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Flexible induction dose regimen for warfarin and prediction of maintenance dose

A FENNERTY, J DOLBEN, P THOMAS, G BACKHOUSE, D P BENTLEY, I A CAMPBELL, P A ROUTLEDGE

Abstract

Fifty patients with venous thromboembolic disease being treated by heparin infusion received a three day warfarin induction regimen tailored according to the prothrombin time (British comparative ratio) measured on days 2 and 3. A prediction of the final maintenance dose of warfarin was made on the basis of a prothrombin time measured on day 4. All patients were safely anticoagulated by day 6, and the prediction was accurate to within 1 mg in 46 patients. Predicted and actual maintenance doses were closely related ($r=0.867$; $n=50$; $p<0.001$).

This scheme should prove helpful in the control of anticoagulation, particularly in patients likely to be sensitive to warfarin, and should shorten hospital stay.

Departments of Medicine, Haematology, and Thoracic Medicine, Llandough Hospital, Penarth, S Glamorgan

A FENNERTY, MB, MRCP, registrar
 J DOLBEN, MB, BS, senior house officer
 P THOMAS, MB, BS, senior house officer
 G BACKHOUSE, FIMLS, technician
 D P BENTLEY, MRCP, MRCPATH, consultant haematologist
 I A CAMPBELL, MD, FRCPED, consultant thoracic physician

Department of Pharmacology and Therapeutics, Welsh National School of Medicine, Heath Park, Cardiff CF4 4XN

P A ROUTLEDGE, MD, MRCP, consultant physician and senior lecturer

Correspondence to: Dr P A Routledge.

Introduction

A relation between the prothrombin time after a loading dose of warfarin and the eventual maintenance dose of warfarin has been well described,¹⁻⁵ and from the derived regression equations a prediction can be made of the maintenance warfarin dose. Until recently the *British National Formulary* suggested a warfarin loading regimen of 10 mg on each of three consecutive days, but this may cause up to 35% of patients to be over anticoagulated by the fourth day.^{6,7} Patients' stay in hospital may be unnecessarily prolonged while their prothrombin time falls to within the therapeutic range and while a tentative maintenance warfarin dose is established.

The current edition of the *British National Formulary* now recommends an induction dose of 10 mg warfarin daily for three days with British comparative ratios measured before the first dose and on the second and third days, so that the subsequent warfarin dose may be modified if required.⁸ No guidelines on dose adjustment are given.

We have attempted to design a flexible three day loading dose regimen, aimed at bringing the British comparative ratio smoothly into the therapeutic range, and to predict the maintenance dose of warfarin on the basis of a British comparative ratio measured on day 4.

Method

Patients with venous thromboembolic disease presenting to physicians, surgeons, and gynaecologists at Llandough Hospital were heparinised using a continuous intravenous infusion maintaining the kaolin-cephalin clotting time (Bell and Alton platelet substitute;

Diagnostic Reagents Ltd, Oxon) within 1.5 and 2.5 times control (roughly 40 s). Each patient received a single 10 mg dose of warfarin at 5 pm on the third day of the heparin infusion (warfarin day 1). Sixteen hours later the British comparative ratio was measured using the Manchester reagent (control time roughly 12 s), and at 5 pm on warfarin day 2 the second dose of warfarin was given according to the schedule set out in the table. The procedure was repeated for the third induction dose on warfarin day 3, and the next day (warfarin day 4) the final maintenance dose of warfarin was predicted (see table) on the basis of a British comparative ratio measured that morning.

