Table 3. *Excretion half-times of PGA_1-^3H radioactivity* in dogs treated with an intravenous dose of PGA_1-17,18-^3H (38 μg kg^{-1}). (I) half-time (h) and (II) interval (h).*

Dog no.	Urine		Faeces		Total	
	I	II	I	II	I	II
1	10·0 66·5	0– 48 48–192	14·8	0–120	36·0	0–144
2	25·9 168·0 10·1	0– 72 72–144 144–192	29·2	0–120	35·6	0–144
3	3·9 60·0	0– 24 24–168	25·6	0–120	36·0	0–120
4	1·7 50·4	0– 24 24–168	21·6	0–120	26·0	0–120

* Tritiated water excreted has been excluded.

After the intravenous administration of PGA_1-^3H to four dogs, urinary excretion accounted for an average of 47% of the radioactive dose (see Table 2). Faecal excretion similarly accounted for an average of 49% of the administered dose. Excretion of the PGA_1-^3H related radioactivity in the urine and faeces was almost complete in 48 h after drug administration (Fig. 1 shows typical curves). An average of 0·5% of the radioactive dose administered was present as tritiated water in the urine (see Table 2). An approximately equivalent fraction may be assumed to have been expired as tritiated water during respiration.

Both urinary and biliary excretion appear to be equally important routes for the elimination of exogenous PGA_1 and related metabolites in the dog (see Table 2). In this respect, the dog appears to differ from the rat (Wickrema Sinha & Shaw, 1977), in which biliary (faecal) excretion was the major route of elimination of exogenous PGA_1 and related metabolites. Comparison of these excretion profiles with those in man (Wickrema Sinha & Shaw, 1977) suggested that man may resemble the rat more closely than the dog in this respect.

The urinary, faecal, and the combined urinary and faecal excretion half-times (which indicate the rate of elimination of total radioactivity from the body) are summarized in Table 3.

Thus, the tritium label in PGA_1-17,18-^3H is metabolically stable, and this material is suitable for use in metabolism studies in man.

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REFERENCES

ATTALLAH, A. & SCHUSSLER, G. C. (1973). *Prostaglandins*, **4**, 479–484.
CAGEN, L. M., PISANO, J. J. & FALES, H. M. (1974). *Fedn Proc. Fedn Am. Socs. exp. Biol.*, **33**, 576.
HSI, R. S. P. (1977). *J. Labelled Compds Radiopharm.*, in the press.
RAZ, A. (1972). *Biochem. J.*, **130**, 631–636.
SMITH, J. A., KOCSIS, J. J., INGERMAN, C. & SILVER, M. J. (1973). *Pharmacologist*, **15**, 208.
WICKREMA SINHA, A. J. & SHAW, S. R. (1977). *J. Pharm. Pharmac.*, **29**, 99–103.

The disposition of timolol in man

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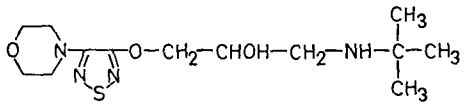
Timolol, 1-(*t*-butylamino)-3-(4-morpholino-1,2,5-thiadiazol-3-yl)-oxy-2-propanol] (I), is a relatively new β_1- + β_2-adrenoceptor blocking drug, resembling propanolol and sotalol in that it has no intrinsic sympathicomimetic activity (Waal-Manning, 1976). Unlike propranolol, it is devoid of local anaesthetic properties and on a molar base it is about 10× more potent (Waal-Manning, 1976; Achong, Piafsky & Ogilvie, 1976).



I

Little is known on the disposition of timolol, and the pharmacokinetic data are scarce and even controversial (Tocco, de Lunn & Duncan, 1975a; Tocco, Duncan & others, 1975b). For these reasons we have examined the pharmacokinetic behaviour of the drug in healthy volunteers.

Three female and 2 male volunteers, ages 22–35 years, 52–85 kg, participated. They did not receive any other drug, took a light breakfast and moved around freely.

Initially, they ingested an aqueous solution of timolol maleate (1·0 mg timolol base ml^{-1}), to give 0·1 mg timolol base kg^{-1}, about 2 h after breakfast. In other experiments, doses up to 0·4 mg kg^{-1}, were also given. Blood samples were taken at regular intervals. Subsequently, in a second series of experiments, 6 weeks later, the same subjects received 3·7 mg timolol given as the commercial preparation†. The

* Correspondence.

† Blocadren (MSD). Tablets containing 10 mg timolol maleate (= 7·4 mg timolol).

Table 1. *Mean plasma timolol concentrations after oral administration of timolol solution, 0·1 mg kg^{-1} (mean ± s.e.m.; n = 5).*

Time (h)	Timolol concn μg litre^{-1}
0·75	17·0 ± 3·6
1·0	23·4 ± 5·4
1·5	26·0 ± 4·5
2·0	24·2 ± 4·5
3·0	18·3 ± 3·5
4·0	15·0 ± 4·0
5·0	11·3 ± 3·0
6·0	9·2 ± 1·7

same dose was continued with a dosing interval of 8 h up to a total of 10 doses. After the first and after the 10th dose series of blood samples (10 ml each) were taken.

