Br. J. clin. Pharmac. (1980), **10**, 561–566

PROPRANOLOL DISPOSITION IN RENAL FAILURE

A.J.J. WOOD, R.E. VESTAL*, C.L. SPANNUTH**, W.J. STONE, G.R. WILKINSON & D.G. SHAND***

Departments of Medicine and Pharmacology,
Vanderbilt University Medical Center
and
Veterans Administration Medical Center,
Nashville, Tennessee 37232, USA

1 Previous studies of propranolol disposition in renal failure have been conflicting.

2 Using simultaneous administration of [^{3}H]-propranolol intravenously and unlabelled propranolol orally the principal determinants of drug distribution were calculated in normals, patients with severe renal impairment (creatinine clearance 14.5 ± 2.8 ml/min) but not on haemodialysis and patients on haemodialysis (creatinine clearance <5 ml/min).

3 The effect of haemodialysis on propranolol binding and free fraction was also examined. The percentage of propranolol unbound rose from 7.1% to 9.9%. ($P < 0.001$) 20 min following heparinization and beginning haemodialysis. This was accompanied by a large rise in free fatty acids from 0.567 ± 0.059 to 3.326 ± 0.691 μmol/ml ($P < 0.005$).

4 The blood to plasma concentration ratios of propranolol were significantly higher in patients with renal failure ($P < 0.02$) and on haemodialysis ($P < 0.001$) and were significantly negatively correlated ($P < 0.001$) with the haematocrit.

5 Although the half-life of propranolol was significantly shortened in the patients with renal failure ($P < 0.02$), there was no change in the apparent liver blood flow, extraction ratio or the principal determinants of steady-state drug concentrations in blood namely oral and intravenous clearance from blood.

6 There is, therefore, no pharmacokinetic basis to adjust the dosage of propranolol in patients with renal failure.

Introduction

The clinical responsiveness to a number of drugs may be altered in patients with renal failure. This is particularly true for those drugs which are predominantly excreted unchanged by the kidneys, where the impaired elimination results in elevated drug levels. However, renal dysfunction may also alter the disposition of drugs which are eliminated primarily by biotransformation (Letteri, Mellk, Louis, Kutt, Durante & Glazko, 1971; Odar-Cederlöf & Borga, 1974; Lichter, Black & Arias, 1973; Maddocks, Wake & Harber, 1975; Reidenberg, 1977). Altered plasma drug binding may account for some of these changes with highly bound drugs such as phenytoin (Odar-Cederlöf & Borga, 1974; Reidenberg, Odar-Cederlöf, von Bahr & Sjöqvist, 1971; Reidenberg, 1976) but perturbations in drug metabolism may also be involved. For example, the rate of elimination of antipyrine is impaired in patients with uremia in the absence of any alterations in the drug's distribution (Licher *et al.*, 1973; Maddocks *et al.*, 1975)

Propranolol is especially useful in the treatment of hypertension in patients with renal failure because of its ability to reduce circulating renin levels. Its disposition in such patients has previously been examined but with conflicting results. The oral absorption of propranolol has been reported to be impaired (Thompson, Joekes & Foulkes, 1972), increased (Lowenthal, Briggs, Gibson, Nelson & Cirksena, 1974) and unchanged (Bianchetti, Granziani, Brancaccio, Morganti, Leonetti, Manfrin, Sega, Gomeni, Ponticelli & Morselli, 1976) in renal failure, whereas its elimination was slowed (Thompson,

Present addresses:
* Dr R.E. Vestal, Research Service (151), V.A. Medical Center, 5th and Fort Streets, Boise, Idaho 83702.
** Dr C.L. Spannuth, 2100 North Roan Street, Johnson City, TN 37601.
*** Dr D.G. Shand, Department of Pharmacology, Duke University, P.O. Box 3813, Durham, North Carolina 27710.

