Background: The activated partial thromboplastin time (APTT) is used to adjust heparin sodium dosage. However, warfarin sodium is often administered concomitantly with heparin and may also affect the APTT and, therefore, heparin dose. We performed a prospective cohort study to quantify the effect of warfarin on the APTT in patients who are being treated with heparin.

Methods: Serial assays of APTT, international normalized ratio, heparin levels, and functional levels of prothrombin (factor II) and factors VII and X were performed in 24 patients with acute venous thromboembolism who were treated with concomitant continuous intravenous heparin and warfarin. The effects of warfarin, as expressed by international normalized ratio and coagulation factor levels, on APTT were determined.

Results: Warfarin markedly affected APTT; for each increase of 1.0 in the international normalized ratio, the APTT increased 16 seconds (95% confidence interval, 10-22 seconds). The effects of warfarin and heparin on APTT were additive. Consequently, warfarin markedly altered the relationship between APTT and heparin levels; of the 29 blood samples with supratherapeutic APTT, 13 had a therapeutic heparin level and 10 had a subtherapeutic heparin level.

Conclusions: In patients receiving concomitant heparin and warfarin therapy, APTT reflects the combined effects of both drugs. Because of the marked effect of warfarin on the APTT, decreasing heparin dose in response to a high APTT frequently results in subtherapeutic heparin levels.

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Heparin Sodium is the standard initial treatment for patients with acute venous thromboembolism. Usual clinical practice in this setting is to start heparin immediately, and warfarin sodium within 24 hours; generally, heparin is discontinued after 5 days. To optimize safety and efficacy, laboratory monitoring of heparin dose is recommended, usually by means of the activated partial thromboplastin time (APTT).

Heparin predominantly exerts its anticoagulant effect by catalyzing antithrombin III, which results in inhibition of thrombin (factor IIa), factor Xa, and to a lesser extent, factors IXa, Xla, and XIIa. Warfarin exerts its anticoagulant effect by reducing functional levels of factors II, VII, IX, and X. The APTT assay is responsive to decreased levels, or inhibition, of factors II, X, and IX and therefore has the potential to be affected by both warfarin and heparin. If the effects of warfarin on the APTT are substantial, adjusting heparin dose in response to APTT in warfarin-treated patients may lead to heparin underdosing.

To determine the independent effects of heparin and warfarin on the APTT, we performed these assays as well as heparin levels and functional levels of factors II, VII, and X on plasma samples from patients with acute venous thromboembolism during the initial phase of treatment.

Results

The following results were obtained in the 77 samples that had detectable levels of heparin: mean (± SD) APTT, 81 ± 24; mean INR, 1.8 ± 0.8; mean heparin level, 0.24 ± 0.12 U/mL; mean factor II level, 89% ± 27%; mean factor VII level, 58% ± 40%; and mean factor X level, 67% ± 30%. Unless otherwise stated, only these samples were included in the analyses. In addition, as a secondary analysis, the effect of warfarin on APTT results was also assessed in 29 samples from the same patients in which heparin could not be detected: mean APTT, 50 ± 26 seconds; mean INR, 2.2 ± 0.86.
PATIENTS AND METHODS

PATIENTS AND INTERVENTIONS

Twenty-four unselected patients with acute deep vein thrombosis or pulmonary embolism were studied. Patients received an initial intravenous bolus of 5000 U of unfractionated heparin sodium (Hepalean; Organon, Scarborough, Ontario) followed by an initial intravenous infusion of 1280 U/h, with subsequent dose adjustment according to APTT by means of a previously published nomogram. Warfarin sodium, 10 mg, was generally started within 24 hours of initiating heparin and subsequent doses were given once daily according to international normalized ratio (INR) results. Heparin was continued for a minimum of 5 days and until the INR was 2.0 or greater for 2 consecutive days. Blood samples were obtained during heparin infusion, or within 12 hours of stopping heparin. All blood samples that had a measurable heparin level (lower limit of detection, 0.05 U/mL) were included in the main analyses. In a secondary analysis, the effect of warfarin on the APTT was assessed in blood samples from the same patients that had either no heparin present (heparin recently discontinued) or heparin levels below the lower limit of detection.

