Pharmacodynamic and pharmacokinetic study of propranolol in patients with cirrhosis and portal hypertension

P. CALÈS¹, D. GRASSET¹, A. RAVAUD¹, C. MESKENS¹, M. BLANC², J. P. VINEL¹, J. COTONAT² & J. P. PASCAL¹

¹Service d'Hépatogastroentérologie, Hôpital Purpan, and ²Laboratoire de Pharmacologie, Hôpital Rangueil and Université Paul Sabatier, Toulouse, France

1 The aim of this study was to investigate the pharmacokinetics and the β -adrenoceptor blocking activity according to time of conventional (C) and long acting (LA) propranolol in cirrhotic patients. Twenty-four patients with alcoholic cirrhosis and oesophageal varices were randomly assigned to receive either 160 mg C propranolol, 160 mg LA propranolol or placebo acutely and then following repeated administration (acute and chronic phases). Thereafter propranolol concentrations and β -adrenoceptor blockade (resting and exercise heart rates) were measured at different intervals.

2 The $C_{\max}$ was significantly higher with C propranolol in both phases. The time of $C_{\max}$ was significantly later with LA propranolol in both phases. The AUCs were significantly higher after chronic administration with both formulations of propranolol.

3 The exercise peaks of β -adrenoceptor blockade were similar between the two formulations and between the two phases of administration of propranolol. The duration of effective β -adrenoceptor blockade was significantly longer in the chronic phase and seemed to be longer with LA than with C propranolol although this was not significant (72 ± 31 vs 48 ± 18 h, respectively).

4 There was a significant correlation between the log propranolol concentration and exercise heart rate but not with resting heart rate. No correlation could be demonstrated between pharmacological data and the Child Pugh score.

5 We conclude that in cirrhotic patients exercise testing was a reliable method in the assessment of β -adrenoceptor blockade. Pharmacology of propranolol was found to be different according to the formulation or to the phase of administration.

Keywords propranolol pharmacokinetics cirrhosis

Introduction

Propranolol is a non-selective, β -adrenoceptor blocking agent. In man propranolol is cleared by hepatic transformation and this process is known to be affected by liver impairment (Wood *et al.*, 1978a). The aim of the present study was to investigate further the pharmacokinetics and β -adrenoceptor blocking activity of propranolol in patients with cirrhosis in order that the duration of action and most suitable dosing interval could be elucidated.

Methods

Patients

Twenty-four patients with histologically proven alcoholic cirrhosis and portal hypertension were studied as inpatients. They were included if they satisfied the criteria for prophylaxis of first variceal bleeding (Pascal *et al.*, 1987). They were excluded if they had taken any cardiovascular drug in the 15 days before entry into the study, if they were older than 75 years of age, or if they

Correspondence: Dr P. Calès, Service d'Hépatogastroentérologie, CHU Purpan, 31059 Toulouse, France

took concomitant drugs other than vitamins. The patients gave informed oral consent and the study was approved by the local ethics committee.

Study design

The patients were randomly assigned to three groups. The first group ($n = 8$) received 160 mg conventional, oral, propranolol (C); the second group ($n = 8$) received 160 mg long-acting, oral, propranolol (LA) and the third group ($n = 8$) received placebo (P).

The day before the first dose, basal measurements were performed. These included a full clinical examination, resting and exercise heart rates (RHR and EHR) (mean of three measures at 8, 11 and 17 h), blood pressure and laboratory measurements which included serum creatinine and liver function tests (albumin, bilirubin, prothrombin time). The severity of hepatic disease was assessed using the Child Pugh score (Pugh *et al.*, 1973).

The pharmacokinetics of propranolol after administration of C and LA formulations are different (McAinsh *et al.*, 1978). Accordingly the times of certain measurements were different between the three groups. In the C propranolol group heart rates were measured and blood samples were taken 0, 2, 4, 6, 8, 10, 14, 24, 36 and 48 h after the acute dose, and additionally at 72 and 96 h after 1 week chronic dosing. In the group receiving the LA formulation additional samples were taken at 60 and 72 h after the acute dose, and 84, 96, 108, 120, 132 and 144 h after the chronic dose. After the end of the study these patients were treated with propranolol so as to avoid the occurrence of a withdrawal syndrome. The placebo patients were sampled at the same time as those during the chronic phase of LA propranolol. In each group the first dose was administered at 08.00 h after an overnight rest which corresponded to time 0.

