tation, where there is only one long term survivor (J Cooper, personal communication). The main advantage of the combined operation is that all diseased tissue is removed and so recurrent infection and an imbalance of ventilation and perfusion from the remaining lung are avoided. In addition, coronary bronchial vascular collaterals, shown at coronary arteriography in these patients, may aid healing of the trachea. Thus no early or late complications have occurred as a result of problems with the tracheal anastomosis after heart and lung transplantation in the Stanford series, which is in sharp contrast to the experience after isolated lung transplantation.[4]

But perhaps the most important practical problem for the future of combined heart and lung transplantation is the lack of suitable donors. Pulmonary changes occur early in patients with brain death as a result of aspiration or infection or both and may be complicated by the development of neurogenic pulmonary oedema. Satisfactory preservation and storage of the heart and lung block have not been achieved, and the donor must be moved to the recipient hospital before the organs are removed. This may result in emotional and logistical difficulties but donors with normal lung function are rare and suitable cases should perhaps be considered for heart and lung donation as a priority. This does not of course preclude the donation of other organs.

It is not only patients with pulmonary hypertension who might benefit from combined heart and lung transplantation. Advances in the diagnosis and treatment of lung rejection should make the procedure a realistic treatment for many other patients with pulmonary failure—especially when improved techniques for preserving the integrity of the lungs result in an increased number of suitable donors.

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Regular Review

Therapeutic ranges in anticoagulant administration

LEON POLLER

Clinicians around the world have reawakened their interest in the use of anticoagulants as less intense ("low dose") therapeutic regimens have come into use. Among the factors that have contributed to this change of attitude have been cumulative experience with national systems of anticoagulant control (particularly in Britain and the Netherlands[1]), new clinical trials, and the wide availability of a standardised thromboplastin, British comparative thromboplastin and its routine counterpart Manchester comparative reagent.

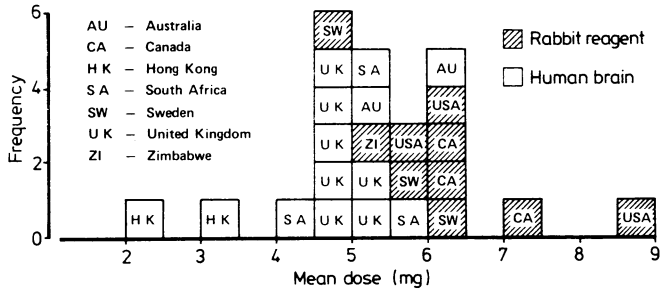
Therapeutic ranges of anticoagulation can be established only by planned randomised clinical trials in the prevention or treatment of the relevant thrombotic disorder. These must be of sufficient size and duration to assess the clinically relevant end point. Many of the early clinical trials overlooked the methods used for laboratory control. The effects on the anticoagulant dose of the technique used for measuring prothrombin time and its method of reporting are of paramount importance. Regimens based on techniques relatively insensitive to the coumarin dependent clotting factors II, VII, and X invariably result in a more intense coagulation defect.[2,3]

A recent international survey of current practice showed that physicians tend to be conservative in dosage with more intense regimens, while important differences in mean dosages may still be seen among countries (see figure).[2] This review will look at current techniques for monitoring anticoagulant treatments and at the main clinical indications.

Therapeutic ranges

The lower limit of a therapeutic range should be the minimum coagulation defect necessary for the prevention of recurrence or extension of an established thrombotic episode. There is no virtue in choosing a coagulation defect

which is safe from haemorrhage if it does not protect against thrombosis. With a prophylactic regimen the upper limit should be the maximum coagulation defect which prevents thrombosis but does not cause either spontaneous bleeding or excessive bleeding in response to haemostatic challenge.



