In animals and man the uncharacterized metabolites of propranolol have a considerably longer half-life in the blood than the parent compound. A representation of the time-course relation between the levels of propranolol and these metabolites in blood of normal volunteers is shown in Fig. 4. With renal impairment the level of such metabolites found in the serum is up to three times higher than that seen in normal subjects. They are also more slowly cleared from the blood as seen by an increase in their half-life (Fig. 5). This is demonstrated only after oral administration when the total radioactivity in the blood was measured at 24 hours. Following intravenous dosage measurements were made only up to six hours after administration.

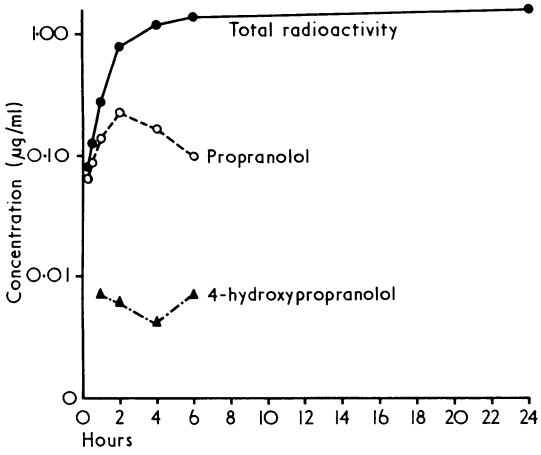

FIG. 5—Time-course relations between levels of propranolol and metabolites in patients with renal impairment.

Discussion

In the presence of renal failure there is a suggestion of delay in absorption of propranolol after an oral dose. There is no delay in the conversion of propranolol to the 4-hydroxymetabolite, nor in the formation of the acid labile conjugates of propranolol and 4-hydroxypropranolol. From observations after intravenous administration of propranolol it is seen that the half-life of both propranolol and the 4-hydroxymetabolite are shorter in the presence of renal functional impairment. There is no current explanation for this phenomenon, particularly as neither of these compounds is excreted to any extent in the urine either in the presence of normal or abnormal renal function.

By using ^{14}C labelling in the ring of the propranolol molecule, it has been possible to observe the handling of the total metabolites of the propranolol. After the disappearance of detectable propranolol and the 4-hydroxy compound the remaining radioactivity is thought to represent their conjugates; the urinary excretion of these compounds is directly related to renal function. The total plasma concentrations of metabolites after a single dose in renal impairment may reach three times that seen in the presence of normal renal function. There is, at present, no convincing evidence that the conjugates have a beta-blocking action. Nevertheless, it might be possible that the conjugates release either propranolol or 4-hydroxypropranolol in sufficient quantities to have a pharmacological effect. Further clinical observations will be necessary to establish whether a dosage regimen in the presence of renal failure will have to take this into account. There are no recognizable side effects due to the accumulation of the conjugates which may occur in such patients.

Higher faecal excretion was observed in the presence of renal failure. This compensatory mechanism is probably of importance in preventing undue accumulation of the conjugate.

In summary, the handling of propranolol in the presence of renal failure is not so altered as to suggest that an alteration in dosage is required from that used in the presence of normal renal function. However, careful long-term studies with continued propranolol dosage for the treatment of hypertension in the presence of renal failure are essential in order to establish this.

We wish to express our thanks for the expert technical help of Mr. R. G. Cooper, Mrs. J. S. Sidall, and Mrs. S. Gillott (I.C.I. Pharmaceuticals Division). We also wish to thank Mr. J. Burns (I.C.I. Pharmaceuticals Division) for the synthesis of radiolabelled propranolol and Mr. David Chew, S.R.N. (St. Philip's Hospital), for organizing the collection of samples.

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Heparin in the Prevention of Deep Vein Thrombosis after Myocardial Infarction

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Summary

A trial of continuous intravenous heparin in the prevention of deep vein thrombosis was undertaken in 48 patients who had suffered a myocardial infarction. Of the 24 control patients who did not receive heparin seven (29%) developed calf vein thrombosis as detected by the radioactive fibrinogen technique. None of the 24 heparinized patients had any evidence of venous thrombosis. This difference is significant at the 1% level.

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Introduction

The M.R.C. (1969) trial of anticoagulant therapy for myocardial infarction showed that its only apparent significant effect was to reduce the incidence of thromboembolism. However, in that trial the diagnosis of deep vein thrombosis was made clinically, and it is now known that this can be misleading (Lambie *et al.*,

1970). Since the introduction of the radioactive fibrinogen test accurate detection of venous thrombosis in the leg has been possible. With this technique a reassessment has been made of the efficacy of heparin in preventing deep vein thrombosis after myocardial infarction.

Patients and Methods

All patients entering the coronary care units of Westminster Hospital and Queen Mary's Hospital, Roehampton, with a clinical diagnosis of myocardial infarction were considered for the trial. Those aged 70 years or more were excluded, as were those known to have a peptic ulcer, hiatus hernia, or severe dyspepsia, and those with a sustained diastolic blood pressure above 120 mm Hg.