Drug assays

Blood was collected immediately before the EHR measurements and the resultant plasma was stored at -20°C . Plasma propranolol concentrations were measured by a high performance liquid chromatography method (Blanc *et al.*, 1987). The plasma half-life ($t_{1/2}$) and the areas under plasma concentrations vs time curves (AUC) were calculated according to a standard method (Gibaldi & Perrier, 1975).

Pharmacodynamic measurements

RHR and EHR were undertaken as an assessment of β -adrenoceptor blockade. The RHR was measured during 1 min after resting in the supine position for 10 min. Then the exercise testing was performed on an upright bicycle ergometer with a work load of 50 watts for 3 min. The peak EHR was recorded by an electrocardiograph monitor. Heart rates were measured as far as possible after standardised meals which were given at 9.15, 12.15 and 18.15 h. The degree of β -adrenoceptor blockade was estimated by expressing the reduction in RHR and EHR as a percentage of the basal heart rate.

Statistical analysis

Results were expressed as means $\pm$ s.d.. χ^2 tests, with Yates correction for small numbers where appropriate, were used for comparisons between qualitative variables. However, if the expected numbers were too small, an Irwin-Fisher-Yates test (exact test) was performed in place of the χ^2 test. Parametric tests (Student's *t*-test) were used for comparisons between quantitative variables. Associations were established by calculation of the correlation coefficient.

Results

The three groups of patients were comparable with respect to age, sex, body weight, smoking habits, ascites, neurologic status, RHR, EHR, albumin, bilirubin, prothrombin time, creatinine, GGT, ASAT and Child Pugh score. No patient had present or past history of encephalopathy. The mean Child Pugh score was 8.0 ± 2.0 .

Pharmacokinetic data

The mean plasma concentrations of propranolol following administration of the C and LA formulations are shown in Figures 1 and 2, respectively. The mean peak plasma levels ($C_{\max}$), times to peak ($t_{\max}$), $t_{1/2}$ s and AUCs are described in Table 1. After multiple dosing, the values for the $C_{\max}$ varied markedly between individuals, i.e. from 142 to 412 ng ml $^{-1}$ with C propranolol and from 38 to 199 ng ml $^{-1}$ with LA propranolol.

Pharmacodynamic data

The basal heart rates in the 24 subjects were 82 ± 11 (range: 56–110) at rest, and 128 ± 18 (range 95–165) beats min $^{-1}$ after exercise.

Figure 1 Conventional propranolol: Plasma propranolol concentration during acute (■) and chronic phases (□) and percentage decrease in exercise heart rate during acute (▲) and chronic phases (△) as a function of time. Each symbol represents the mean value of each group of eight subjects.

Figure 2 Long acting propranolol: Plasma propranolol concentration during acute (■) and chronic phases (□) and percentage decrease in exercise heart rate during acute (▲) and chronic phases (△) as a function of time. Each symbol represents the mean value of each group of eight subjects.

The degree of β -adrenoceptor blockade as a function of time is described in Figures 1 and 2. There was no significant correlation between the percentage decrease in RHR and that of EHR for LA propranolol but a significant correlation was found with C propranolol, albeit only during the last three measurements in the chronic phase. The pharmacodynamic data are listed in Table 2. In every patient the maximum percentage decrease of heart rate (peak β -adrenoceptor blockade) and the time corresponding to this value (time of peak β -adrenoceptor blockade) were calculated.

As shown in Figure 3, in the placebo group the heart rates varied significantly at rest, i.e. $-5.4 \pm 6.1\%$ at time 8 h ($P < 0.05$) and $4.5 \pm 4.0\%$ at time 120 h ($P < 0.05$) whereas no significant variation was observed with exercise testing, range: $-3.5 \pm 7.3\%$ and $4.2 \pm 7.7\%$, at times 8 and 108 h, respectively (Figure 3).

