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A prospective comparison of three argatroban treatment regimens during hemodialysis in end-stage renal disease

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A prospective comparison of three argatroban treatment regimens during hemodialysis in end-stage renal disease.

Background. We prospectively evaluated 3 treatment regimens of argatroban, a direct thrombin inhibitor, for providing adequate, safe anticoagulation in patients with end-stage renal disease (ESRD) during hemodialysis.

Methods. In this randomized, 3-way crossover study, ESRD patients underwent hemodialysis sessions of 3- or 4-hour duration using high-flux membranes and each of 3 argatroban treatment regimens (A: 250-μg/kg bolus, with an additional 250-μg/kg bolus allowed; B: 250-μg/kg bolus followed by 2-μg/kg/min infusion; C: steady-state, 2-μg/kg/min infusion initiated 4 hours before dialysis). Pharmacodynamic effects including activated clotting times (ACTs); hemodialysis efficacy including single-pool Kt/V, urea reduction ratio (URR), and circuit flow; and safety through a 3-day follow-up were monitored. Argatroban pharmacokinetic parameters including dialytic clearance were evaluated during regimen C.

Results. Thirteen patients completed 38 hemodialysis sessions (1 patient withdrew consent after 2 sessions). Mean ± SD ACTs increased from 131 ± 14 seconds at baseline to 153 ± 24, 200 ± 30, and 197 ± 33 seconds, respectively, after 60 minutes of hemodialysis using regimens A, B, and C. Across regimens, mean Kt/Vs (1.5–1.6) and URRs (70%-73%) were comparable. No dialyzer was changed; 1 session was shortened 15 minutes because of circuit clot formation. Systemic argatroban clearance increased ∼20% during hemodialysis, without clinically significantly affecting ACTs. Upon argatroban discontinuation, ACTs and plasma argatroban decreased concurrently (elimination half-life, 35 ± 6 min). No thrombosis, bleeding, serious adverse events, or clinically significant changes in vital signs or routine laboratory measures occurred.

Conclusion. Argatroban, administered by each treatment regimen, provides safe, adequate anticoagulation to enable successful hemodialysis in ESRD patients. Argatroban dialytic clearance by high-flux membranes is clinically insignificant.

Key words: argatroban, anticoagulation, hemodialysis, end-stage renal disease.

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Anticoagulation is generally required for effective hemodialysis, and unfractionated heparin is most commonly used for this purpose. However, there are limitations associated with heparin, including dependence on adequate antithrombin levels, unpredictable anticoagulant effects, no inhibition of clot-bound thrombin, and heparin-induced thrombocytopenia (HIT), which is an immune-mediated, prothrombotic reaction to heparin [1]. Antibodies that cause HIT have been detected in up to 12% of patients with end-stage renal disease (ESRD) receiving chronic dialysis [2]. Adverse effects commonly make some alternative anticoagulant options impractical during hemodialysis, such as metabolic and hemodynamic complications with citrate [3], bleeding complications with warfarin [4], and cross-reactivity with HIT antibody with low-molecular-weight heparin and danaparoid [5]. Although used successfully during hemodialysis in some patients, hirudins such as lepirudin, which directly inhibit thrombin, are predominantly renally cleared and associated with an increased elimination half-life and bleeding risk in renal failure, frequent formation of antihirudin antibodies that may alter the agent's pharmacokinetics, poor correlation between plasma drug concentrations and the level of anticoagulation assessed by the activated partial thromboplastin time (aPTT), differences in drug filtration characteristics according to the type of dialyzer used, and possible allergic or anaphylactoid reactions [6, 7].

Argatroban is a rapidly acting, direct thrombin inhibitor that effectively inhibits free and clot-bound thrombin without need of a cofactor [8], has predictable anticoagulant effects [9, 10], and does not induce or potentiate HIT [11]. Unlike hirudins, argatroban is hepatically metabolized [10], is not associated with formation of antibodies to itself [12], and its pharmacokinetics and pharmacodynamics are not significantly affected by renal dysfunction [10]. Prospective data on argatroban anticoagulation during hemodialysis are limited, mainly including Japanese case reports or small studies in patients with antithrombin deficiency [13, 14] or HIT

[15–17]. However, these data consistently indicate that argatroban may be used successfully during dialysis and, hence, suggest that an optimal protocol for its use during high-flux hemodialysis should be developed. Potential dialytic removal of argatroban by high-flux membranes has not yet been precisely estimated.

We report a prospective, randomized, crossover study conducted to establish the adequacy of anticoagulation and safety of 3 treatment regimens of argatroban in patients with ESRD during high-flux hemodialysis. We also investigated the pharmacokinetics of argatroban in this setting, including its dialytic clearance.

