

Studies of the Absorption and Removal of Propranolol in Hypertensive Patients during Therapy

By C. A. CHIDSEY, M.D., P. MORSELLI, M.D., G. BIANCHETTI, M.D.,
A. MORGANTI, M.D., G. LEONETTI, M.D., AND A. ZANCHETTI, M.D.

SUMMARY

The variability of plasma propranolol concentrations has been determined in a large group of patients being treated with the drug. Although the average patient achieved a therapeutic plasma level with 160 mg/day, there was marked interpatient variation. This was found to be primarily the result of differences in effective absorption of the drug, which averaged 46% of the oral dose but ranged from 20 to 80%. Propranolol disappeared from plasma with a half-life of 4.7 hours and its removal appeared to follow dose independent kinetics with no evidence of saturation of hepatic metabolism. The derived pharmacokinetic values of volume of distribution and clearance rate have been used to provide guidelines for initiating propranolol therapy intravenously, and the schedule of 8 mg as a loading dose and 0.02 mg/min as a sustaining dose has been suggested.

THERE ARE NOW a considerable number of therapeutic indications for the use of propranolol in the treatment of cardiovascular disease¹⁻⁶ and it is probable that the action of the drug in most, if not all, of these is mediated through inhibition of beta-adrenergic receptors.^{7, 8} To achieve the optimal therapeutic response in certain clinical situations it should be important to maintain continuous pharmacologic activity. However, the initial estimates of the pharmacokinetics of propranolol indicated rapid oral absorption and a 2-hour plasma half-life with plasma levels widely variable among subjects.⁹ Therefore, it would seem unlikely that blood levels of propranolol producing effective beta blockade could be maintained continuously with the usual clinical practice of administering the drug on a 2-4 times daily schedule.

Because of the apparent discrepancy between the reported pharmacokinetics of propranolol and its therapeutic use, the present study was undertaken to re-examine this question. Since differences may occur in the way some drugs are handled in chronic as opposed to acute administration,¹⁰ we have done these

studies in a group of patients on therapy with propranolol, measuring blood levels at doses customarily used clinically (10-80 mg given four times daily) to determine whether blood levels in patients on therapy are as variable after a single oral dose as after acute administration. We have also reassessed the kinetics of absorption and elimination in these patients to see whether elimination is indeed that reported previously and to determine the relative contributions of absorption and elimination to the variability of handling of propranolol among patients. Finally, a newly developed method for administering propranolol has been employed which overcomes the sensitivity and specificity problems of methods previously used.¹¹

Methods

We have studied 40 patients with hypertension. Propranolol therapy was being instituted in these patients and they were given the drug incrementally, using doses of 10, 20, 40, and 80 mg administered every six hours. Blood samples were drawn into heparinized tubes two hours after dosing on the third to fifth day after instituting that dose. The plasma, separated by centrifugation, was stored at 4°C until assay. No change in propranolol level was observed in samples after as much as four weeks of storage at this temperature. In four of these patients propranolol was given intravenously two days before starting oral medication in a dose of 0.1 mg/kg infused over 10 min. Following the intravenous administration, an estimate of plasma half-life was made using blood samples taken over an 8 hour time interval. In these four patients a similar half-life determination was also made after two to three weeks of treatment when 40 to 80 mg orally every six hours was being administered and the half-life was estimated from plasma concentration determined during 24 hours following the last oral dose. In six other hypertensive patients on chronic therapy (40 to 80 mg administered every six hours) similar

From the Departments of Medicine and Pharmacology, University of Colorado, Medical Center, Denver; Istituto di Ricerche Farmacologiche "Mario Negri," Milano; and Istituto di Ricerche Cardiovascolari, Milano.

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Address for reprints: Charles A. Chidsey, III, M.D., Professor of Medicine and Pharmacology, Head, Division of Clinical Pharmacology, University of Colorado Medical Center, 4200 East Ninth Avenue, Denver, Colorado 80220.