After any necessary initial treatment had been given patients were admitted to the trial, provided: (*a*) the clinical diagnosis was still that of myocardial infarction, (*b*) the patient had not been in hospital longer than 12 hours, and (*c*) the estimated time of infarction was within the previous 24 hours.

Allocation to a treatment group was made by drawing a sealed envelope. Separately randomized envelopes were provided at each of the two hospitals. The treatment groups were: (1) *heparin*—5,000 units intravenously as a loading dose, followed by 20,000 units every 12 hours by continuous intravenous infusion, using either an electric (Handley, 1967) or clockwork (Handley, 1970a) infusion pump; and (2) *control*—no anticoagulants.

Heparin was continued for two weeks, the dose being adjusted as necessary to maintain the whole-blood clotting time between two-and-a-half and three-and-a-half times the normal. Since active treatment involved a prolonged intravenous infusion double-blind control was not considered justified. All the patients remained in bed for at least two weeks; they were instructed to exercise their legs, but were given no other leg physiotherapy. As soon as possible after admission to the trial all patients were given an intravenous injection of 100 μCi of ^{125}I-labelled human fibrinogen (Radiochemical Centre, Amersham). The same dose was given about a week later to maintain the level of radioactivity. Oral potassium iodide 120 mg daily was given for three weeks to block thyroid uptake of the radioisotope. The patients' lower limbs were examined for deep vein thrombosis on alternate days for two weeks with a Pitman 235 isotope-localization monitor. The technique was based on that of Kakkar *et al.* (1970). The counts at 6-cm intervals from inguinal ligament to ankle were expressed as percentages of the precordial count. A 20% difference between similar positions on each limb, or adjacent positions on the same limb, is considered diagnostic of venous thrombosis, provided this difference persists over the course of three days or more (Kakkar *et al.*, 1970; Pai and Negus, 1971).

Results

Sixty patients were admitted to the trial. A diagnosis of myocardial infarction was considered proved only if characteristic changes occurred in the electrocardiogram (Wood, 1968) and/or serum levels of aspartate aminotransferase and serum hydroxybutyrate dehydrogenase. Seven patients were subsequently withdrawn because proof of infarction was lacking. A further four died and in one heparin was stopped because of frank haematuria. None of the patients who were withdrawn from the trial (Table I) had any evidence of venous thrombosis or pulmonary embolism. This left 24 in each of the treatment groups. The two groups were well matched with regard to age, sex, presence of varicose veins, severity of infarction, previous thromboembolic episodes, and obesity (Table II).

During the course of the two-week follow-up period seven (29%) of the control patients developed evidence of deep vein thrombosis. Thrombosis was not detected in any of the patients receiving heparin. This difference is significant at the 1% level ($P = 0.009$ by Fisher's Exact Test; twice the single-tail probability). All the thromboses were found below the knee; one occurred two days after admission, three on Day 4, one on Day 5, and two on Day 10. Four patients developed bilateral thrombosis. Two of those with positive tests also had clinical and radiological evidence of pulmonary infarction. One died three weeks after admission to hospital and necropsy confirmed the presence of multiple pulmonary emboli and venous thrombosis below the iliofemoral region.

Apart from the one patient who had haematuria, there were no other haemorrhagic complications.

TABLE I—*Patients Withdrawn from Trial*

	Treatment Group	
	Heparin	Control
Diagnosis of myocardial infarction not proved	3	4
Died	2	2
Haemorrhagic complication	1	0
	6	6

TABLE II—*Comparison of Patients in Each Treatment Group*

		Heparin	Control
Age	<50 years	4	3
	50-54 „	4	6
	55-59 „	6	5
	60-64 „	8	5
	65-69 „	2	5
Sex	Male	22	20
	Female	2	4
Significant varicose veins		5	4
Mean prognostic indices	Peel *et al.* (1962)	9·4	8·6
	Norris *et al.* (1969)	4·8	4·9
Previous thromboembolic episode		2	1
Obesity—10% or more above average weight for age, sex and height (Documenta Geigy, 1970)		5	5

Discussion

The radioactive fibrinogen test has been shown to correlate well with venographic evidence of lower limb deep vein thrombosis (Negus *et al.*, 1968; Browse *et al.*, 1971). With this technique the incidence of venous thrombosis in the control group was 29%. This is slightly lower than that reported by other authors (Murray *et al.*, 1970; Maurer *et al.*, 1971; Nicolaides *et al.*, 1971), presumably because they included the high-risk older age group (Maurer *et al.*, 1971).

In most published trials of anticoagulant therapy after myocardial infarction heparin has been used only to cover the period until an oral anticoagulant has had time to produce its effect. There is laboratory evidence that heparin is the better prophylactic against venous thrombosis (Johnson and Reeve, 1969).