0306–5251/80/060561–06 $01.00

Joekes, Foulkes, 1972 and Bianchetti *et al.*, 1976), and the volume of distribution increased on a dialysis day in patients undergoing haemodialysis (Bianchetti *et al.*, 1976). A lack of appreciation of (a) the difference in a single oral *v* a steady-state dose (Wood, Carr, Vestal, Belcher, Wilkinson & Shand, 1978) (b) the effect of aging on elimination (Vestal, Wood, Branch, Shand & Wilkinson, 1979) and (c) the effect of heparin on plasma binding (Wood, Shand & Wood, 1979a; Wood, Shand & Wood, 1979b; Wood, Robertson, Robertson, Wilkinson & Wood, 1980) of propranolol may account for some of these discrepancies. Also, the use of plasma levels of total (bound plus unbound) drug may have compounded the problem. Accordingly, we have studied the complete steady-state disposition of propranolol following simultaneous oral and intravenous administration in a group of patients with severe renal failure but not on haemodialysis, a similar group receiving haemodialysis and age-matched control subjects.

Methods

Eighteen males were studied, seven of whom had severe renal failure (creatinine clearance 14.6 ± 2.8 ml/min, weight 77.7 ± 6.7 kg) but were not on haemodialysis (mean age 50.7 ± 3.4 years), five patients on haemodialysis (creatinine clearance < 5 ml/min, weight 73.1 ± 4.6 kg) were studied on an inter-dialysis day (mean age 52.3 ± 3.7 years) and six were healthy age matched controls (creatinine clearance 87.3 ± 10.0 ml/min; mean age 52.0 ± 1.6 years, weight 80.4 ± 3.9 kg) with no evidence of disease on routine history, physical examination or laboratory testing. Neither the subjects nor patients received any drugs, other than propranolol, in the week preceding the study. After obtaining informed consent all subjects were admitted to the Vanderbilt Hospital Clinical Research Center.

Propranolol was administered by mouth in a dose of 80 mg every 8 h for at least 2 days. Simultaneous with the morning oral dose on the third day, 45 μCi of [^{3}H]-propranolol was administered intravenously and blood samples taken by separate venepuncture over the next 8 h. Propranolol was determined in blood by the high pressure liquid chromatography method of Wood *et al.* (1978) with the [^{3}H]-propranolol corresponding to the propranolol peak being collected and, following the addition of 10 ml 'Unogel', counted by liquid scintillation spectrometry.

The fraction of propranolol free in plasma was measured by equilibrium dialysis of 3 ml plasma against 6 ml phosphate buffer to which had been added 2.7 ng of [^{3}H]-propranolol in 50 μl of saline as previously described (Kornhauser, Wood, Vestal, Wilkinson, Branch & Shand, 1978). The free fraction of drug in plasma was then calculated as the concentration of radioactive propranolol in the buffer divided by the concentration in the plasma. The blood to plasma concentration ratio (blood/plasma) was determined by measuring the [^{3}H]-propranolol concentration in an aliquot from 1 ml plasma to which had been added 2.7 ng of [^{3}H]-propranolol and dividing by the [^{3}H]-propranolol concentration in plasma obtained after adding 2.7 ng [^{3}H]-propranolol to 1 ml blood and centrifuging.

Systemic or intravenous clearance (Cl_s) was estimated from the relationship of [^{3}H]-propranolol as:

$$Cl_s = \frac{D_{i.v.}}{AUC_{i.v.}}$$

where $D_{i.v.}$ is the dose of [^{3}H]-propranolol intravenously and $AUC_{i.v.}$ is the total area under the concentration/time curve extrapolated to infinity. Volume of distribution ($V_d\beta$) was calculated as:

$$V_d\beta = \frac{Cl_s T_{1/2}}{0.693}$$

where $T_{1/2}$ is the half-life measured from the terminal portion of the concentration/time curve from 1 to 8 h. The apparent oral clearance (Cl_o) was calculated as:

$$Cl_o = \frac{D_o}{AUC_o}$$

where D_o is the oral dose and AUC_o is the area under the concentration/time curve following oral administration during the dosing interval.

It has previously been shown (Wilkinson & Shand, 1975) that if the venous equilibration model (Rowland, Benet & Graham, 1973) applies and the drug is fully absorbed, and metabolized only by the liver then:

$$Cl_o = Cl_{int}$$

in which Cl_{int} is the total intrinsic clearance of the drug, a measurement of the activity of the drug metabolizing enzymes.