METHODS

This prospective, randomized, open-label, 3-way crossover, 2-center, pharmacokinetic-pharmacodynamic study characterized and compared the safety and effects of 3 treatment regimens of argatroban in patients with ESRD undergoing maintenance hemodialysis. The institutional review board at each center approved the study. Subjects gave informed consent. A sufficient number of patients was to be enrolled so that 12 patients completed the study.

Patients and treatment

Patients between 21 and 75 years in age with ESRD on maintenance hemodialysis for at least 3 months were eligible. All patients had a urine output <100 mL/day, Kt/V ≥1.2 within the previous month, an estimated dry weight within 30% of ideal body weight, and were able to achieve dialysis blood flow rates ≥300 mL/min, and to tolerate a study session of up to 9 hours. Females of childbearing potential were required to use medically approved methods of birth control for 7 days before the study and throughout the study. Patients were excluded if they had any clinically relevant abnormality (other than ESRD); uncontrolled cardiovascular, hematologic, respiratory, central nervous system, or gastrointestinal disease; significant hepatic insufficiency (defined as total bilirubin >1.5 mg/dL or transaminase elevations >2 times the upper limit of normal); history of bleeding diathesis, drug allergy of clinical significance, regular alcohol consumption, or chronic alcoholism; surgery or significant physical trauma within the past 3 months; systolic blood pressure >180 mm Hg or diastolic blood pressure >100 mm Hg, unless the investigator felt this would not endanger the subject during the study; morbid obesity; usage of warfarin, other anticoagulants, or nonsteroidal antiinflammatory drugs except aspirin currently, or of phenytoin, cimetidine, rifampin, cyclosporine, or tacrolimus within the past month; or serum albumin <2.5 g/dL, activated clotting time (ACT) >200 seconds, prothrombin time (PT) >16 seconds, international normalized ratio (INR) >1.4, an unexplained aPTT >2 times the upper limit of normal, hematocrit <30%, or hemoglobin <8 g/dL. Patients were also excluded if they had been treated with an investigational drug within the past month, previously randomized into the study, donated >500 mL blood within the past 56 days, or were >3 kg above their estimated dry weight.

Patients were assigned in the order of their enrollment to an argatroban treatment sequence according to a randomized schedule. Patients underwent 3 hemodialysis sessions, each 3 to 4 hours in duration and separated by >48 hours, using high flux CT 190 dialyzer membranes (Baxter, Deerfield, IL, USA) and argatroban (GlaxoSmithKline, Philadelphia, PA, USA) anticoagulation. Ultrafiltration was set to reach the patient's current estimated dry weight. The argatroban treatment regimens were designed to achieve ACTs >180% of baseline (i.e., predosing) during most of the hemodialysis session, and >140% of baseline at the end of the session. In regimen A, patients received a 250-μg/kg bolus at the start of the hemodialysis session and, at the investigator's discretion, an additional 250-μg/kg bolus after 2 hours if the ACT was <140% of baseline. In regimen B, patients received a 250-μg/kg bolus at the start of the hemodialysis session, followed by continuous infusion of 2 μg/kg/min. The infusion was discontinued 1 hour before the end of the session. In regimen C, a continuous infusion of 2 μg/kg/min was started 4 hours before hemodialysis to allow achievement of steady-state concentrations before initiation of hemodialysis. The infusion was maintained during hemodialysis, and discontinued at the termination of hemodialysis. Dose titration up to 5 μg/kg/min was permitted if desired to achieve adequate anticoagulation.

Treatment was not permitted if the baseline ACT exceeded 200 seconds. Argatroban was discontinued if the ACT was >400 seconds for 2 consecutive hours, or if any clinically significant bleeding event occurred.

Assessments

Pharmacodynamics. In each hemodialysis session, the whole blood HemoTec (Medtronic, Englewood, CO, USA) ACT, plasma aPTT, and plasma PT/INR were measured before argatroban was administered; at 15, 30, 60, 120, and 180 minutes after the start of hemodialysis; at the end of hemodialysis (for sessions that lasted longer than 180 min); and at 15 (regimens B and C), 30 (regimens B and C), and 60 minutes after the end of hemodialysis. For regimen C treatment, coagulation assessments were also made 210 and 240 minutes after starting argatroban (i.e., at −30 and 0 minutes, respectively, before hemodialysis).

Pharmacokinetics. During regimen C treatment, plasma samples for pharmacokinetic analysis were obtained at the same times that pharmacodynamic specimens were obtained. Dialyzer effluent was collected

before the start of dialysis and quantitatively for successive 1-hour periods during dialysis. The total volume of each hourly collection was recorded, and 20 mL aliquots were retained for argatroban analysis. Samples were stored at −70°C until assayed.

