COMPARISON OF THE PHARMACOKINETICS OF INTRAVENOUS AND ORAL PROPRANOLOL IN OBESE AND NORMAL VOLUNTEERS

Bowman, S.L., Hudson, S.A., Munro, J.F., Simpson, G., Clements, J.A.
Department of Pharmacy, Heriot-Watt University and Eastern General Hospital, Edinburgh.

The consequences of pathophysiological differences between obese and normal subjects for dose adjustment of most drugs are not well documented (Abernethy and Greenblatt, 1982). In particular, no comparison of propranolol pharmacokinetics in these subject groups appears to have been reported. We have measured the pharmacokinetics of propranolol in obese and normal volunteers. Six obese patients (mean weight 136.5 ± 35.8 kg SD) and six control subjects (66.8 ± 11.3 kg), matched for age and sex and with no known contra-indication to the drug, gave informed consent to participate in the study.

Pharmacokinetic values were determined on separate occasions after intravenous (IV) infusion of propranolol hydrochloride 10 mg over 15 minutes and after a single oral dose of propranolol hydrochloride 40 mg ('Inderal', ICI Ltd) and were compared by Student's t-test ($p<0.05$). Plasma samples (3 ml) were analysed for propranolol by a modification of the HPLC method of Terao and Shen (1982). 4-methylpropranolol was added as internal reference standard before extraction into diethyl ether, evaporation under nitrogen and uptake into eluent (50 µl) of acetonitrile: 0.05M sodium hydrogen sulphate (pH 2.7) 25:75. The eluent flow rate was 3.0 ml/min. Injection of the sample (20 µl) on to a column of 100 mm x 4.6 mm of Partisil ODS-10 gave peaks with capacity factors of 3.33 and 5.44 for propranolol and internal standard respectively. UV detection was at 293 nm and the limit of detection was 10 ng/ml.

After IV infusion, propranolol elimination half-life ($t_{\frac{1}{2}}$ ± SEM) was significantly prolonged in the obese compared to controls (5.0 ± 0.3 h vs 3.0 ± 0.1 h) and there was an increase in volume of distribution Vd_{β} (339 ± 22 l vs 198 ± 8 l). No difference in clearance was noted between groups (0.78 ± 0.02 l/min vs 0.78 ± 0.01 l/min).

After oral administration, absorption kinetics did not differ significantly between the two groups. Bioavailability was 35% (± 4%) in the obese compared with 27% (± 2%) in controls ($p>0.05$). Time to peak was 1.5 (± 0.1) h in the obese compared with 1.4 (± 0.1) h in the controls ($p>0.05$). Elimination half-life was significantly prolonged in the obese group (4.89 ± 0.45 h vs 2.85 ± 0.22 h) and there was a larger volume of distribution (325 ± 30 l vs 184 ± 14 l). Apparent clearance was not significantly different between the two groups (2.4 ± 0.2 l/min vs 3.0 ± 0.3 l/min). The changes in half-life in the obese therefore reflect alterations in drug distribution rather than differences in clearance.

The volume of distribution correlated significantly with Body Mass Index (weight, kg/(height, m)^2) and body weight after both IV and oral administration. Propranolol appears to distribute into excess body weight over "ideal" body weight to the extent of about 70%. Therefore, after IV administration, Vd_{β} (l/kg body weight) was significantly lower in the obese (2.6 ± 0.1 l/kg vs 3.0 ± 0.1 l/kg). This finding may be explained in part by an increase in propranolol protein binding in the obese (fraction unbound 0.09 ± 0.002 vs 0.10 ± 0.002) determined in vitro.

The marked increase in the volume of distribution in obese subjects indicates that the loading dose of propranolol needs to be larger in the obese. In the absence of a loading dose, the time to reach steady-state will be prolonged but this finding is unlikely to be clinically significant. Clearance is not significantly different in obese subjects and, therefore, degree of obesity will not affect the selection of the maintenance dose. Prolongation of half-life may allow less frequent administration of propranolol in the obese in the treatment of ischaemic heart disease. The small reduction in the proportion of unbound propranolol in the plasma of the obese is unlikely to be important clinically.

Abernethy, D.R. & Greenblatt, D.J. (1982) Clinical Pharmacokinetics 7: 108-124
Terao, N. & Shen, D.D. (1982) Chromatographia 15: 685-687