Interpreting the International Normalized Ratio (INR) in Individuals Receiving Argatroban and Warfarin

S.B. Sheth, R.A. DiCicco, M.J. Hursting¹, T. Montague, D.K. Jorkasky

SmithKline Beecham Pharmaceuticals, Presbyterian Medical Center, University of Pennsylvania Health System, Philadelphia, PA, and ¹Texas Biotechnology Corporation (as consultant), Houston, TX, USA

Key words
Argatroban, warfarin, direct thrombin inhibitors, International Normalized Ratio

Summary
The effects of argatroban, a direct thrombin inhibitor, on the International Normalized Ratio (INR), activated partial thromboplastin time (aPTT) and functional factor X during warfarin co-administration were established to provide means to interpret INRs during argatroban/warfarin co-therapy. Twenty-four subjects receiving warfarin (7.5 mg, day 1; 3-6 mg/day, days 2-10) and argatroban (1-4 µg/kg/min over 5 h, days 1-11) were assessed daily for these coagulation parameters prior to argatroban infusion (warfarin “monotherapy”) and at its conclusion (“co-therapy”). Argatroban increased aPTTs dose-dependently. Co-therapy INR increased linearly with monotherapy INR, with slope sensitive to argatroban dose and thromboplastin used. Prediction errors for monotherapy INRs were ≤±0.4 for argatroban 1-2 µg/kg/min but ±± 1.0 for higher doses. Despite co-therapy INRs >7, no major bleeding occurred. Factor X remained ≥37% of normal. Therefore, the predictable effect of argatroban (≤2 mg/kg/min only) on INRs during warfarin co-therapy allows for reliable prediction of the level of oral anticoagulation.

Introduction
Direct thrombin inhibitors are gaining use in the treatment and prevention of thromboembolic diseases (1-3). One advantage of direct thrombin inhibitors over heparin is the ability to inhibit effectively bound thrombin (3). The anticoagulant effect of direct thrombin inhibitor is typically monitored using the activated partial thromboplastin time (aPTT) (1, 2, 4, 5), although dose-dependent increases also occur in the prothrombin time (PT) (6-11) and International Normalized Ratio (INR) (4, 7). Patients on intravenous anticoagulation with a direct thrombin inhibitor who require long-term oral anticoagulation with the vitamin K-antagonist warfarin are likely to receive both agents during the induction period (3 to 5 days) of warfarin. Routinely, warfarin dosage is individualized according to a patient’s response to the drug, as assessed by the INR, with a therapeutic range of 2.0-3.0 recommended for most indications (12). Since direct thrombin inhibitors also increase the PT/INR, a reliable means to monitor warfarin therapy during co-administration of a direct thrombin inhibitor is important.

Argatroban is a reversible, synthetic direct thrombin inhibitor that inhibits thrombin-catalyzed or induced reactions, including fibrin formation, activation of factors V, VIII, and XIII and protein C, and platelet aggregation (10, 13). Efforts to characterize argatroban’s effect on the INR during concurrent warfarin therapy have been reported. In one study (14), argatroban 1-2 µg/kg/min and warfarin 2.5-5.0 mg/day were administered concurrently to healthy subjects over 6 days. Argatroban (elimination half-life, 39-51 min) (15) was temporarily discontinued daily to simulate warfarin monotherapy. Within 4 h of stopping argatroban, mean INRs decreased almost two-fold although mean functional factor X levels remained unchanged. Although therapeutic INRs were not attained (i.e., the maximum INR during warfarin monotherapy was 1.8), results indicated that revised guidelines were needed for interpreting INRs during argatroban/warfarin co-therapy. Subsequent in vitro studies (16) using plasma from warfarin-treated patients demonstrated a linear relationship between the INR in the presence versus absence of exogenous argatroban. The slope of the relationship was affected by plasma argatroban concentration and the sensitivity (International Sensitivity Index, ISI) of the thromboplastin used in measuring the PT/INR. Validation of this linear relationship in individuals throughout the therapeutic INR range, plus further characterization of the variables influencing this relationship, would facilitate establishment of guidelines for interpreting INRs during argatroban and warfarin co-therapy.