LABORATORY ASSAYS

Blood samples were drawn into specimen tubes (BD Vacutainers; Becton Dickinson Co, Mountain View, Calif) containing buffered sodium citrate, 0.102 mol/L, double centrifuged at 1700g to ensure removal of the platelets, and plasma was extracted and frozen at -70°C for batch analysis. Prothrombin times were determined with a commercial human placental thromboplastin (Thromborel S, international sensitivity index, 1.06; Behring Diagnostics, Montreal, Quebec) and reported as INR values. The APTT was assayed by means of an automated coagulation instrument (ACL 810 Coagulation Analyzer; Coulter, Burlington, Ontario) and a commercial APTT reagent (Dade Activ- FS; Dade International, Mississauga, Ontario). The therapeutic range for heparin with this APTT assay is 60 to 85 seconds in our laboratory. Plasma heparin levels were measured with protamine sulfate titration, by the method of Refn and Vestergaard with modifications as described by Kitchen and Preston. The therapeutic range for heparin with this assay is 0.2 to 0.4 U/mL. Functional levels of factors II, VII, and X were assayed by means of a 1-stage clotting method.

ANALYSIS

Regression analysis was used to assess the influence of variables (ie, INR results, coagulation factor levels, heparin levels) on APTT. To investigate whether a variable (ie, INR) had an additional influence on APTT over and above the influence of another variable (ie, heparin level), both were included as explanatory variables in an additive multiple regression model. With this technique, the coefficient associated with each variable (ie, INR or heparin level) reflects its additional explanatory effect independent of the other variables in the regression model. The further addition of a product variable (ie, INR times heparin level) allows one to investigate whether the 2 variables have a multiplicative interactive effect on the outcome of interest (ie, APTT). The proportions of the variances of the APTT that were accounted for by different factors ( singly or in combination) are reported as $r^2$ value. All P values are 2 tailed.

FACTORS INFLUENCING THE APTT

There was a significant, direct relationship between APTT and INR (Figure 1); on average, the APTT increased 16 seconds (95% confidence interval, 10-22 seconds) for each increase in the INR of 1.0 ($r^2 = 0.28; P < .001$). The APTT was significantly related to levels of factor II ($r^2 = 0.24, P < .001$), factor VII ($r^2 = 0.33, P < .001$), and factor X ($r^2 = 0.32, P < .001$). The relationship between APTT and INR was accounted for by differences in vitamin K-dependent coagulation factor levels; after controlling for difference in levels of factors X and II, the relationship between APTT and INR was no longer significant ($P = .1$).

The direct relationship between APTT and heparin levels did not achieve statistical significance ($P = .1$) (Figure 2). However, after controlling for differences in INR, a relationship between APTT and heparin levels was evident (Figure 3); for each increase in the heparin level of 1.0 U/mL, on average, the APTT increased 48 seconds (95% confidence interval, 10-87 seconds). There was no evidence of a multiplicative interactive effect of heparin levels and INR on APTT ($P = .6$); the effects of warfarin and heparin on the APTT, therefore, appeared to be additive (Figure 3).

Analyses were performed to explore the mechanism of the increase in the APTT caused by warfarin. After controlling for differences in heparin levels, the APTT was more closely related to a decline in factor X activity than to levels of factors II or VII, or the INR. In addition, APTT was statistically significantly ($P < .05$) related to levels of factor X even after controlling for differences in levels of factor II, factor VII, or INR. However, none of the levels of factor II, factor VII, or INR was statistically significantly associated with APTT after controlling for differences in levels of factor X.

CLINICAL IMPLICATIONS: AGREEMENT BETWEEN APTT AND HEPARIN LEVELS

Blood samples were categorized as supratherapeutic, therapeutic, or subtherapeutic according to APTT (therapeutic range, 60-85 seconds) and heparin levels (therapeutic range, 0.2-0.4 U/mL) (Table). There was agreement between APTT and heparin levels in only 36 of the 77 samples. Of the 41 samples with discordant results, the intensity of heparin therapy was higher according to APTT results in 36 and higher according to heparin levels in 5. Only 6 of the 29 samples that had supratherapeutic APTT results also had high heparin levels. Consistent with previously described analyses that demonstrated a marked influence of warfarin on APTT, samples with high APTT relative to heparin levels had elevated INR (Table).
This study shows that, in patients who are being treated with concomitant heparin and warfarin, APTT reflects the effects of both drugs. Unexpectedly, APTT was more closely related to INR and factor X levels than to heparin levels. Consequently, in patients treated with oral anticoagulation, decreasing heparin dose in response to high APTT often results in subtherapeutic heparin levels. However, when APTT was low, heparin levels were usually low also; therefore, increasing heparin dose in response to low APTT increases the chance of achieving a therapeutic heparin level.

