Prospective Assessment of a Nomogram for the Initiation of Oral Anticoagulation Therapy for Outpatient Treatment of Venous Thromboembolism

M.J. Kovacs^a D.A. Anderson^b P.S. Wells^c

^aDepartments of Medicine, ^aLondon Health Sciences Centre, London, Ontario, ^bQueen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia, ^cOttawa Civic Hospital, Ottawa, Ontario, Canada

Key Words

Warfarin · Nomogram · Venous thromboembolism

Abstract

Venous thromboembolism is a common medical problem. Recently, the emphasis has been on a switch to outpatient low molecular weight heparin therapy. Previous warfarin nomograms have been developed only for inpatients. We prospectively assessed a warfarin initiation nomogram in 105 consecutive outpatients; the nomogram requires International Normalized Ratio (INR) testing on only days 3, 5, and 8. Eighty-three percent had a therapeutic INR by day 5 and 98% by day 8. There were no major bleeds and only 6 instances of INR >4.5. This outpatient warfarin nomogram appears to be safe and efficacious in obtaining timely therapeutic levels of warfarin and deserves further study.

Copyright © 2002 S. Karger AG, Basel

Introduction

Venous thromboembolism is a common medical problem with significant morbidity and mortality, especially if untreated [1]. Until recently, conventional therapy has been with unfractionated heparin for 5–7 days together with oral anticoagulant therapy (such as with warfarin for a minimum of 3 months). More recent work has estab-

lished that low molecular weight heparin is at least equivalent to unfractionated heparin for the acute management of deep vein thrombosis and pulmonary embolism [2–4]. This has led to the treatment of many if not most of these patients as outpatients because of the pharmacological advantages of low molecular weight heparin over unfractionated heparin [5].

To make outpatient management of venous thromboembolism feasible, nurses or pharmacists are involved and nomograms are often used to adjust oral anticoagulant dosing. Warfarin, however, has traditionally been prescribed initially on a daily basis, according to the International Normalized Ratio (INR) for at least 5 days and until the INR is >1.9 for 24 h.

Nomograms for the initiation of warfarin have been described in the past and have been shown to be superior to standard care [6–8]. Recently, a warfarin nomogram published based on initiation of a maintenance dose (5 mg) has been suggested to be as efficacious as traditional higher doses of initiation [9, 10]. This 5-mg nomogram has a number of limitations: it requires daily INR assessments; it was developed using some inpatients in whom warfarin dose requirements may be less than for outpatients; it used some patients without a diagnosis of venous thromboembolism and finally, the dose of warfarin required for a given day was not explicitly stated but rather indicated as a range.

Since the nomograms that have been developed to date are not ideal for outpatient management, the objectives of

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

© 2002 S. Karger AG, Basel
1424–8832/02/0323–0131\$18.50/0

Accessible online at:
www.karger.com/journals/pht

Dr. Michael J. Kovacs
Room 2760, Phase 1, London Health Sciences Centre
800 Commissioners Road East
London, Ontario N6A 4G5 (Canada)
Tel. +1 519 685 8475, Fax +1 519 685 8477, E-Mail michael.kovacs@lhsc.on.ca

Day-3 INR	Days 3, 4 Dose (mg)	Day-5 INR	Days 5, 6, 7 Dose (mg)
< 1.3	15, 15	< 2.0	15, 15, 15
1.3–1.4	10, 10	2.0–3.0	7.5, 5, 7.5
		3.1–3.5	0, 5, 5
		> 3.5	0, 0, 2.5
1.5–1.6	10, 5	< 2.0	7.5, 7.5, 7.5
1.7–1.9	5, 5	2.0–3.0	5, 5, 5
		3.1–3.5	2.5, 2.5, 2.5
		> 3.5	0, 2.5, 2.5
2.0–2.2	2.5, 2.5	< 2.0	5, 5, 5
2.3–3.0	0, 2.5	2.0–3.0	2.5, 5, 2.5
		3.1–3.5	0, 2.5, 0
		> 3.5	0, 0, 2.5
> 3.0	0, 0	< 2.0	2.5, 2.5, 2.5
		2.0–3.0	2.5, 0, 2.5
		3.1–4.0	0, 2.5, 0
		> 4.0	0, 0, 2.5

Fig. 1. 10-mg warfarin nomogram. Day 1 = 1st day of warfarin. All patients receive 10 mg on day 1 and day 2. INR in the morning; drug is given in the evening.

this study were to develop a warfarin initiation nomogram requiring blood work only every 48 h tailored explicitly for outpatient therapy and to obtain a therapeutic INR by the 5th day.