This study was conducted to describe the effect of argatroban on the INR during warfarin co-administration in healthy subjects over a range of argatroban doses and throughout the therapeutic INR range in an effort to guide anticoagulant monitoring during co-therapy. Also characterized were the effects of different thromboplastins on the relationship between INRs during co-therapy versus warfarin monotherapy, the effects of argatroban on the aPTT and factor X levels during warfarin co-administration, and the general tolerability of co-therapy. This report presents the first comprehensive evaluation of these multiple parameters in individuals receiving warfarin concurrently with a direct thrombin inhibitor.

Methods
Study Design and Subjects
Twenty-four healthy volunteers (3 groups, 8 subjects each) between 18 to 55 years old were enrolled in this open-label, parallel-group, repeat-dosing study. Sample size was anticipated (16) to provide sufficient data for characterizing the effect of argatroban on the INR throughout the therapeutic INR range. Inclusion criteria included weight >50 kg (within 25% of ideal) and negative drug and pregnancy tests. Exclusion criteria included any clinically significant abnormality on physical or laboratory examination; abnormal PT, aPTT, factor X or protein C functional levels; thrombocytopenia; heme-positive stools; personal or family history of abnormal bleeding/bruising (including gastrointestinal-

Downloaded from www.thrombosis-online.com on 2018-03-16 | ID: 1001066444 | IP: 54.70.40.11
For personal or educational use only. No other uses without permission. All rights reserved.
nal or menstrual); or ulcer. Subjects were also excluded for prior stroke; liver disease, alcoholism or drug abuse within the past 6 months; surgery within the past 3 months; blood donation >500 mL within 56 days; unwillingness to accept blood products; or use of investigational drugs within 30 days (or 5 half-lives), aspirin or nonsteroidal anti-inflammatory agents within 3 weeks, or any medication within 2 weeks of dosing. The Institutional Review Board, University of Pennsylvania, Philadelphia, PA approved the study prior to its initiation. Subjects gave written informed consent before study entry.

Treatments and Assessments

Subjects were admitted to the clinical unit 2 h prior to initial dosing for a 12-day stay. An intravenous, 5-h infusion of argatroban (Texas Biotechnology Corporation, Houston, TX; SmithKline Beecham Pharmaceuticals, Philadelphia, PA) was administered starting at 9:00 AM at a dose of 2 µg/kg/min on days 1-8 and of 1, 3 and 4 µg/kg/min, respectively, on days 9, 10 and 11. On days 10-11, if the investigator estimated that aPPTTs would exceed 90 s at the planned dose, argatroban 1 or 2 mg/kg/min could be repeated. Argatroban doses were selected to reflect those administered patients with heparin-induced thrombocytopenia (1). Steady-state argatroban levels were expected within 4 h of drug initiation (15).

Subjects also received 7.5 mg of warfarin (DuPont Pharma, Wilmington, DE) at 9:00 PM on day 1, followed by a fixed dose of 3-6 mg at the same time on days 2-10. The first group of subjects was randomized to receive 3 or 5 mg; the second group was randomized to receive 3, 4, 5 or 6 mg; the third group received 5 mg. Warfarin doses were selected to achieve a distribution of INRs between 1.0-3.0, as assessed using a thromboplastin with ISI of 0.88. No dose adjustments were made after day 2. To ensure subject safety, those attaining INRs >3.0 prior to argatroban infusion were withdrawn from the study, however all available data was analyzed. Warfarin-induced changes in the INR during the daily, 5-h infusion of argatroban were expected to be clinically negligible (17). Vital signs, physical examination and adverse events were assessed prior to, during and at completion of the study. Blood was collected daily into evacuated tubes (3.8% sodium citrate) for assessment of plasma INR, functional factor X, and aPPTT immediately prior to the initiation and cessation of argatroban infusion. Samples collected on days 2-11 prior to argatroban initiation (i.e., warfarin “monotherapy”) and prior to argatroban cessation (i.e., “co-therapy”) were considered paired for analysis purposes.

