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Pharmacokinetics of Pindolol in Man

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Summary. The kinetics of absorption, distribution and excretion of pindolol have been investigated in 17 volunteers after an oral dose or intravenous infusion of 5 mg. The calculated absorption was 92%. The time course of the plasma levels appeared to follow first order kinetics with an apparent half life of 3.6 (oral) and 3.1 (i.v.) hours. The cumulative urinary excretion at $t = \infty$ was 36.1% and 39.2% of the dose administered, respectively, indicating extensive metabolism of the drug. The distribution volume was 136 l. Peak plasma levels were found 80 min after oral administration and they showed up to 4-fold variation after identical doses. Renal clearance was 216 ml × min^{-1} and total clearance was 483 ml × min^{-1}. In plasma 57% of pindolol was bound to protein.

Key words: Pindolol, beta-blockade, pharmacokinetics, man.

Pindolol (Visken®)*, DL-4-(2-hydroxy-3-isopropylaminopropoxy)-indole, is a potent β-adrenoceptor blocking agent with a negligible effect on cardiovascular function in normal individuals (Levy, 1971). It is 5 to 10 times more potent than propranolol on a weight basis and, unlike that drug, possesses intrinsic agonist activity (Barrett and Carter, 1970). It is chemically related (Fig. 1) to other β-blocking

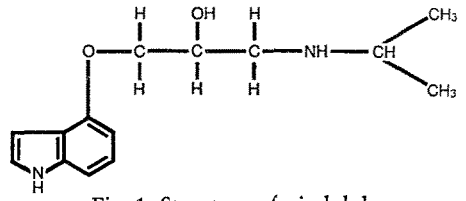

Fig. 1. Structure of pindolol

compounds, all of which have an isopropylamine side chain, although all these drugs differ in the intensity of their effects on the several β-receptors in different organs. The pharmacokinetic behaviour of pindolol in man is somewhat different from other β-blockers and could not have been predicted from its chemical structure (Fitzgerald and Scales, 1968; Shand *et al.*, 1970; Johnsson *et al.*, 1971; Åblad *et al.*, 1972; George *et al.*, 1972; Bodem and Chidsey, 1973). Basic pharmacokinetic information is required to establish suitable dosage schedules for a new drug and although the pharmacological activities of pindolol have been widely investigated (Saameli, 1967; Hill and Turner, 1967, 1969; Giudicelli *et al.*, 1969; Lubawski and Wale, 1969; Barrett and Carter, 1970; Levy, 1971), little is known about its pharmacokinetic behaviour in man. Preliminary data (Hicks *et al.*, 1972) after the intravenous administration of 0.6 mg of pindolol to 4 subjects showed a mean plasma half-life of 3.4 h. The plasma concentrations were quite variable, however, perhaps because they were all less than 4 ng/ml, which is near the lower limit of detection of the analytical method employed (Pacha, 1969).

The present study describes the absorption, distribution, and excretion of pindolol in man after oral and intravenous administration of the same dose.

* Sandoz Ltd., Basle, Switzerland.

Materials and Methods

Estimation of Pindolol in Plasma and Urine

Pindolol concentration was measured using a slight modification of the method described by Pacha (1969).

A. Plasma. 5 ml of plasma from blood containing 2 drops of heparin (Liquemin®) were made alkaline by adding 1 ml of 1 N sodium hydroxide and extracted with 12 ml of diethylether by mechanical shaking for 10 min. The compound was extracted from 10 ml of the organic phase into 2 ml of 0.1 N hydrochloric acid. 1.5 ml of the latter was incubated with 0.5 mg of O-phthalaldehyde by heating in a water bath at 50°C for 30 min. The solution was stabilized by addition of 0.5 ml of ascorbic acid and examined in an Aminco Bowman spectrophotofluorimeter at excitation and emission maxima of 390 and 440 nm, respectively.

B. Urine. 5 ml of urine were diluted with 5 ml of distilled water. 2 ml of 10% zinc sulphate solution

and 1 ml of 1 N sodium hydroxide were added and the precipitate separated by brief centrifugation. 1 ml of 1 N sodium hydroxide was added to the solution and the drug extracted into 10 ml of 1.5% benzene-isoamyl alcohol. After reextraction into 2 ml of 0.1 N hydrochloric acid the same procedure was followed as for plasma.