Methods

Consecutive outpatients with an objectively confirmed new diagnosis of venous thromboembolism (by previously described criteria [2, 5]) were potentially eligible. Patients were excluded if they required hospitalization, had received oral anticoagulant therapy within the previous 2 weeks, had a baseline INR > 1.4, were less than 18 years of age, or were pregnant or of child-bearing potential but not using adequate contraception. Patients were chosen for outpatient therapy based on our previous published criteria [5]. The study was performed at three Canadian tertiary care centres and informed consent was obtained from all participants. There was no external funding support.

All patients were treated with low molecular weight heparin (either tinzaparin 175 U/kg subcutaneously daily or dalteparin 200 U/kg subcutaneously daily). This was given for a minimum of 5 days and until the INR was greater than 1.9. All patients had a baseline complete blood count (CBC), serum creatinine and INR.

Warfarin (Coumadin®) was ordered according to a nomogram as illustrated in figure 1. This was designed and extrapolated from our previously published nomogram [6]. Anecdotal experience at our centres demonstrated the need for 10-mg initiation (rather than 5 mg) and this nomogram was designed to eliminate the need for daily INR testing. The first day of warfarin therapy for this study was termed day 1 regardless of how many days of low molecular weight heparin the patient had already received. All patients received a loading dose of 10 mg on day 1 and day 2 given in the early evening after dinner.

Patients had an INR determined on day 3 in the morning. The warfarin dose was then relayed to the patient by study nurse for day 3 and day 4. The patient then had an INR taken on day 5 and the warfarin dose was prescribed from the nomogram for days 5, 6 and 7. Finally, all patients then had an INR taken on day 8. The warfarin was continued for at least 3 months and all patients were followed for 3 months.

All laboratory measurements after the baseline were done at the local laboratory that was closest to the patient. All prothrombin reagents used were of low International Sensitivity Index.

The primary outcome of the study for efficacy was the proportion of patients therapeutic by day 5 and for safety, the proportion of patients with an INR > 4.5. Secondary outcomes were recurrence of venous thromboembolism and episodes of major bleeding, defined as per previous studies over the subsequent 3 months from diagnosis [2, 5].

Results

There were a total of 105 consecutive patients from three teaching hospitals. There were 55 men and 50 women. Eighteen patients had pulmonary embolism with 87 proximal deep vein thrombosis. Thrombosis was due to cancer in 35 patients, transient risk factors in 19 and was idiopathic in 51. The average age was 57 years. All patients had an INR determined on days 3 and 5, while 94 patients had an INR determined on day 8. Eleven patients did not get an INR determined until day 9 or later due to poor compliance or poor availability of testing on a weekend but were all therapeutic on that day and were all followed for 3 months.

Eighty-seven patients (83%) had a therapeutic INR (2.0–3.0) by day 5 and 98% were therapeutic by day 8. Of the 18 patients with an INR less than 2.0 on day 5, 6 had an INR of 1.9 and 8 had an INR of 1.7. There were only 6 instances in 6 patients of INR >4.5 out of 297 measurements. Three of these were suspicious for compliance issues while no reasons were apparent in the other 3 patients. On day 3, 1 patient had an INR greater than 4.5, on day 5, 3 patients had an INR greater than 4.5, on day 8, 2 patients had an INR greater than 4.5. As assessed by the 3rd month, 5 patients (4.8%) had recurrent venous thromboembolism and there were no major bleeds. Fifteen patients were excluded because warfarin had already been initiated prior to consent.

Discussion

We have developed a nomogram for the initiation of warfarin which is specific for the outpatient management of venous thromboembolism. The efficacy of this nomogram is established by the fact that 83% of patients were therapeutic by day 5 (the usual minimum duration of heparin therapy). The safety is demonstrated by the fact that there were only 6 instances of INR determinations over 4.5 despite a loading dose of 10 mg for 2 days. Moreover, the recurrence of venous thromboembolism at 3 months was only 4.8% (5 patients) and there were no major bleeds over the same time period.