We have defined the effective β -adrenoceptor blockade as a decrease in EHR $\geq 25\%$ and the duration of effective β -adrenoceptor blockade as the difference between the time of administration of propranolol and the last time of effective β -adrenoceptor blockade. By these definitions,

Table 1 Comparison of pharmacokinetics between: 1) conventional and long acting propranolol (*P**) and 2) single (S) and repeated (R) administration (*P***)

	<i>Conventional</i>	<i>Propranolol</i>		<i>P**</i>	<i>P*</i>
		<i>P**</i>	<i>Long acting</i>		
$t_{1/2}$ (h)	S 9.5 ± 3.0 R 14.2 ± 5.5	) NS	16.3 ± 5.8 18.9 ± 12.0	) NS	< 0.05 NS
C_{max} (ng ml ⁻¹)	S 103 ± 38 R 225 ± 118	) < 0.05	30 ± 16 119 ± 51	) < 0.05	< 0.01 < 0.05
t_{max} (h)	S 3.2 ± 1.2 R 2.4 ± 0.6	) NS	14.1 ± 6.2 9.9 ± 1.8	) NS	< 0.01 < 0.0001
AUC (ng ml ⁻¹ h)	S 2055 ± 1212 R 4616 ± 2821	) < 0.05	1420 ± 922 5616 ± 3342	) < 0.05	NS NS
Accumulation ratio	2.1 ± 0.4		4.0 ± 1.9		< 0.05
Minimum plasma propranolol level (ng ml ⁻¹) for effective β -adrenoceptor blockade	S 14 ± 7 R 27 ± 22	) NS	10 ± 6 17 ± 6	) < 0.05	NS NS

Values are expressed as mean ± 1 s.d.

Table 2 Comparison of pharmacodynamic data between: 1) conventional and long acting propranolol (*P**) and 2) single (S) and repeated (R) administration (*P***)

	<i>Conventional</i>	<i>Propranolol</i>		<i>P**</i>	<i>P*</i>
		<i>P**</i>	<i>Long acting</i>		
Resting peak β -adrenoceptor blockade (%)	S 29.2 ± 4.9 R 35.3 ± 4.8	) NS	26.2 ± 8.8 31.1 ± 8.7	) < 0.05	NS NS
Exercise peak β -adrenoceptor blockade (%)	S 36.3 ± 10.7 R 37.3 ± 10.2	) NS	30.8 ± 7.6 36.3 ± 4.7	) NS	NS NS
Time of exercise peak β -adrenoceptor blockade (h)	S 4.3 ± 2.4 R 3.5 ± 0.9	) NS	21. ± 12.0 9.6 ± 8.4	) < 0.05	< 0.01 NS
Duration of effective β -adrenoceptor blockade (h)	S 34.0 ± 17.1 R 48.2 ± 17.6	) < 0.05	52.3 ± 23.6 72.0 ± 31.4	) < 0.05	NS NS

Values are expressed as mean ± 1 s.d.

Figure 3 Placebo: Percentage variations in resting (Δ) and exercise ($\square$) heart rates as a function of time. Each symbol represents the mean value of the eight subjects. A black symbol denotes a significant variation ($P < 0.05$).

the duration of effective β -adrenoceptor blockade was greater during the chronic phase than during the acute phase for both formulations of propranolol (Table 2). The minimum concentration required for effective β -adrenoceptor blockade, i.e. the concentration of propranolol corresponding to the last time of effective β -adrenoceptor blockade (Table 2) was also calculated.

Relationship between pharmacokinetic and pharmacodynamic data

For each period of measurement a correlation was sought between the log plasma propranolol concentration and the percentage decrease in EHR. A significant correlation was found in 12 instances out of 14 for C propranolol and in 7 out of 25 for LA propranolol. By contrast, no correlation could be found between the log plasma propranolol concentration and the percentage decrease in RHR for either formulation. The duration of effective β -adrenoceptor blockade was significantly correlated with the AUC either with C propranolol ($r = 0.94$, $P < 0.05$) or with LA propranolol ($r = 0.91$, $P < 0.01$), during the chronic phase, but not during the acute phase. This duration was not correlated with $t_{1/2}$ nor with $C_{\max}$ whichever the formulation of propranolol. Furthermore no significant correlation was found between the Child-Pugh score and any pharmacokinetic or pharmacodynamic variable but the shortest individual durations of β -adrenoceptor blockade were observed in patients with well compensated cirrhosis.