Clinical Studies

17 volunteers (9 males and 8 females) agreed to take part in the study. They were between 19 and 30 years of age and weighed from 50 to 80 kg. All the subjects appeared healthy according to their clinical history and the results of physical examination and laboratory tests, including creatinine clearance.

Oral administration: 12 subjects fasted overnight and then swallowed a single 5 mg tablet of pindolol. Blood samples were obtained before and at the following times after administration: 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 h. Blood was centrifuged immediately and the plasma stored at 4° C for up to one day before analysis. Urine was collected during the periods 0—4, 4—8, 8—12 and 12—24 h after dosing.

Intravenous administration: 5 mg of pindolol were infused in 50 ml saline at a constant flow rate over 3 h. Any drug remaining in the ampoule and infusion system afterwards was washed out, and the amount actually administered determined by subtracting the residue from the nominal content of the ampoules. Blood samples were usually obtained after 15, 90, 165 and 180 min of the infusion, and at 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 h afterwards. Urine was collected during the infusion (3 h) and for periods of 0—4, 4—8, 8—12 and 12—24 h following it.

Blood pressure and heart rate were recorded in sitting position whenever a blood sample was collected.

Protein Binding

Protein binding was studied by the method of Krieglstein & Kuschinsky (1968) using gel chromatography on Sephadex G 25 and a 4% solution of human serum albumin. The drug concentration used was 60 ng/ml of protein solution, which is the same as the upper range of plasma levels produced by the oral dose.

Calculations

Calculations were performed on an Olivetti Programma P 602 or a Wang 300 desk computer.

Results

Clinical

No change in blood pressure at rest was observed in any of the experiments. In some subjects the resting heart rate declined slightly but not to a significant degree. The only adverse effects were moderate headaches in two cases.

Plasma Levels

The plasma levels found in all the investigations are shown in Tables 1 and 2. The time course of the mean plasma concentrations after oral administration is shown in Fig. 2 ($\bar{x} \pm S_{\bar{x}}$). The majority of the individual plasma level-time curves are compatible with a one-compartment model and can be described by the Bateman function. There was a rapid increase in concentration during the first hour and maximum levels determined graphically were reached after about 80 min, followed by a linear decline in the semilogarithmic plot between 3 h and the end of the experiment. The correlation coefficients of individual regression lines in the linear parts of the slopes were between 0.92 and 0.99. The mean maximum plasma level was 33.1 ± 5.2 ng/ml, with a range in individuals of 19 to 81 ng/ml plasma, i.e. there was a 4-fold difference in the plasma concentration reached in different subjects.

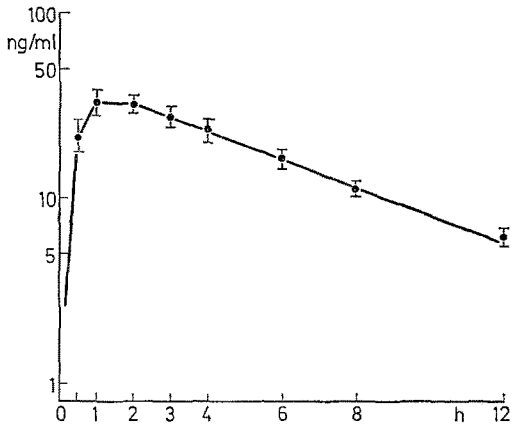

Fig. 2. Time course of plasma levels ($\bar{x} \pm S_{\bar{x}}$) after oral administration of 5 mg of pindolol

After intravenous infusion of pindolol, the fall in plasma levels was strictly linear on a semilogarithmic plot (Fig. 3) in 4 of the 5 subjects tested. This was proved by calculating the regression lines twice, once from the final point of estimation of plasma level back to 2 h after the end of the infusion period, and again from the final point back to the very end of the infusion period. This procedure showed that the

correlation was not made worse by inclusion of the first 2 h of the falling concentration-time graphs after the end of the infusion; in 3 instances they even improved. In one subject (C) there was biphasic decline of the plasma level curve with a terminal slope beginning after 60 min. The same subject had the surprisingly high urinary excretion of 76.8% after 24 h (see below). There was wide individual variation in the maximum plasma level reached after the infusion (17—59 ng/ml).