Hemodialysis efficacy. All circuits were visually inspected for blood flow and evidence of clot formation during hemodialysis. Serum blood urea nitrogen (BUN) was assessed 5 minutes before hemodialysis, and at the completion of hemodialysis. Hemodialysis efficacy was assessed for each treatment session by means of the single-pool Kt/V, calculated using the Daugirdas formula [18], and the urea reduction ratio (URR), calculated as the change in BUN between the start and end of hemodialysis, divided by the BUN at the start of hemodialysis. During each treatment session, arterial and venous pressures were measured 15, 30, 60, 120, and 180 minutes after the start of hemodialysis, and at the end of hemodialysis. Dialyzer fiber bundle volumes were measured during each regimen at one center according to the unit's protocol using a Renatron II dialyzer reprocessing system with Renalin solution (Minntech Corporation, Minneapolis, MN, USA).

Safety. Patients underwent physical exams 7 days before the first hemodialysis session, and 3 days after the final session, and sitting blood pressure and heart rate, routine clinical laboratory tests (albumin, alkaline phosphatase, total bilirubin, BUN, creatinine, calcium, cholesterol, chloride, glucose, lactate dehydrogenase, potassium, total protein, sodium, transaminases, triglycerides, uric acid, CO_2, hemoglobin, hematocrit, platelets, red blood cells, white blood cells, neutrophils, lymphocytes, monocytes, eosinophils, and basophils), and stool guiac were assessed. Vital signs were also monitored during and after hemodialysis when pharmacodynamic assessments were done. Adverse events were assessed during hemodialysis and at 3-day follow-up.

Analyses

Pharmacodynamics, hemodialysis efficacy, and safety. Pharmacodynamic, hemodialysis efficacy, and safety data were summarized by treatment regimen (and overall for safety), and descriptive statistics were computed. The frequency of ACTs >180% or >140% of baseline values was determined for each assessment time during hemodialysis. For pharmacodynamic and safety data, percentage changes in responses from the baseline value were compared with a change of "0" using the signed rank test (significance level of 0.05). Single-pool Kt/V and URR values were compared between treatment regimens using the analysis of variance (ANOVA) with Bonferroni test (Graphpad Instat program, version 3.05, San Diego, CA, USA).

Pharmacokinetics. Plasma and dialysate concentrations of argatroban during regimen C treatment were measured using liquid chromatography/tandem mass spectrometry [19] at the Worldwide Bioanalysis Department, GlaxoSmithKline, King of Prussia, PA, USA. The argatroban concentration-time profile for each patient was analyzed using Winnonlin version 4.0.1 (Pharsight Corporation, Mountain View, CA, USA). Systemic argatroban clearance (CL) before and during hemodialysis was calculated as the argatroban infusion rate divided by the steady-state plasma concentration. Dialytic clearance was determined using the dialysate recovery method and calculated as the ratio A_{hd}/AUC_{hd}, where A_{hd} was the total recovery of argatroban in dialyzer effluent during hemodialysis (determined by summation of individual recoveries during the successive 1-hour collection periods), and where AUC_{hd} was the area under the plasma concentration-versus-time curve during hemodialysis. The elimination half-life ($t_{\frac{1}{2}}$) was determined by analysis of declining argatroban concentrations following cessation of infusion. The elimination rate constant (k_e) was calculated as $0.693/t_{\frac{1}{2}}$, and the volume of distribution as CL/k_e.

RESULTS

Patients and treatment

The study population included 13 patients with ESRD who completed a total of 38 hemodialysis sessions using argatroban anticoagulation administered as a 250-μg/kg bolus (regimen A), 250-μg/kg bolus plus 2-μg/kg/min infusion (regimen B), or steady-state infusion of 2 μg/kg/min (regimen C). Twelve patients completed the study. One patient completed sessions using regimens A and B, but withdrew consent during the regimen C session; data from this patient were included in the pharmacodynamic and efficacy analyses for regimens A and B and in all safety analyses.

The population was predominantly male ($N = 9$) and African American ($N = 11$; 2 Caucasian patients), with a mean (SD) age of 54 (12) years. Their mean baseline systolic and diastolic blood pressures were 139 (21) and 86 (12) mm Hg, respectively. Their chronic renal failure arose secondary to hypertension ($N = 8$), diabetes mellitus and hypertension ($N = 3$), or polycystic kidney disease ($N = 2$). Vascular access was provided by a tunneled catheter ($N = 5$), arteriovenous fistulas ($N = 6$), or arteriovenous graft ($N = 2$). Seven patients took aspirin daily. At study entry, coagulation measures included a mean (SD) ACT of 131 (14) seconds, aPTT of 43 (12) seconds, and INR of 1.1 (0.1).