Discussion

Pharmacokinetics

With C propranolol, $C_{\max}$ during the chronic phase and the degree of accumulation were similar to other reports (Wood *et al.*, 1978b). After multiple dosing of LA propranolol, mean $C_{\max}$ was higher than that observed in non cirrhotic subjects (Leahey *et al.*, 1980; Serlin *et al.*, 1983) but near to that previously found in cirrhotic patients (Arthur *et al.*, 1985). The difference may be the consequence of higher degree of accumulation in cirrhotic patients: 4.0 instead of 1.7 to 1.8 in non cirrhotic subjects, (Leahey *et al.*, 1980; Serlin *et al.*, 1983) possibly arising from a reduced first pass effect (Wood *et al.*, 1978b) due to enzyme saturation and/or a slight decrease in hepatic blood flow (Kornhauser *et al.* 1978). The degree of accumulation was greater with LA propranolol than with C propranolol and this has been reported in normal subjects (Leahey *et al.*, 1980). The absorption of propranolol is prolonged for the LA formulation, thus the saturation of the hepatic metabolic activity may also be more prolonged leading to a greater accumulation for the sustained release formulation. The pharmacokinetic comparison between C and LA propranolol was similar to that reported previously in normal subjects (Leahey *et al.*, 1980; McAinsh *et al.*, 1978) or in cirrhotic patients (Watson *et al.*, 1987) i.e. with LA propranolol $C_{\max}$ was lower and occurred later while plasma levels were higher after 24 h.

Like others (Jiron *et al.*, 1985) we did not find

any correlation between the severity of cirrhosis and pharmacokinetic data. However this result should be interpreted with caution since: a) the number of patients studied was small, b) the Child Pugh score is an approximate reflection of hepatic function (Barbare *et al.*, 1985), c) the most prominent abnormalities of kinetics have been found in patients with serum albumin concentration below 30 g l^{-1} (Arthur *et al.*, 1985; Branch *et al.*, 1976). Finally a decrease in propranolol clearance was not only dependent on liver activity but also on the volume of blood shunted away from the hepatocytes. This could explain the absence of a correlation (Jiron *et al.*, 1985).

Pharmacodynamics

In our study, as reported in normal subjects (McDevitt, 1977), RHR was not found to be reliable in the assessment of β -adrenoceptor blockade, since it was correlated neither to propranolol concentration nor to EHR, and it significantly varied with time in the placebo group. The value of the exercise peak β -adrenoceptor blockade was similar to that observed in non cirrhotic patients, 28 to 40% (Leahey *et al.*, 1980; Serlin *et al.*, 1983; Coltart & Shand, 1970; Hager *et al.*, 1981; Mullane *et al.*, 1982; Pine *et al.*, 1975) and in cirrhotic patients, 36% (Mills *et al.*, 1984). Thus, unlike others (Arthur *et al.*, 1985), we consider that the different pharmacokinetics of propranolol in patients with cirrhosis does not result in excessive β -adrenoceptor blockade. Unlike the result reported for non cirrhotic subjects (Leahey *et al.*, 1980; Serlin *et al.*, 1983), the degree of β -adrenoceptor blockade was not significantly different between C and LA propranolol in these cirrhotic patients. Furthermore chronic administration of LA propranolol increased the degree of β -adrenoceptor blockade unlike non cirrhotic subjects (Serlin *et al.*, 1983). This may be explained by high accumulation in cirrhotic patients.

After a single dose, the duration of effective β -adrenoceptor blockade was about 1.5 days with C propranolol and 2 days with LA propranolol. After repeated dosing, this was increased to about 2 days with C propranolol and 3 days with LA propranolol. These figures are much higher than those observed in patients without liver disease, namely about 12 h with C propranolol (Leahey *et al.*, 1980; Aellig, 1976) and about 1 day with LA propranolol (Leahey *et al.*, 1980; McAinsh *et al.*, 1978). Therefore the LA formulation may be preferable in cirrhotic patients, since i) the lack of compliance with

propranolol is significantly associated with an increase in bleeding risk (Poynard *et al.*, 1987), ii) the duration of effective β -adrenoceptor blockade with LA propranolol was longer than with C propranolol which might contribute to lower the risk of haemorrhage following withdrawal (Poynard *et al.*, 1987) in poorly compliant patients. Since effective β -adrenoceptor blockade was observed more than 48 h after an acute dose in six out of eight patients, LA propranolol may be administered every other day to most cirrhotic patients.