Subjects were discharged if the INR was <3.0 on day 12 and decreasing from the previous value. Subjects received 10 mg of vitamin K (Merck & Co., Inc., West Point, PA) subcutaneously plus a vitamin K-rich meal prior to discharge, then returned for follow-up assessments 1 and 7-10 days later.

Coagulation Testing

PT, aPPTT and factor X assays were performed using the Automated Coagulation Laboratory (ACL) Analyzer (Beckman Coulter, Fullerton, CA). The aPPTT was measured using IL Test aPPTT-C Activated Partial Thromboplastin Time reagent (Instrumentation Laboratory Co., Lexington, MA). PT assays were performed using two different thromboplastins with ISIs of 0.88 (recombinant human tissue factor; Innovin®, Dade Behring, Miami, FL) and 1.78 (rabbit brain; Thromboplastin C Plus®, Dade Behring). Calibration curves were generated for each thromboplastin. The INR was calculated from the PT (12), using ISI values in accordance with the reagent/instrument combination as determined by the World Health Organization.

After the clinical study, INRs were also determined for specimens from days 2-8 from 10 randomly-selected subjects using thromboplastins with ISIs of 1.31 (rabbit brain; PT-Fibrinogen HS Thromboplastin, Beckman) and 2.13 (rabbit brain; PT-Fibrinogen Thromboplastin, Beckman Coulter) and 0.88 (Innovin®, same lot as previously used). Plasma, which had been stored at -70°C, was quick-thawed at 37°C prior to assay.

Functional factor X was measured photometrically by a two-stage method (Chromogenix AB, Franklin, OH) adapted for the ACL. In stage one, functional factor X is activated in the presence of calcium by exogenous Russell’s Viper venom. In stage two, generated factor Xc cleaves a factor Xc-specific chromogenic substrate. The rate of color formation relates to the functional factor X level. A calibration curve is generated using normal plasma. The assay, which depends on neither clot formation nor thrombin activity, is insensitive to argatroban at supratherapeutic (i.e., up to 5 mg/mL) concentrations (18).

Statistical Methods

For each argatroban dose (1, 2, 3 and 4 µg/kg/min) and thromboplastin (ISIs of 0.88 and 1.78), co-therapy INRs were modeled separately as a linear function of monotherapy INR. Ninety-five (95) percent inverse individual prediction intervals (PIs) were calculated based on estimates of the model parameters and the residual error (19). The half-width of these 95% prediction intervals were interpreted as the “prediction error” for a monotherapy INR predicted from a co-therapy INR. The subset of INRs measured using different thromboplastins (ISIs of 1.31 and 2.13) was similarly analyzed.

Changes from baseline (calculated as the value immediately prior to argatroban cessation minus the value immediately prior to argatroban initiation, on a given day) for INR and aPPTT on day 1 and aPPTT on days 8-11 were descriptive-ly summarized by argatroban dose. Summary statistics for co-therapy INR, monotherapy INR and factor X were calculated for values grouped by monotherapy INR ranges of <1.0, 1.0-1.5, 1.5-2.0, 2.0-2.5, 2.5-3.0 and >3.0.

Results

Subjects and Dosing

Twenty-four subjects (16 Caucasian, 6 African-American, 2 Hispanic) were enrolled and received argatroban and warfarin. Randomization resulted in 6, 2, 14, and 2 subjects administered daily warfarin doses of 3, 4, 5 and 6 mg, respectively. All subjects were male, with a mean (range) age of 33 (20-53) years and weight of 79 (58-102) kg. Seventeen subjects completed the study. Six subjects were withdrawn (2 each on days 5 and 6, 1 each on days 9 and 10) due to INRs >3.0 during warfarin monotherapy; one subject was withdrawn (day 4) due to an adverse event, hematochezia. Two subjects received argatroban 2 µg/kg/min on day 11 due to concerns that their aPPTTs would exceed 90 s at the planned dose of 4 µg/kg/min. Altogether, 19, 24, 18 and 15 subjects, respectively, received argatroban at a dose of 1, 2, 3 and 4 mg/kg/min. All subjects received 10 mg of vitamin K subcutaneously prior to discharge and, by the next day, had decreased INRs (mean ± SD INR of 1.5 ± 0.3 [ISI of 0.88]).