Hemodialysis in each session lasted for 4 hours ($N = 8$), 3.5 hours ($N = 2$; 1 of whom had 1 session shortened by 15 min), or 3 hours ($N = 3$). Eleven (85%) of 13 patients received a second bolus at a mean (SD) 125 (14) minutes

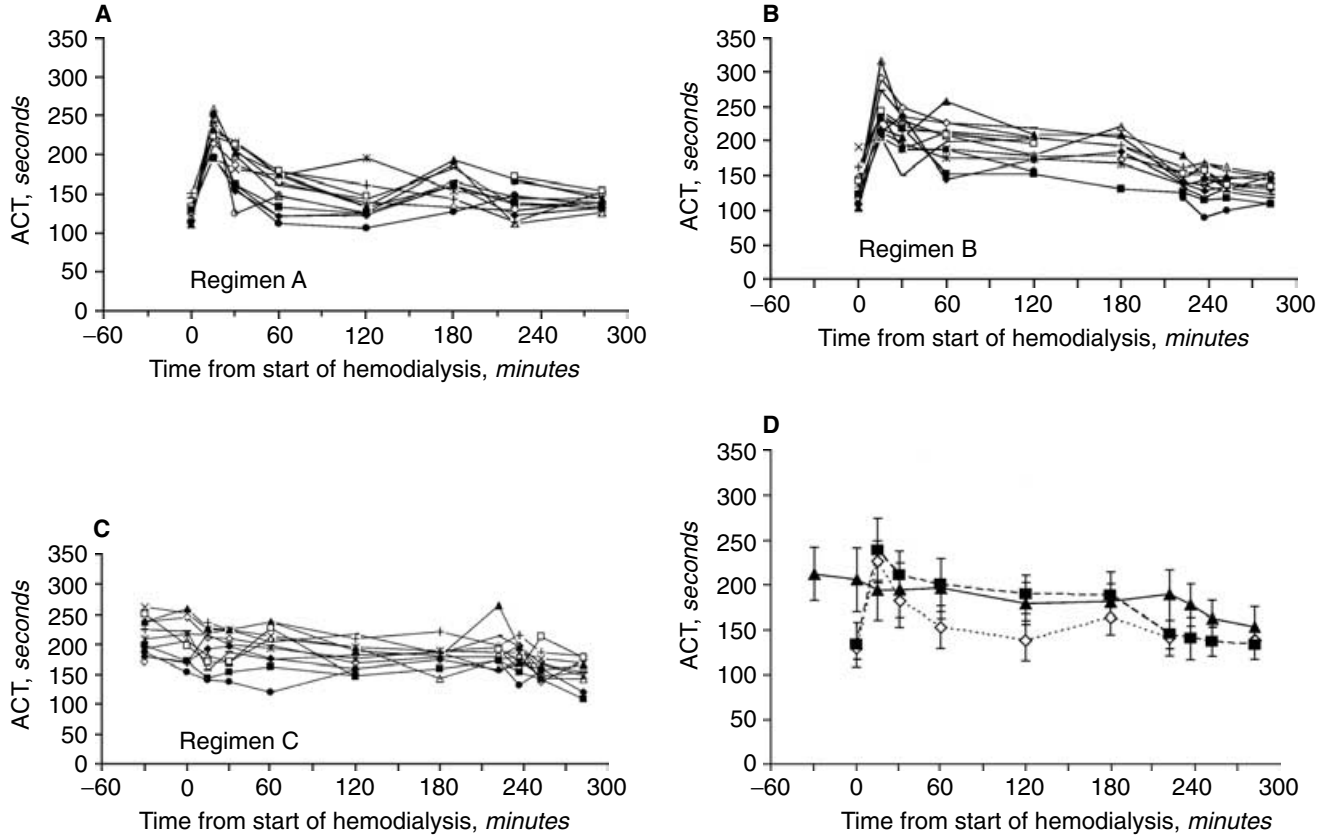

Fig. 1. ACTs in ESRD patients undergoing hemodialysis using argatroban anticoagulation. Argatroban was administered as a bolus (regimen A; *A*), bolus plus infusion (regimen B; *B*), or steady-state infusion (regimen C; *C*). Summarized responses are compared by regimen in (*D*) (regimen A, diamonds; regimen B, squares, regimen C, triangles). Data obtained at the end of hemodialysis and 15, 30, and 60 minutes after the end of hemodialysis are presented, respectively, at 222 minutes (the mean duration of the hemodialysis sessions), and 237, 252, and 282 minutes after the start of hemodialysis. For patients whose sessions lasted 3 hours ($N = 3$), data obtained 180 minutes after the start of hemodialysis are shown with the "end of hemodialysis" results. For figure clarity purposes only, regimen C's predose mean (SD) ACT of 132 (25) seconds is not shown in (D).

after regimen A treatment was initiated. During regimen C treatment, the infusion dose remained 2 μg/kg/min in all but 1 patient, whose dose was adjusted to 3 μg/kg/min after 22 minutes of hemodialysis. Patients received mean (SD) total argatroban doses of 461 (94) μg/kg during regimen A, 573 (52) μg/kg during regimen B, and 912 (143) μg/kg during regimen C.