It can be concluded that, at least after intravenous infusion of pindolol 5 mg over 3 h as in this study,

Table 1. *Plasma concentrations (ng/ml) after oral administration of pindolol 5 mg*

	Hours								
Subject	0.5	1	2	3	4	6	8	12	24
I	2.4	10.8	17.6	19.4	16.6	9.2	10.0	4.8	—
II	9.8	21.8	32.0	26.8	18.2	12.0	5.2	4.0	—
V	44.5	43.3	51.3	44.5	32.0	25.0	20.0	9.0	—
VIII	31.0	81.4	56.2	55.2	52.4	45.0	26.2	17.5	0.55
IX	7.3	16.9	32.0	25.4	22.0	14.1	9.3	4.52	0.28
X	5.9	21.8	24.6	22.6	18.5	12.6	7.2	2.82	2.05
XII	18.9	28.8	22.2	20.0	14.0	8.5	7.0	4.4	0.26
XV	5.0	29.4	26.9	17.5	13.3	6.9	3.8	3.4	1.25
XVI	31.7	38.1	38.5	32.1	30.2	24.5	16.6	10.5	0.76
XIX	18.1	26.3	25.8	23.3	21.35	15.9	10.6	5.3	0.99
XXI	9.9	25.7	19.7	16.1	13.2	5.4	2.4	0.6	—
XXIV	67.4	44.6	36.0	28.7	23.0	16.0	10.7	6.7	0.33
$\bar{x}$	21.01	33.08	31.9	27.6	22.89	16.26	10.75	6.12	0.81
S	19.53	18.16	12.0	11.59	11.1	10.96	6.98	4.46	0.61
$S_{\bar{x}}$	5.63	5.24	3.47	3.34	3.2	3.17	2.01	1.28	0.22

Table 2. *Plasma level (ng/ml) during and after 3 h intravenous infusion of pindolol 5 mg*

	Hours												
Subject	−2.75	−1.5	−0.25	0[a]	0.25	0.5	1	2	3	4	6	8	12
A	8.8	11.7	13.9	14.2	13.4	12.9	12.1	11.4	8.0	6.5	4.5	3.9	1.5
B	4.5	13.5	14.7	17.3	15.7	16.0	13.6	10.6	8.3	6.7	3.8	1.6	—
C	5.9	15.2	24.3	27.5	21.3	19.5	16.1	12.0	9.3	7.5	5.3	4.5	3.4
D	13.5	39.5	55.9	54.9	50.0	43.9	36.5	25.9	23.2	14.1	6.5	3.8	1.1
E	4.0	34.4	36.8	38.4	38.4	33.8	29.4	24.8	12.8	11.2	5.5	2.4	0.8
$\bar{x}$	7.0	22.9	16.4	30.5	27.8	25.2	21.5	16.9	12.3	9.2	5.1	3.2	1.7
$S_{\bar{x}}$	2.2	5.2	9.7	8.3	7.1	5.4	4.9	3.4	2.9	1.5	0.5	0.5	0.6

[a] Time when infusion ceased.

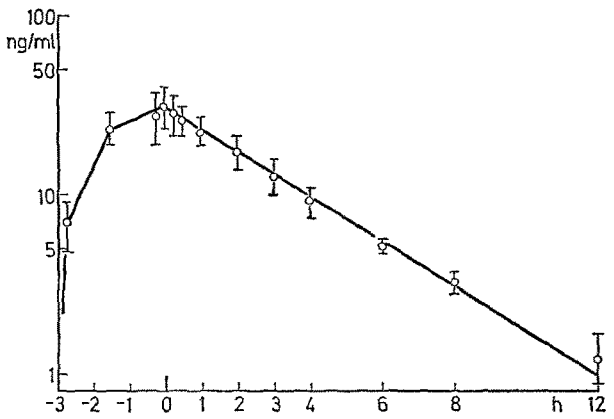

Fig. 3. Plasma level time course ($\bar{x} \pm S_{\bar{x}}$) during and after intravenous administration of 5 mg of pindolol

there was usually a monoexponential decline of the plasma concentration-time curve. It seemed permissable, therefore, to assume that the pharmacokinetics of pindolol obeyed an open one-compartment model.