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interruption of dosing was done on two occasions giving the last dose once orally in a postabsorptive state and then at another time intravenously, in the latter case using 15–20 mg dose infused at 1.0 mg/min. One of these six patients was uremic with a serum creatinine of 13.8 mg/100 ml and a creatinine clearance of 4 ml/min.

In these studies effective oral absorption and plasma half-life were determined in the same patient. Effective oral absorption in these studies represents the material absorbed from the GI tract and escaping first pass removal or metabolism by the liver in the course of entering the systemic circulation.

Propranolol was measured in plasma samples by a gas liquid chromatographic method using electron capture.¹¹ This method has both the sensitivity and the specificity required for the chronic observations which we wished to make. The coefficient of variation (standard deviation : mean) determined on 35 duplicate determinations was 8%. It is possible to detect 1 ng/ml of propranolol in plasma and no interfering peaks have been found in samples either from patients not on propranolol but taking a variety of other cardiovascular medication or from patients in renal insufficiency or heart failure. We have previously found that, using the standard fluorometric method, values in untreated, uncomplicated hypertensive patients were sometimes high, and in one patient variable from day to day, even though these patients were maintained on a constant diet and were receiving no drugs (fig. 1). This was true despite meticulous washing of all collection vessels and glassware with acid as previously recommended.⁹ In fact, the fluorometric method would not have allowed accurate quantification of the many samples in the present study in which propranolol was found in a concentration of less than 30 ng/ml.

Calculation of the effective oral absorption and the plasma half-life was accomplished by simple computer analysis of the data. A program employing nonlinear regression analysis was used to fit equations to the time concentration curves of plasma propranolol which had been measured after either oral or intravenous administration. These equations were either (1) $C = A \cdot e^{-k_1 t} - B \cdot e^{-k_2 t}$ to describe the curve after oral dosing, or (2) $C = A \cdot e^{-k_1 t} + B \cdot e^{-k_2 t}$ to describe the curve after intravenous dosing. Thus, the difference of exponentials described the rise and fall of concentration after the oral dose and the sum of exponentials described the initial rapid fall and later slower fall in concentration after the intravenous dose (fig. 5). The value of k_1 , the rate constant of removal, was not significantly different after oral or intravenous dosing and an average of the two was used to calculate the plasma half-life ($0.693 \div k_1$). The net time-plasma propranolol concentra-

tion curve resulting from the final dose of drug was obtained by extrapolating the preabsorptive plasma concentration, using the decay rate constant (k_1) determined in the computer fitting described above, and then subtracting these extrapolated values from the actual curve to obtain the net time-concentration curve. This process of curve subtraction was accomplished algebraically without trapezoidal integration by actually using only the parameters of the curves directly generated by the computer analysis of the plasma concentration data.* The resulting net time concentration curve after oral dosing was divided by that after intravenous dosing making suitable correction for the difference in dose administered by these two routes. This resulted in a determination of the fraction of the oral dose delivered into the systemic circulation which we chose to term the effective oral absorption. The clearance rate and the volume of distribution were calculated from the time concentration curve and the elimination rate constant, k_1 .¹²

Results

The peak concentration of propranolol in plasma of treated patients averaged 18 ± 15 , 52 ± 51 , 121 ± 98 , and 245 ± 110 ng/ml (mean \pm standard deviation) on doses of 40, 80, 160, and 320 mg/day, respectively. Although these plasma concentrations generally related to the dose in a linear fashion, there was marked variability in plasma propranolol among patients reflected in the large standard deviation which was almost equal to the average concentration at the lower doses and was about half that concentration at 320 mg/day. Thus, there was a fourfold range of variability of plasma propranolol at usual therapeutic doses. When the dose was related to body weight (fig. 2), this variability was still present, but the concentration was shown to increase progressively with the administered dose with a correlation coefficient of 0.80. Considering more specifically the relationship between peak concentration and dose, propranolol concentration could be shown to increase linearly with dose in 11 of the 40 treated patients, all of whom received each of the four dose levels of drug, 40 to 320 mg/day (fig. 3). In the other 29 patients not all dose levels were given to each patient. These data suggest that the kinetics of removal of propranolol are first order and independent of the concentration or the administered dose to at least 400 ng/ml or 6 mg/kg/day (320 mg/day).