With the use of an intravenous infusion pump heparin may be given for prolonged periods without the problems of fluctuation of the infusion rate and fluid overload associated with a drip infusion (Handley, 1967; Martyn and Janes, 1971). Some authors (Flute, 1969; Kakkar, 1971) allege that continuous infusion of heparin produces more episodes of bleeding than intermittent administration. This has not been supported by experimental evidence (Handley, 1970b). Haemorrhage was not a serious problem in the present study. One patient developed haematuria, but this was not severe and heparin might well have been continued had it not already been given for nearly a week, thus covering the period of maximum risk (Maurer *et al.*, 1971).

The question arises whether calf vein thromboses, demonstrated by the radioactive fibrinogen technique, are of clinical importance. It has been suggested that there is a significant risk of pulmonary embolism only if clot occurs in the veins above the knee (Kakkar *et al.*, 1969). However, in the two patients in the

present series who developed pulmonary emboli deep vein thrombosis was apparently confined to the calf; in the patient who died this was confirmed at necropsy. These findings agree with those of Murray *et al.* (1970); they found evidence of pulmonary embolism after myocardial infarction in 4 out of 12 patients with thrombosis below the knee, but in none of those with normal radioactivity counts. It is accepted that the fibrinogen test cannot detect thrombi above mid-thigh level with any degree of accuracy (Flanc *et al.*, 1968; Negus and Evans, 1971), so some of these patients may also have had undetected iliofemoral thrombosis. Notwithstanding this, the only patients in either series who had pulmonary emboli also had fibrinogen-detectable thrombosis of the calf vein. These thrombi, therefore, seem worth preventing. In the present trial heparin, given by continuous intravenous infusion, seemed to be capable of doing this effectively.

The decision to give this drug routinely after myocardial infarction is still a difficult one, which would be easier to make if a safer regimen could be shown to be effective. Sharnoff and DeBlasio (1970) and Williams (1971) reported favourably on low-dose subcutaneous heparin prophylaxis in surgical cases. The possibility of using such a regimen after myocardial infarction is being explored.

We should like to thank the physicians of the Westminster Hospital Group for allowing us to study patients under their care; and Dr. Ian Sutherland for statistical advice. A.J.H. is in receipt of the H.A.M. Thompson Fellowship from the Royal College of Physicians of London. We are grateful to the British Heart Foundation, the Peel Medical Research Trust, and the Board of Governors of Westminster Hospital for financial help.

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Splenic Atrophy in Dermatitis Herpetiformis

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Summary

Twenty-four patients with dermatitis herpetiformis were investigated for splenic atrophy by splenic scan and clearance of ^{51}Cr-labelled heat-damaged red blood cells. Eight of them had definite splenic atrophy. The average splenic cross-sectional area of the remaining 16 with normal clearance times was substantially smaller than normal, suggesting some degree of splenic atrophy. No relationship of splenic hypofunction to intestinal biopsy findings, folate status, reticulin antibody, or treatment with a gluten-free diet or dapsone was evident.

Introduction

Considerable interest has been shown in the recent finding that patients with dermatitis herpetiformis show an enteropathy similar to that of coeliac disease (Marks *et al.*, 1966; Fraser *et al.*, 1967; Fry *et al.*, 1967; Brow *et al.*, 1971). Because they found that both the skin and gut lesions improved when patients with dermatitis herpetiformis received a gluten-free diet, and relapsed on reintroduction of gluten, Fry *et al.* (1969) suggested a direct relation between the skin and small intestine in this disorder.

Seah *et al.* (1971a, 1971b) demonstrated the presence of reticulin antibodies in the sera of a proportion of patients with both dermatitis herpetiformis and coeliac disease. Since the spleen is the largest organized collection of lymphoreticular tissue in the body and the occurrence of splenic atrophy in coeliac disease is well established (Martin and Bell, 1965; McCarthy *et al.*, 1966; Ferguson *et al.*, 1970; Marsh and Stewart, 1970), we have investigated splenic size and function in a group of patients with dermatitis herpetiformis to further clarify the relation between dermatitis herpetiformis and coeliac disease.

Patients and Methods

Twenty-four consecutive patients attending a dermatitis herpetiformis clinic were studied (see Table). There were 14 men aged 28-75 (average 52) and 10 women aged 26-65 (average 38). At the time of these studies seven patients had their rash controlled by a gluten-free diet alone, nine were receiving a gluten-free diet, and dapsone, and eight were receiving dapsone only.

Assessment of Splenic Function.—Autologous red cells were labelled with 150 μCi of ^{51}Cr and damaged by heating for 20 minutes at 49·5°C. Splenic function was assessed by measuring the rate of clearance of the ^{51}Cr-labelled cells. After the intravenous injection of these cells, blood samples were taken at 3, 10, 20, 30, and 60 minutes, haemolysed, and radioactivity counted

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