Argatroban for anticoagulation in continuous renal replacement therapy*

Andreas Link, MD; Matthias Girndt, MD; Simina Selejan, MD; Alexander Mathes, MD; Michael Böhm, MD; Hauke Rensing, MD

Objective: **Argatroban, a direct thrombin inhibitor, was evaluated for anticoagulation in continuous renal replacement therapy (CRRT) in critically ill patients with heparin-induced thrombocytopenia type II and acute renal failure. The investigation focused on predictors for the maintenance doses of argatroban with efficacy and safety of argatroban being secondary outcomes.**

Design: **Prospective, dose finding study.**

Setting: **Two intensive care units (medical and surgical) of a university hospital.**

Patients: **Medical and surgical patients (n = 30) with acute or histories of heparin-induced thrombocytopenia type II and acute renal failure with necessity for CRRT.**

Intervention: **CRRT with argatroban for anticoagulation.**

Measurements and Main Results: **Critical illness severity scores Acute Physiology and Chronic Health Evaluation (APACHE)-II, Simplified Acute Physiology Score (SAPS) II, and the indocyanine green plasma disappearance rate (ICG-PDR) were correlated to the argatroban maintenance doses. These diagnostic tools can help to identify patients with the necessity for decreased argatroban doses. The following recommendations for argatroban dosing during CRRT could be determined: a loading dose of 100 μg/kg followed by a maintenance infusion rate (μg/kg/min), which can be calculated from the scores as follows: for APACHE II: 2.15–0.06 × APACHE II ($r = -.81$, $p < 0.001$); for SAPS II: 2.06–0.03 × SAPS II ($r = -.8$, $p < 0.001$); and for ICG-PDR: −0.35 + 0.08 × ICG-PDR ($r = .89$, $p < 0.001$). The efficacy and safety of anticoagulation during CRRT were determined by the steady state of blood urea nitrogen (32.16 ± 18.02 mg/dL), mean filter patency at 24 hrs (98%), and the rate of bleeding episodes. Only two patients developed minor bleeding; no patient developed severe bleeding episodes.**

Conclusion: **In critically ill patients with heparin-induced thrombocytopenia type II and necessity for CRRT critical illness scores (APACHE II, SAPS II) or ICG-PDR can help to predict the required argatroban maintenance dose for anticoagulation. These predictors identify decreased argatroban dosing requirements resulting in effective and safe CRRT. (Crit Care Med 2009; 37: 105–110)**

KEY WORDS: continuous renal replacement therapy; heparin-induced thrombocytopenia II syndrome; argatroban; multiple organ failure

Continuous renal replacement therapy (CRRT) is proven effective for critically ill patients with (acute) renal failure (1, 2). In patients with heparin-induced thrombocytopenia type II (HIT-II) requiring CRRT effective anticoagulation, it is necessary to avoid thrombembolic complications (3, 4). The options for anticoagulant treatment in critically ill patients with HIT-II requiring CRRT are limited and include danaparoid and direct thrombin inhibitors. Although danaparoid has been used in HIT-II for a long time several major drawbacks have been reported. Cross-reactivity with heparin/platelet factor 4 antibodies in 15% of cases (5), prolongation of half-life in renal failure up to 36–48 hours (6), and an increased risk for bleeding events in 46% (7) have been described. Direct thrombin inhibitors, including argatroban and lepirudin, differ in their mode of elimination. The major route of elimination of lepirudin is renal clearance. In anuria prolonged half-lives up to 50 hrs have been reported (8). Furthermore, after 5 days 44% of the patients developed lepirudin antibodies that decrease renal clearance, increase activity, and thus, augment the risk of bleeding (9) contributing to major bleeding complications (10, 11).

In contrast, argatroban is mainly eliminated by hepatic metabolism. As such, argatroban may be the more appropriate direct thrombin inhibitor in critically ill patients with renal impairment and with the necessity for CRRT. Prospective data on argatroban under hemodialysis include case reports and small studies only in patients on intermittent hemodialysis (12–14) or in patients after cardiovascular surgery with cardiopulmonary bypasses (15).

In our study, critically ill patients with HIT-II-syndromes or histories of HIT-II and necessity for CRRT were assigned to an argatroban treatment. The investigation focused on predictors for the maintenance doses of argatroban with efficacy and safety of argatroban being secondary outcomes.