Pharmacodynamics

Effects of argatroban alone or with warfarin on the aPPTT. For subjects receiving only argatroban 2 mg/kg/min (day 1), the mean (SD increase in aPPTT over baseline was 24.3 ± 6.3 s. For subjects receiving concurrent warfarin, argatroban increased the aPPTT dose-depentently. When stable warfarin effects were expected (20), argatroban at doses of 1, 2, 3 and 4 µg/kg/min produced mean aPPTT increases over baseline of 20.5 ± 5.6, 27.8 ± 7.5, 39.6 ± 10.4 and 42.4 ± 13.1 s, respectively (days 9, 8, 10 and 11, respectively). Coefficients of variation (26-31%) were consistent with low intersubject variability.

Effect of argatroban alone on the INR. Prior to warfarin initiation (day 1), subjects receiving argatroban 2 mg/kg/min demonstrated increases in INR over baseline that were dependent upon the sensitivity of the thromboplastin used. The INR, as measured using thromboplastins with ISIs of 0.88 and 1.78, respectively, increased on average (± SE) 0.43 ± 0.03 and 0.74 ± 0.03.

Effect of argatroban 2 mg/kg/min on the INR during warfarin co-therapy. Among subjects receiving warfarin monotherapy on days 2-8, the INR ranges, as assessed using the lower (0.88) and higher (1.78) ISI thromboplastins, respectively, were 0.9-3.8 and 0.7-3.6. During warfarin co-therapy with argatroban 2 µg/kg/min, maximum INRs as assessed using the lower and higher ISI thromboplastins, respectively, were 6.4 and 8.3.
The relationship between the INR during argatroban 2 µg/kg/min and warfarin co-therapy versus warfarin monotherapy is shown for each thromboplastin in Fig. 1A. Co-therapy INRs related linearly to monotherapy INRs for each thromboplastin, with a correlation coefficient ($r^2 \geq 0.92$). The relationship was sensitive to the thromboplastin used, with a steeper slope associated with the higher (1.78) versus lower (0.88) ISI thromboplastin (i.e., slope $\geq$SE values of 2.24 ± 0.05 versus 1.75 ± 0.04).

For argatroban 2 mg/kg/min, inverse prediction equations for estimating a warfarin monotherapy INR (INR$_{monotherapy}$) from a co-therapy INR (INR$_{co-therapy}$) were

- (ISI = 0.88) INR$_{monotherapy}$ = 0.19 + (0.57 × INR$_{co-therapy}$)  
  (Equation 1)

- (ISI = 1.78) INR$_{monotherapy}$ = 0.18 + (0.45 × INR$_{co-therapy}$)  
  (Equation 2)

The inverse prediction error for a warfarin monotherapy INR from a co-therapy INR was ± 0.3 for each thromboplastin, hence allowing for reliable, clinically relevant, inverse predictions.

**Effect of argatroban 1 µg/kg/min on the INR during warfarin co-therapy.** On day 9, the INR range during warfarin monotherapy was 1.1-3.4 for the lower ISI (0.88) thromboplastin and 1.0-3.0 for the higher ISI (1.78) thromboplastin. Within these INR ranges, the relationship between the INR during argatroban 1 mg/kg/min and warfarin co-therapy versus warfarin monotherapy was also linear for each thromboplastin ($r^2 \geq 0.94$; Fig. 1B). As seen for argatroban 2 µg/kg/min, the linear relationship was sensitive to the thromboplastin used, with a steeper slope associated with the higher versus lower ISI thromboplastin (i.e., slope values of 1.73 ± 0.11 versus 1.52 ± 0.08). The linear relationship was also sensitive to argatroban dose, with greater slopes associated with 2 µg/kg/min than 1 µg/kg/min. For argatroban 1 mg/kg/min, the inverse prediction error for a monotherapy INR from a co-therapy INR was > ±1 for each thromboplastin, disallowing reliable inverse predictions.