Our finding that oral anticoagulation has a marked effect on the APTT is consistent with earlier reports. Hauser and Rozek reported that warfarin caused a similar increase in the APTT ratio and the prothrombin time ratio in patients who were not receiving heparin. Consequently, in patients treated with oral anticoagulation, decreasing heparin dose in response to high APTT often results in subtherapeutic heparin levels. However, when APTT was low, heparin levels were usually low also; therefore, increasing heparin dose in response to low APTT increases the chance of achieving a therapeutic heparin level.

Our finding that oral anticoagulation has a marked effect on the APTT is consistent with earlier reports. Hauser and Rozek reported that warfarin caused a similar increase in the APTT ratio and the prothrombin time ratio in patients who were not receiving heparin. However, as the international sensitivity index of the thromboplastin that was used to measure the prothrombin ratio was not reported, these data are difficult to interpret. Mungall and Floyd reported that the dose of continuous intravenous heparin sodium required to achieve a therapeutic APTT dropped from 1800 to 1000 U/h after warfarin was started (intensity of oral anticoagulation not specified). Our study quantifies the effects of warfarin and heparin on APTT results and supports the concept that these effects are additive.

It is important to emphasize that this study was performed with the use of a single thromboplastin and a single APTT reagent. The relationship of APTT to heparin levels varies with different reagents and other technical factors, and consequently, quantitative interactions are expected to differ among laboratories. However, major differences are unlikely, and the interactions we have described should be generalizable to clinical practice.

Our finding that, independent of heparin levels, factor X levels were most closely related to APTT suggests that a decrease in the level of this factor is an important mediator of warfarin-induced prolongation of the APTT. However, because there were strong interrelationships between the levels of the vitamin K–dependent coagulation factors, and because factor IX activity was not assessed in this study, this finding is inconclusive.

There was evidence that heparin had a minor effect on INR (analyses not shown), suggesting that the relationship between APTT and INR is partly accounted for by the confounding effect of heparin levels on both assays. However, the finding that APTT was no longer related to INR after controlling for differences in levels of
factors II and X in the regression analysis strongly supports that the relationship between the APTT and INR is predominantly mediated by vitamin K antagonism. Indirectly, our findings question the role of laboratory monitoring of heparin therapy. Laboratory monitoring of heparin therapy by means of the APTT was introduced at a time when it was usual to postpone starting warfarin therapy for at least 5 days, and when there was limited understanding of optimal heparin dosing. With recognition that (1) an average initial intravenous infusion rate of approximately 1300 U/h rather than the previously selected 1000 U/h is more appropriate, (2) weight adjustment of heparin dose is advantageous, and (3) oral anticoagulants interfere with APTT, the value of APTT monitoring of heparin therapy, provided an adequate starting dose is used, is uncertain. Consistent with these observations, a recent meta-analysis failed to find an association between subtherapeutic APTT during the first 48 hours of therapy and subsequent recurrent venous thromboembolism in patients with acute venous thromboembolism who were treated with an average dose of at least 30 000 U of continuous intravenous heparin per day. Similarly, the importance of achieving a predefined (ie, therapeutic) heparin level is also uncertain. Five days of heparin therapy is effective treatment for patients with acute venous thrombosis despite the possibility that heparin levels may be subtherapeutic for much of this time because of the concomitant effect of warfarin on the APTT. Currently, it is not known whether achieving predefined heparin levels, or APTT, optimizes combined efficacy and safety in patients who are receiving both heparin and warfarin. Indeed, the value of any form of laboratory monitoring is uncertain if patients are being treated with appropriate doses of heparin. In summary, this study identifies that warfarin has a major effect on APTT and questions the appropriateness of reducing heparin dose in response to high APTT in patients who are receiving oral anticoagulants.

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