Pharmacodynamics

For each regimen, argatroban therapy produced generally similar temporal response profiles during hemodialysis for ACTs (Fig. 1), aPTTs (Fig. 2), and, although not routinely used for monitoring parenteral anticoagulation, INRs (data not shown). With the exception of the ACT at 120 minutes and the end of hemodialysis during regimen A treatment, all argatroban regimens significantly prolonged these effect measures (relative to baseline) at each assessment during hemodialysis. Peak responses occurred at the first assessment (i.e., 15 minutes) after bolus administration in regimens A and B. During much of the treatment period, the level of anticoagulation was comparable between regimens B and C. At 60 minutes after the start of hemodialysis, mean (SD) ACTs were 153 (24) seconds in regimen A, 200 (30) seconds in regimen B, and 197 (33) seconds in regimen C; aPTTs in these respective regimens were 66 (15), 91 (28), and 84 (23) seconds. When argatroban was discontinued, coagulation measures began returning to baseline levels in each regimen. Within an hour of the end of hemodialysis, mean (SD) ACTs in regimens A, B, and C, respectively, were 141 (9), 134 (15), and 154 (23) seconds.

ACTs >180% of baseline were relatively infrequent during hemodialysis, occurring in no patient on regimen A, 1 (8%) patient on regimen B, and 2 (17%) patients on regimen C at 60 minutes after the start of hemodialysis. By contrast, ACTs >140% of baseline occurred during hemodialysis with each treatment regimen (Fig. 3). This level of anticoagulation was more consistently achieved when a continuous infusion (with or without a bolus) was used. After 60 minutes of hemodialysis, approximately 70% of patients receiving regimens B or C, compared with 8% patients receiving regimen A, had an ACT >140% of baseline. With the exception of 2 patients

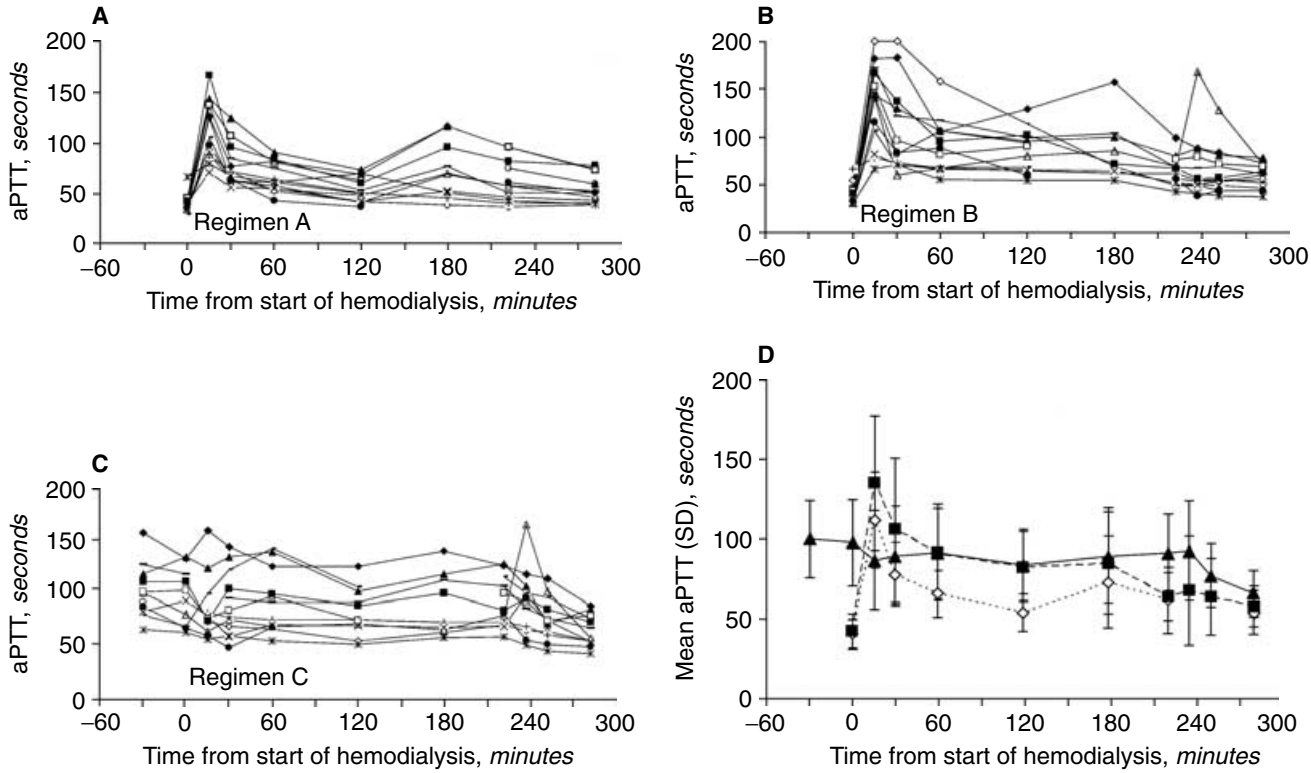

Fig. 2. aPTTs in ESRD patients undergoing hemodialysis using argatroban anticoagulation. Data are presented as described in Figure 1. For figure clarity purposes only, regimen C's predose mean (SD) aPTT of 39 (11) seconds is not shown in (D).