The clearance from plasma following oral or intravenous clearance was calculated as:

$$Cl_{Plasma} = Cl_{Blood} \times [Blood] / [Plasma]$$

Apparent liver blood flow $\hat{Q}$ was estimated by (Wilkinson & Shand, 1975):

$$\hat{Q} = \frac{D_o D_{i.v.}}{AUC_{i.v.} D_o - AUC_o D_{i.v.}}$$

Bioavailability (F) was calculated as:

$$F = \frac{AUC_o D_{i.v.}}{AUC_{i.v.} D_o}$$

In theory, again assuming complete absorption and

hepatic elimination, bioavailability is determined by flow and intrinsic clearance as:

$$F = (1-E) = \frac{\hat{Q}}{\hat{Q} + Cl_{int}}$$

where E is the hepatic extraction ratio.

In addition, eleven patients undergoing haemodialysis had blood samples taken prior to starting haemodialysis and prior to heparinization, 20 min after the start of haemodialysis, and at the end of haemodialysis for the measurement of the fraction of propranolol free in plasma, haematocrit and free fatty acid levels (Dole & Meinertz, 1960).

The results were analysed using Student's t-test for unpaired values $P < 0.05$ being accepted as the minimal level of significance.

Results

The mean propranolol levels in blood at the various sampling times in the three groups are shown in Table 1. Although the half-life of propranolol (Table 2) was significantly ($P < 0.02$) shortened in patients with renal failure not on haemodialysis, compared to controls, there was no significant difference in either the oral or systemic clearance of propranolol from blood.

Table 1 Effect of renal failure on propranolol levels in blood (ng/ml ± s.e. mean)

Time after dose (min)	*Normals*	*Haemodialysis*	*Renal failure*
0	58 ± 14	78 ± 28	56 ± 8
5	51 ± 9	82 ± 32	49 ± 7
15	55 ± 10	87 ± 34	55 ± 8
30	67 ± 13	94 ± 25	60 ± 13
60	97 ± 27	131 ± 43	86 ± 19
120	115 ± 22	135 ± 37	129 ± 21
240	93 ± 18	134 ± 31	109 ± 17
360	68 ± 11	97 ± 28	74 ± 14
480	49 ± 8	73 ± 23	65 ± 17

Nor was there any significant alteration in apparent liver blood flow or extraction ratio (Table 2). The fraction of propranolol free in plasma was unchanged but the blood to plasma ratio (Table 3) was increased in both groups of patients with renal failure. The haematocrits (Table 3) were significantly lower in the patients with renal failure ($P < 0.02$) and on haemodialysis ($P < 0.001$) than in the age matched controls. In addition there was a significant ($P < 0.001$) negative correlation between the blood/plasma ratio and haematocrit (Figure 1). When the clearance following both oral and intravenous administration and the volume of distribution were expressed in terms of free drug in blood (Table 4) no significant difference was found between either of the two groups of patients with renal failure and the age matched controls. The calculated clearance from plasma following intravenous administration was significantly ($P < 0.02$) greater in the patients with renal failure compared to patients with normal renal function (Table 2).

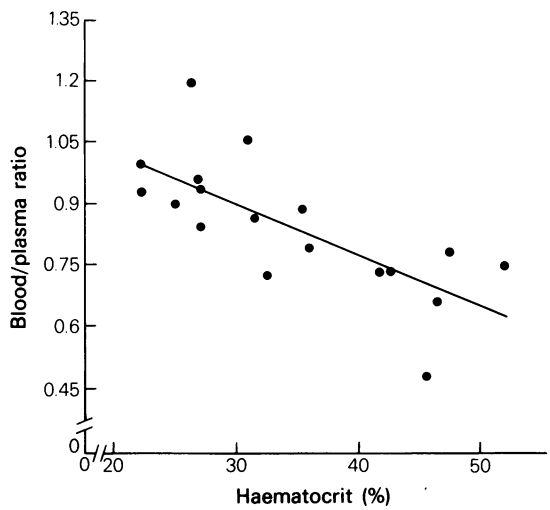

Figure 1 Relationship between blood/plasma concentration ratio and haematocrit, $r = -0.722$, $P < 0.001$.

Table 2 Pharmacokinetic parameters of total propranolol in normal controls, patients with renal failure and patients receiving haemodialysis on an interdialysis day (mean ± s.e. mean).