Urinary Excretion

The time course of the cumulative excretion in urine after oral and intravenous administration is shown in Fig. 4. The amount rose rapidly during the first 12 h and then flattened out during the 12—24 h period. It seems likely, therefore, that the amount of drug excreted in urine after 24 h is not important in its total urinary excretion. After an oral dose the mean cumulative excretion at 24 h was 32.3 ± 3.0%,

and, after intravenous infusion 38.9 ± 0.9%. The results obtained after the infusion in one subject, C, have not been included in the calculation as he was the only one of 17 subjects who had the enormously high total excretion of 76.8% after 24 h. The excretion rates ($\mu g \times h^{-1}$) for individual subjects

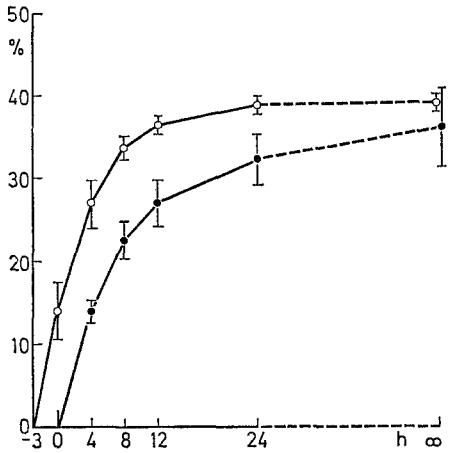

Fig. 4. Cumulative urinary excretion of pindolol after oral administration (●——●) and intravenous infusion (o——o) of 5 mg of pindolol

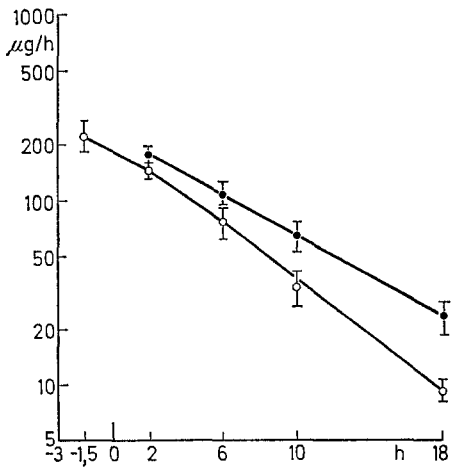

Fig. 5. Urinary excretion rates of oral (●——●) and intravenous (o——o) pindolol

declined linearly with time when plotted on a semilogarithmic scale (Fig. 5), thus making it possible to calculate the half lives of urinary excretion for both routes of administration. They were 5.41 ± 0.68 h after oral and 3.68 ± 0.37 h after intravenous administration of pindolol. The latter figure did not differ significantly from the plasma half life after i.v. administration, but the plasma half life after an oral dose (3.65 = 0—24 h) was significantly shorter than that of its urine excretion ($p < 0.05$; Table 3).

Protein Binding

In three experiments the average amount of pindolol bound to serum protein was 57.2%.

Pharmacokinetic Data

The pharmacokinetic parameters of pindolol calculated from analysis of plasma levels and urinary excretion are listed in Tables 3 and 4. As the time course of plasma levels after intravenous infusion suggested that the data was compatible with a linear open one-compartment system, they may be described by the Bateman function.

The plasma elimination rate constant k_2 was estimated by calculation of the regression lines of the linear declining slope after both oral and intravenous administration and dividing the calculated slopes by log *e*. The mean value of k_2 was -0.20 ± 0.01 h^{-1} after oral and -0.25 ± 0.04 h^{-1} after intravenous dosing (Tables 3, 4). The difference between the two slopes was not significant by Student's t-test. According to

$$t_{0.5} = \frac{ln\,2}{k_2}$$

the plasma half lives were 3.65 ± 0.24 h (oral) and 3.13 ± 0.55 h (i.v.) respectively.

After oral administration, the initial concentration C_o can be calculated by extrapolating the plasma concentration regression line to zero time. It averaged 33.08 ± 5.24 ng/ml with the 4-fold variation mentioned previously. After intravenous infusion *a* is the initial concentration which would have been obtained had the total dose been administered as a bolus injection. *a* may be calculated by $a = F_o^\infty \times k_2$. F_o^∞ is the total area below the serum curves determined by summing the areas according to $F_o^\infty = F_o^n + F_n^\infty$, where F_o^n is calculated by the trapezoidal rule, and $F_n^\infty = \frac{C_o}{k_2}$; C_n = concentration at time $t = n$. C_o was 41.18 ± 9.55 ng/ml. The cumulative urinary excretion at $t = \infty$ was calculated by approximating the cumulative excretion by an exponential equation of the form $E_u^t = E_u^\infty (1 - e^{-k_2 t})$; see Tables 3, 4. Mean values of cumulative urinary excretion at $t = \infty$ were 39.18 ± 0.91% after intravenous and 36.14 ± 4.37% after oral administration, respectively.