Mean dosages of warfarin used in various countries. (Results of an international survey.[2])

In normal practice clinicians have to accept that the greater the chosen coagulation defect inevitably the higher must be the incidence of haemorrhage. The incidence of bleeding side effects can be kept low in long term administration—one episode in 23 treatment years in Britain[4] and one severe event in 25 treatment years in the Netherlands Thrombosis Service.[5] Table I gives the recommendations on treatment ranges of the British Society for Haematology. Whether even further reduction is possible without loss of protection, by lowering the recommended upper limits given in table I, remains to be established.

TABLE I—*Proposed therapeutic ranges (British Society for Haematology guidelines on oral anticoagulants, 1984)*

British ratio (INR)*	Clinical state
2·0-2·5	Prophylaxis of deep vein thrombosis including high risk surgery
2·0-3·0	Treatment of deep vein thrombosis, pulmonary embolism, transient ischaemic attacks
3·0-4·5	Recurrent deep vein thrombosis and pulmonary embolism; arterial disease including myocardial infarction; arterial grafts; cardiac prosthetic valves and grafts

*British ratios and international normalised ratios (INR) are virtually identical within the therapeutic range.

The British Society for Haematology based its proposals on clinical trial reports (for example, Sevitt and Gallagher, Taberner *et al*, and Hull *et al*),[3 6-8] cumulative experience of the British system for anticoagulant control, and a national survey of current practice in 1983. Whereas the limits for the prophylaxis and the treatment of venous thrombosis have been clearly defined, they are less clear for arterial thrombosis.

The introduction of a new World Health Organisation system for international standardisation of the prothrombin time has allowed comparison of anticoagulant control regimens based on a common system of reporting, termed international normalised ratios (INR).[9] All manufacturers are now expected to calibrate their reagents and provide the relevant international normalised ratio values, making it easier to derive more precise therapeutic equivalents with individual reagents. The system can be adopted easily in Britain because British ratios and the international normalised ratios are virtually identical over the therapeutic range. For the different Quick test thromboplastins Wessler has provided a useful simplified guide to equivalents to the British range of 2·0 to 4·0.[10 11] This is reproduced in table II with the addition of international normalised ratio equivalents.

TABLE II—*Therapeutic ranges for various thromboplastins equivalent to conventional range with British comparative thromboplastin (ratio 2·0-4·0) (modified from Wessler[19])*

Reagent	Range of ratios
British comparative thromboplastin (INR)	2·0-4·0
Thrombotest	2·0-4·0
Rabbit thromboplastin—brain/lung	1·5-2·1
Rabbit thromboplastin—brain	1·3-1·7

Some thromboplastin reagents show poor sensitivity to the coumarin dependent clotting factors—a problem which is only partly resolved by the international normalised ratio system because the correlations of values may be poor, particularly in the induction phase of anticoagulation. When plasma samples were tested in parallel with Manchester comparative reagent which gave a ratio of 2·0 with Simplastin the results showed a wide scatter, with extremes of 25 to 100 seconds (INR 2·1 to 8·5). The explanation lies in the relative insensitivity of the Simplastin rabbit brain reagent to the predominant depression of factor VII which is seen in the first few days of treatment owing to the short half life of this clotting factor. Efforts must be made by the manufacturers to improve their reagents' sensitivity to the coumarin dependent clotting factors (II, VII, and X) measured by the prothrombin time if we are to achieve safer and more effective anticoagulation.

When oral anticoagulants were first introduced for myocardial infarction the claims made were exaggerated; but, as Mitchell commented, the discipline required for sound clinical trials had not been developed at that time.[12]

Furthermore, the introduction of new laboratory methods (such as the "P+P test" and Thrombotest) specifically designed for control of oral anticoagulants led organisers of trials in the 1960s—unsuspectingly—to provide a less intense coagulation defect than previously. For example, dosage in an important Danish study based on the P and P test aimed at 10-25% activity, which is equivalent to only 1·2 to 1·5 in terms of British ratios/international normalised ratios.[13] The British Medical Research Council's short term study published in 1969 was regarded as a model of trial design but regrettably used a homoeopathic coagulation defect of 15% Thrombotest activity (about 1·6 British ratio/international normalised ratio[14]) in place of the more intense defect in its previous, more favourable long term studies.[15 16] The importance of this change escaped the organisers of the trial, though they were concerned by the resulting paradox. By the early 1970s few physicians were prepared to subject their patients with myocardial infarction to a potentially dangerous form of long term treatment with benefits that seemed doubtful or at best marginal.