	Normals	*Haemodialysis*	*Renal failure*
$T_{1/2}$ (h)	4.33 ± 0.12	4.01 ± 0.66	3.50* ± 0.26
V_d (l)	308.5 ± 28.4	241.5 ± 24.3	254.9 ± 21.9
Cl_o (blood), (ml/min)	2305.5 ± 337.8	1953.8 ± 541.4	2120.2 ± 310.5
$Cl_{i.v.}$ (blood), (ml/min)	814.8 ± 55.5	776.0 ± 140.9	856.0 ± 80.9
$\hat{Q}$ (ml/min)	1349.4 ± 114.2	1347.9 ± 203.6	1561.5 ± 158.9
E	0.616 ± 0.046	0.567 ± 0.035	0.564 ± 0.045
Cl_o plasma (ml/min)	1561.3 ± 187.6	1835.7 ± 550.9	1870.4 ± 210.3
$Cl_{i.v.}$ plasma (ml/min)	562.2 ± 48.0	721.3 ± 136.1	770.2 ± 51.4*

* $P < 0.02$ (v normals)

Table 3 Effect of renal failure on the unbound fraction of propranolol in plasma, the blood to plasma ratio and haematocrit (mean ± s.e. mean)

	Normals	*Haemodialysis*	*Renal failure*
Percentage unbound in plasma	6.0 (± 0.6)	6.7 (± 1.1)	7.7 (± 0.9)
Blood/plasma ratio	0.69 (± 0.05)	0.93** (± 0.03)	0.92* (± 0.06)
Haematocrit (%)	44.4 (± 2.3)	24.6*** (± 1.1)	33.3* (± 2.8)

* $P < 0.02$ (v normals)
** $P < 0.005$
*** $P < 0.001$

Table 4 Pharmacokinetic parameters of propranolol in patients with renal failure based on unbound levels (mean ± s.e. mean)

	Normals	*Haemodialysis*	*Renal failure*
Free Cl_o (l/min)	26.0 ± 2.7	28.2 ± 6.4	26.7 ± 4.4
Free $Cl_{i.v.}$ (l/min)	9.6 ± 0.9	11.8 ± 2.6	10.9 ± 1.5
Free V_d (l)	3583 ± 266	3588 ± 541	3203 ± 391

The binding of propranolol was also studied during haemodialysis (Table 5). The percentage of propranolol free in plasma increased significantly ($P < 0.001$) from 7.1% to 9.9% 20 min following heparinization and beginning haemodialysis. This was accompanied by a large rise in free fatty acids from 0.567 (± 0.059) to 3.326 (± 0.691) μmol/ml ($P < 0.005$). The percentage of unbound propranolol remained elevated immediately post-dialysis at 9.8% (± 0.7) ($P < 0.001$) as did the free fatty acid concentration ($P < 0.001$).

Discussion

The simultaneous administration of labelled propranolol intravenously along with unlabelled drug orally allows the determination of oral and intravenous kinetics under identical conditions (Wood *et al.*, 1978; Vestal *et al.*, 1979; Kornhauser *et al.*, 1978). In addition, by measuring the blood/plasma ratio and drug binding in plasma it is possible to determine all of the parameters controlling propranolol's disposition in man and to express those, where appropriate, in terms of free drug.

The factors controlling the elimination of propranolol vary according to its route of administration. Since with chronic oral dosing of propranolol the hepatic extraction ratio is about 66% (Wood *et al.*, 1978) the principal factors controlling the systemic or intravenous clearance of propranolol are its rate of delivery to the liver, that is the liver blood flow, and the total intrinsic clearance. In contrast, following oral administration propranolol is avidly removed by the liver prior to entering the systemic circulation resulting in high apparent oral or total intrinsic clearance, and low systemic availability. The principal factor controlling total intrinsic clearance is the drug metabolizing ability of the liver.

We have shown that the oral and systemic clearance of propranolol from blood are unaffected by chronic renal failure. In addition, we found no alteration in apparent liver blood flow in either of the groups of patients with renal failure. However, the half-life of propranolol was significantly ($P < 0.02$) shorter in patients with renal failure not on haemodialysis compared to normal age matched controls. Drug half-life is dependent on both the ability to eliminate drug (clearance) and volume of distribution. The volume of distribution was lower though not significantly so in the patients with renal failure compared to normal controls and this coupled with the similar clearances resulted in the reduced-half-life.