The cause of the marked variability of plasma levels achieved with propranolol was examined by measuring plasma half-life and effective absorption. The duration of administration of the drug was found to be a very important influence on the rate of elimination of a given dose (fig. 4). Thus, a dose of 80 mg administered to a patient who was not previously

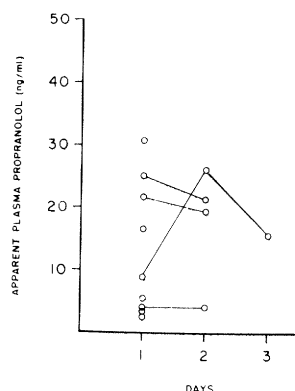


Figure 1

The apparent concentration of propranolol found in plasma using the fluorometric method of analysis. Blood samples were obtained from patients during hospitalization when no propranolol or other drugs were given and the diet was constant.

*We wish to express our gratitude to Dr. Philip Archer of the Department of Biometrics at the University of Colorado Medical Center for assistance in these computations.

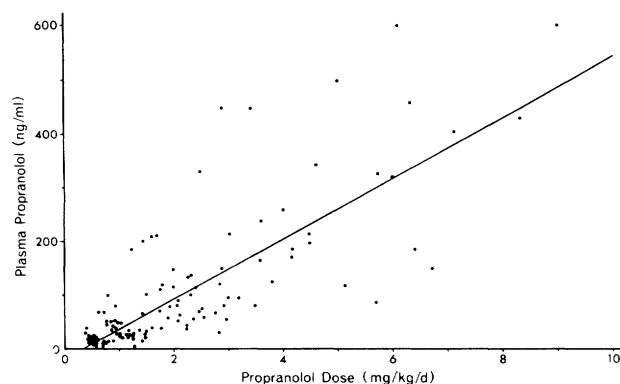


Figure 2

Propranolol concentrations in the plasma of 40 patients receiving 40 to 320 mg/day given orally in a divided 6 hourly schedule. The doses have been related to the total body weight of the patient and expressed as mg/kg/day. A linear correlation between dose and concentration ($r = 0.80$) is demonstrated.

receiving propranolol resulted in a lower peak plasma level, 50 ng/ml versus 100 ng/ml, a shorter apparent half-life, 2.6 hours versus 5.2 hours, and a smaller area under the curve than 80 mg administered to the same patient on chronic treatment with this same dose. Examining further the effect of duration of dosing on plasma half-life, four patients had an average propranolol half-life of 1.9 ± 0.1 hours (mean \pm standard error of the mean) following intravenous admin-

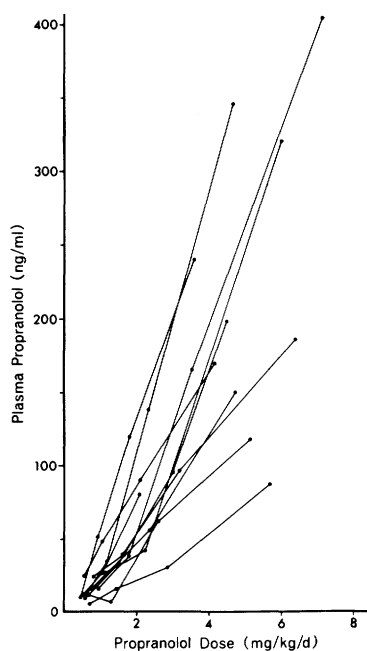


Figure 3

Propranolol concentrations in plasma of 11 patients, each of whom received all 4 dose levels (40, 80, 160, and 320 mg/day). The linear increase in concentration as dose is increased is seen with each individual patient, confirming the validity of the linear correlation observed in the data obtained from the entire group of patients (fig. 2).

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istration whereas after 14–21 days of oral treatment this value was 5.0 ± 0.4 hours following administration of an oral dose.

