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A comparison of the pharmacokinetics of propranolol in obese and normal volunteers

S. L. BOWMAN[1]*, S. A. HUDSON[1,2], G. SIMPSON[2], J. F. MUNRO[2] & J. A. CLEMENTS[1]
[1]Department of Pharmacy, Heriot-Watt University and [2]Eastern General Hospital, Edinburgh

The pharmacokinetics of intravenous and oral propranolol have been compared in six obese and six normal subjects matched for age and sex. After intravenous administration there was no difference in plasma clearance but the volume of distribution was greater (V = 339 l *vs* 198 l) and the half-life was longer ($t_{1/2}$ = 5.0 h *vs* 3.0 h) in the obese group. No important difference in the rate of oral absorption was observed. A trend towards higher systemic availability in the obese group (35% *vs* 27%) was not statistically significant.

Keywords propranolol pharmacokinetics obesity

Introduction

Propranolol pharmacokinetics have been studied extensively in patient and volunteer groups (Routledge & Shand, 1979) but do not appear to have been reported for the obese. The incidence of hypertension and ischaemic heart disease are increased in obesity and propranolol may be indicated. Because propranolol is highly lipophilic and is almost totally cleared by the liver, differences in the obese might be expected. Accordingly, we have measured its pharmacokinetics after intravenous and oral administration to normal and obese volunteers matched for age and sex.

Methods

Six subjects (three male) were in each group. Mean weight for the obese was 136.5 ± 35.8 kg (s.d.), mean age 33 ± 6 years, ideal body weight (equal to X kg + 2.3 kg per inch over 5 feet, where X = 45.5 (female) or 50.0 (male); Anon, 1959) was 68.4 ± 4.0 kg and body mass index (defined as weight in kg (height in m)$^{-2}$; Garrow, 1981) was 46.2 ± 4.2. For control subjects mean weight was 66.8 ± 11.3 kg, mean age 33 ± 6 years, ideal body weight 63.8 ± 5.0 kg and body mass index 22.5 ± 0.7. None was receiving concurrent medication. There was no evidence of renal or hepatic disease and all had normal liver function tests. All gave informed consent. The study was approved by the Area Hospital Ethics Committee.

After an overnight fast, propranolol hydrochloride (10 mg) was infused over 10 min or administered as a single oral dose of 40 mg (Inderal) with 150 ml water. At least 1 week separated the studies. Venous samples (8 ml) were withdrawn through a cannula at 0 (pre-dose), 5, 15 and 30 min, 1, 2, 4, 6, 8 and 12 h (intravenous study) and at 0 (pre-dose), 15, 30, 60 and 90 min, 2, 3, 5, 8, 12 and 24 h (oral study).

Propranolol in plasma was determined by h.p.l.c. (Terao & Shen, 1982) with u.v. detection at 293 nm. Peak height ratios (propranolol/4-methylpropranolol) were proportional to propranolol concentrations of 10 to 200 ng ml^{-1}. The coefficients of variation at concentrations of 15 and 50 ng ml^{-1} were 7.1% and 3.0%, respectively, and known metabolites of propranolol (4-hydroxypropranolol, α-naphthoxyacetic and α-naphthoxylactic acids) were shown not to interfere.

Data were fitted to compartmental models by non-linear regression (Clements & Prescott, 1976). The area under the concentration–time curve (AUC) after oral administration was obtained by trapezoidal rule with addition of

* Present address: Pharmacy Department, Bangour General Hospital, West Lothian

area beyond the last point. Pharmacokinetic parameters were calculated from standard equations (Gibaldi & Perrier, 1979). Means are shown with s.e. mean and were compared by unpaired t-test ($P < 0.05$).

For protein binding studies propranolol (150 ng ml^{-1}) was added to samples of pooled plasma from normal and obese subjects. After centrifugation at 2000 rev min^{-1} for 15 min in Centriflo membranes the protein-free filtrates were assayed for propranolol.

Results

There was no significant difference between the obese and non-obese in plasma clearance of propranolol after intravenous infusion (Table 1) and there was no correlation between clearance and body weight ($r^2 = -0.002$). However the volume of distribution was significantly larger in the obese group and the half-life was longer. Plasma concentrations at the end of the infusion were higher in normal subjects than in the obese (Figure 1).

There was a highly significant correlation between half-life and the volume of distribution ($r^2 = 0.953$; $P < 0.001$) whereas no correlation existed between half-life and clearance ($r^2 = 0.0002$). Volume of distribution was correlated with body weight ($r^2 = 0.966$; $P < 0.001$) and with body mass index ($r^2 = 0.962$; $P < 0.001$).

After oral administration there was no difference in absorption kinetics between groups and although the bioavailability was higher in the obese (mean 35%, range 24–48%) compared to normal subjects (mean 27%, range 17–33%) the difference was not significant (Table 1). Amongst obese subjects there was a significant correlation ($r^2 = 0.68$; $P < 0.05$) between bioavailability and actual body weight. There was no difference in apparent clearance whereas the apparent volume of distribution and half-life were significantly greater in the obese. As with the intravenous study, half-life correlated with apparent volume of distribution but not with apparent clearance ($r^2 = 0.978$; $P < 0.001$; $r^2 = 0.142$, respectively).