It is now well recognized that the free fraction of several drugs (Reidenberg, 1976) is increased in patients with renal failure. It was, therefore, of importance to examine the effect of renal failure on the plasma binding of propranolol. Renal failure did not appear to alter the plasma binding of propranolol. However, there was a significant elevation of the blood to plasma ratio in the patients with renal failure and a significant negative correlation between blood to plasma ratio and haematocrit. The relationship

Table 5 Effect of haemodialysis on the percentage of propranolol unbound in plasma and on free fatty acid levels (mean ± s.e. mean)

	Pre-dialysis	*20 min after start of dialysis*	*Post-dialysis*
Percentage unbound in plasma	7.1 ± 0.42	9.9* ± 0.64	9.8* ± 0.7
Free fatty acids (μmol/ml)	0.567 ± 0.059	3.326** ± 0.691	1.771* ± 0.190

* $P < 0.001$ (v pre-dialysis)
** $P < 0.005$

between haematocrit (H) and blood to plasma concentration ratio can be computed as follows:

$$[\text{Blood}] = [\text{Plasma}](1-H)+[BC]\times H.$$

$$\frac{[\text{Blood}]}{[\text{Plasma}]} = \frac{[\text{Plasma}]\text{-}H\,([\text{Plasma}]\text{-}[BC])}{[\text{Plasma}]}$$

$$\frac{[\text{Blood}]}{[\text{Plasma}]} = 1-H\left(1-\frac{[BC]}{[\text{Plasma}]}\right)$$

where [Blood], [Plasma] and [BC] are the drug concentration in blood plasma, and formed elements respectively. Thus, the rise in blood to plasma concentration ratio found in the patients with renal failure would be expected because of the reduced haematocrit seen in renal failure.

By the use of both the blood/plasma ratio and the free fraction in plasma it was possible to calculate clearances and volume of distribution in terms of free drug in blood. We found no significant effect of renal impairment on either intrinsic free clearance, free intravenous clearance or free volume of distribution.

Thus, besides clinical importance the critical value of using drug clearance rather than half-life as a measure of drug metabolizing ability is re-emphasized by this study as is the importance of examining drug binding and free clearance in disease states. The difference between our findings and those of previous workers are explained partly by lack of attention to these and other concepts more specifically applicable to propranolol. We have previously shown (Vestal *et al.*, 1979) that age affects propranolol's elimination in man. Thus, it is critical to ensure that patients and controls are adequately age matched and this was not done in previous studies of propranolol's elimination in renal disease. Additionally, because the bioavailability increases and the total intrinsic clearance of propranolol falls between the first and seventh oral dose (Wood *et al.*, 1978) it is not possible to extrapolate (as was done in previous studies) the findings from single oral dose studies of propranolol to the usual therapeutic situation which involves chronic oral dosing.

The elevation of the free fraction of propranolol following heparinization at the beginning of haemodialysis is particularly interesting because of the previous report of increased volume of distribution during this procedure (Bianchetti *et al.*, 1976). Elevation of the free fraction of propranolol will result in more drug being available for distribution. The administration of heparin results in a large and significant rise in the free fraction of propranolol and a number of other drugs during other procedures (Wood *et al.*, 1979a, 1979b; Wood *et al.*, 1980; Desmond, Roberts, Wood, Dunn, Wilkinson & Schenker, 1980) and it is likely therefore that the rise in free fraction of propranolol which we found 20 min after beginning haemodialysis and heparinization was due to the heparin administration. Thus, it is likely that the apparent increase in volume of distribution reported by Bianchetti *et al.* (1976) was due to the effect of heparin prior to haemodialysis.

This study has shown that oral clearance which is the determinant of steady-state drug levels, is unaltered by renal failure either in patients on haemodialysis or those not yet receiving it. There is therefore no pharmacokinetic reason to make any adjustment to the customary dosage of propranolol in renal failure.

We are grateful to Sylvia Belcher for her excellent technical assistance. This work was supported by USPHS GM 15431 and 5 MOIRR-95 and the Veterans Administration. Reprint requests should be addressed to Dr A.J.J. Wood.

References

BIANCHETTI, G., GRAZIANI, G., BRANCACCIO, D., MORGANTI, A., LEONETTI, G, MANFRIN, M., SEGA, R., GOMENI, R., PONTICELLI, C. & MORSELLI, P.L. (1976). Pharmacokinetics and effects of propranolol in terminal uraemic patients and in patients undergoing regular dialysis treatment. *Clin. Pharmacokin.*, **1**, 373–384.