The advantages of our nomogram are that in the first 8 days of therapy only 3 INR determinations are required. This increases the feasibility for outpatient management supervised by nurses or pharmacists and might decrease

the need for physician involvement. The other major advantage is that the INR was therapeutic in over 80% of patients by the 5th day. The results of the study are likely generalizable due to the prospective nature of our study, the relatively simple inclusion/exclusion criteria and the fact that a homogeneous patient population was included that specifically excluded inpatients and included only patients with a diagnosis of acute venous thromboembolism.

Compared to other nomograms that have been published, this nomogram is much more convenient due to the lack of a need for daily INR testing and that the dose for a given day is explicitly stated [6–10]. Moreover, this nomogram has been developed specifically for outpatients whereas others included inpatients [6–10].

A recent publication suggested that a 5-mg starting dose for the first 2 days was as efficacious as a 10-mg dose [9, 10]. That study is likely not generalizable to outpatients due to inclusion of inpatients as well as patients without a diagnosis of venous thromboembolism. Finally, unlike the 10-mg nomogram in that study we did not have an excess of prolonged INRs. This nomogram may not be safe for inpatients due to a greater sensitivity to warfarin compared to outpatients [6]. This could lead to more prolonged INRs and so this nomogram should first be studied in inpatients prior to general use.

In conclusion, this warfarin initiation nomogram that we have developed exclusively for outpatients with venous thromboembolism has the potential to increase the feasibility of outpatient management supervised by nurses and/or pharmacists. Randomized studies need to be performed comparing the effectiveness of this nomogram with others, especially the 5-mg nomogram.

References

- Weinmann EE, Salzman EW: Deep-vein thrombosis. *N Engl J Med* 1994;331:1630–1641.
- Levine M, Gent M, Hirsh J, Leclerc J, Anderson D, Weitz J, Ginsberg J, Turpie AG, Demers C, Kovacs M, Geerts W, Kassis J, Desjardins L, Cusson J, Cruickshank M, Powers P, Brien W, Haley S, Willan A: A comparison of low-molecular weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep-vein thrombosis. *N Engl J Med* 1996;334:667–681.
- Brandjes DP, Heijboer H, Buller HR, de Rijk M, Jagt TH, ten Cate JW: Acenocoumarol and heparin compared with acenocoumarol alone in the initial treatment of proximal-vein thrombosis. *N Engl J Med* 1992;327:1485–1489.
- Koopman MM, Prandoni P, Piovella F, Ockelford PA, Brandjes DP, van der Meer J, Gallus AS, Simonneau G, Chesterman CH, Prins MH: Treatment of venous thrombosis with intravenous unfractionated heparin administered in the hospital as compared with subcutaneous low-molecular-weight heparin administered at home. The TASMAN Study Group. *N Engl J Med* 1996;334:682–687.
- Wells PS, Kovacs MJ, Bormanis J, Forgie MA, Goudie D, Morrow B, Kovacs J: Expanding eligibility for outpatient treatment of deep venous thrombosis and pulmonary embolism with low-molecular-weight heparin. *Arch Intern Med* 1998;158:1809–1812.
- Kovacs MJ, Cruickshank M, Wells PS, Kim H, Chin-Yee I, Morrow B, Boyle E, Kovacs J: Randomized assessment of a warfarin nomogram for initial oral anticoagulation after venous thromboembolic disease. *Haemostasis* 1998;28:62–69.
- Fennerty A, Bolben J, Thomas P, Backhouse G, Bentley DP, Campbell IA, Routledge PA: Flexible induction dose regimen for warfarin and prediction of maintenance dose. *Br Med J Clin (Res Ed)* 1984;288:1268–1270.
- Doecke CJ, Cosh DG, Gallus AS: Standardized initial warfarin treatment: Evaluation of initial treatment response and maintenance dose prediction by randomized trial, and risk factors for an excessive warfarin response. *Aust NZ J Med* 1991;21:319–324.
- Harrison L, Johnston M, Massicotte MP, Crowther M, Moffat K, Hirst J: Comparison of 5-mg and 10-mg loading doses in initiation of warfarin therapy. *Ann Intern Med* 1997;126:133–136.
- Crowther MA, Harrison L, Hirsh J: Warfarin: Less may be better. *Ann Intern Med* 1997;127:332–333.