Tailored loading dose schedule for warfarin administration according to British comparative ratio

Day	British comparative ratio	Warfarin dose (mg)
1	<1.4	10.0
2 (16 hours after first 10 mg dose)	<1.8	10.0
	1.8	1.0
	>1.8	0.5
	<2.0	10.0
3 (16 hours after second dose)	2.0-2.1	5.0
	2.2-2.3	4.5
	2.4-2.5	4.0
	2.6-2.7	3.5
	2.8-2.9	3.0
	3.0-3.1	2.5
	3.2-3.3	2.0
	3.4	1.5
	3.5	1.0
	3.6-4.0	0.5
>4.0	Nil	
4 (16 hours after third dose)	<1.4	Predicted maintenance dose >8.0
	1.4	8.0
	1.5	7.5
	1.6-1.7	7.0
	1.8	6.5
	1.9	6.0
	2.0-2.1	5.5
	2.2-2.3	5.0
	2.4-2.6	4.5
	2.7-3.0	4.0
	3.1-3.5	3.5
	3.6-4.0	3.0
	4.1-4.5	Miss out next day's dose, then give 2 mg
	>4.5	Miss out 2 days' doses, then give 1 mg.

The schedule was calculated from the data of Routledge *et al* using the thrombotest to predict maintenance dose.¹ All British comparative ratios were measured while the patients were receiving heparin. The maintenance dose (defined as that giving a therapeutic ratio⁹—that is, between 2.0 and 4.0—on three consecutive occasions, each separated by at least 24 hours) was determined independently by the clinician in charge of the patient. The relation between predicted and actual maintenance dose was examined by linear least squares correlation analysis.

Results

Fifty consecutive patients were studied. In addition to a diagnosis of venous thromboembolic disease, three patients had congestive cardiac failure and two had chronic liver disease. Mean age of the group was 52 years (range 24-81), and 29 were men.

All patients received two 10 mg induction doses of warfarin, and by the third day 26 patients were already in the therapeutic range; of the remainder, three were above the range (ratio 4.0-5.0) and 21 below the range. By warfarin day 4, 32 patients were within the therapeutic range, 15 below the range, and the three patients above the range on day 3 continued above the range despite missing a warfarin dose. All but two patients were within the therapeutic range by warfarin day 5 and all by warfarin day 6. The predicted maintenance dose of warfarin correlated closely with the actual maintenance dose ($r=0.867$; $p<0.001$) (figure).

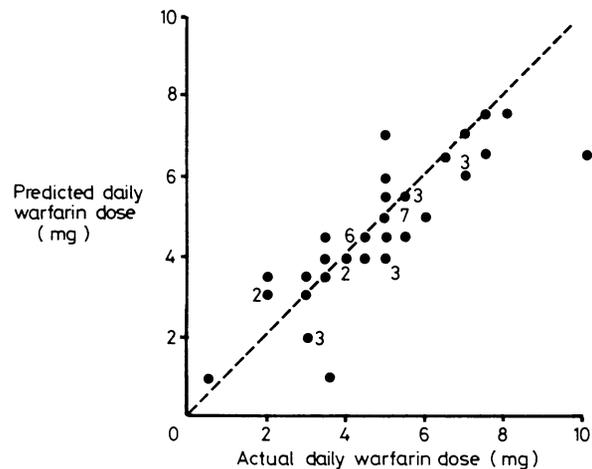
Patients first received what proved to be their maintenance dose of warfarin a median of five days after beginning the drug. The predicted dose was exact in 26 patients and accurate to within 1 mg in 46. Patients were subsequently followed up for a median of 21 days,

and at the end of follow up 44 of the patients were within the therapeutic range and taking a dose of warfarin within 1 mg of the predicted dose. The mean difference between the actual and predicted daily maintenance doses was -0.12 (SE 0.12) mg.

Discussion

Several studies have examined the feasibility of predicting warfarin requirements¹⁻⁵ but none has enabled the physician to tailor the loading dose according to the individual patient's need.

