12.5 u/kg heparin stimulated lipolytic activity within 15 min but failed to depress coagulation over 60 min. As the anticoagulant action of heparin is known to develop within 30 s of the administered dose (Robinson & Harris, 1959) provided that a therapeutic dose is given, these investigations clearly establish the lower dose range of heparin at which the anticoagulant and lipolytic activities of the drug can be separated.

In this regard it is of interest that the 20 u/kg dose which produces therapeutic anticoagulation is considerably lower than the 'low dose' heparin regimen advocated in the prophylaxis of venous thrombosis (Sherry, 1975).

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PLASMA PIMOZIDE PROFILES IN CHRONIC SCHIZOPHRENICS

The intermittent administration of neuroleptics has practical advantages as maintenance therapy in chronic schizophrenia and can be as effective as the same medication given continuously (Prien & Klett, 1972). There have however been no studies on intermittent pimozide. Before embarking on clinical trials to investigate different schedules of intermittent administration more work has been done on the pharmacokinetics of pimozide.

The subjects, nine male chronic schizophrenic inpatients, were given, firstly 6 mg pimozide daily for 4 days, and, secondly, 12 days later, a single 24 mg dose. Blood was withdrawn at regular intervals and plasma pimozide levels estimated by a radioimmuno-assay technique with which the major metabolites of pimozide do not interfere (Michiels, Hykants, Knaeps & Jansen, 1975).

Extrapyramidal side effects were assessed daily by a 4-point rating scale (McCreadie & McDonald, 1977).

The study was approved by the Western District Ethical Committee, Greater Glasgow Health Board.

The mean plasma level—time curves for the single and multiple dose schedules are shown in Figure 1. Pimozide was slowly absorbed, reaching peak plasma levels around 8 h (range 4–12 h). The plasma level after the single dose was then four times higher than after the first of the 6 mg doses. Eight hours after the third of the multiple doses plasma levels were equal and after the fourth dose, the single dose plasma level was almost 35% lower.

The mean plasma half-lives, estimated by regression analysis, were similar for both dose schedules: 55 ± 6.8 h (mean $\pm$ s.e. mean) for the multiple and 53 ± 3.1 h for the single dose schedule.

Systemic availability, measured by the area under the curve ($AUC_{0-\infty}$), was on average 27% greater with the single dose (range -7 to $+71\%$; $P < 0.05$, Wilcoxon matched pairs test). The reason for this is not clear but it is unlikely that this small difference is of clinical significance. There was a high correlation between systemic availability and single determinations of pimozide concentration; for example, the correlation (r) in the single dose schedule between systemic availability and plasma concentration at 24 h was $+0.99$. Therefore systemic availability can

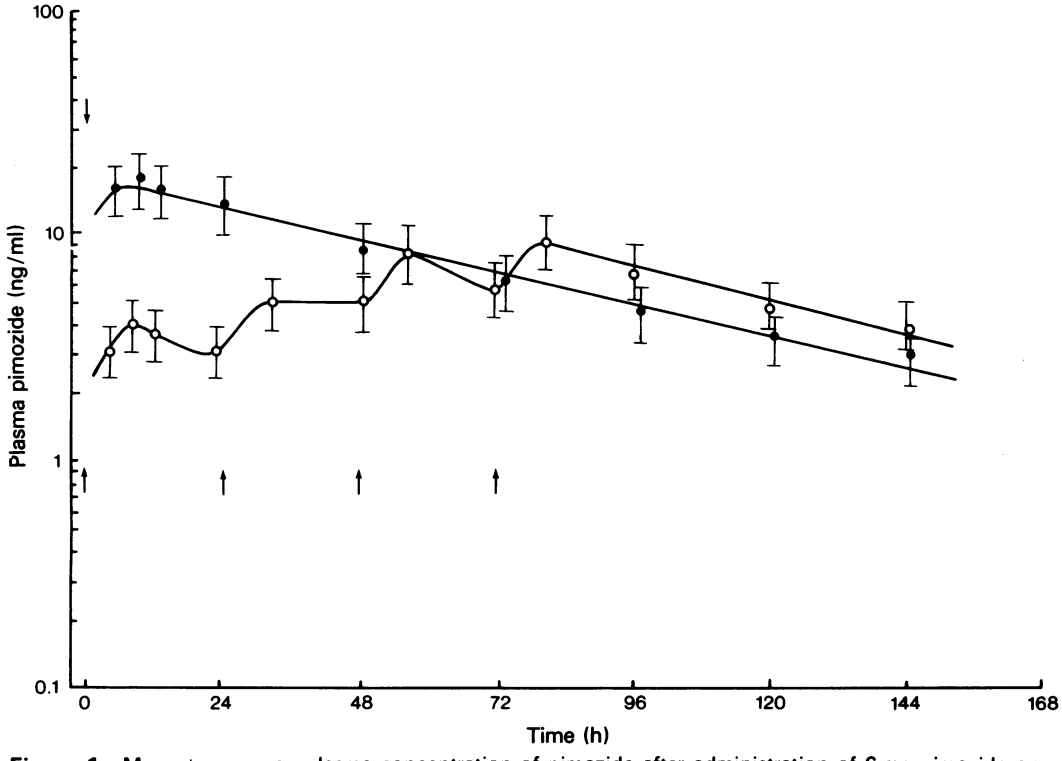

Figure 1 Mean ± s.e. mean plasma concentration of pimozide after administration of 6 mg pimozide once daily for 4 days (○) and after a single 24 mg dose (●). ↓: administration of 24 mg dose; ↑: administration of 6 mg doses.

be predicted from a single pimozide estimation.

There was, with the multiple doses and single dose respectively, a 17- and 9-fold interindividual difference in peak levels and 13- and 12-fold difference in the AUC.

There were no clinically or statistically significant changes in extrapyramidal side effects during either dose schedule.

The present study, the first to use on a large scale the radioimmunoassay technique to measure pimozide, has shown that the average plasma half-life, 53 h, is very much longer than that of chlorpromazine, which has been successfully used as intermittent therapy (Greenberg & Roth, 1966); therefore intermittent pimozide might also be effective. The following findings would suggest that a single higher-than-usual weekly dose might also be useful: the multiple doses did not give continuously higher plasma levels until the fourth day; with the single dose there was a higher peak concentration; finally, there were no serious extrapyramidal side effects with the single dose.

In current clinical practice the dose range of pimozide (2–10 mg daily) is fairly narrow. The present study, which has found large individual differences in pimozide systemic availability, suggests that a somewhat higher dose, when given either continuously or intermittently, may be needed in some patients to produce a therapeutic effect.

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