Mitchell, J. R., Jollow, D. J., Potter, W. Z., Gillette, J. R., Brodie, B. B. (1973) J. Pharmacol. Exp. Ther. 187: 211–217

Olsson, R. (1978) Lancet ii: 152–153

Rose, P. G. (1969) Br. Med. J. 1: 381–382

Willson, R. A., Hart, F. E. (1977) Gastroenterology 73: 691–696

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

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# High capacity for pulmonary first-pass elimination of propranolol in rats

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Plasma propranolol concentrations after i.v. and i.a. 1, 2·5, 5 and 10 mg kg$^{-1}$ doses of the drug given intravenously or intra-arterially have been compared in 7-week-old male Wistar rats. The areas under the curves after i.a. dosing were almost twice those after i.v. dosing at any dose, despite the elimination half-lives being the same. The difference in total body clearance after i.a. dosing from that after i.v. dosing indicated a significant contribution by pulmonary clearance, which ranged from about 20 to 30 mL min$^{-1}$ kg$^{-1}$, to the overall first-pass elimination after the i.v. administration. The pulmonary extraction ratio was approximately 0·4 to 0·5 at the i.v. doses used. Mean pulmonary transit time was estimated to be about 1 to 2 min. There was no dose-dependence in the pulmonary first-pass elimination kinetics of propranolol.

Propranolol has been thought to be eliminated predominantly by the liver in both man and animals (Shand et al 1971; Shand & Rangno 1972; Shand et al 1972). However, the recent reports have demonstrated that it is also extensively taken up by dog (Pang et al 1982) and rat (Schneck et al 1977; Rikihisa et al 1981) lung after the direct injection into the pulmonary artery or i.v. injection via the tail vein. Furthermore, the hepatic clearance of propranolol after in-vitro perfusion has been found to be substantially lower than the in-vivo total body clearance in rats (Iwamoto et al 1986). However, there have been no reports showing direct evidence of pulmonary first-pass elimination after its i.v. administration. We have compared plasma propranolol levels after i.v. and i.a. administration at 1, 2·5, 5 and 10 mg kg$^{-1}$ in 7-week-old rats to estimate pulmonary clearance, extraction ratio and mean transit time during the first-passage through the lung.

## *Methods*

Male Wistar rats (7-week-old, 210–225 g) were chronically cannulated into both jugular vein and artery with silicone polymer tubing (i.d. 1·0 mm; o.d. 1·5 mm, Dow Corning) and fasted overnight. The intravascular end of the venous cannula was inserted into the right atrium as reported by Iwamoto et al (1982) and that (with 1·2 cm tip of bevelled PE-50) of the arterial cannula was inserted into the right pulmonary vein.

Unanaesthetized, chronically cannulated rats (n = 4) were given propranolol (ICI) at 1, 2·5, 5 or 10 mg kg$^{-1}$ either intravenously (via jugular vein) or intra-arterially (via pulmonary vein). Each rat was sham-injected with the same volume (1 mL kg$^{-1}$) of 0·9% NaCl (saline) into an alternative cannula. Periodic blood samples (approximately 0·12 mL at nine time points) were withdrawn from the venous cannula into heparinized micro tubes over 2 h. Plasma (0·05 mL) propranolol concentration was determined according to Iwamoto & Watanabe (1984).

Plasma propranolol concentration (C)-time curves were analysed according to the least-squares regression analysis program MULTI (Yamaoka et al 1981) for a bi-exponential decline expressed as $C = Ae^{-\alpha t} + Be^{-\beta t}$, where A, B, $\alpha$ and $\beta$ are hybrid parameters. Area under the concentration-time curve (AUC) was estimated by the equation, $AUC = A/\alpha + B/\beta$. Total body clearance ($CL_{tot}$) was estimated by the equation,

$$CL_{tot} = \text{dose}/AUC.$$

Pulmonary clearance ($CL_p$) and extraction ratio ($E_p$) were calculated by the equations,

$$CL_p = (CL_{tot})_{i.v.} - (CL_{tot})_{i.a.}$$

and

$$E_p = 1 - (AUC)_{i.v.}/(AUC)_{i.a.},$$

respectively, where the subscripts i.v. and i.a. stand for the intravenous and intra-arterial administration, respectively. Mean residence time (MRT) after i.v. or i.a. dosing was estimated by the equation,

$$MRT \int_0^\infty t\,C\,dt/AUC.$$

Mean transit time in the lung ($MTT_p$) was calculated by the equation,

$$MTT_p = (MRT)_{i.v.} - (MRT)_{i.a.}.$$

## *Results and discussion*

Fig. 1 represents plasma propranolol concentration-time profiles after i.v. and i.a. administration at

* Correspondence.