Comparison of the β -adrenoceptor blockade vs time data after C and LA propranolol leads to the same conclusion as in normal subjects (Leahey *et al.*, 1980) i.e. the effects of LA propranolol were more evenly distributed throughout the whole day. Moreover, peak β -adrenoceptor blockade during the chronic phase of LA propranolol was flat so that the time of β -adrenoceptor blockade assessment was extended. In Figures 1 and 2 parallelism between the curves of β -adrenoceptor blockade and propranolol concentration is observed. One may be surprised by a persisting decrease in EHR at a time when no propranolol was detectable in plasma. However the decrease in EHR is not the result of physical training (Jennings *et al.*, 1986), or of an improvement in patient condition since EHR did not vary significantly in the placebo group. In fact, the persistence of β -adrenoceptor blockade without plasma propranolol has been previously ascribed to diffusion of the drug in spaces other than plasma, or to a receptor fixation (Leaman *et al.*, 1976; Wilson *et al.*, 1976). A more likely pharmacokinetic explanation is the contribution of an active metabolite to the pharmacological effect, i.e. the 4-hydroxypropranolol which was not detected by assay.

The value of the minimum concentration for effective β -adrenoceptor blockade was similar to that reported in non cirrhotic patients (Mullane *et al.*, 1982). The higher minimum propranolol level required for effective β -adrenoceptor blockade after repeated dosing can be ascribed to the well documented increase in the density of β -adrenergic receptors after chronic administration of β -adrenoceptor blockers (Neve & Mollinoff, 1986).

In conclusion exercise testing seemed to be reliable in the assessment of β -adrenoceptor blockade in cirrhotic patients. LA propranolol seemed to be the most suitable formulation for use in cirrhotic patients since it could decrease the risks following a lack of compliance in such patients. A dose of 160 mg LA propranolol could be administered every other day in most patients but the level of compliance to this drug

regimen should be controlled. It may however be interesting to study further the pharmacology of the lower dose preparation (80 mg LA propranolol) in cirrhotic patients.

We are indebted to Dr C. Dupont, Mr D. Allsopp, Dr J. McAinsh & Dr H. Cameron (ICI-France and England) for their help.

