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

ischaemia-induced release of lactate dehydrogenase from 18.8 ± 2.5 (s.e. mean) to 5.0 ± 0.9 u/gm wet weight ($P < 0.01$). In addition, the recovery of mechanical performance following restoration of coronary perfusion was substantially improved in the presence of LHPG.

The degree of myocardial ischaemic injury following coronary artery occlusion in pentobarbitone-anaesthetised dogs during infusions of isoprenaline, as assessed by epicardial ST-mapping (Maroko *et al.*, 1972) was reduced by approximately 40% after LHPG (2×10^{-5} mol/kg i.v.); the effect persisted for at least 2 h.

Preliminary studies in healthy volunteers (L. Carlson, personal communication) and in patients with coronary artery disease (D. Jewitt, personal communication) have demonstrated myocardial metabolic effects similar to those described above. This profile of activity suggests that LHPG may be useful in the treatment of angina, in limiting infarct size or in reducing the incidence of dysrhythmias following acute myocardial infarction.

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Potential protective value of enhanced myocardial carbohydrate utilisation with reduced free fatty acid uptake after UK 25842 in patients with coronary artery disease

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The influence of UK 25842 (L-4-hydroxyphenylglycine) in a dose of 4–12 mg/kg body weight, given by intravenous infusion over 5 min, on haemodynamics and myocardial metabolism was investigated in 20 patients with obstructive coronary artery disease before and during angina pectoris induced by atrial pacing. Heart rate, intra-cardiac pressures, cardiac output and coronary venous blood flow were measured. Myocardial uptake and extraction ratios (E.R.) of lactate, pyruvate, free fatty acids (F.F.A.), acetoacetate, glycerol and triglycerides were determined from systemic arterial and coronary sinus blood samples.

No major haemodynamic changes or any side effects occurred after UK 25842. Atrial pacing time to the onset of angina increased from 289 ± 33 to 360 ± 35 s UK 25842 (12 mg/kg). Both myocardial F.F.A. uptake and extraction ratios fell. During angina, myocardial F.F.A. E.R. was reduced from 20.2 ± 4.0 to 9.4 ± 2.3% ($P < 0.05$). There was a corresponding increase in myocardial E.R. of lactate (−14.4 ± 11.6 to 11.1 ± 4.2%) and pyruvate (9.3 ± 6.9 to 29.2 ± 5.1%), ($P < 0.01$), with reversal of lactate production in 60% of patients. Myocardial glucose uptake was also increased. This change from F.F.A. to carbohydrate utilisation by the myocardium was confirmed by an increase in the myocardial R.Q. from 0.7 to 0.81 ($P < 0.05$). These changes were associated with a reduction in myocardial oxygen consumption (MVO_2) from 27.4 ± 2.7 to 24.8 ± 2.8 ml/min ($P < 0.05$).

This reduction in MVO_2 associated with enhanced myocardial carbohydrate utilisation, produced by UK 25842, has great potential value not only in patients with angina but also in those with myocardial infarction, when jeopardised areas of the myocardium may be salvaged.