METHODS

Patients and Registration

With approval of the Institutional Review Board, we evaluated all critically ill patients with necessity for CRRT and clinical signs or history of HIT-II syndromes on the medical and surgical intensive care units of the University Hospital of the Saarland from January 2006 to June 2007. HIT-II was defined clinically as an unexplained decrease of more than 50% in platelet count from the patients base-

***See also p. 342.**

From the Klinik für Innere Medizin III (AL, SS, MB,); Klinik für Innere Medizin IV (MG); Klinik für Anästhesiologie und Intensivmedizin (AM, HR), Universitätsklinikum des Saarlandes; D-66421Homburg/Saar, Germany.

The authors have not disclosed any potential conflicts of interest.

For information regarding this article, E-mail: link@med-in.uni-saarland.de

DOI: 10.1097/CCM.0b013e3181932394

line, or a platelet count lower than 100 × 10^9/L while on heparin therapy, or by positive local laboratory tests. HIT-II screening tests were performed at the University Hospital Laboratory using the particle gel immunoassay (ID-HPF-4, DiaMed, Switzerland) for rapid detection and the enzyme-linked immunosorbent assay for discovering antibodies (IgG, IgA, IgM) to heparin-platelet factor 4 complexes. Both HIT-II tests were done for all patients. Critical illness was defined by commonly used scores in intensive care medicine: Acute Physiology and Chronic Health Evaluation II (APACHE-II, 16) and Simplified Acute Physiology Score II (SAPS-II, 17). Thus, critical illness and multiple organ dysfunction syndromes were defined as a minimum SAPS-II score of 30 points.

Inclusion and Exclusion Criteria

Critically ill patients with manifestation or history of HIT-II and necessity for CRRT were treated with argatroban after exclusion of clinically relevant bleeding signs, transient thrombocytopenia, disseminated intravasal coagulopathy, and preexisting chronic hepatic dysfunction (Child-Pugh C). Concomitant treatment was performed according to best medical practice. The decision to anticoagulate with argatroban was made by the physician in charge according to clinical needs and the inclusion and exclusion criteria.

Continuous Renal Replacement Therapy

Continuous venovenous hemodialysis was performed with a polysulfone high-flux hemodialyzer using a roller-pump-driven hemofiltration device manufactured by Fresenius AG (ADM 08; Bad Homburg, Germany) with a bicarbonate dialysate at a flow rate of 2000 mL/hr. The blood flow was 100 mL/min. The ultrafiltration rate depended on clinical requirements (0–200 mL/hr). The hemodialysis tubes and filters were renewed every 24 hrs.

Argatroban Pharmacokinetics

Argatroban (molecular weight 526.66 daltone) is a rapidly acting direct thrombin inhibitor with moderate protein binding (54%), primarily to albumin (20%) and α1-acid glycoprotein (34%). Its short elimation half-life of 35–51 mins and major route of hepatic metabolism (70%) are important aspects for use of argatroban in patients with renal failure; ~14% of the unchanged drug is eliminated via feces and 16% is eliminated renally. During hemodialysis, the dialytic clearance of argatroban was 0.3–0.7 mL/min/kg, suggesting an increase of ~20% in argatroban clearance (15).

Management and Monitoring of Anticoagulation

At the beginning of CRRT, all patients received argatroban at a dose of 100 μg/kg as a bolus injection followed by a continuous infusion of 1 μg/kg/min. Argatroban was applied into the extracorporeal circulation (prefilter injection/infusion). The monitoring of anticoagulation was performed by repetitive measurements of the systemic activated partial thromboplastin time (aPTT) according to standard methods. The anticoagulation regimen was designed to result in a 1.5- to 3-fold elevation of aPTT. The first measurement of aPTT was done 30 minutes after starting CRRT, followed by further controls every 60 minutes until a 1.5- to 3-fold elevated aPTT was reached. If aPTT was below the therapeutic range, the argatroban dose was increased stepwise (in steps of 0.25 μg/kg/min). If aPTT was more than 3-fold elevated, argatroban was discontinued for 2 consecutive hours and stepwise reduced (0.25 μg/kg/min). When the hemofilter systems were routinely changed, the argatroban infusion was continued and no further boluses were given. In all surgical cases, CRRT with argatroban started 24–48 hrs after the surgical procedure.