Although the drug is not officially available for intravenous administration, two of the volunteers agreed to receive the drug intravenously as an infusion of a sterile solution of about 0·02 mg kg^{-1} in dextrose 5%, administered in 15 min.

Blood samples were taken from a cubital vein (Venoject tubes with 143 mg sodium heparin each). Plasma was separated immediately and kept at 4° until assay (usually 1–2 days later).

Timolol was assayed by g.l.c. (Vermeij, 1977), using a simplification of the method of Tocco & others (1975a) and a Pye gas-chromatograph with a ^{63}Ni-EC-detector. Determinations were in duplicate. After addition of the internal standard (45 ng desmethyl-timolol)‡, 1·0 ml plasma was made alkaline and extracted with benzene. Timolol was back extracted into 0·1 M HCl and, subsequently, after making alkaline again, taken up into benzene. An aliquot of the benzene phase was evaporated at 60° under nitrogen and derivatized with HFBI¶ and handled further as described by Tocco & others (1975a).

Pharmacokinetic parameters were calculated from the experimental data for each individual. The parameters after oral administration could be calculated assuming a one compartment open model. After intravenous administration a two compartment open model was taken as a base of the calculations. For the calculations a computer program was used§. Accordingly optimal estimates for the various pharmacokinetic parameters could be obtained.

The volume of distribution was calculated as V_d area.

The fraction f that reaches the systemic circulation after oral administration was calculated by the formula of Gibaldi, Boyes & Feldman (1971).

C_{max}^{∞} and C_{min}^{∞} after oral administration could be calculated according to Ritschel (1973).

The mean plasma concentrations of timolol of the five subjects at different times after intake of the solution (dose: 0·1 mg kg^{-1}) are listed in Table 1. The mean pharmacokinetic parameters that could be calculated from the data obtained in each individual are presented in Table 2. In addition to the data obtained after administration of the oral solution, some data acquired after administration of the tablets are also given. Obviously no important differences exist between the data calculated after the administration of an aqueous solution and the pharmaceutical

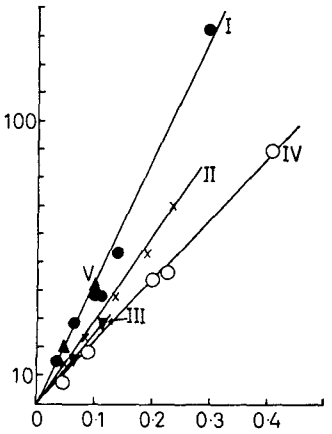


FIG. 1. Linear relation of $C_{t_{peak}}$ *vs* dose administered orally in the five volunteers (I-V). Ordinate: $C_{t_{peak}}$ (μg litre^{-1}); abscissa: dose (mg kg^{-1}).

‡ Gift from R. J. Bergmans, associate medical Director, Merck, Sharp & Dohme, Haarlem, The Netherlands.

¶ Heptafluorobutyrylimidazole, Pierce nr 44210.

§ Non-linear regression programme FARMFIT, developed and used at the Computer Centre of the University of Nijmegen and run on the computer of SARA (Stichting Academisch Rekencentrum Amsterdam) for the Department of Pharmacotherapy of the University of Amsterdam.

Table 2. *Pharmacokinetic parameters of timolol (oral administration) (mean ± s.e.m.; n = 5).*

Parameter	After oral sol.	After 1st tablet	After 10th tablet
Kel	0·286 ± 0·017 h^{-1}	0·348 ± 0·020 h^{-1}	0·324 ± 0·015 h^{-1}
$t_{\frac{1}{2}}$ el	2·47 ± 0·15 h	1·99 ± 0·14 h	2·17 ± 0·10 h
k_{abs}	5·04 ± 1·06 h^{-1}	2·38 ± 0·46 h^{-1}	—
Lag time	0·6 ± 0·1 h	0·19 ± 0·19h	—
t_{peak}	1·2 ± 0·1 h	1·14 ± 0·2h	—
V_d. kg^{-1}	1·33 ± 0·09 h	—	—
f	0·48 ± 0·04	—	—

preparation. The availability of the tablet with respect to the solution was 0·84 ± 0·09 (mean ± s.e.m.; n = 5). After administration of higher doses no significant differences in the pharmacokinetic parameters were seen.