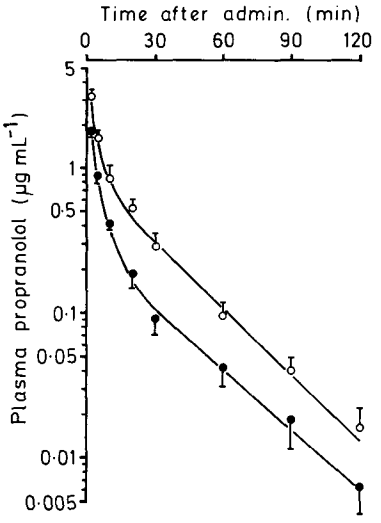


FIG. 1. Plasma concentration-time curve for propranolol after intra-arterial (○) and intravenous (●) administration at 1·0 mg kg$^{-1}$ to 7-week-old male Wistar rats. The solid lines represent the computer-fitted bi-exponential curves weighted with the reciprocal of the squared concentration. Each point is the mean ± s.d. of four rats.

1 mg kg$^{-1}$ to 7-week-old rats. The solid lines represent computer-fitted bi-exponential curves. The terminal elimination phase seemed to decline in almost parallel fashion after i.v. and i.a. dosing. Similar profiles were obtained at 2·5, 5 and 10 mg kg$^{-1}$. The plasma level after i.a. dosing was always higher than that after i.v. dosing. Estimated pharmacokinetic parameters are summarized in Table 1. At each tested dose, there was no significant difference in either α or β between routes, elimination half-lives after both routes being almost identical. There was no dose-dependence of total body clearance estimated after either route of dosing. However, the AUC after the i.v. dosage was always approximately half of that after the i.a. dosage and the results suggest an extensive pulmonary first-pass elimination of propranolol after i.v. administration to rats.

Effect of dose on pulmonary first-pass clearance, extraction ratio and mean transit time is summarized in Table 2. Although each parameter fluctuated slightly with dose, there was no dose-dependence in these parameters after the present doses. The larger value for $MTT_p$ of propranolol as compared with the MTT of pulmonary blood flow (i.e. usually several seconds) suggests an extensive extraction of this drug by rat lung. According to organ clearance concept (Rowland et al 1973; Wilkinson & Shand 1975), $E_p = CL_{int}/(CL_{int} + Q)$, where $CL_{int}$ is the intrinsic clearance and Q the blood flow. $CL_{int}$ for the pulmonary elimination of propranolol at 1 to 10 mg kg$^{-1}$ was then estimated as only about 70 to 100% of Q, i.e. only about 130 to 180 mL min$^{-1}$ kg$^{-1}$ in 7-week old rats of 210 to 225 g (Bischoff et al 1971). This also suggests that the lung may act as a 'pseudo-eliminating organ' by principally taking up or binding propranolol during its first-passage through the lung after i.v. administration. Furthermore, the absence of dose-dependence at every parameter ($CL_p$, $E_p$ or $CL_{int}$) of propranolol at the doses used suggests a high capacity for the lung to extract this drug.

Table 1. Pharmacokinetic parameters for propranolol after intravenous or intra-arterial administration of 1·0 to 10·0 mg kg$^{-1}$ to rats (n = 4).

| | Dose (mg kg$^{-1}$) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 1·0 | | 2·5 | | 5·0 | | 10·0 | |
| Parameter[a] | i.v. | i.a. | i.v. | i.a. | i.v. | i.a. | i.v. | i.a. |
| A (μg mL$^{-1}$) | 1·94 (0·31)[b] | 3·27 (1·40) | 3·07 (0·29) | 2·57 (0·78) | 7·62 (1·85) | 4·44 (1·29) | 13·1 (3·39) | 14·8 (3·17) |
| B (μg mL$^{-1}$) | 0·295 (0·136) | 0·969 (0·273) | 0·522 (0·111) | 1·98 (0·440) | 0·671 (0·205) | 2·77 (0·61) | 2·65 (0·315) | 5·92 (0·289) |
| α (min$^{-1}$) | 0·222 (0·051) | 0·288 (0·067) | 0·114 (0·015) | 0·101 (0·061) | 0·131 (0·057) | 0·105 (0·013) | 0·636 (0·192) | 0·566 (0·201) |
| β (min$^{-1}$) | 0·0313 (0·0135) | 0·0376 (0·0071) | 0·0222 (0·0022) | 0·0326 (0·0098) | 0·0223 (0·0088) | 0·0189 (0·0032) | 0·0171 (0·0049) | 0·0169 (0·0015) |
| AUC[c] (μg min mL$^{-1}$) | 18·2 (4·8) | 37·1 (9·8) | 50·5 (8·9) | 86·2 (17·1) | 88·2 (15·1) | 189 (57·2) | 176 (38·7) | 376 (89·2) |
| $CL_{tot}$[d] (mL min$^{-1}$ kg$^{-1}$) | 55·1 (19·7) | 26·9 (6·90) | 49·5 (7·77) | 29·0 (6·13) | 56·7 (10·1) | 26·4 (6·02) | 56·8 (11·3) | 26·6 (7·8) |

[a] Weighted with reciprocal of the squared concentration.
[b] s.d.
[c] Estimated by the equation, $AUC = A/\alpha + B/\beta$.
[d] Estimated by the equation, $CL_{tot}$ = dose/AUC.