DOLE, V.P. & MEINERTZ, H. (1960). Microdetermination of long-chain fatty acids in plasma and tissues. *J. biol. Chem.*, **235**, 2595–2599.

DESMOND, P.V., ROBERTS, R.K., WOOD, A.J.J., DUNN, G.D., WILKINSON, G.R., & SCHENKER, S. (1980). Effect of heparin administration of plasma binding on benzodiazepines. *Br. J. clin. Pharmac.*, **9**, 171–175.

KORNHAUSER, D.H., WOOD, A.J.J., VESTAL, R.E., WILKINSON, G.R., BRANCH, R.A. & SHAND, D.G. (1978). Biological determinants on propranolol disposition in man. *Clin. Pharmac. Ther.*, **23**, 165–174.

LETTERI, J.M., MELLK, H., LOUIS, S., KUTT, H., DURANTE, P. & GLAZKO, A. (1971). Diphenylhydantoin metabolism in uraemia. *New Engl. J. Med.*, **285**, 648–652.

LICHTER, M., BLACK, M. & ARIAS, I.M. (1973). The metabolism of antipyrine in patients with chronic renal failure. *J. Pharmac. exp. Ther.*, **187**, 612–619.

LOWENTHAL, D.T., BRIGGS, W.A., GIBSON, T.P., NELSON, H. & CIRKSENA, W.J. (1974). Pharmacokinetics of oral propranolol in chronic renal disease. *Clin. Pharmac. Ther.*, **16**, 761–769.

MADDOCKS, J.L., WAKE, C.J. & HARBER, M.J. (1975). The plasma half-life of antipyrine in chronic uraemic and normal subjects. *Br. J. clin. Pharmac.*, **2**, 339–343.

ODAR-CEDERLÖF, I. & BORGÅ, O. (1974). Kinetics of diphenylhydantoin in uraemic patients: Consequences of decreased plasma protein binding. *Eur. J. Clin. Pharmac.*, **7**, 31–37.

REIDENBERG, M.M. (1976). The binding of drugs to plasma proteins from patients with poor renal function. *Clin. Pharmacokin.*, **1**, 121–125.

REIDENBERG, M.M. (1977). The biotransformation of drugs in renal failure. *Am. J. Med.*, **62**, 482–485.

REIDENBERG, M.M., ODAR-CEDERLÖF, I., VON BAHR, C., BORGÅ, O. & SJÖQVIST, F. (1971). Protein binding of diphenylhydantoin and desmethylimipramine in plasma from patients with poor renal function. *New Engl. J. Med.*, **285**, 264–267.

ROWLAND, M., BENET, L.Z. & GRAHAM, G.G. (1973). Clearance concepts in pharmacokinetics. *J. Pharmacokin. Biopharm.* **1**, 123–136.

THOMPSON, F.D., JOEKES, A.M. & FOULKES, D.M. (1972). Pharmacodynamics of propranolol in renal failure. *Br. med. J.*, **2**, 434–436.

VESTAL, R.E. WOOD, A.J.J., BRANCH, R.A., SHAND, D.G. & WILKINSON, G.R. (1979). Effects of age and cigarette smoking on propranolol disposition. *Clin. Pharmac. Ther.*, **26**, 8–15.

WILKINSON, G.R. & SHAND, D.G. (1975). A physiological approach to hepatic drug clearance. *Clin. Pharmac. Ther.*, **18**, 377–390.

WOOD, A.J.J., CARR, K., VESTAL, R.E., BELCHER, S., WILKINSON, G.R. & SHAND, D.G. (1978). Direct measurement of propranolol bioavailability during accumulation to steady-state. *Br. J. clin. Pharmac.*, **6**, 345–350.

WOOD, M., SHAND, D.G. & WOOD, A.J.J. (1979a). Propranolol binding in plasma during cardiopulmonary bypass. *Anesthesiology*, **51**, 512–516.

WOOD, M., SHAND, D.G. & WOOD, A.J.J. (1979b). Altered drug binding due to the use of indwelling heparinized canulas (heparin lock) for sampling. *Clin. Pharmac. Ther.*, **25**, 103–107.

WOOD, A.J.J., ROBERTSON, D., ROBERTSON, R.M., WILKINSON, S.R. & WOOD, M. (1980). Elevated plasma free drug concentrations of propranolol and diazepam during cardiac catheterization. *Circulation*, (in press).

(Received March 25, 1980)