Assessments for Anticoagulation, Efficacy, and Safety

Anticoagulation. For argatroban dose titration, plasma aPTT was measured before, 30 minutes after starting CRRT, and every hour until a 1.5- to 3-fold aPTT was reached. In cases of a steady state, aPTT was measured twice daily. All hemodialysis tubes and filters were visually inspected for blood flow and evidence of clot formation.

Hemodialysis Efficacy. The hemodialysis efficacy was assessed by the average fall in blood urea nitrogen to steady state, which occurred after a mean of 3.8 days after the beginning of CRRT.

Safety. Patients underwent physical examination, hemodynamic measurements (blood pressure, heart rate) and clinical laboratory tests (hemoglobin, hematocrit, sodium, potassium, platelets, red and white blood cells, urea, creatinine) daily on the intensive care units. Bleeding episodes were defined as actual bleeding noted. They were classified as minor when argatroban infusion had to be paused to restore coagulation and as major when transfusion of blood or coagulation factors became necessary.

Assessments for Hepatic Function

Transaminases, total bilirubin, albumin, and cholinesterase were measured. For dynamic liver function, indocyanine green (ICG-PULSION, Pulsion Medical Systems, Germany) was injected central venously (0.5 mg/kg). ICG is nearly exclusively eliminated in an unconjugated form by the liver into the bile and does not undergo enterohepatic recirculation. Its elimination may be expressed as plasma disappearance rate (ICG-PDR) and can be measured noninvasively at the bedside by transcutaneous pulse densitometry with a finger clip (LiMON monitoring, Pulsion Medical Systems, Germany). Normal values for ICG-PDR are considered to be over 18%/min. In general, ICG removal from the blood depends on liver blood flow, parenchymal cellular function, and biliary excretion (18, 19).

Statistical Analysis

Demographical data and data on efficacy and safety were summarized and descriptive statistics were computed (means ± SD). For all patients the individual argatroban maintenance infusion rates were correlated to the initial cholinesterase levels, ICG-PDR, SAPS II, and APACHE II score (Pearson). Furthermore a regression analysis was performed. A α-error of less than 0.05 was considered statistically significant.

RESULTS

Within 18 months, 34 critically ill patients with clinical signs or history of HIT-II and necessity for CRRT were studied. The incidence for the acute manifestation or history of HIT-II of our critically ill patients on medical and surgical intensive care units during the study period was 1.3%. A manifest HIT-II syndrome was diagnosed in 28 cases; a history of HIT-II in 2 cases. These findings were confirmed by laboratory tests in 26 cases, indicating a specificity of 86%.

Treatment with argatroban was performed on 30 patients. Four patients were excluded from the anticoagulation regimen with argatroban because of preexisting chronic hepatic dysfunction (n = 3) and disseminated intravascular coagulation (n = 1) (Fig. 1). In those cases lepirudin was used for anticoagulation. None of the included patients had been diagnosed with acute or chronic hepatic disease before onset of critical illness. Patient characteristics, diagnosis underlying critical illness, and acute renal failure are shown in Table 1.

Argatroban Infusion Rate and Anticoagulation

Patients received an initial argatroban bolus of 100 μg/kg bolus at the start of

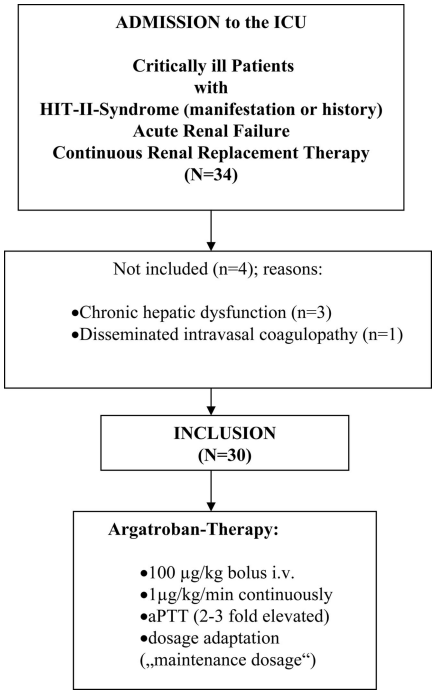

Figure 1. Study flow chart for registered critically ill patients with acute manifestation or history of heparin-induced thrombocytopenia type-II (*HIT*) syndrome and acute renal failure with necessity for continuous renal replacement therapy. Thirty patients were included and argatroban therapy was initiated; four patients were excluded. *ICU*, intensive care unit; *i.v.*, intravenous; *aPTT*, activated partial thromboplastin time.