References

- Aellig, W. H. (1976). β -adrenoceptor blocking activity and duration of action of pindolol and propranolol in healthy volunteers. *Br. J. clin. Pharmacol.*, **3**, 251–257.
- Arthur, M. J. P., Tanner, A. R., Patel, C., Wright, R., Renwick, A. G. & George, C. F. (1985). Pharmacology of propranolol in patients with cirrhosis and portal hypertension. *Gut*, **26**, 14–19.
- Barbare, J. C., Poupon, R. E., Jaillon, P., Prod'homme, S., Darnis, F. & Poupon, R. Y. (1985). Intrinsic hepatic clearance and Child-Turcotte classification for assessment of liver function in cirrhosis. *J. Hepatol.*, **1**, 253–259.
- Blanc, M., Cales, P., Grasset, D., Ravaut, A., Meskens, C., Cotonat, J. & Pascal, J. P. (1987). Etude des paramètres de biodisponibilité du propranolol chez des malades cirrhotiques, après administration orale de la forme retard. *Thérapie*, **42**, 187–191.
- Branch, R. A., James, J. A. & Read, A. E. (1976). A study of factors influencing drug disposition in chronic liver disease, using the model drug (+)-propranolol. *Br. J. clin. Pharmacol.*, **3**, 243–249.
- Coltart, D. J. & Shand, D. G. (1970). Plasma propranolol levels in the quantitative assessment of β -adrenergic blockade in man. *Br. med. J.*, **3**, 731–734.
- Gibaldi, M. & Perrier, D. (1975). *Pharmacokinetics*. New-York: Marcel Dekker.
- Hager, W. D., Pieniaszek, H. J., Perrier, D., Mayersohn, M. & Goldberger, V. (1981). Assessment of β -blockade with propranolol. *Clin. Pharmac. Ther.*, **30**, 283–290.
- Jennings, G., Nelson, L., Nestel, P., Esler, M., Korner, P., Burton, D. & Bazelmans, J. (1986). The effects of changes in physical activity on major cardiovascular risk factors hemodynamics, sympatric function, and glucose utilization in man: a controlled study of four levels of activity. *Circulation*, **73**, 30–40.
- Jiron, M. I., Delhotal, B. & Lebrec, D. (1985). Relationship between dose, blood level and hemodynamic response in patients with cirrhosis receiving propranolol. *Eur. J. clin. Pharmacol.*, **28**, 353–355.
- Kornhauser, D. M., Wood, A. J. J., Vestal, R. E., Wilkinson, G. R., Branch, R. A. & Shand, D. G. (1978). Biological determinants of propranolol disposition in man. *Clin. Pharmac. Ther.*, **23**, 165–173.
- Leahy, W. J., Neill, J. D., Varma, M. P. S. & Shanks, R. G. (1980). Comparison of the efficacy and pharmacokinetics of conventional propranolol and a long acting preparation of propranolol. *Br. J. clin. Pharmacol.*, **9**, 33–40.
- Leaman, D. M., Levenson, L. W., Shiroff, R. A., Babb, J. D., Dejos, E. P. H. R. L., Hayes, A. H. & Zelis, R. (1976). Persistence of biologic activity after disappearance of propranolol from the serum. *J. Thor. Cardiol. Surg.*, **72**, 67–72.
- McAinsh, J., Baber, N. S., Smith, R. & Young, J. (1978). Pharmacokinetic and pharmacodynamic studies with long acting propranolol. *Br. J. clin. Pharmacol.*, **6**, 115–121.
- McDevitt, D. G. (1977). The assessment of β -adrenoceptor blocking drugs in man. *Br. J. clin. Pharmacol.*, **4**, 413–425.
- Mills, P. R., Rae, A. P., Farah, D. A., Russel, R. I., Lorimer, A. R. & Carter, D. C. (1984). Comparison of three adrenoreceptor blocking agents in patients with cirrhosis and portal hypertension. *Gut*, **25**, 73–78.
- Mullane, J. F., Kaufman, J., Dvornik, D. & Coelho, J. (1982). Propranolol dosage, plasma concentration, and beta blockade. *Clin. Pharmac. Ther.*, **32**, 692–700.
- Neve, K. A. & Molinoff, P. B. (1986). Effects of chronic administration of agonists and antagonists on the density of β -adrenergic receptors. *Am. J. Cardiol.*, **57**, 17F–22F.
- Pascal, J. P., Calès, P. and a multicenter group study. (1987). Propranolol in the prevention of first upper gastrointestinal tract hemorrhage in patients with cirrhosis of the liver and esophageal varices. *New Engl. J. Med.*, **317**, 856–861.
- Pine, M., Favrot, L., Smith, S., McDonald, K. & Chidsey, C. A. (1975). Correlation of plasma propranolol concentration with therapeutic response in patients with angina pectoris. *Circulation*, **52**, 886–893.
- Poynard, T., Lebrec, D., Hillon, P., Sayegh, R., Bernuau, J., Naveau, S., Chaput, J. C., Klepping, C., Rueff, B. & Benhamou, J. P. (1987). Propranolol for prevention of recurrent gastrointestinal bleeding in patients with cirrhosis: a prospective study of factors associated with rebleeding. *Hepatology*, **7**, 447–451.
- Pugh, R. N. H., Murray-Lyon, J. M., Dawson, J. L., Pietroni, M. C. & Williams, R. (1973). Transection of the oesophagus for bleeding oesophageal varices. *Br. J. Surg.*, **60**, 646–649.
- Serlin, M. J., Orme, M. L., McIver, M., Green, G. J., Sibeon, R. G. & Breckenridge, A. M. (1983). The pharmacodynamics and pharmacokinetics of conventional and long acting propranolol in patients with moderate hypertension. *Br. J. clin. Pharmacol.*, **15**, 519–527.
- Watson, R. G. P., Bastain, W., Larkin, K. A., Hayes, J. R., McAinsh, J. A. & Shanks, R. G. (1987). A comparative pharmacokinetic study of conventional

- propranolol and a long acting preparation of propranolol in patients with cirrhosis and normal controls. *Br. J. clin. Pharmac.*, **24**, 527-535.
- Wilson, M., Morgan, G. & Morgan, T. (1976). The effect on blood pressure of β -adrenoceptor blocking drugs administered once daily and their duration of action when the therapy is ceased. *Br. J. clin. Pharmac.*, **3**, 857-861.
- Wood, A. J. J., Kornhauser, D. M., Wilkinson, G. R., Shand, D. G. & Branch, R. A. (1978a). The influence of cirrhosis on steady-state blood concentrations of unbound propranolol after oral administration. *Clin. Pharmacokin.*, **3**, 478-487.
- Wood, A. J. J., Carr, K., Vestal, R. E., Belcher, S., Wilkinson, G. R. & Shand, D. G. (1978b). Direct measurement of propranolol bioavailability during accumulation to steady state. *Br. J. clin. Pharmac.*, **6**, 345-350.

(Received 15 January 1988,
accepted 7 February 1989)