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Argatroban for elective percutaneous coronary intervention: The ARG-E04 multi-center study

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ABSTRACT

The synthetic arginine-derived direct thrombin inhibitor argatroban is an attractive anticoagulant for percutaneous coronary intervention (PCI), because of its rapid onset and offset, and its hepatic elimination. Argatroban was approved for PCI in patients with heparin-induced thrombocytopenia (HIT). However, there are limited data about argatroban in non-HIT patients. The objective of this open-label, multiple-dose, controlled study was to examine the safety and efficacy of argatroban in patients undergoing elective PCI.

Methods and results: Of 140 patients randomized to three argatroban dose groups (ARG250, ARG300, and ARG350 with 250, 300, or 350 μg/kg bolus, followed by 15, 20, or 25 μg/kg/min infusion) and one unfractionated heparin (UFH) group (70–100 IU/kg bolus), 138 patients were analyzed. Argatroban dose-dependently prolonged activated clotting time (ACT) with more patients reaching the minimum target ACT after the initial bolus injection (ARG250: 86.1%, ARG300: 89.5%, and ARG350: 96.8%) compared to 45.5% in UFH ($p<0.001$). The patient proportion who did not require additional bolus injections to start PCI was significantly higher in argatroban than in UFH ($p\leq0.002$). Consequently, the time to start of PCI was shortened in argatroban groups. Composite incidences of death, myocardial infarction, and urgent revascularization until day 30 were not significantly different between the groups (ARG250: 2.8%, ARG300: 0.0%, ARG350: 3.2% vs. UFH: 3.0%). Major bleeding was observed only in UFH (3.0%), while minor bleeding occurred in ARG350 (3.2%) and UFH (6.1%, n.s.).

Conclusion: Argatroban dose-dependently increases coagulation parameters and, compared to UFH, demonstrates a superior predictable anticoagulant effect in patients undergoing elective PCI.

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1. Introduction

Argatroban is a synthetic arginine-derived direct thrombin inhibitor recognized to be used for heparin-induced thrombocytopenia (HIT) [1]. Argatroban has favorable pharmacokinetic properties, because it is hepatically eliminated not requiring dose adjustment in patients with renal failure, and has a short plasma half-life [2]. Reversible inhibition of thrombin, in addition to the short half-life, may, thus, translate into a well-defined cessation of its anticoagulation effect. Therefore, argatroban could be a suitable agent for anticoagulation during percutaneous coronary intervention (PCI) especially in conditions that may prohibit the use of heparin.

Argatroban has been approved by the U.S. FDA for anticoagulation in patients with or at risk of HIT undergoing PCI, based on the prospective historically controlled studies ARG-216, ARG-310, and ARG-311. In these studies, 91 aspirin-treated patients with present or previous diagnosis of HIT underwent 112 procedures with a dose of 350 μg/kg given as an intravenous bolus plus 25 μg/kg/min as an intravenous infusion which was adjusted to activated clotting time

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(ACT) of 300–450 s [3]. The concomitant use of argatroban with aspirin, a thienopyridine, and a GPIIb/IIIa inhibitor was studied in a prospective single-arm study with 152 patients at doses of 250 or 300 μg/kg bolus plus 15 μg/kg/min infusion to target an ACT of 275–325 s [4]. However, controlled dose–response data of argatroban in reference to unfractionated heparin is lacking when argatroban is used in combination with dual antiplatelet therapy in patients undergoing contemporary stent-PCI. Therefore, the ARG-E04 trial was designed to study the anticoagulation pharmacodynamics, efficacy and safety in three different dose groups of argatroban in combination with dual antiplatelet therapy compared to standard treatment with unfractionated heparin (UFH).

2. Materials and methods

2.1. Study design

ARG-E04 was a randomized, open, parallel-group, multi-center, multiple-dose study to examine the pharmacodynamics, safety and efficacy of 3 doses of argatroban in patients undergoing elective PCI in comparison with UFH, when both anticoagulants were used in combination with clopidogrel and aspirin. The study was approved by the institutional review board at the University of Frankfurt before its initiation. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. Patient informed consent was obtained. Men and non-pregnant women ≥18 years were eligible. Target population were patients with stable CAD or troponin (Tn)-negative unstable angina (UA) undergoing elective PCI for one or more de novo or restenotic lesions of their native coronary vessels with low to moderate anatomic risk. Patients, who had severe hepatic disorder defined by levels of liver function tests elevated >3 times above the upper limit of normal range (ULN), renal insufficiency defined by serum creatinine >2.0 mg/dl, thrombocytopenia <125,000/μl, documented coagulation disorders or bleeding diathesis, a lumbar puncture within the past 2 weeks, or a history of previous cerebral aneurysm, hemorrhagic stroke, or recent thrombotic stroke within the past 6 months, were excluded. The study was registered with www.clinicaltrials.gov, number NCT00508924.