Table 1. Baseline characteristics of argatroban treated patients

Characteristic	Argatroban in Continuous Renal Replacement Therapy
n	30
Age (yrs)	67.1 ± 14.2
men/women (n/n)	15/15
HIT-II diagnosis	
By history	2
By clinical signs	28
By laboratory test	26
Reasons for critical illness and acute renal failure	
Septic shock	9
Cardiogenic shock	10
Acute decompensation of a chronic renal failure	3
Acute ischemia (limb ischemia; mesenteric infarction)	2
Polytrauma	1
“open heart” surgery	5
Critical illness prognostic scores	
Acute Physiology and Chronic Health Evaluation II	26 (18; 34)
Acute Physiology Score II	45 (30; 66)
Dialysis efficacy	
Activated partial thromboplastin time (sec)	82 ± 16
CRRT duration (hr)	132 ± 122
BUN	
Pretreatment BUN (mg/dL)	55.1 ± 25.9
Steady-state BUN during continuous renal replacement therapy (mg/dL)	32.2 ± 18.0
Filter patency at 24 hrs (%)	98
Liver function	
CHE*10^3 U/L	2.8 ± 1.1
Albumin (g/L)	25.5 ± 6.3
Bilirubin (mg/dL)	2.8 ± 5.9
Indocyanine green plasma disappearance rate (%/min)	14.6 ± 3.9
Bleeding signs and thrombembolic complications	
Major bleedings (patients, n)	0
Minor bleedings (patients, n)	2
Thrombembolic complications (patients, n)	1

Age, gender, reasons for critical illness and acute renal failure, critical illness prognostic scores (Acute Physiology and Chronic Health Evaluation II, Simplified Acute Physiology Score II), dialysis efficacy, liver function test (e.g., indocyanine green plasma disappearance rate), bleeding signs and thrombembolic complications. Parameters are given as mean ± SD respectively range (prognostic score).

HIT-II, heparin-induced thrombocytopenia; CCRT, continuous renal replacement therapy; CHE, cholinesterase.

CRRT followed by continuous infusion of 1 μg/kg/min. The bolus administration resulted in a peak response of anticoagulation with aPTT >140 seconds within 30 minutes without registration of any bleeding signs. The following argatroban infusion rate of 1 μg/kg/min resulted in an effective anticoagulation with 2- to 3-fold elevated aPTT within 60 minutes. In 22 cases the infusion rate had to be reduced (average rate 0.7 μg/kg/min; range, 0.1–1.5 μg/kg/min). In 5 cases the infusion rate was increased up to 1.2–1.5 μg/kg/min. The median duration before patients reached their target aPTT was 5 hours (range 0–14 hours). After achieving therapeutically effective levels of anticoagulation (aPTT 70–90 seconds) the infusion rate of the continuous argatroban application remained unchanged during the whole treatment period. There was no evidence of loss of the argatroban effect during the whole CRRT period. Five patients with a CRRT were treated for more than 10 days. In these cases no loss of effect of argatroban was observed and no increase of the infusion rate was necessary.

Argatroban Infusion Rate in Critically Ill Patients

Although none of our critically ill patients included for argatroban anticoagulation had a history of liver disease the clinical chemistry tests for hepatic function were changed in many individuals. Laboratory parameters for hepatic destruction such as aspartate aminotransterase and alanine aminotransterase had a wide range (318 U/L; minimum 10, maximum 2168 U/L). Parameters for hepatic function of synthesis, e.g., cholinesterase ranged from normal to decreased levels (2.86×10^3 U/L; minimum 0.87, maximum 5.48×10^3 U/L). The maintenance argatroban dose showed no statistically significant correlation to parameters of hepatic synthetic function, like albumin concentration and cholinesterase activity ($r = .53$, not significant, n = 30, Fig. 2). At low argatroban dosages (0.1 μg/kg/min), patients had a wide scatter of albumin and cholinesterase levels. Therefore, the adequate argatroban dose could not be predicted from these parameters. The present data show that patients with reduced clinical chemistry markers of liver synthesis (albumin, cholinesterase) required up to 90% less argatroban infusion rate compared to the manufacturer's recommendations. Using dynamic hepatic tests of liver clearance activity like ICG-PDR we measured a significant correlation to the effective argatroban maintenance infusion rate ($r = .89$, $p < 0.001$, n = 23, regression analysis: argatroban infusion rate [μg/kg/min] = $-0.35 + 0.08 \times$ ICG-PDR, Fig. 3). Individuals with the need for low argatroban maintenance doses could not be