The absorption rate was determined by the following method: the cumulative urinary excretion of pindolol after oral and intravenous administration were compared as this can give exact data (Nüesch, 1973) about absorption rate, provided that excretion is calculated at $t = \infty$, and the model is linear. Experience has shown that this method may also be

employed when oral and i.v. studies have been performed in different subjects. The absorption rate of pindolol calculated from these data was 92%.

Another method of determination of absorption rates, based on comparison of the total areas below the plasma level curves ($c \times t$) after oral and intravenous doses of a drug, might also be applicable to interindividual trials, as suggested by Dengler (1970, 1973) for sparteine and digitalis glycosides. The total f is the absorption quotient. After i.v. application f is 1.0 and, in the case of oral pindolol, $f = 0.92$ (92% absorption). The mean volume of distribution calculated after both methods of administration was 136 ± 32 l (i.v.) and 142 ± 17 l (oral), respectively. When corrected for the body weights of the subjects, the relative distribution volumes were 2.0 ± 0.48 l/kg (i.v.) and 2.1 ± 0.24 l/kg (oral), respectively.

Table 3. *Pharmacokinetic parameters of pindolol after oral administration of 5 mg*

Subject	a (ng/ml)	k_1[a] (h^{-1})	Inv.-$t_{0.5}$[a] (h)	t_{max}[a] (h)	k_2 (h^{-1})	El.-$t_{0.5}$ (h)	F_0^∞ ($\mu g \cdot h \cdot ml^{-1}$)	E_{cum} (%)	V (l)	Cl_{tot} ($ml \cdot min^{-1}$)	Cl_{ren} ($ml \cdot min^{-1}$)
I	23.9	0.898	0.77	2.40	0.148	4.66	161.6	25.3	227	515.5	153.4
II	40.0	1.668	0.42	1.39	0.224	3.10	178.8	27.3	135	466.7	144.0
V	64.1	1.910	0.36	1.39	0.169	4.10	379.6	—	85	219.7	—
VIII	116.2	6.800	0.10	0.53	0.210	3.31	533.9	59.3	47	150.5	77.3
IX	41.3	1.112	0.62	1.85	0.214	3.23	193.0	41.1	131	431.6	198.9
X	35.7	1.285	0.54	1.65	0.224	3.10	159.3	66.6	152	522.7	317.4
XII	32.4	3.920	0.18	0.80	0.198	3.49	163.2	25.3	168	511.5	160.3
XV	20.1	1.088	0.64	2.14	0.138	5.04	145.6	29.1	270	572.7	197.4
XVI	60.0	3.161	0.22	0.97	0.177	3.91	339.5	28.0	90	244.9	73.4
XIX	33.3	1.675	0.41	1.57	0.152	4.56	218.9	34.9	163	380.0	154.9
XXI	36.9	2.545	0.27	0.96	0.352	1.97	100.5	22.6	147	792.0	190.4
XXIV	57.5	—	—	—	0.208	3.34	276.1	38.1	95	301.6	128.0
$\bar{x}$	46.8	2.360	0.41	1.42	0.200	3.65	239.2	36.1	142	425.8	163.2
$S_{\bar{x}}$	7.5	0.520	0.06	0.17	0.010	0.24	37.2	4.4	17	51.5	20.0

[a] According to Diller (1961).

a = initial concentration (cf page 22); k_1 = invasion rate constant; Inv.-$t_{0.5}$ = invasion half life; t_{max} = time of maximum plasma concentration; k_2 = elimination rate constant; El.-$t_{0.5}$ = elimination half life; F_0^∞ = total area below the serum curve; E_{cum} = cumulative urinary excretion; V = volume of distribution; Cl_{tot} = total clearance; Cl_{ren} = renal clearance.