**Effect of the thromboplastin used on the relationship between INRs during co-therapy versus warfarin monotherapy.** Because primary analyses indicated that the relationship between co-therapy and warfarin monotherapy INRs was sensitive to the thromboplastin used, INRs were determined for a subset of samples from days 2-8 using two additional thromboplastins (ISIs of 1.31 and 2.13). As a control, these samples were also re-assayed using the lower ISI (0.88) thromboplastin to validate consistency of the methods over time; initial and re-assay INR values correlated strongly ($r^2 = 0.98$) with no significant absolute changes noted.

For the two additional thromboplastins, INRs during warfarin co-therapy with argatroban 2 µg/kg/min increased linearly with warfarin monotherapy INR ($r^2 \geq 0.87$). Prediction errors were ± 0.4. The inverse prediction equations were

- (ISI = 1.31) INR$_{monotherapy}$ = 0.21 + (0.44 × INR$_{co-therapy}$)  
  (Equation 5)

- (ISI = 2.13) INR$_{monotherapy}$ = 0.26 + (0.40 × INR$_{co-therapy}$)  
  (Equation 6)

Fig. 2 summarizes the INR relationships having prediction errors of ≤ ±0.4, by argatroban dose (1 and 2 µg/kg/min) and the ISI of the thromboplastin used.

**Effect of argatroban on functional factor X during warfarin co-therapy.** Mean functional factor X levels (and INRs) during warfarin monotherapy and co-therapy with argatroban 2 µg/kg/min were determined for 6 different ranges of warfarin monotherapy INR (Table 1). Within each INR range, factor X levels during warfarin monotherapy and co-therapy were similar. Mean factor X remained ≥37% of normal throughout the study, even at co-therapy INRs > 7, suggesting that the increased INR on co-therapy relative to warfarin monotherapy was not the result of increased vitamin K-dependent anticoagulant effect.

**Safety**

Twenty-one subjects reported 65 adverse events, each being self-limiting and none requiring treatment. The most common events included injection site reaction (9 subjects, 38%), purpura (7 subjects,
Fig. 2 Summary of INR relationships for warfarin/argatroban co-therapy versus warfarin monotherapy, by argatroban dose and ISI of thromboplastin used (prediction errors ≤±0.4). Two sets of lines are superimposed due to similarity in slope and intercept.

Table 1 Mean (SD) INR and functional factor X levels during warfarin monotherapy versus warfarin/argatroban co-therapy, by monotherapy INR range

<table>
<thead>
<tr>
<th>INR Range (warfarin alone)</th>
<th>n</th>
<th>INR&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Factor X (% of normal)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Warfarin Alone</td>
<td>Warfarin and Argatroban</td>
</tr>
<tr>
<td>0.0-1.0</td>
<td>37</td>
<td>0.91 (0.06)</td>
<td>1.73 (0.30)</td>
</tr>
<tr>
<td>1.0-1.5</td>
<td>79</td>
<td>1.21 (0.14)</td>
<td>2.38 (0.62)</td>
</tr>
<tr>
<td>1.5-2.0</td>
<td>46</td>
<td>1.76 (0.15)</td>
<td>3.81 (1.27)</td>
</tr>
<tr>
<td>2.0-2.5</td>
<td>29</td>
<td>2.21 (0.15)</td>
<td>5.69 (2.26)</td>
</tr>
<tr>
<td>2.5-3.0</td>
<td>12</td>
<td>2.70 (0.15)</td>
<td>6.28 (1.68)</td>
</tr>
<tr>
<td>&gt; 3.0</td>
<td>4</td>
<td>3.32 (0.23)</td>
<td>7.67 (1.10)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Paired values assessed immediately prior to (warfarin monotherapy) and after (co-therapy) a 5-hour infusion of argatroban (1-4 µg/kg/min) in individuals receiving warfarin

<sup>b</sup>Measured using thromboplastin with ISI of 1.78

29%), gingival bleeding (6 subjects, 25%), diarrhea and headache (5 subjects each, 21%), and rectal bleeding (4 subjects, 17%). Injection site reactions and purpura, which occurred at venipuncture and catheter sites, were consistent with trauma from venipuncture or catheter manipulation. Gingival bleeding events were mild in intensity and associated with toothbrushing. Rectal bleeding events were also mild in intensity, described as “blood on toilet tissue [after bowel movement]” or associated with rectal fissure. The timing of these events varied with no trend for association with higher INRs.