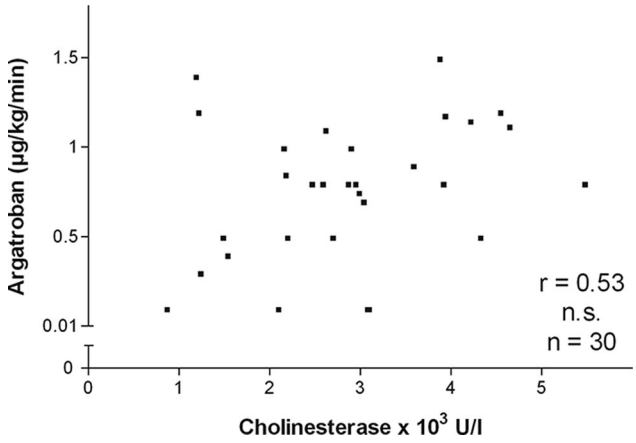

Figure 2. Correlation between serum-cholinesterase and argatroban infusion rate during continuous renal replacement therapy in critically ill patients ($r = .53$, n.s., n = 30). *N.S.*, not significant.

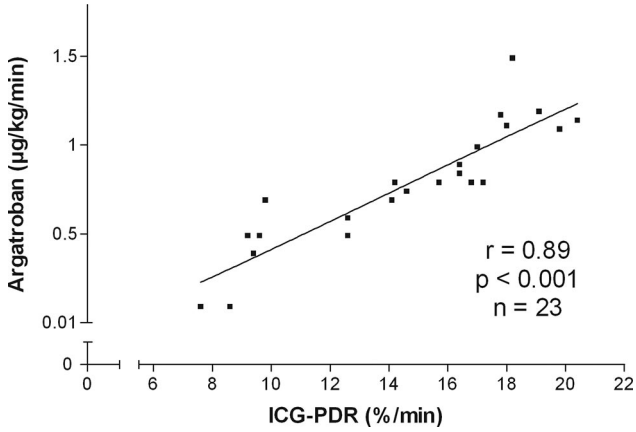

Figure 3. Correlation between indocyanine green plasma disappearance rate (*ICG-PDR*) and argatroban infusion rate during continuous renal replacement therapy in critically ill patients ($r = .89, p < 0.001$, n = 23). Regression analysis: Argatroban infusion rate [µg/kg/min] = $-0.35 + 0.08 \times$ ICG-PDR.

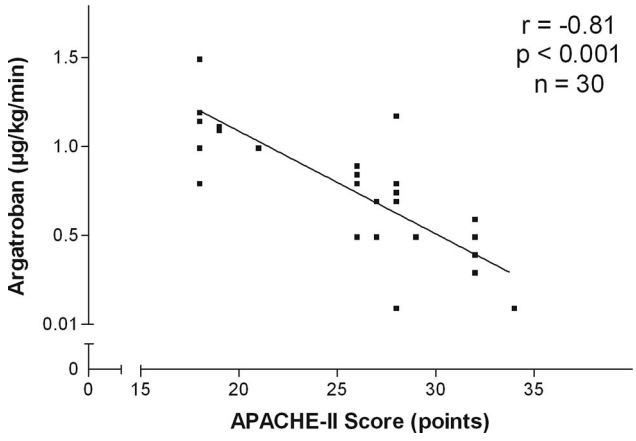

Figure 4. Correlation between Acute Physiology and Chronic Health Evaluation (*APACHE*) II score and argatroban infusion rate during continuous renal replacement therapy in critically ill patients ($r = -.81, p < 0.001$; n = 30). Regression analysis: Argatroban infusion rate [µg/kg/min] = 2.15–0.06 × APACHE II.

identified reliably by cholinesterase levels since some of those with normal or slightly reduced cholinesterase had impaired ICG clearances and low argatroban requirements.

