Approximately 12 h after the administration of either the oral or the i.v. preparations there was a second peak in plasma EE concentrations. The oral bioavailability of EE (50 μg), calculated from the areas under the plasma concentration: time curves was 42.4%.

In order to permit determination of the apparent terminal plasma half-life, another group of five women each received EE alone (3 mg) by mouth with subsequent blood sampling over 48 h. A terminal half-life of 12.2 ± 0.83 h was shown following the secondary peak.

The bioavailability of EE is lower than that of the synthetic progestogen, norethisterone (64%) (Back, Breckenridge, Crawford, MacIver, Orme, Rowe & Smith, 1978). The secondary peak of plasma EE concentration is most readily explained as resulting from enterohepatic circulation, since it is already known that EE sulphate is the major metabolite of EE in human bile (Cargill, Steinetz, Gosnell, Beach, Meli, Fujimoto & Reynolds, 1969). The occurrence of enterohepatic circulation may be of clinical significance in drug interactions with antibiotics.

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Pharmacokinetics of disopyramide administered by intramuscular, intravenous and oral routes to normal volunteers

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Disopyramide is an effective agent in the prevention and treatment of cardiac arrhythmias, particularly ventricular arrhythmias. It can be given by mouth or by intravenous injection. The intravenous route should be used with caution as the drug has a hypotensive effect if given too quickly. The intravenous preparation has been given outside hospital to patients with acute myocardial infarction (Ward & Holbrow, unpublished), however, it was considered that the intramuscular route could provide an alternative which would rapidly lead to safe yet effective serum levels. A preliminary pharmacokinetic study was, therefore, performed.

Single doses of disopyramide (100 mg) were administered in random order by the intravenous, intramuscular and oral routes to eight healthy male volunteers and serial blood samples taken. Disopyramide was estimated by gas liquid chromatography (Hayler & Flanagan, 1978).

As the intravenous injection was given over a period of 10 min with the first blood sample being taken on completion of the injection, the highest

Table 1 Means of peak plasma levels, times to peak and elimination half-lives of disopyramide (100 mg) following its intravenous, intramuscular and oral administration to volunteers

Route of Administration	*Mean peak disopyramide plasma level (mg/l) (± s.e. mean)*	*Mean time to peak (min)*	*Mean β half-life (hours)*
Intravenous	3.87 (±0.38)	0*	7.35
Oral	2.08 (±0.15)	90	8.36
Intramuscular	2.31 (±0.15)	15	6.78

* The intravenous injection was made slowly over 10 min and the first blood sample taken on completion of the injection.

observed plasma level is likely to be below the true peak. In other respects the data from oral and intravenous administrations are in accord with those of other authors (Ward & Kinghorn, 1976; Bryson, Whiting & Lawrence, 1978).

Following intramuscular injection significant plasma levels were present within 5 min and were within the recognised therapeutic range of 2–4 mg/l (Karim, 1975) in 10 min. The injections were well tolerated and did not produce any adverse reactions, in particular the hypotension and bradycardia observed in some of the volunteers during and immediately after the intravenous administration.

From these results the intramuscular administration of disopyramide would merit further study in patients.

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Protection against experimental myocardial ischaemia by L-4-hydroxy-phenylglycine, a new agent which alters myocardial metabolic balance in favour of carbohydrate utilisation

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There is much evidence that free fatty acid (FFA) utilisation by the heart may be harmful during ischaemia, especially when accompanied by elevated sympathetic activity. Interventions which depress myocardial FFA utilisation have been shown to reduce myocardial oxygen consumption (MVO_2) in animals (Mjøs, 1971) and man (Simonsen & Kjekshus, 1978) and to protect against ischaemic injury (Kjekshus and Mjøs, 1973; Maroko, Libby, Sobel, Bloor, Sybers, Shell, Covell & Braunwald, 1972).

We initially identified L-4-hydroxyphenylglycine (LHPG; UK-25,842) during a search for agents which enhanced carbohydrate utilisation at the expense of that of FFA. Thus, LHPG (0.25–2.0 mM) stimulated the depressed oxidation of [1 or 2-^{14}C]-pyruvate (up to 1.5-fold) or [U-^{14}C]-glucose (up to 3-fold) by diaphragm muscle obtained from fat-fed rats.

In isolated rat hearts, perfused as described previously (Higgins, Morville & Burges, 1978) in the presence of glucose (5.55 mM), insulin (0.1 U/ml) and albumin-bound palmitate (0.8 mM), LHPG (2.0 mM) markedly stimulated glycolytic flux, increased glucose oxidation 4-fold and increased myocardial efficiency (i.e. the ratio $dF/dT.HR/MVO_2$) by about 40%.

The depression of rat myocardial pyruvate dehydrogenase (PDH) activity induced by fat-feeding was reversed in a dose-dependent fashion by parenteral or oral LHPG. For example, the proportion of PDH in the active form was increased from a control level of 10–12% to 28% by LHPG (5×10^{-5} mol/kg i.v.) and to about 80% at a dose of 6×10^{-4} mol/kg s.c. or p.o. However, LHPG had no effect on isolated preparations of PDH, or on its regulatory enzymes, PDH kinase and PDH phosphatase.

The effects of LHPG (2×10^{-5} mol/kg i.v.) on myocardial metabolism *in vivo* were studied in closed-chest, pentobarbitone-anaesthetised dogs by means of coronary sinus sampling,; coronary flow was measured by the hydrogen-clearance technique (Aukland, Bower & Berliner, 1964). Myocardial uptakes of pyruvate and lactate were substantially increased and that of FFA decreased for at least 2 h following LHPG; these effects were enhanced during infusion of isoprenaline. The increase in MVO_2 following isoprenaline was attenuated by 40%, whereas the haemodynamic effects of isoprenaline were unaltered. No changes were observed in the circulating levels of intermediary metabolites.

The hypothesis that the metabolic and oxygen-sparing properties of LHPG would protect against the deleterious effects of FFA during myocardial ischaemia was examined both *in vitro* and *in vivo*. In globally ischaemic, working rat hearts (Waldenström, Hjalmarson, Jodal & Waldenström, 1977) perfused with Krebs-Henseleit solution containing glucose (10 mM), insulin (2 mu/ml) and albumin-bound palmitate (1.5 mM), LHPG (10^{-4} M) reduced the