One subject receiving warfarin 5 mg/day was withdrawn on day 4 due to 5 episodes of bloody stools, with no bleeding between bowel movements. The warfarin monotherapy INR was 1.5. Physical examination revealed active bowel sounds with a soft abdomen and no evidence of hemorrhoids or fissure; the event resolved without treatment. Subsequent colonoscopy revealed internal hemorrhoids.

No major bleeding occurred. No clinically significant changes occurred in vital signs, physical examination or routine clinical laborato-

Discussion

These results suggest that a reliable estimation of the warfarin monotherapy INR can be predicted from a co-therapy INR, allowing smooth transition from the direct thrombin inhibitor argatroban to warfarin anticoagulation in patients requiring long-term anticoagulation after an acute event. A linear relationship exists between the INR during warfarin monotherapy versus argatroban/warfarin co-therapy that is sensitive to argatroban dose and the ISI of the thromboplastin used. Further, it is linear for each combination of argatroban dose (1, 2, 3 and 4 µg/kg/min) and thromboplastin (ISIs of 0.88 and 1.78) studied for monotherapy INRs up to 3.8 (i.e., throughout the therapeutic range). Hence, this study confirms and augments previous observations concerning the effect of argatroban in vitro on the INR of warfarinized plasma (16).

The inverse prediction equation for a given combination of argatroban dose and thromboplastin can be used to predict monotherapy INRs from INRs during warfarin co-therapy with argatroban 1 or 2 µg/kg/min for thromboplastins used in this study. At these doses, the prediction error is acceptably low (≤±0.4), allowing relatively accurate assessments. For an INR of 4.0 during argatroban 2 µg/kg/min and warfarin co-therapy, the predicted warfarin monotherapy INR would equal 2.5 (95% PI: 2.2 to 2.8) for the lower ISI (0.88) thromboplastin (using Equation 1) and 2.0 (95% PI: 1.7 to 2.3) for the higher ISI (1.78) thromboplastin (using Equation 2). For a dose of 1 µg/kg/min, similar calculations can be performed using Equations 3-4.

Premature discontinuation of argatroban before adequate oral anticoagulation is achieved could potentially lead to new or recurrent thrombosis. Upon cessation of argatroban, it would be prudent to check the INR when the effect of argatroban is negligible (approximately 4 h later [15]) to ensure an actual therapeutic value reflective of warfarin monotherapy.

Linear relationships between co-therapy versus warfarin monotherapy INRs were also demonstrated for the combinations of argatroban 2 µg/kg/min and thromboplastins with ISIs of 1.31 and 2.13. For these thromboplastins, a co-therapy INR of 4.0 predicts warfarin monotherapy INRs of 2.0 (95% PI: 1.6 to 2.4) and 1.9 (95% PI: 1.5 to 2.3), respectively (Equations 5-6). The predicted monotherapy INRs agree closely with that estimated for the combination of argatroban 2 µg/kg/min and the higher ISI (1.78) thromboplastin, suggesting that, in general, argatroban can be discontinued when the co-therapy INR is ≥4.0. Further, for interpreting the relationship between co-therapy versus monotherapy INRs, there appears to be minimal, if any, clinically significant differences among the three thromboplastins with ISIs of 1.31-2.13. While those thromboplastins were of rabbit brain composition, the lower ISI (0.88) thromboplastin contained recombinant human tissue factor. Hence, the differential effects of thromboplastins on the INR relationship may be related to the ISI and/or other variables, such as reagent composition.