Table 4. *Pharmacokinetic parameters of pindolol after intravenous administration of 5 mg*

Subject	Dose (mg)	a (ng/ml)	k_2 (h^{-1})	$t_{0.5}$ (h)	F_0^∞ ($\mu g \cdot h \cdot ml^{-1}$)	E_{cum} (%)	V (l)	Cl_{tot} ($ml \cdot min^{-1}$)	Cl_{ren} ($ml \cdot min^{-1}$)
A	4.26	22.6	0.150	4.42	150.8	37.7	210	525.0	176.3
B	4.71	29.7	0.281	2.46	105.6	40.1	160	749.3	282.7
C	4.71	25.3	0.153	4.53	165.5	79.9	190	484.5	371.5
D	4.83	59.6	0.326	2.13	282.8	37.6	50	271.7	106.5
E	4.72	68.7	0.331	2.10	207.5	41.3	70	386.2	143.2
$\bar{x}$	4.65	41.2	0.248	3.13	179.8	39.2	136	483.3	216.1
$S_{\bar{x}}$	0.10	9.6	0.040	0.55	30.7	0.9	32.2	79.6	48.3

C_0 = initial concentration; k_2 = elimination rate constant; $t_{0.5}$ = elimination half life; F_0^∞ = total area below the serum curve; E_{cum} = cumulative urinary excretion; V = volume of distribution; Cl_{tot} = total clearance; Cl_{ren} = renal clearance.

areas below the plasma level curves, corrected for the slightly different amounts administered, were 239.2 ± 37.2 ng × h × ml^{-1} after the oral dose, and 195.6 ± 29.6 ng × h × ml^{-1} after the intravenous dose. The difference is not significant ($t = 0.71$; $p > 0.05$).

The distribution volume V_D is defined by the equation

$$V_D = \frac{D \cdot f}{k_2 \cdot F_0^\infty}$$

where D is the dose administered intravenously, and

The invasion rate constant k_1 after the oral administration of pindolol has also been calculated in two ways:

1. The Sigma-minus method is based on plotting semilogarithmically the "residuals" between the extrapolated regression line and the plasma levels actually measured at different times during the invasion period, and then calculating the invasion rate constant from k_1 = slope/log e [21].

2. According to Diller (1961) the rate constant of invasion is described by

$$k_1 = k_2 \cdot \frac{C_o}{C_o - a}$$

where C_o is the initial plasma concentration obtained by extrapolating the regression line to $t = o$ and a is calculated as

$$a = F_o^{\infty} \times k_2$$

The mean invasion constant calculated by method I was 1.23 ± 0.14 h^{-1}, and that calculated by method II was 2.36 ± 0.52 h^{-1}. Using the k_1-values of the individual curves, the invasion half life time was calculated to be 0.63 ± 0.07 h and 0.41 ± 0.06 h, respectively.

The time of peak plasma level after oral administration of pindolol may be calculated by

$$t_{max} = \frac{1}{k_1 - k_2} \cdot ln \frac{k_1}{k_2}$$

It was found to be 1.42 ± 0.17 h when the Diller method was employed and 1.88 ± 0.15 h when the Sigma-minus method was used. From the k_1 values obtained by the Diller method, the calculated t_{max} was in better agreement with that determined graphically from individual plasma level-time curves. Accordingly, a t_{max} of 1.42 h was considered a realistic parameter of the practical situation.

Wagner's (1969) method was used to estimate renal clearance, which was defined as the relationship between the amount of drug excreted in urine at $t = n$ (A_u; ^{n}) to the area below the plasma concentration-time curve at time n (F_o^n),

$$Cl_{ren} = \frac{A_u;\, {}_o^n}{F^n}$$

The renal clearance of pindolol was found to be 163.2 ± 20 ml · min^{-1} ($\bar{x} \pm S_{\bar{x}}$) after oral administration and 216.1 ± 48.4 ml · min^{-1} after intravenous infusion. Total clearance calculated by $Cl_{tot} = k_2 \cdot V$ was 425.8 ± 51.5 ml · min^{-1} and 483 ± 79.6 ml · min^{-1}, respectively. The difference between the two clearances is not significant.

Discussion

The pharmacokinetics of pindolol after oral and intravenous administration may be interpreted in terms of an open one-compartment model. Although Gibaldi *et al.* (1969) have suggested that an open two-compartment model would be more appropriate in most instances, it seemed reasonable to evaluate the present data in the simpler way as it would not lead to any major changes in the pharmacokinetic parameters. In order to avoid adverse reactions, it was considered impossible to employ the technique of rapid injection of doses sufficiently large to produce plasma levels that could readily be assayed, and instead a slow infusion of pindolol was given over 3 h.