Linear kinetics could be demonstrated to occur in each of the subjects, since we observed a linear relation between the administered dose and the maximal plasma concentration (Fig. 1). The plasma concentrations after intravenous infusion of timolol during 15 min in the two volunteers are presented graphically in Fig. 2. The initial distribution of drug is rapid, with a half-life of the α-phase of 4 and 7 min. The half-life of the β-phase (2·6 and 1·8 h) and the volume of distribution (1·7 and 1·4 litres kg^{-1}) did not differ greatly from that found after oral administration in the same volunteers.

The plasma half-life of timolol in this investigation (about 2·5 h) is substantially shorter and more precise than the data published by Tocco & others (1975a, b), who give only approximate data (*viz* 3 and 4·5 h, respectively).

The volume of distribution is large and points towards considerable distribution in the tissues. It is of the same order of magnitude as that of, e.g. oxprenolol (Mason & Winer, 1976). In fact, the pharmacokinetic parameters of timolol as determined in our investigation are comparable to a large extent with those of oxprenolol as presented by Mason & Winer (1976).

Using the formula of Gibaldi & others (1971), the fraction *f* that reaches the systemic circulation after oral administration amounts to 0·48. Taking 0·73 as the fraction F that is absorbed after oral administration (Hucker, Strauffer & others, 1971) this would mean that timolol is subject to a moderate first pass effect in the liver.

As can be anticipated from the values found for k_{el} and k_{abs}, accumulation after repeated oral administration (dosing interval 8 h) is not large. C_{max}^{∞} after oral administration of 5 mg timolol maleate as a tablet amounted to 17·1 ± 3·6 μg $litre^{-1}$ (mean ± s.e.m.; n = 5). This value will be reached at the fourth administration. The 10th administration, therefore, really represents the steady state situation. C_{min}^{∞} was calculated to be 0·89 ± 0·6 μg $litre^{-1}$ (mean ± s.e.m.; n = 5).

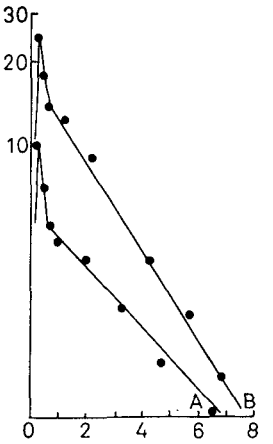


FIG. 2. Plasma concentration time curves after intravenous administration of timolol in two volunteers. Infusion time: 15 min. subj. A: dose 0·011 mg kg^{-1}; subj. B: dose 0·028 mg kg^{-1}. Ordinate: concentration (μg $litre^{-1}$); abscissa: time (h).

The pharmacokinetic data obtained suggest that the distribution and elimination of timolol occur by linear rate processes, at the plasma concentrations reached in this investigation (which cover the therapeutic dose range recommended). However, since no plasma concentration-effect data of timolol are available, no predictions about the optimal dose regimen can be made as yet. It may be expected that the short plasma half-life of the drug will lead to large fluctuations during the dose intervals, which should be regarded as a disadvantage. Large differences in pharmacokinetic parameters appear to exist between the three β-sympatholytic drugs propranolol (Johnsson & Regårdh, 1976), sotalol (Anttila, Arstila & others, 1976) and timolol.

Plasma timolol determinations were performed very skilfully by Mrs W. Ramp-Koopmanschap.

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REFERENCES

ACHONG, M. R., PIAFSKY, K. M. & OGILVIE, R. J. (1976). *Clin. Pharm. Thér.*, **19**, 148–152.

ANTTILA, M., ARSTILA, M., PFEFFER, M., TIKKANEN, R., VALLINKOSKI, V. & SUNDQUIST, H. (1976). *Acta pharmac. tox.*, **39**, 118–128.

GIBALDI, M., BOYES, R. N. & FELDMAN, S. (1971). *J. pharm. Sci.*, **60**, 1338–1340.

HUCKER, H. B., STRAUFFER, S. C., GATES, T. N. & ARNOLD, J. D. (1971). *Pharmacology*, **13**, 294.

JOHNSSON, G. & REGÅRDH, C.-G. (1976). *Clin. Pharmacokin.*, **1**, 223–263.

MASON, W. D. & WINER, N. (1976). *Clin. Pharm. Thér.*, **20**, 401–412.

RITSCHEL, W. (1973). *Angewandte Biopharmazie*, p. 544. Stuttgart: Wissenschaftliche Verlag Gesselschaft mbH.

TOCCO, D. J., DE LUNA, F. A. & DUNCAN, A. E. W. (1975a). *J. pharm. Sci.*, **64**, 1879–1881.

TOCCO, D. J., DUNCAN, A. E. W., DE LUNA, F. A., HUCKER, H. B., GRUBER, V. F. & VANDENHEUVEL, W. J. A. (1975b). *Drug Metab. Disp.*, **3**, 361–370.

VERMEIJ, P. (1977). *Kinetische aspecten van enkele β-blokkeerders*. Ph.D. Thesis, University of Amsterdam.

WAAL-MANNING, H. (1976). *Drugs*, **12**, 412–441.