Since scores such as APACHE II or SAPS II are validated for severity and mortality of critical illness, we compared these scores to the maintenance argatroban infusion rate by correlation analysis. We found a highly significant correlation between the continuous argatroban dose and APACHE II score ($r = -.81$, $p < 0.001$, n = 30, regression analysis: argatroban infusion rate [µg/kg/min] = $2.15 - 0.06 \times$ APACHE II, Fig. 4) and SAPS II score ($r = -.8$, $p < 0.001$, n = 30, regression analysis: argatroban infusion rate [µg/kg/min] = $2.06 - 0.03 \times$ SAPS II, Fig. 5). In patients with elevated APACHE II or SAPS II scores, argatroban infusion rates had to be considerably reduced compared with the manufacturer's recommendations.

Argatroban Efficacy and Safety During CRRT

CRRT with argatroban was performed effectively, as evidenced by the average fall in blood urea nitrogen to steady state (32.16 ± 18.02 mg/dL). The hemodialysis tubes and filters were renewed every 24 hours. In three cases a 24-hr period was interrupted because of the appearance of fibrin strands, early sludging or thrombus material in the drip chamber of the dialyzing system. A cumulative number of 165 dialyzing systems were used, and only 2% of the systems had to be changed earlier than the 24-hr standard period.

Two patients developed minor bleeding; argatroban infusion was discontinued until restoration of coagulation. No patient developed severe bleeding episodes or required transfusion. One thrombembolic complication during evaluation of the diagnosis and starting of the CRRT occurred. No new thromboembolic complications were detected during treatment with argatroban.

DISCUSSION

The anticoagulation of critically ill patients with HIT-II requiring CRRT is limited on danaparoid and the direct thrombin inhibitor lepirudin (3, 4) with high risks for bleeding events caused by drug accumulation because of their renal clearance. The new direct thrombin inhibitor argatroban is mainly cleared hepatically. Its recommendations are limited on patients with hemodynamic stability, the absence of chronic liver disease (Child-Pugh score >6), and in cases of renal failure on an intermittent renal replacement therapy (14).

In critically ill patients, hepatic clearance is often impaired by shock-induced reduced liver perfusion. Thus, a de-

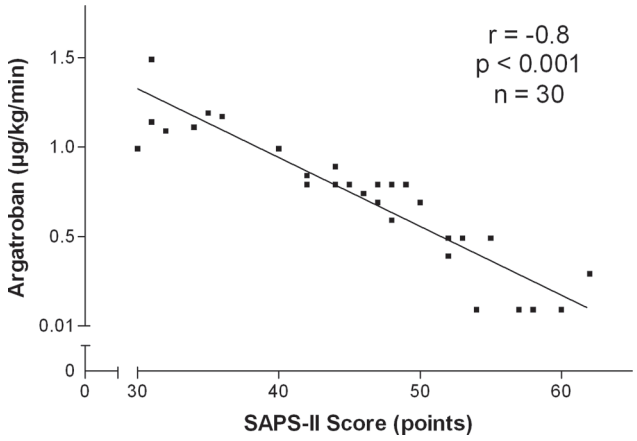

Figure 5. Correlation between Simplified Acute Physiology Score (*SAPS*) II and argatroban infusion rate during continuous renal replacement therapy in critically ill patients ($r = -.8$, $p < 0.001$, n = 30). Regression analysis: Argatroban infusion rate [µg/kg/min] = 2.06–0.03 × SAPS II.

creased hepatic clearance is associated with an increased elimation half-life of argatroban. In critically ill patients with multiple organ dysfunction syndromes a dose reduced ten-fold (0.2 µg/kg/min) is reported to be sufficient and safe for effective anticoagulation (20–23). To evaluate reliable predictors for effective argatroban doses in critically ill patients "static" and "dynamic" hepatic tests and critical illness prognostic scores (APACHE II, SAPS II) were correlated to the argatroban maintenance infusion rate. Monitoring of liver enzymes and hepatic protein synthesis have only limited diagnostic, therapeutic, and prognostic value in hepatic dysfunction (24, 25). We found no statistically significant correlation between the argatroban infusion rate and cholinesterase. Our data show that patients with reduced hepatic protein synthesis required up to 90% decrease of the argatroban infusion rate, but normal hepatic protein synthesis does not exclude the need for a dose reduction.