At this time new arguments but no new data were put forward.[17-20] The United States Veterans study used thromboembolism as its main end point and found a reduction in strokes and systemic embolism, though the mortality was little different in the treated patients and controls.[21] In a cumulative review Douglas and McNicol concluded that 40 to 50 lives would be saved for every 1000

patients treated, with greater benefit in men and younger age groups.[22]

The report of the Sixty-plus Reinfarction Group of the Netherlands Thrombosis Service has revived the issue.[5] This was a well designed randomised double blind study of 878 patients (mean age 61·6 years with 85% men) based on sound clinical and laboratory control. The target therapeutic range of 5% to 10% Thrombotest activity (INR 2·0 to 4·5) was achieved in 72% of tests. All patients had, however, received long term treatment with anticoagulants for at least six months before randomisation. The mortality was 13·4% in a two year follow up in the placebo group but 7·6% in those treated with coumarin. The cynic could reasonably argue that the conclusion to be drawn from the sixty plus study is that once oral anticoagulant treatment has been established for six months it is dangerous to stop. Favourable results from current Norwegian and Dutch studies will therefore be needed before the use of long term anticoagulation is again to be considered routinely for myocardial infarction or in addition to alternative treatments such as intracoronary streptokinase[23] or tissue type plasminogen activator.[24]

Furthermore, the reported low incidence of severe haemorrhagic events (one in 25 treatment years) in the Dutch study would be unlikely to be matched in countries where more intense anticoagulation is still practised—but the new international normalised ratio system may go some way to overcome this difficulty.

Venous thrombosis and pulmonary embolism

Administration of oral anticoagulants to patients after deep vein thrombosis with or without associated pulmonary embolism has been accepted clinical practice since the early 1940s.

The only controlled prospective randomised trial among the early studies was reported from Britain, but it has been criticised because of the small numbers—indeed the trial was abandoned before completion because of the apparent higher risk in the untreated group.[25] Since that time on ethical grounds no investigators have felt justified in including untreated controls in clinical trials of anticoagulants in deep vein thrombosis, but the validity of the treatment has been challenged repeatedly.

In fact, there have been some studies at McMaster University which have clarified the value of warfarin in deep vein thrombosis.[3 8 26] Warfarin was given to patients with acute deep vein thrombosis after 14 days of administration of heparin. In the first study the patients were randomised into two groups given warfarin and low dose subcutaneous heparin (5000 units three times a day). There were nine recurrences of deep vein thrombosis in 35 patients given low dose heparin but no recurrence in the 33 patients given warfarin.[26] In this study and the follow up study using the same target prothrombin ratios with Simplastin, 1·5 to 2·0 (INR equivalent 3·0-4·5), the incidence of bleeding with oral anticoagulants was 21% to 22%.[3] Bleeding complications are, however, relatively uncommon using the therapeutic ranges usual in Britain. In the third randomised study a less intense, British type of range based on a 2·0 to 2·5 ratio range with Manchester comparative reagent (INR 2·0-2·5) was compared with the 1·5 to 2·0 Simplastin ratio range.[8] The incidence of bleeding was 22·4% with Simplastin control but only 4·3% with the Manchester comparative reagent control ($p=0·015$), though both regimens were equally successful in preventing rethrombosis. The mean doses of warfarin were 5·8 mg and 4·9 mg respectively. The McMaster trials have convincingly shown not only the value of warfarin in the treatment of deep vein thrombosis but also the greater safety from haemorrhage that comes from a combination of a sensitive control technique with an international normalised ratio range of 2·0 to 2·5. Unfortunately, with most of the present commercial reagents overdosage may still occur even with this low range, particularly in the early days of treatment, owing to their relative insensitivity to the coumarin induced defect at this stage.[3]

Prophylaxis against deep vein thrombosis

Oral anticoagulants are still regarded as the most certain protection against deep vein thrombosis, though they have not proved popular with surgeons because of their fear of bleeding.[27] Low dose heparin and some non-invasive procedures have therefore been preferred—despite their failures in high risk patients.