These findings suggested either that fractional rate of metabolism is lower at higher concentrations of the drug, i.e., the metabolic rate is saturated, obeying zero order kinetics, or that the more rapid disappearance from plasma on first dosing reflects removal into a large extravascular volume of distribution and not actual clearance from the body by either excretion or metabolism. The former suggestion would seem unlikely from the previous data (fig. 3) which showed that peak concentrations increased linearly with administered dose even to high concentrations and doses.

Because it was apparent from these observations that the pharmacokinetics of propranolol could be assessed only in patients receiving the drug chronically, we studied six hypertensive patients on long-term therapy. Net time concentration curves were calculated for a single dose, administered both orally and intravenously (fig. 5). Plasma half-life in these six patients was the same after oral and intravenous dosing and averaged $4.7 \pm .2$ hours (fig. 6). The fractional rate of decline of propranolol during the elimination period in each of these patients was constant even to very low concentrations (1 ng/ml), indicating also by this approach that there was no evidence for saturation of metabolism during chronic drug administration. The effective absorption, calculated from the time concentration curves of the two propranolol administrations, averaged $46 \pm 10\%$ of the oral dose. The interpatient variation in this value was much greater than in the half-life, with some patients having effective absorption as low as

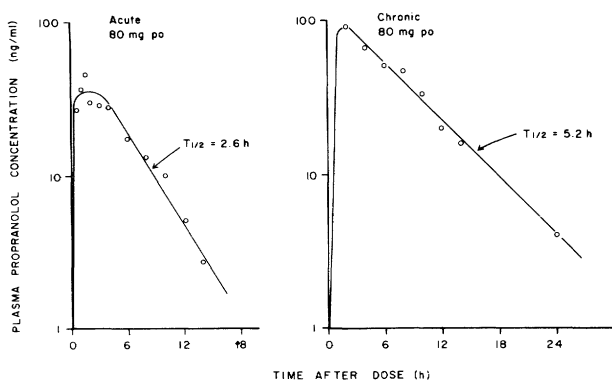


Figure 4

The plasma propranolol concentration following an oral dose of the drug. The curve on the left was obtained when the patient had not been receiving a drug and that on the right during chronic oral dosing, and the latter was corrected to the net curve for a single 80 mg dose by the method of subtraction (see Methods).

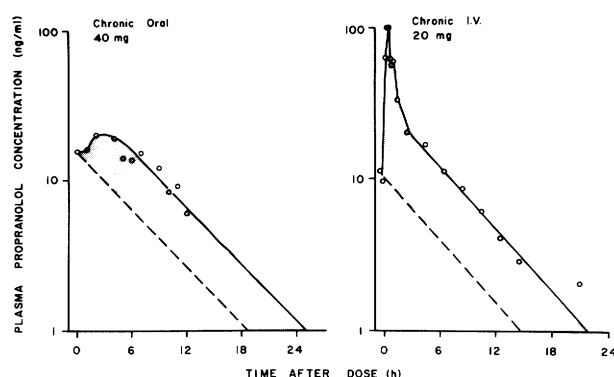


Figure 5

The plasma propranolol time concentration curve after oral and intravenous dosing. This illustrates the disappearance of propranolol and demonstrates how the net time concentration curve for the last dose was obtained. By curve fitting, either an equation for the difference of two exponentials (oral) or the sum of two exponentials (i.v.) was obtained to describe the data. The elimination rate constant (k_1) and the preabsorptive plasma propranolol were used to determine the dotted line, and by difference, the net area was calculated.

20% of the oral dose whereas in others absorption was 80%. This is indicative that the rate of removal of drug may not be as important as its absorption (gastrointestinal absorption and first pass metabolism of drug passing through the portal circulation) in causing the variability of plasma drug levels between patients. One of these patients was uremic (serum creatinine = 13.8 mg/100 ml) and there was no apparent difference in effective absorption or plasma half-life because of the renal insufficiency.