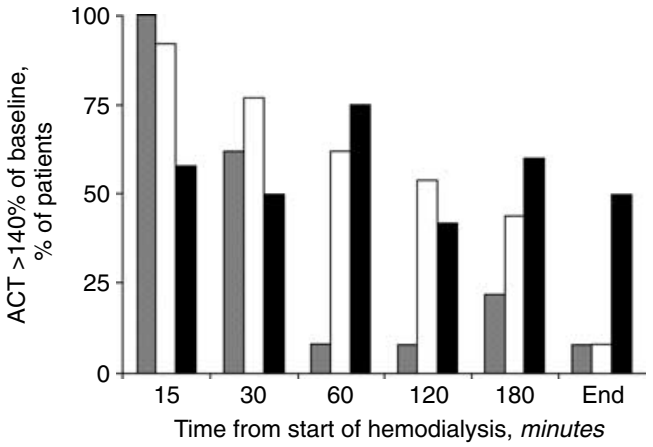

Fig. 3. Frequency of ACTs >140% of baseline during hemodialysis. Patients received argatroban as a bolus (regimen A; striped bars), bolus plus infusion (regimen B, white bars), or steady-state infusion (regimen C, black bars).

receiving regimen C, all patients, irrespective of treatment regimen, had ACTs <140% of baseline within 60 minutes of completing hemodialysis.

Pharmacokinetics

The mean (SD) steady-state plasma argatroban concentration following 4 hours of continuous infusion at 2 μg/kg/min was 673 (176) ng/mL. Systemic clearance was 3.1 (0.9) mL/min/kg before hemodialysis, and 3.4 (1.0) mL/min/kg during dialysis. Dialytic clearance of argatroban measured by the recovery method was 0.7 (0.3) mL/min/kg, suggesting an increase of ~20% in argatroban clearance by hemodialysis. Table 1 summarizes these and other pharmacokinetic parameters of argatroban in ESRD patients, including a mean (SD) elimination half-life of 35 (6) minutes.

Table 1. Argatroban pharmacokinetic parameters in ESRD patients

Parameter	Mean (SD) ($N = 12$)
Steady-state concentration[a] *ng/mL*	
240 minutes after infusion started	673 (176)
360 minutes after infusion started[b]	605 (187)
Clearance *mL/min/kg*	
Systemic, before hemodialysis	3.1 (0.9)
Systemic, during hemodialysis	3.4 (1.0)
Dialytic	0.7 (0.3)
Volume of distribution *L/kg*	0.15 (0.03)
Elimination rate constant, min^{-1}	0.020 (0.003)
Elimination half-life *minutes*	35 (6)

[a] Infusion dose, 2 μg/kg/min.
[b] Equivalent to 120 minutes after start of hemodialysis.

Hemodialysis efficacy

Dialysis dose was effectively delivered using each argatroban treatment regimen, as evidenced by mean URRs

Table 2. Hemodialysis efficacy with argatroban anticoagulation

Parameter	Regimen A ($N = 13$)	Regimen B ($N = 13$)	Regimen C ($N = 12$)
Urea reduction ratio % mean (SD)[a]	73 (4)	72 (5)	70 (4)
Single-pool Kt/V, mean (SD)[a]	1.5 (0.2)	1.6 (0.3)	1.5 (0.2)
Circuit inspection *N*			
Fibrin strands[b]	11	6	7
Dialyzer changed	0	0	0
Session shortened	0	1[c]	0

Regimen A: 250-μg/kg bolus, with additional 250-μg/kg bolus allowed; regimen B: 250-μg/kg bolus plus 2-μg/kg/min infusion; regimen C: steady-state infusion of 2 μg/kg/min.

[a] $P = 0.23$ for urea reduction ratio, and $P = 0.48$ for Kt/V.

[b] Appearance of fibrin strands, early sludging, or early thrombus in the drip bulb of the system; saline flushing was used to prevent further coagulation or thrombus organization.