The dynamic hepatic clearance test ICG-PDR is currently a valuable tool for assessment of liver function in critically ill patients and correlates well with the outcomes in critcally ill patients (18, 26, 27). It has the advantage of noninvasive testing at the bedside by a transcutaneous system and providing results within a few minutes. We measured a significant correlation between the effective argatroban infusion rate and ICG-PDR. Our data suggest that ICG-PDR can help to identify those patients who have decreased argatroban dosing requirements, presumably related to occult hepatic dysfunction. Beiderlinden et al (23) did not observe a correlation between argatroban maintenance doses and ICG-PDR. They have investigated a population of critically ill patients in whom almost 45% did not require CRRT whereas in our population all patients received CRRT. Therefore, hepatic clearance appears to be effective to estimate argatroban dosages in patients with completely extinct kidney function. Nevertheless, ICG-PDR has not reached a widespread clinical application. We therefore tested the relation between the severity of critical illness scores, APACHE II (16) and SAPS II (17), and the argatroban maintenance infusion rate. For both scores, a strong correlation was observed. In critically ill patients with necessity for CRRT our argatroban dosing recommendations can be summarized as follows: after a loading dose of 100 µg/kg, the maintenance infusion rate may be calculated from the current ICG-PDR value, APACHE II value, or SAPS II value based on regression analysis. The use of these regression equations could result in a more rapid target aPTT attainment and lower cases of argatroban overdose.

Efficacy of hemodialysis was demonstrated by an adequate decrease in blood urea nitrogen and the high mean filter patency at 24 hours (98%). Only minor bleedings were observed in only 6.6% of the patients. This bleeding rate was comparable to rates for argatroban-treated patients overall from the multicenter retrospective studies (28).

One might argue that the study is limited by the small sample size and missing measurements of argatroban concentrations, its clearance and metabolites. As described recently the dialytic clearance of argatroban with high-flux membranes is clinically insignificant (~20%) (15). There is no specific antidote for direct thrombin inhibitors; however, effect measures typically return to baseline within 4–6 hrs after discontinuation of the argatroban therapy, and it has been suggested that recombinant factor VIIa may be a useful pharmacologic agent for reversing severe bleeding (29). The observed safety and efficacy of argartoban were achieved by targeting a high PTT range, daily dialyzer changes, low blood flow rates, and low filtratrion fractions. However, this first report on argatroban anticoagulation in critically ill patients with HIT and CRRT sets the stage for a larger trial in these complex medical conditions.

In conclusion, this study is important for several reasons. First, the initial SAPS II evaluation and/or ICG-PDR measurement are suitable tools for the prediction of the required argatroban maintenance dose in critically ill patients with HIT-II syndromes and necessity for CRRT. Second, the anticoagulation with argatroban is efficient and safe, but dose reductions down to 0.1–1.0 µg/kg/min are required. Third, argatroban appears to be a suitable anticoagulant in critically ill patients with HIT syndrome undergoing CRRT.

ACKNOWLEDGMENTS

We are indebted to Project Director Dr. S. Graeber (Institute for Medical Biometry, Epidemiology and Medical Informatics, University of the Saarland, Germany) for statistical support and reviewing the manuscript.

REFERENCES

1. Buchardi H: History and development of continuous renal replacement techniques. *Kidney Int Suppl* 1998; 66:S120–S124
2. Bellomo R, Ronco C: Continuous renal replacement therapy in intensive care unit. *Intensive Care Med* 1999; 25:781–789
3. Keeling D, Davidson S, Watson H: The management of heparin-induced thrombocytopenia. *Br J Haematol* 2006; 133:259–269
4. Oudemans-van Straaten MH, Wester JPJ, de Pont ACJM, et al: Anticoagulation strategies in continuous renal replacement therapy: Can the choice be evidence based? *Intensive Care Med* 2006; 32:188–202
5. Magnani HN: Heparin-induced thrombocytopenia (HIT): An overview of 230 patients treated with Orgaran (Org 10172). *Thromb Haemost* 1993; 70:554–561
6. Polkinghorne KR, McMahon LP, Becker GJ: Pharmocokinetic studies of dalteparin (Fragmin), enoxaparin (Clexane), and danaparoid