It is also possible to calculate the apparent volume into which propranolol distributes after absorption and this figure is of value in determining the loading dose of drug required to achieve a given plasma con-

centration. The volume of distribution determined in these six patients was 320 ± 82 liters. The magnitude of this apparent volume indicates extensive extravascular binding of the drug. The rate of clearance of propranolol can be calculated from the volume of distribution and the plasma half-life and this value may be used to determine the rate of administration of propranolol that will be required to maintain a given plasma concentration. This was calculated to be 810 ± 82 ml/min. The variability in these values was not reduced when a correction for body size was introduced and so we have presented the data as mean values representative of the average patient.

Discussion

These data provide quantitative information on the fate of orally administered propranolol which is relevant to its use in man. It is apparent that the plasma half-life measured in these studies is consistent with clinical experience with the drug. Thus, the average half-life of 4.7 hours together with absorption kinetics of an oral dose giving a peak concentration at two hours (figs. 4 and 5) would allow for maintenance of minimal effective beta-blocking blood levels, without excessive peak concentrations necessitated by very large doses, on a 4 times daily schedule.

The initial estimates of plasma propranolol disappearance suggesting a two hour half-life have recently been qualified by studying disappearance after nine oral doses in normal subjects.¹³ Although plasma half-life data roughly comparable to ours have been outlined, these investigators attributed the slower plasma removal to reduced metabolism due to saturation of hepatic enzymes. However, we cannot agree with this interpretation and rather believe that the initial rapid plasma clearance reflects prolonged removal into a large volume of distribution (fig. 4). It may have been difficult to measure propranolol at the low level present during the elimination phase, and thus, this elimination was missed in earlier studies. The drug is concentrated in tissues, especially the liver and lung,¹⁴ and it is apparent that this tissue-binding would result in a large volume of distribution. There is no evidence that the enzymes responsible for propranolol's metabolism are saturated in the range of doses used clinically. Thus, the decline of plasma concentration was always observed to be an exponential function of time, indicating that the rate of metabolism is dependent on concentration and not saturation (figs. 4 and 5). Furthermore, our studies have shown a linear increase in peak plasma propranolol as the dose is increased (figs. 2 and 3). Consequently, there is no evidence for saturation of hepatic metabolism within the range of 1 to 400 ng/ml.

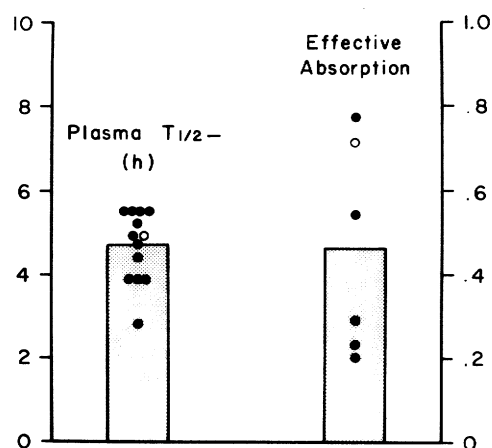


Figure 6

The plasma half-life and effective oral absorption of propranolol determined in patients chronically treated with the drug. The open circle represents data obtained from a single patient with severe uremia (creatinine clearance 4 ml/min).

It is apparent from these data that patients will achieve considerably different plasma propranolol concentrations at any given dose. On the average a total daily dose of 160 mg administered on an every 6 hour schedule will achieve a plasma concentration of 121 ng/ml, a value in excess of the 100 ng/ml reported to be necessary to inhibit maximally adrenergic stimulation of heart rate during exercise.^{7, 8, 15} However, there is considerable variation in individual patient responses and a significant number of patients will be well below this value (fig. 2). In the absence of measurement of plasma levels, it is difficult to predict the degree of blockade from resting pulse rate or any simple clinical maneuver and under these circumstances it would seem wisest to assess the clinical response at progressively increasing daily doses of 40, 80, 160, and 320 mg and maintain the patient on the lowest level of drug necessary to achieve maximum therapeutic response.¹⁵

The interpatient variability in plasma propranolol is due in part to differences in the rate of removal as estimated by plasma half-life, but more importantly by differences in the extent of effective absorption. Although only one uremic patient was studied, it would appear that neither absorption nor removal are notably affected by renal insufficiency, which is consistent with other studies of propranolol in uremic patients.¹⁶ That the effective absorption, or delivery into the circulation, is primarily the result of removal of the drug from the portal blood during absorption has been suggested by other studies.¹⁷ It would seem that this removal is the consequence of binding and not metabolism¹⁸ and our findings would support the suggestion that the binding is saturable but requires only minimal and repetitive doses (40 mg/day and greater) under usual circumstances to achieve this saturation and produce effective concentrations of propranolol in the circulating blood.