[c] A 3.5-hour session using regimen B was shortened by 15 minutes.

of 70% to 73% and single-pool Kt/V values of 1.5 to 1.6, which were not different across the regimens (Table 2). In 4 patients with available data, pre- and postdialysis fiber bundle volumes were not significantly different, with the mean (SD) postdialysis values in regimens A, B, and C, respectively, being 95% (1%), 97% (8%), and 96% (6%) of the predialysis values.

No dialyzer was changed. Upon appearance of fibrin strands or early sludging in the dialysis system drip bulb during regimens A ($N = 11$), B ($N = 6$), or C ($N = 7$), saline flushing was used successfully to prevent further coagulation or thrombus organization. One (2.6%) of 38 hemodialysis sessions was shortened due to circuit clot formation. This event occurred after 3.25 hours of hemodialysis (regimen B), and because only 15 minutes remained in the patient's session, the dialyzer was not changed. In this patient, ACT values during hemodialysis using regimens A, B, and C, respectively, were 122 to 228, 151 to 206, and 185 to 224 seconds, and the infusion dose was adjusted to 3 μg/kg/min during regimen C.

Safety

Adverse events were all mild or moderate in severity, and none occurred consistently across regimens or was considered related to study drug (Table 3). The only adverse events reported by more than 1 patient were headache ($N = 3$, with 1 event during hemodialysis in each of 2 patients and 1 event afterwards), peripheral edema ($N = 3$), pain ($N = 2$), and hypotension ($N = 2$).

No patient died or experienced a thrombotic, hemorrhagic, or otherwise serious adverse event. There were no clinically significant changes in heart rate, blood pressure, or clinical laboratory values (excluding the ACT, aPTT, PT/INR, and BUN) during the study.

DISCUSSION

Prevention of hemodialyzer clot formation and maintenance of vascular access patency are challenging problems in ESRD patients managed with hemodialysis. Hemodialyzer clot formation may result in interruption or early termination of hemodialysis sessions, or in subclinical loss of dialyzer fiber bundle volume, causing diminished dialysis delivery. Similarly, vascular access thrombosis may impair or ultimately preclude performance of hemodialysis. Chronic hemodialysis patients are at risk for HIT, a hypercoagulable state triggered by heparin. The antibodies that cause HIT have been detected in up to approximately 1 in 8 ESRD patients [2]. The presence of these antibodies, even in the absence of thrombocytopenia, has been associated with significantly increased thrombotic morbidity in patients with acute coronary syndrome [20, 21]. Although catastrophic thrombotic events associated with HIT such as stroke, peripheral occlusion with gangrene, and myocardial infarction [22, 23] are clinically obvious, more subtle events including arteriovenous graft and hemodialyzer clot formation may not be recognized as associated with heparin treatment. Likewise, the platelet count in HIT may fall more than 30% from baseline yet still be within the "normal" range, further obscuring the association. These concerns, together with other known limitations of heparin [1], has led to increasing interest in the use of alternative anticoagulants in patients with ESRD, including those at risk for HIT, during hemodialysis.

Direct thrombin inhibitors, including argatroban and hirudins, represent an anticoagulant class distinct from heparins. These agents exert their anticoagulant effects by directly inhibiting thrombin-catalyzed or induced reactions without need of a cofactor. Direct thrombin inhibitors may be distinguished from one another in part on the basis of their mode of elimination. The major route of elimination of argatroban, unlike the hirudins, is hepatic metabolism, and not renal clearance. As such, argatroban may be a direct thrombin inhibitor of choice in patients with renal impairment, including those with ESRD who are dialysis dependent [6, 24]. There is no specific antidote for direct thrombin inhibitors; however, effect measures typically return to baseline within 4 to 6 hours of discontinuing argatroban therapy [9], and it has been suggested that recombinant factor VIIa may be a useful pharmacologic agent for reversing severe bleeding [25]. Among its other uses, argatroban is approved as an anticoagulant in the United States for prophylaxis or treatment of thrombosis in HIT [22, 23] and in patients with or at risk for HIT undergoing percutaneous coronary interventions [26], and in Japan in nonlacunar stroke [27], chronic arterial occlusion [28], and during hemodialysis in patients with antithrombin deficiency [13, 14]. For prophylaxis or treatment of thrombosis in HIT, the

Table 3. Adverse events

Adverse event	*N* with event (13 patients/regimen)				Total *N* (%)	Total events[a]
	Regimen A	Regimen B	Regimen C	3-day Follow-up		
Headache	1	0	2	0	2 (15.4)	3
Peripheral edema	0	1	2	0	2 (15.4)	3
Pain	1	1	0	0	2 (15.4)	2
Hypotension	0	1	1	0	2 (15.4)	2
Respiratory disorder	1	0	0	1	1 (7.7)	2
Back pain	1	0	0	0	1 (7.7)	1
Anorexia	0	0	1	0	1 (7.7)	1
Dyspepsia	0	0	1	0	1 (7.7)	1
Nausea	0	0	1	0	1 (7.7)	1
Vomiting	0	0	1	0	1 (7.7)	1
Myalgia	0	1	0	0	1 (7.7)	1
Dizziness	0	0	1	0	1 (7.7)	1
Cough increased	1	0	0	0	1 (7.7)	1
Rhinorrhea	1	0	0	0	1 (7.7)	1
Upper respiratory infection	0	0	1	0	1 (7.7)	1

Regimen A: 250-μg/kg bolus, with additional 250-μg/kg bolus allowed; regimen B: 250-μg/kg bolus plus 2-μg/kg/min infusion; regimen C: steady-state infusion of 2 μg/kg/min.