sodium (Orgaran) in stable hemodialysis patients. *Am J Kidney Dis* 2002; 40:990–995
7. Lindhoff-Last E, Betz C, Bauersachs R: Use of a low-molecular-weight heparinoid (danaparoid sodium) for continuous renal replacement therapy in intensive care patients. *Clin Appl Thromb Hemost* 2001; 7:300–304
8. Fischer KG: Hirudin in renal insufficiency. *Semin Thromb Hemost* 2002; 28:467–482
9. Eichler P, Friesen HJ, Lubenow N, et al: Antihirudin antibodies in patients with heparin-induced thrombocytopenia treated with lepirudin: Incidence, effects on aPTT, and clinical relevance. *Blood* 2000; 96:2373–2378
10. Kern H, Ziemer S, Kox WJ: Bleeding after intermittent or continuous r-hirudin during CVVH. *Intensive Care Med* 1999; 25: 1311–1314
11. Muhl E, Siemens HJ, Kujath P, et al: Therapy and monitoring of heparin-induced thrombocytopenia type II in critically ill patients during continuous venovenous hemodiafiltration: Comparison of aPTT and ecarin clotting time for monitoring of r-hirudin therapy. *J Intensive Care* 2002; 17:34–40
12. Matsuo T, Yamada T, Yamanashi R, et al: Anticoagulant therapy with MD805 of a hemodialysis patient with heparin-induced thrombocytopenia. *Thromb Res* 1990; 58:663–666
13. Koide M, Yamamoto S, Matsuo M, et al: Anticoagulation for heparin-induced thrombocytopenia with spontaneous platelet aggregation in a patient requiring haemodialysis. *Nephrol Dial Transplant* 1995; 10:2137–2140
14. Murray PT, Reddy BV, Grossman EJ, et al: A prospective comparison of three argatroban treatment regimes during hemodialysis in endstage renal disease. *Kidney Int* 2004; 66: 2446–2453
15. Koster A, Buz S, Hetzer R, et al: Anticoagulation with argatroban in patients with heparin-induced thrombocytopenia antibodies after cardiovascular surgery with cardiopulmonary bypass: First results from the ARG-E03 trial. *J Thorac Cardiovasc Surg* 2006; 132:699–700
16. Knaus W, Draper E, Wagner D, et al: APACHE II: A severity of disease classification system. *Crit Care Med* 1985; 13:818–832
17. Le Gall JR, Lemeshow S, Saulnier F: A new simplified acute physiology score (SAPS II) based on a European/North American multicenter study. *JAMA* 1993; 270:2957–2963
18. Kimura S, Yoshioka T, Shibuya M, et al: Indocyanine green elimination rate detects hepatocellular dysfunction early in septic shock and correlates with survival. *Crit Care Med* 2001; 29:1159–1163
19. Sakka SG, Reinhart K, Meier-Hellmann A: Prognostic value of the indocyanine green plasma disappearance rate in critically ill patients. *Chest* 2002; 122:1715–1720
20. Arpino PA, Hallisey RK: Effect of renal function on the pharmacodynamics of argatroban. *Ann Pharmacother* 2004; 38:25–29
21. Williamson DR, Boulanger I, Tardif M, et al: Argatroban dosing in intensive care patients with acute renal failure and liver dysfunction. *Pharmacotherapy* 2004; 24:409–414
22. Levine RL, Hurstling MJ, McCollum D: Argatroban therapy in heparin-induced thrombocytopenia with hepatic dysfunction. *Chest* 2006; 129:1167–1175
23. Beiderlinden M, Treschan TA, Görlinger K, et al: Argatroban anticoagulation in critically ill patients. *Ann Pharmacother* 2007; 41: 749–754
24. Reichling JJ, Kaplan MM: Clinical use of serum enzymes in liver disease. *Dig Dis Sci* 1988; 33:1601–1614
25. Shakil AO, Kramer D, Mazariegos GV, et al: Acute liver failure: Clinical features, outcome analysis, and applicability of prognostic criteria. *Liver Transpl* 2000; 6:163–169
26. Sakka SG: Assessing liver function. *Curr Opin Crit Care* 2007; 13:207–214
27. Sakka SG, Reinhart K, Meier-Hellmann A: Prognostic value of the indocyanine green plasma disappearance rate in critically ill patients. *Chest* 2002; 122: 1715–1720
28. Lewis BE, Wallis DE, Berkowitz SD, et al: Argatroban anticoagulant therapy in patients with heparin-induced thrombocytopenia. *Circulation* 2001; 103:1838–1843
29. Alving BM: How I treat heparin-induced thrombocytopenia and thrombosis. *Blood* 2003; 101:31–37