Table 2. Clearance ($CL_p$), extraction ratio ($E_p$) and mean transit time ($MTT_p$) for propranolol in rat lung (n = 4).

| Parameter | Dose (mg kg$^{-1}$) 1·0 | 2·5 | 5·0 | 10·0 |
|---|---|---|---|---|
| $CL_p$[a] (mL min kg$^{-1}$) | 28·2 (7·9)[b] | 20·5 (4·6) | 30·3 (5·4) | 30·2 (5·3) |
| $E_p$[c] | 0·509 (0·139) | 0·415 (0·117) | 0·533 (0·126) | 0·532 (0·141) |
| $MTT_p$[d] (min) | 1·2 (0·6) | 1·1 (0·4) | 1·8 (0·6) | 1·9 (0·5) |

[a] Estimated by the equation,

$$CL_p = (CL_{tot})_{i.v.} - (CL_{tot})_{i.a.}$$

[b] s.d.

[c] Estimated by the equation,

$$E_p = 1 - (AUC)_{i.v.}/(AUC)_{i.a.}$$

[d] Estimated by the equation,

$$MTT_p = (MRT)_{i.v.} - (MRT)_{i.a.}$$

It has recently been reported that benzo(a)pyrene (Wiersma & Roth 1983), doxorubicin (Minchin et al 1984), harmol (Mudler et al 1984), isoprenaline (Brazzell et al 1982), isosorbide dinitrate (Mayer et al 1983), lignocaine (Bertler et al 1978), meperidine (Kramer et al 1985), phenol (Cassidy & Houston 1980) and verapamil (Gillespie et al 1984) are subject to pulmonary extraction and/or metabolism after i.v. administration or in-vitro perfusion in some animals. The present work is the first report showing the first-pass elimination kinetics of propranolol in rat lung by comparison of the plasma levels after i.v. and i.a. administration.

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REFERENCES

Bertler, A., Lewis, D. H., Lofstron, J. B., Post, C. (1978) Schriften. Intensivmed. Anesthesiol. 16: 87–92

Bischoff, K. B., Dedrick, R. L., Zaharko, D. S., Longstreth, J. A. (1971) J. Pharm. Sci. 60: 1128–1133

Brazzell, R. K., Smith, R. B., Kostenbauder, H. B. (1982) Ibid. 71: 1268–1274

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

Gillespie, M. N., Felder, T. B., Blanford, S. L., Reinsel, C. N., Kostenbauder, H. B. (1984) J. Cardiovasc. Pharmacol. 6: 802–807

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., Satoh, M., Deguchi, N., Sugiyama, H. (1986) Biochem. Pharmacol. 35: 1149–1152

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

Mayer, P. R., Lubawy, W. C., McNamara, P. J., Kostenbauder, H. B. (1983) Ibid. 72: 785–789

Minchin, R. F., Johnson, M. R., Aiken, M. R., Boyd, M. R. (1984) J. Pharmacol. Exp. Ther. 229: 193–198

Mudler, G. J., Weitering, J. G., Schotens, E., Dowson, J. R., Pang, K. S. (1984) Biochem. Pharmacol. 33: 3081–3087

Pang, J. A., Blackburn, J. P., Butland, R. J. A., Corrin, B., Williams, T. R., Geddes, D. M. (1982) J. Appl. Physiol. 52: 393–402

Rikihisa, T., Okhuma, T., Mori, M., Otsuka, M., Suzuki, T. (1981) Chem. Pharm. Bull. 29: 2035–2042

Rowland, M., Benet, L. Z., Graham, G. G. (1973) J. Pharmacokinet. Biopharm. 1: 123–136

Schneck, D. W., Pritchard, J. F., Hayes, A. H. (1977) J. Pharmacol. Exp. Ther. 203: 621–629

Shand, D. G., Rangno, R. E. (1972) Pharmacology 7: 159–168

Shand, D. G., Evans, G. H., Nies, A. S. (1971) Life Sci. 10: 1417–1421

Shand, D. G., Rangno, R. E., Evans, G. H. (1972) Pharmacology 8: 344–352

Wiersma, D. A., Roth, R. A. (1983) J. Pharmacol. Exp. Ther. 226: 661–667

Wilkinson, G. R., Shand, D. G. (1975) Clin. Pharmacol. Ther. 18: 377–390

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