[a]All were mild or moderate in severity, and deemed unlikely to be related or unrelated to drug.

recommended argatroban starting dose is 2 μg/kg/min (reduced to 0.5 μg/kg/min in patients with hepatic impairment), adjusted to a target aPTT of 1.5 to 3 times the baseline value.

We conducted this prospective, randomized, crossover study to establish the adequacy of anticoagulation and safety of 3 treatment regimens of argatroban in 13 patients with ESRD during hemodialysis. We also aimed to characterize the pharmacokinetic profile of argatroban in this setting, and determine the extent and significance of any dialytic argatroban removal. The argatroban treatment regimens (250-μg/kg bolus, 250-μg/kg bolus followed by 2-μg/kg/min infusion, or steady-state infusion of 2 μg/kg/min) were designed to target ACTs >180% of baseline values during most of the hemodialysis session. However, such ACTs were infrequently attained and, indeed, unnecessary for adequate anticoagulation with argatroban during hemodialysis. Rather, ACTs >140% of baseline were more common, particularly when the treatment regimen included continuous infusion. Also, with infusion treatment, aPTT values typically were approximately 2 times the baseline value. At the levels of anticoagulation achieved using each of the treatment regimens, argatroban therapy provided adequate, safe anticoagulation to enable effective hemodialysis. Efficacy of hemodialysis was demonstrated by the acceptable delivered dialysis doses and the high frequency of session completions. There was some evidence that the treatment regimens using continuous infusion, compared with bolus only, were more efficacious at minimizing the appearance of fibrin strands or sludging in the dialyzer circuit, perhaps related to their achievement of generally higher levels of anticoagulation. Safety was demonstrated by a lack of thrombotic, hemorrhagic, serious, or drug-related adverse events, as well as no clinically significant changes in vital signs or routine laboratory values. The most common adverse events, which were headache and peripheral edema, are not unexpected in this setting. Furthermore, argatroban's elimination half-life of approximately 40 minutes led to rapid normalization of coagulation parameters after therapy was discontinued. This half-live value and other estimated pharmacokinetic parameters in ESRD patients agreed closely with values reported previously for healthy subjects and patients with severe renal impairment [10, 19]. Additionally, our data indicate that dialytic clearance of argatroban with high-flux membranes, as determined by the dialysate recovery method, is clinically insignificant (approximately 20%).

CONCLUSION

These results help provide practical guidance regarding argatroban treatment strategies in patients undergoing hemodialysis. For example, in hospitalized patients receiving a steady-state argatroban infusion of 2 μg/kg/min for other needs (e.g., prophylaxis or treatment of thrombosis in HIT), and who require hemodialysis, the infusion could simply be maintained during hemodialysis. Although patients in our study did not have active HIT, it is anticipated that this treatment approach would be adequate in such patients. Our findings of a clinically insignificant ~20% increment in argatroban clearance, with no evidence of loss of effect (i.e., stable intradialytic ACTs and aPTTs), suggest no significant risk of dialytic argatroban removal precipitating thrombosis. Also, for most outpatients requiring hemodialysis, or hospitalized patients not currently receiving argatroban, the preferable argatroban treatment regimen for hemodialysis may be a 250-μg/kg bolus followed by a 2-μg/kg/min infusion. If desired, the infusion could be stopped up to an hour in

advance of the anticipated completion of hemodialysis session. In our study, this regimen, compared with bolus treatment only, resulted in more consistent levels of anticoagulation, less fibrin strand formation, and a 112-μg/kg increase in the mean total dose. In a recent case series of critically ill HIT patients with liver dysfunction and acute renal failure requiring continuous renal replacement therapy, the steady-state argatroban dose associated with aPTTs of 1.5 to 2.5 times baseline was approximately 0.5 μg/kg/min [29]. Although our study excluded patients with significant hepatic insufficiency, we recommend a generally similar reduction in argatroban dose (and careful monitoring using the aPTT or ACT) for hemodialysis of the subset of ESRD patients with comorbid hepatic impairment; this remains to be prospectively evaluated. Overall, this treatment guidance should further facilitate safe and effective hemodialysis using alternative anticoagulation with argatroban in ESRD patients.

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