relevant pharmacological property is smooth muscle contraction, either of the uterus or the coronary arteries. However, the nature of the receptors activated by ergometrine, and in particular the role of α-adrenoceptors, remains a matter of contention (Muller-Schweinitzer & Weidmann 1978; Sakanashi & Yonemura 1980; Brazenor & Angus 1981). Experiments on neural tissue have suggested that ergometrine may act as a partial agonist on α_2-adrenoceptors (Marshall et al 1977; Brown & Caulfield 1979), but few studies have focussed on α-adrenoceptor interactions on smooth muscle. Apart from the uterus and coronary arteries, ergometrine is generally considered to have little contractile effect on smooth muscle (Bowman & Rand 1980). However, during an investigation of α-adrenoceptor function in the mouse anococcygeus muscle, it was found that ergometrine produced strong contractions which were reduced by phentolamine, suggesting α-adrenoceptor activation (Gibson unpublished observation). In the present communication, we examine these contractions in more detail. In particular, the experiments were designed to clarify two points. First, the anococcygeus muscle is very sensitive to contraction by indirect sympathomimetics (Gillespie 1981; Gibson & Wedmore 1981) and therefore experiments were carried out to determine whether ergometrine-induced contractions of the mouse anococcygeus were direct or indirect. Secondly, the nature of the α-adrenoceptor activated by ergometrine was determined.

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Methods

Male mice (LACA strain; 25–35 g) were killed by stunning and exsanguination. The paired anococcygeus muscles were dissected out and set up in series, joined at the ventral bar, in 1 mL glass organ baths containing Krebs-bicarbonate solution (composition mM: NaCl 118·1; KCl 4·7; $MgSO_4$ 1·0; KH_2PO_4 1·2; $CaCl_2$ 2·5; $NaHCO_3$ 25·0; glucose 11·1) maintained at 37°C and gassed continuously with 95% O_2:5% CO_2. A resting tension of 200–400 mg was placed on the tissue and changes in tension recorded with a Grass FTO3 force-displacement transducer attached to a Lectromed pen-recorder. Muscles were allowed to equilibrate for 45 min before the experiment was begun.

Ergometrine was added to the organ bath in volumes not exceeding 50 μL and was left in contact with the tissue for 5 min or until any consequent rise in tone had reached a peak. Following washout, further concentrations of agonist were not added until muscle tone had returned to baseline. pD_2 values (−log of the molar concentration of agonist producing 50% of the maximum response, Ariëns & van Rossum 1957) were calculated by regression analysis of the straight line portion of the concentration-response curve (between 20–80% of the maximum response).

Antagonist drugs of the competitive type (prazosin, phentolamine, yohimbine) were added to the Krebs reservoir at the appropriate concentration and were in contact with the tissue for 30 min before testing their effect on ergometrine sensitivity.