The *British National Formulary* now recommends that the British comparative ratio should be measured daily during the induction phase but no guidelines concerning dosage adjustment are given. Our scheme gives effective guidance during the induction period, enabling most patients to be safely anticoagulated rapidly and avoiding the overanticoagulation which



Relation between predicted and actual daily warfarin dose. Hatched line represents line of identity.

occurs in up to 35% of patients who receive a fixed, unmonitored dose of 10 mg warfarin on three consecutive days.^{6,7} The scheme may be particularly useful in those patients likely to be sensitive to warfarin—for example, the elderly and patients with liver disease or congestive heart failure.¹⁰ We also find that the maintenance dose of warfarin may be predicted using the British comparative ratio on day 4 even when a variable induction dose is used and that this prediction indicates the maintenance requirements for several weeks after the initiation of treatment.

A flexible induction regimen depends on the measurement of the British comparative ratio while the patient is still receiving heparin; as already shown, however, provided that the kaolin-cephalin clotting time is within the therapeutic range of 1.5 to 2.5 times control the ratio is unlikely to be raised by more than 10%. In the event of a prolonged kaolin-cephalin clotting time protamine (0.4 μ g) may be added to the sample (1 ml) to neutralise the effect of heparin.¹¹

None of the patients in this study had their dose of warfarin modified on day 2. Nevertheless, we think that this part of the scheme (see table) should be retained. One patient who was excluded from the study because of non-adherence to the protocol was given a second 10 mg induction dose despite having a British comparative ratio of 1.83 after the first 10 mg dose of warfarin. The ratio after the second 10 mg dose rose to 6.7.

We also recommend measurement of the British comparative ratio on warfarin day 1 to identify patients likely to be particularly sensitive to warfarin. Unfortunately, this value was obtained

for only a third of our patients. Only one subject had a pre-treatment ratio greater than 1.4 and, although she was not overanticoagulated after the first 10 mg dose, she became overanticoagulated towards the end of the induction phase. We therefore recommend that any patient with a baseline ratio of 1.4 or greater—provided that this is not due to excessive anticoagulation by heparin¹¹—should have a lower initial induction dose of warfarin than suggested in the table. The subsequent guidelines will of course not apply to such patients, and doses will have to be chosen empirically.

This scheme appears to offer a useful means of predicting the maintenance dose of warfarin in a broad range of patients. Also the incidence of potentially dangerous overanticoagulation and the duration of inpatient stay should be reduced. The British comparative ratio should still be monitored regularly after the patient has been discharged from hospital, however, because of the many factors that may alter warfarin dose requirements during prolonged administration.

We thank the consultant physicians, surgeons, and gynaecologists at Llandough Hospital for allowing us to study patients under their care and their junior staff for their cooperation.

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SHORT REPORTS

Poisoning with cadmium fumes after smelting lead

Inhalation of cadmium fumes may cause pneumonitis and even death, but only three deaths have been reported in the United Kingdom within the past 17 years.¹⁻³ Crude lead and lead ores are usually contaminated with cadmium, and people working with lead may be exposed to cadmium fumes.

Case report

A fit 36 year old man was admitted with a 24 hour history of vomiting and profuse watery diarrhoea. He had generalised diffuse, dull, aching abdominal pains, a severe headache, and generalised myalgia with tightness of his chest. He was slightly confused, restless, and dehydrated but had no fever, lymphadenopathy, or rash. He was shocked, with a regular pulse rate of 108 beats/min and blood pressure of 80/40 mm Hg. His chest was clear. His abdomen was diffusely tender without peritonism. Severe gastroenteritis was diagnosed, and he was treated symptomatically. Initial investigations showed blood urea concentration 15.7 mmol/l (94 mg/100 ml), serum creatinine concentration 470 μ mol/l (5.3 mg/100 ml), serum sodium concentration 138 mmol(mEq)/l, serum potassium concentration 3.6 mmol(mEq)/l, serum amylase activity 710 U/l, haemoglobin concentration 14.2 g/dl, and white cell count $8.9 \times 10^9/l$. A chest radiograph was normal. Blood cultures and viral agglutinin titres yielded negative results.