The first controlled study of oral anticoagulants was at the Birmingham Accident Hospital.[6] Three hundred patients with recent hip fractures were allocated to oral anticoagulant or control groups according to day of admission. The target for anticoagulant control was a ratio of 2·0 to 3·0 using a Quick test thromboplastin matched against Manchester comparative reagent (INR equivalent 2·0 to 3·0). The incidence of clinical deep vein thrombosis was reduced from 28·7% to 2·7% by oral anticoagulants; the more reliable necropsy data indicated a reduction of deep vein thrombosis from 83% to 14%. In a further controlled necropsy study Sevitt and Innes found that a 10–25% Thrombotest range of activity was inadequate to protect against deep vein thrombosis but ratios (INR) greater than 2·0 with the Quick test calibrated against Manchester comparative reagent did give protection.[28]

Taberner *et al* carried out a controlled randomised study which showed the effectiveness of oral anticoagulation in prophylaxis in a group of patients at moderate risk undergoing surgery for gynaecological disorders.[7] The therapeutic range target of 2·0 to 2·5 with Manchester comparative reagent (INR 2·0 to 2·5) was achieved preoperatively. This reduced the incidence of deep vein thrombosis without increasing operative bleeding. Probably the best compromise is to use low dose heparin prophylaxis for patients in low and moderate risk categories and warfarin for the high risk categories—hip surgery, fracture of the femur, and malignancies.

Prosthetic heart valves

Oral anticoagulants are given long term, usually on a lifelong basis, for patients with prosthetic heart valves. The indications are strong for patients with mitral valve prostheses, whereas tissue valves are safer, particularly in the aortic position, and may not need anticoagulant protection.[29] The therapeutic range of 3·0 to 4·5 British ratios (INR) given in table I represents current practice based on the 1983 survey from 270 major British centres. There have been no controlled randomised trials: the decision on anticoagulation is based on general clinical experience of the high incidence of embolic events in unprotected patients and their reduction by warfarin. Randomised studies have been limited to the evaluation of the benefit of antiplatelet drugs as an adjunct to warfarin. It has rarely been possible to discern whether

aspirin or dipyridamole gives real benefit or merely compensates for inadequate oral anticoagulation. For instance, the Mayo Clinic study compared the effects of warfarin and aspirin and warfarin and dipyridamole against a non-randomised control group of patients with mechanical prosthetic heart valves receiving warfarin alone.[30] The report does not state the intensity of warfarin anticoagulation, but the very low incidence of excessive bleeding requiring blood transfusion or hospitalisation (1·2 per 100 patient years) in the warfarin control group suggests that the treatment may have been less intense than the moderate dose ("low dose") regimens current in Britain and the Netherlands. The correct intensity of anticoagulation for prosthetic heart valves therefore still remains to be established but may be resolved by studies currently in progress.

Embolism

The recommended range shown in table I for rheumatic heart disease with embolism and atrial fibrillation with embolic complications is based on the current practice. Strong evidence for the value of oral anticoagulants was put forward in early trials and has remained unchallenged. Embolic incidents per treatment months were compared with months "off treatment" in the same patients. The results were so favourable that adequate randomised studies have never been performed.

The same strictures on lack of adequate trials apply to treatment for systemic embolism with a presumed cardiac source, but routine practice is to give prolonged long term treatment after a single episode using the range 3·0 to 4·5 British ratios (INR).

In this report international normalised ratio equivalents for the clinical trials are given retrospectively in the light of contemporaneous calibrations of prothrombin time methods against the Quick test using British comparative thromboplastin/Manchester comparative reagent.

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