The fraction of unbound propranolol in the plasma of obese and normal subjects was 0.089 ± 0.002 and 0.099 ± 0.002, respectively ($n = 6$).

Discussion

Pathophysiological changes associated with the development of obesity may be expected to alter the pharmacokinetics of drugs through alterations in clearance and distribution (Abernethy & Greenblatt, 1982).

As expected, propranolol distributed into excess body weight (EBW). Distribution into EBW was approximately 70% of that into IBW, which is less than that for more lipophilic drugs such as benzodiazepines (Abernethy *et al.*, 1981; Greenblatt *et al.*, 1984) but is likely to be more than that for most other β-adrenoceptor blocking drugs which are more hydrophilic than propranolol.

Our demonstration that propranolol plasma clearance is similar in obese and control subjects is in accord with the findings for other drugs. The increased half-life of propranolol is a consequence of the larger volume of distribution in the obese, as has been found, for example, with benzodiazepines (Abernethy & Greenblatt,

Table 1 Pharmacokinetic parameters in obese and normal subjects after administration of propranolol hydrochloride by intravenous infusion (10 mg over 10 min) or orally (Inderal, 40 mg) (mean + s.e. mean)

Intravenous infusion			*Oral administration*		
Pharmacokinetic parameter	*Subject group*		*Pharmacokinetic parameter*	*Subject group*	
	Obese	*Normal*		*Obese*	*Normal*
V (l)	339 ± 22*	198 ± 8	CL (l min^{-1})	2.4 ± 0.2	3.0 ± 0.3
V (l kg^{-1})	2.6 ± 0.1*	3.0 ± 0.1	V (l kg^{-1})	2.4 ± 0.1	2.8 ± 0.2
V (l kg^{-1} IBW)	5.0 ± 0.3*	3.2 ± 0.2	AUC (μg l^{-1} h)	260 ± 25	207 ± 18
V_{ss} (l)	326 ± 21*	187 ± 7	F (%)	35 ± 4	27 ± 2
CL (ml min^{-1})	780 ± 20	780 ± 10	ka (h^{-1})	1.83 ± 0.1	1.68 ± 0.13
CL (ml min^{-1} kg^{-1})	6.1 ± 0.6*	11.9 ± 0.7	C_{max} (μg l^{-1})	31 ± 2	38 ± 6
$t_{½}$ (h)	5.0 ± 0.3*	3.0 ± 0.1	t_{max} (h)	1.5 ± 0.1	1.4 ± 0.1
			$t_{½}$ (h)	4.9 ± 0.5*	2.8 ± 0.2

* Significantly different from normal group.
F % = oral bioavailability; C_{max} = calculated peak concentration.
t_{max} = calculated peak time

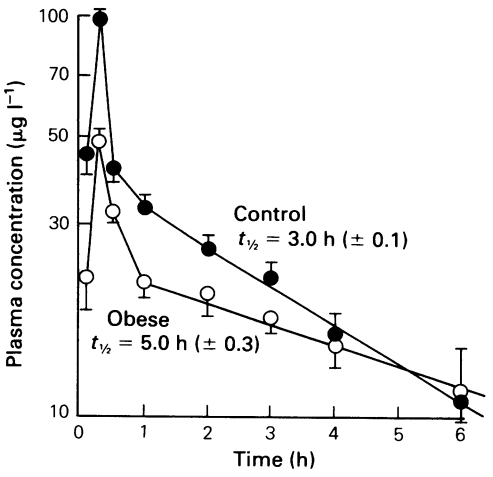

Figure 1 Plasma propranolol concentration *vs* time during and after intravenous infusion of 10 mg propranolol HCl over 10 min to obese (○) and normal (●) subjects.

1982), theophylline (Gal *et al.*, 1978) and lignocaine (Abernethy & Greenblatt, 1984).

The influence of obesity on oral absorption rate and bioavailability has received scant attention in the literature. Our data suggest that the rate of propranolol absorption is similar in the two groups. The bioavailability of propranolol in our normal subjects (27%) is similar to that reported previously (22%) in single dose studies (Wood *et al.*, 1978). The lower peak plasma concentration in the obese can be explained by the larger volume of distribution. Although there was a trend towards higher bioavailability in the obese than in normal subjects (35% *vs* 27%) the difference was not significant. There was marked inter-subject variation and further studies are required.

Abernethy *et al.* (1984) have described the effect of obesity on the pharmacokinetics of oral triazolam. Whereas the larger AUC for the obese group was attributed to a lower clearance, it is also consistent with a higher systemic availability. Obesity does not appear to affect the bioavailability of midazolam (Greenblatt *et al.*, 1984).

The effects of obesity on the action of propranolol are dependent on the study of the overall pharmacodynamic response and the influence of other factors such as the extent of formation of the active metabolite 4-hydroxypropranolol. However, there are several possible practical implications of these results. Intravenous doses of propranolol may need to be larger in the obese but plasma concentrations will decline more slowly because of the longer half-life. Since clearance is unaffected by obesity, no alteration of maintenance dose is likely to be required. During multiple dose therapy the longer half-life in the obese will lead to smaller fluctuations in plasma concentration and twice-daily dosing of propranolol in the obese may be possible. The longer time taken to reach steady-state is unlikely to be important clinically.

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