Two practical applications of these pharmacokinetic parameters describing propranolol's absorption and disposition are the volume of distribution and the clearance rate which can be used to predict the dose of propranolol necessary to produce effective blockade when there is need to initiate and maintain therapy acutely by the intravenous route. Thus, the volume of distribution averaging 320 L is the apparent volume into which propranolol mixes. Since this value greatly exceeds any body compartment, we can conclude that the drug is bound in extravascular sites in man as it has been shown to be bound in experimental animals.¹⁴ However, it is this volume that must be saturated to achieve a given plasma concentration of propranolol and the loading dose can be calculated by multiplying the desired concentration by the volume of distribution. The clearance rate,

calculated from this volume and the plasma half-life, allows estimation of the volume capacity of the removal system. Propranolol is almost totally metabolized in the liver and its large clearance value, 810 ml/min, would suggest that its hepatic extraction ratio is close to 100%, which is in agreement with other reported estimates of hepatic metabolism.¹³ Using this clearance, the rate of infusion of propranolol required to maintain a given level can be calculated by multiplying the desired plasma concentration by the clearance rate. Although these mean estimates of volume of distribution and clearance rate indicate there may be considerable variability among patients, they will be of some value in approximating an intravenous dose of propranolol for sustained therapy, as in a postoperative patient with supraventricular arrhythmia. Thus, if one wishes to achieve a moderately effective level of blockade, a plasma propranolol of 25 ng/ml would be selected, a value slightly in excess of the ED₅₀ or the dose producing 50% of maximal effect.¹⁵ To achieve this value, loading and sustaining doses can be estimated for this purpose. With a volume of distribution of 320 L and a clearance rate of 810 ml/min on chronic therapy, the recommendation can be made to give a loading dose of 8 mg (given over 20 minutes) to be followed by a sustaining infusion of 0.02 mg/min. We have recently tested this recommendation in a few patients and found it to be a close approximation of the amount desired for adequate but not excessive blood levels.

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Corrections

Gould et al.: *Circulation* **51**: 1085, 1975. On page 1093, the sentence which begins 13 lines from the end of the article should read as follows:

Such a vicious cycle would explain why patients with chronic, anatomically stable coronary disease might develop a myocardial infarction without total occlusion or thrombosis, particularly a subendocardial infarction.

Willerson et al.: *Circulation* **51**: 1046, 1975. The following table was mistakenly dropped from page 1048:

Table 1

Patients with Acute Myocardial Infarction with Positive ^{99m}Tc-PYP Myocardial Scintigrams

| Location of myocardial infarction by ECG | Location of myocardial infarction by scintigram | Intensity of ^{99m} Tc-PYP scintigrams |
|--|---|---|
| 1) Anterior or anterolateral —39 | Anterior or anterolateral —36 Inferior or posterolateral —3 | 4+ scintigram —12 3+ scintigram —19 2+ scintigram — 8 |
| 2) Inferior, inferolateral or inferoposterolateral —36 | Inferior, inferolateral or inferoposterolateral —32 Posterior or posterolateral —4 | 4+ scintigram — 9 3+ scintigram —21 2+ scintigram — 6 |
| 3) True posterior myocardial infarction —3 | True posterior myocardial infarction —3 | 4+ scintigram — 1 3+ scintigram — 2 |
| 4) Acute subendocardial myocardial infarction —18 | Diffuse uptake of ^{99m} Tc-PYP that was difficult to localize —9 Anterior —2 Posterior or inferoposterior —6 Inferior or inferolateral —1 | 4+ scintigram — 1 3+ scintigram — 6 2+ scintigram —11 |