Absorption of the oral dose occurred rapidly, as shown by $t_{max} = 1.42$ h; other beta-receptor blocking agents have given almost identical t_{max}, according to graphical evaluation of plasma level-time curves, e.g. propranolol (Paterson *et al.* 1970), practolol (Bodem and Chidsey, 1973), and alprenolol (Ablad *et al.*, 1972).

It is of interest that the maximum plasma concentrations of pindolol exhibited 4-fold variation after either oral or i.v. dosing. The fact that the same range was found after intravenous administration means that it cannot be due to differences in absorption rate between subjects. Similar results have been reported for propranolol (Shand *et al.*, 1970) and have been used to support the thesis that the plasma level of a drug correlates better with its effect than does the dose given (Koch-Weser, 1972). However, another study has shown that, despite good correlation between the logarithm of the plasma concentration of pindolol and its beta-blocking activity in individual subjects, there are considerable intersubject differences in the relationship between beta-blocking effect and the plasma level of pindolol (Gugler *et al.*, 1973).

The plasma half life of pindolol, which may be considered the most important pharmacokinetic parameter of any drug, was 3.65 ± 0.24 h after oral and 3.13 ± 0.55 h after intravenous administration; the difference is not significant. Comparable findings have been reported for propranolol, the corresponding half lives being 3.0 ± 0.79 h (oral) and 2.34 ± 0.22 h (i.v.), respectively (Shand *et al.*, 1970).

A plasma level of 10 ng/ml of pindolol has been reported as the minimum concentration that will produce beta-receptor blockade (Gugler *et al.*, 1973); although this may require modification because recent results have shown that the effect of pindolol lasts more than 24 h after a single oral dose (Olsson and Varnauskas, 1973). As shown in Fig. 2, an oral dose of 5 mg will produce a plasma level of 10 ng/ml within 30 min and the plasma concentration will exceed this level for 6—8 h. The shorter half life of propranolol (2.3—3.0 h) necessitates shorter dose intervals or the use of larger doses. Alprenolol is reported to have a plasma half life of about 3.5 h (Åblad *et al.*, 1972) and practolol is the only compound of this group of drugs known to have a longer plasma half life — about 13 h (Bodem and Chidsey, 1973). The half life of urinary excretion of pindolol

was 3.68 ± 0.37 h (i.v.) and 5.41 ± 0.68 h (oral); only the latter differed significantly from the corresponding plasma half life.

The absorption rate of pindolol of 92% agrees with those of practolol (Bodem and Chidsey, 1973) and propranolol (Paterson *et al.*, 1970). The cumulative excretion rate of 40% at $t = \infty$ means that the drug is extensively metabolized. Propranolol is metabolized to an even greater extent, but practolol is not metabolized at all in man. All these compounds have the same side chain, which is considered to be responsible for their beta-receptor blocking activity. It seems likely that the side chain has no influence on their metabolism and it is the nucleus that mainly determines the rate of biological degradation.

If elimination routes other than renal are excluded, the difference between total and renal clearance of a drug is considered to be the metabolic 'clearance' and is some guide to the degree of metabolism of the compound. In the case of practolol, total clearance and renal clearance are identical, which confirms the finding that the compound is not metabolized. The total clearance of pindolol was 483 ml $\times$ min^{-1}, and its renal clearance was 216 ml $\times$ min^{-1}, indicating a high metabolic clearance of 267 ml $\times$ min^{-1}. The metabolic fate of pindolol in man is not yet known.

Calculation of the invasion constant k_1 always introduces certain difficulties if absorption is rapid and if only a limited number of plasma level determinations have been done during the invasion period. Both of the methods employed to calculate k_1 are imprecise to some degree, although the validity of the Sigma-minus method can be estimated by determining the correlation coefficient of the calculated regression line, 0.92 in the case of pindolol. In addition, the variability of k_1 was less when the Sigma-minus procedure was used, indicating that this method was to be preferred. On the other hand, t_{max} calculated from k_1-values obtained by Diller's method was a better fit with t_{max} actually observed in the plasma curves of individual subjects. It appears that both methods were applicable in the present study, albeit with certain reservations.

The volumes of distribution of pindolol were 136 l and 142 l, after i.v. and oral administration, respectively. Similar values have been reported for propranolol and practolol (Shand *et al.*, 1970; Bodem and Chidsey, 1973), which implies similar distribution patterns of these compounds that are closely related in terms of chemical structure, partition coefficient, and pK_a-values.

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