INTRAVENOUS PROPRANOLOL IN PATIENTS WITH INFLAMMATION

Higher than normal plasma propranolol concentrations have been reported in coeliac disease (Parsons *et al.*, 1976; Schneider *et al.*, 1976), Crohn's disease and rheumatoid arthritis (Schneider *et al.*, 1979). Explanations which have been offered include increased absorption of the drug, improved bioavailability due to a reduction in 'first-pass' metabolism across the liver, or a change in the distribution volume of the drug. It is not possible to distinguish between these possibilities without dosing intravenously. The present study reports the disposition pharmacokinetics of propranolol administered intravenously to patients with inflammatory disease.

Eleven patients aged 26–78 years were studied: seven had Crohn's disease and four rheumatoid arthritis. All gave informed consent to the procedure which involved insertion of cannulae into veins of both forearms; one was used for intravenous dosing and the other for blood sampling. Propranolol was infused intravenously in a dose of 0.15 mg/kg at a rate of 1 mg/min. Blood samples were drawn from the contralateral arm prior to propranolol administration and at 0, 10, 20, 30, 45, 60, 75, 90, 120, 180, 240 and 360 min after the end of the infusion. Plasma propranolol concentrations were measured by high performance liquid chromatography (Nation *et al.*, 1978) and areas under the plasma concentration-time curves (AUC) were calculated by the trapezoidal rule and extrapolated to infinity: clearance was calculated from dose/AUC. Binding to serum proteins was determined by equilibrium dialysis using [^{3}H]-propranolol at a concentration of 10 ng/ml.

Plasma propranolol concentrations were higher than normal in patients with evidence of active inflammation (Figure 1) and were associated with smaller distribution volumes and increased binding to serum proteins (Table 1). A significant correlation was found between the area under the total plasma concentration-time curve for propranolol and the ESR ($r = 0.59$, $P < 0.05$). In addition, a significant negative correlation was found between the ESR and the apparent distribution volume ($r = -0.73$, $P < 0.01$). Finally, there was a highly significant negative relationship found between the unbound fraction of propranolol in plasma and the AUC: for AUC 0–∞ ($r = -0.78$, $P < 0.01$) and AUC 0–1 h ($r = -0.84$, $P < 0.01$).

Previous studies of propranolol pharmacokinetics in patients with inflammation have been confined to oral dosing. The present study indicates that in patients with active inflammation, propranolol concentrations are elevated because of a reduction in the apparent distribution volume which is probably the result of increased binding to plasma protein. Propranolol binds not only to albumin but also α_1-acid glycoprotein (Piafsky *et al.*, 1978). The concentration

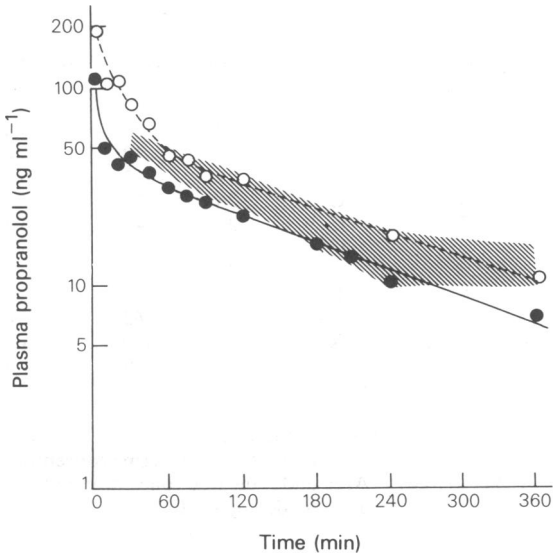

Figure 1 Plasma propranolol concentrations obtained after intravenous administration of 0.15 mg/kg to a patient with rheumatoid arthritis. On the first occasion (○----○) he had a sedimentation rate of 100 mm/h and on the second (●——●) it had fallen to 39 mm/h. The shaded area represents the range of concentrations achieved with this dose in 15 normal individuals aged between 19 and 87 years. Active inflammation is associated with delayed distribution of the drug and higher than normal propranolol concentrations.

of the latter is raised in a variety of inflammatory conditions including Crohn's disease and rheumatoid arthritis. Thus, when total propranolol concentrations are measured in the blood of patients who have active inflammation, the values are elevated irrespective of the route of administration. These higher values might be interpreted as an indication to reduce the dose of propranolol in patients with inflammatory disease. However, since it is the free concentration which is active (McDevitt *et al.*, 1976) and this is not increased, it would be inappropriate to reduce the dose. Indeed, in the present study there was a significant positive correlation between the free fraction and the AUC_{free} ($r = 0.774$, $P < 0.01$). This confirms previous findings of De Leve & Piafsky (1981) for +-propranolol. It is, therefore, possible that drug effects will be smaller for the same dose in patients with rheumatoid arthritis or Crohn's disease than in normals.

We are grateful to the British Heart Foundation for

Table 1 Pharmacokinetics of i.v. propranolol (0.15 mg/kg) in patients with Crohn's disease (C) and rheumatoid arthritis (RA)

Patient	*Condition*	*Age (years)*	*ESR (mm/h)*	*Free fraction (%)*	*AUC (0–1 h)*	*AUC (0–∞) (μg ml⁻¹ min)*	*AUC (free) (0–∞)*	*V_d (l/kg)*	*$T_{½}$ (min)*
1	C	30	11	14.9	107	445	66.3	6.28	215
2	C	54	12	13.4	106	385	51.6	4.76	141
3	C	27	32	6.7	241	—	—	—	*
4	C	26	37	8.2	158	430	35.3	4.18	139
5	C	37	42	8.1	158	658	53.3	4.04	205
6	C	35	44	5.6	297	835	46.8	2.27	146
7	C	27	64	7.0	217	646	45.2	2.39	119
8	RA	78	51	3.9	359	914	35.6	1.80	127
9	RA	67	62	7.4	218	556	41.1	2.55	109
10 (a)	RA	42	100	4.1	289	798	32.7	2.34	144
10 (b)	RA	42	39	5.8	171	537	31.1	3.34	138
11	RA	71	112	7.0	241	734	51.4	2.23	126

* = insufficient data
AUC = Area under the total plasma concentration-time curve in $\mu g\ ml^{-1}$ min.
AUC (free) = Area under the free concentration-time curve in $\mu g\ ml^{-1}$ min.
V_d = dose divided by AUC × β.

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A SIMPLE AND SENSITIVE H.P.L.C. METHOD FOR THE ASSAY OF PROCHLORPERAZINE IN PLASMA

Prochlorperazine [2-chloro-10-(3,4′-methylpiperazin-1-pylpropyl)phenothiazine; Stemetil] is widely used for the treatment of nausea, vomiting, migraine, anxiety and schizophrenia. Hitherto, it has not been possible to monitor plasma levels of this drug during therapy because of the lack of adequately sensitive assay procedures, although for some other phenothiazines suitable methods, based on gas-liquid