For argatroban 3 or 4 µg/kg/min, estimates of warfarin monotherapy INR from the co-therapy INR are more imprecise (prediction error ≥±1) and hence cannot be used to interpret reliably INRs on co-therapy. It may be reasonable in this situation to temporarily reduce the argatroban dose to 2 µg/kg/min and, after re-attaining steady state (approximately 4 h later), use inverse prediction equations for 2 µg/kg/min to assess INR status.
These INR relationships were established in healthy, young males and may vary by laboratory and thromboplastin reagent. Although females were study eligible, males filled enrollment per chronological application. Because vitamin K status and age are important factors in warfarin response, the established INR relationships may be different in females or patients. However, generally similar relationships were demonstrated in vitro when argatroban was added at clinically relevant concentrations to plasma from patients receiving warfarin or healthy donors (16). Variables impacting the INR relationships for argatroban (e.g., dose, choice of thromboplastin) may also be relevant for other direct thrombin inhibitors during oral anticoagulation. The INR system itself has limitations that should be considered when monitoring warfarin monotherapy or co-therapy with a direct thrombin inhibitor. Imprecision of the INR increases with the PT ratio, and higher ISI thromboplastins are associated with a loss of system accuracy and precision, particularly in the upper therapeutic range (21, 22). These limitations probably contributed to the increased variability in INR data in this study at higher argatroban doses, wherein higher co-therapy INRs were typically measured. Confirmation of the reliability of these relationships for interpreting INRs during argatroban/warfarin co-therapy remains to be established in patients.

Co-therapy INRs >7 were attained without major bleeding in this study, and there were no differences between paired factor X levels during warfarin monotherapy versus warfarin/argatroban co-therapy. In the rabbit model, depression of factor X and prothrombin are required for warfarin to protect effectively against tissue factor-induced intravascular coagulation; by extrapolation, factor X depression is required for warfarin’s antithrombotic effects (23). Herein, co-therapy INRs of 2.4 were associated with factor X levels that occur in individuals not adequately anticoagulated with warfarin. Therefore, such increased INRs during co-therapy do not reflect increased warfarin-specific anticoagulant activity but rather synergistic effects on the INR that can be modeled (Equations 1-6).

Co-therapy of argatroban 1-4 µg/kg/min and warfarin 3-6 mg/day was generally safe and well tolerated for 11 days in healthy volunteers. Some minor bleeding occurred, as expected from the pharmacology of anticoagulant drugs. However, there was no apparent relationship between minor bleeding and either the INR or anticoagulant dosage. Also, bleeding did not increase upon continued warfarin dosing and escalated argatroban dosing. For monitoring argatroban, the aPTT is relatively more sensitive than the INR – no subjects receiving argatroban 2 µg/kg/min alone had INRs >2.0 whereas 10 (42%) subjects had aPTTs >2x control. Further, during argatroban and warfarin co-therapy, aPTTs can be used effectively to monitor argatroban, and factor X assays that are insensitive to argatroban interference (e.g., the chromogenic method used herein) may prove useful for supplemental monitoring, if desired.

The ability to prolong the PT/INR is a characteristic of direct thrombin inhibitors as a class (4-11). INRs of 1.4-2.3 were demonstrated using a high ISI (2.9) thromboplastin in patients receiving hirudin 0.1-0.3 mg/kg/h intravenously (4), which includes clinically relevant doses (2, 24). INRs of 1.3-2.4 have been attained with intravenous hirulog 0.05-0.6 mg/kg given over 15 min, although the ISI of the thromboplastin used was not reported (7). Argatroban 2 µg/kg/min also increases the INR, the magnitude of which is sensitive to the thromboplastin used. The differential effects of the thromboplastin used on the prolongation of the PT/INR by other direct thrombin inhibitors remain to be investigated. Further, the INR relationships for other thrombin inhibitors during warfarin co-therapy need to be established to promote safe, efficient transition from intravenous anticoagulation to oral warfarin.

References


Received July 24, 2000 Accepted after resubmission October 31, 2000