Despite adequate rehydration he produced only 50 ml of urine over the next 18 hours. He became increasingly dyspnoeic and developed bilateral fine basal crepitations and radiological appearances consistent with gross pulmonary oedema. Electrocardiography showed varying rhythms of atrial fibrillation, nodal rhythm, and sinus tachycardia. He became feverish and his myalgia worsened. Investigations showed blood urea concentration 26.1 mmol/l (157 mg/100 ml), serum creatinine concentration 697 μ mol/l (7.9 mg/100 ml), sodium concentration 136 mmol/l, potassium concentration 6 mmol/l, bicarbonate concentration 18 mmol(mEq)/l, calcium concentration 1.7 mmol/l (6.8 mg/100 ml), and haemoglobin concentration 13.2 g/dl. Twenty four hours after admission we learnt that he had been smelting about 182 kg lead for about 24 hours in an enclosed environment without wearing adequate protective clothing. He had felt unwell towards the end of that session. Acute lead poisoning from inhaled fumes seemed likely from the clinical picture. Microcup absorption spectrometry showed blood lead and cadmium concentrations to be 0.5 μ mol (10.4 μ g/100 ml) (normal < 1.8 μ mol (< 37 μ g/100 ml)) and 32 nmol/l (0.36 μ g/100 ml) (normal < 10 nmol (< 0.11 μ g/100 ml)) respectively and urinary lead and cadmium concentrations to be < 100 nmol/l (< 2.1 μ g/100 ml) (normal < 400 nmol (< 8.3 μ g/100 ml)) and 102 nmol/l (1.1 μ g/100 ml) (normal < 10 nmol (0.11 μ g/100 ml)) respectively. As he was anuric chelating agents were not indicated. Although he was treated with peritoneal dialysis, his condition deteriorated. He remained dyspnoeic and cyanotic and died 72 hours later.

On postmortem examination his lung and gastric mucosae were appreciably

congested, with moderate hyperaemia throughout the large and small intestines and slight cerebral congestion. Histological investigation showed mild hepatic fatty infiltration and severe acute centrilobular necrosis; acute cellular necrosis in the loops of Henle; mild interstitial oedema, infiltration with eosinophils, lymphocytes, and histiocytes in the myocardium; depletion of adrenal lipid content and mild focal haemorrhages; and congestion and acute inflammatory cell infiltration of the spleen.

Samples of tissue were analysed for lead and cadmium concentrations (table). Samples from a control patient without renal disease were analysed simultaneously.

Tissue concentrations of lead and cadmium in samples taken post mortem from our patient and from a 60 year old man without renal disease

	Lead (ppm)		Cadmium (ppm)	
	Patient	Control	Patient	Control
Kidney	1.00	0.97	67.95	9.38
Liver	1.66	1.28	1.37	0.63
Lung	0.79	0.87	0.82	0.086
Skin	0.89	0.45	0.24	0.035
Muscle	0.67	0.80	0.21	0.058
Heart	0.73		0.42	
Brain	0.60	0.92	0.08	0.066
Stomach	0.94		0.43	
Small intestine	0.85		0.90	
Spleen		0.92		0.062

ppm = Parts per million.

Comment

Clinical and histological evidence was consistent with acute poisoning with cadmium after lead smelting. Cadmium is more volatile than lead and has a much lower boiling point, hence fumes produced when impure lead is smelted will contain an increased proportion of cadmium.

Tissue and body fluid cadmium concentrations after exposure to cadmium fumes are not necessarily greater than those found in chronic cadmium poisoning.¹⁻³ Concentrations in the liver and lungs in our patient were similar to those in other affected subjects, and the raised kidney cadmium concentration was probably secondary to previous chronic occupational exposure. There was evidence, however, of recent exposure, with a considerably increased urinary cadmium concentration and accumulation in other tissues. When a patient is known to have been exposed to lead fumes, concurrent exposure to cadmium should be considered, particularly if an acute illness affecting the lungs suddenly develops.