2.2. Patients

A total of 140 patients (8 from one Belgium center and 132 from 7 contributing German centers) with defined coronary anatomy were randomized to four parallel study arms: three groups with increasing doses of argatroban and one unfractionated heparin (UFH) group. For analysis including activated clotting time (ACT) and clinical events, 2 patients were excluded, in whom PCI was not performed (Full Analysis Set). Although, there was no formal power calculation for this phase II dose-finding study, the sample size was considered sufficient to investigate the tendency of the dose–response as well as the adequacy of anticoagulation in reference to UFH.

2.3. Drug treatments

After randomization, the patients were to receive clopidogrel loading dose (300 mg at least 3 h prior to PCI or 600 mg within 3 h prior to PCI) and oral aspirin 100 mg. Patients in one of the three argatroban arms were treated either (1) with an intravenous (i.v.) bolus of 250 μg/kg argatroban administered over 3 to 5 min before the start of the procedure, followed by the i.v. infusion of argatroban at 15 μg/kg/min until the end of the procedure (ARG250), or (2) with an i.v. bolus of 300 μg/kg argatroban, followed by 20 μg/kg/min i.v. infusion (ARG300), or (3) with an i.v. bolus of 350 μg/kg argatroban, followed by 25 μg/kg/min i.v. infusion (ARG350). Patients in the unfractionated heparin arm received an i.v. bolus of 70–100 IU/kg unfractionated heparin (UFH) before the start of the procedure. A PCI procedure was not to be started until ACT reached the minimum target level of 250 s. ACT was to be checked 5 to 10 min after a bolus dose. If ACT remained below the target of 250 s, patients in one of the three argatroban arms received additional i.v. bolus injections of 150 μg/kg argatroban, whereas patients in the unfractionated heparin arm received additional i.v. bolus injections of 2000–5000 IU UFH to reach and maintain the target ACT. In cases where ACT was 450–800 s or over 800 s, it was recommended to halve the infusion dose or stop infusion, respectively. Subsequent to PCI, the patients were to be treated with dual platelet inhibition by a combination of clopidogrel 75 mg per day together with oral aspirin 100 mg per day. The use of GPIIb/IIIa inhibitors was restricted to bail-out situations or to the patients in whom the target ACT of 250 s could not be reached.

2.4. Endpoints and follow-up

As a primary efficacy endpoint, ACT was determined to establish a dose–ACT response relationship among argatroban groups in reference to standard unfractionated heparin. Based on these assessments, the proportion of patients reaching a minimum target ACT of 250 s after initial bolus injection was analyzed. As a secondary endpoint, the proportion of patients who did not require additional bolus injections to start PCI and during PCI was determined. Further efficacy analyses included specific markers of coagulation mentioned in Laboratory assessments below. Clinical endpoints were the composite incidence and each of all-cause death, myocardial infarction defined by enzymatic (CK-MB≥3×ULN), clinical (clinical syndrome and supportive ECG or CK-MB or CK≥2×ULN), or additional criteria (clinical syndrome and troponin≥2×ULN), or urgent revascularization at day 30, and the incidence of hemorrhagic events during hospital stay according to the definition of major and minor bleeding by Thrombolysis In Myocardial Infarction (TIMI) study group [5], which, except for minor bleeding, were adjudicated by an independent committee. PCI-induced troponin (Tn) elevations were defined as Tn values ≥ULN for the assays used (troponin T≥0.03 ng/ml; Elecsys; Roche Diagnostics, Indianapolis, IN, and troponin I≥0.08 ng/ml; AxSym(R)® TnI reader; Abbott Laboratories, Abbott Park, Ill., USA, or Access® AccuTnI™ assay; Beckman Coulter, Fullerton, CA) measured at approximately 24 h following PCI.

2.5. Laboratory assessments

Plasma samples were obtained from patients at baseline immediately before start of initial bolus of argatroban or UFH, at 5–10 min, 30 min, and every 30 min after the end of initial bolus, at the end of the procedure, and at every 30 min up to 2 h as well as 24 h after the end of the procedure. Two samples of venous blood were collected via a catheter inserted into the cubital vein. One sample was immediately used for on-site determination of ACT using ACT Plus™ (Medtronic GmbH, Düsseldorf, Germany). The other sample was immediately centrifuged at 2000 *g* for 10 min to obtain platelet-poor plasma (PPP), which was kept frozen at −20 °C until analysis in the central laboratory. After transfer of the samples to the central laboratory, activated partial thromboplastin time (aPTT) was determined by aPTT-SP-Liquid (Instrumentation Laboratory, Munich, Germany, normal range 22–26 s) on a coagulation analyzer (ACL® 7000, Instrumentation Laboratory; Milan, Italy).

2.5.1. Ecarin clotting time (ECA-T)

The ECA-T is based on the cleavage of prothrombin to meizothrombin by venom from the snake *Echis carinatus*. Meizothrombin binds to direct thrombin inhibitors, but exhibits only 5% of the clotting activity of thrombin. This test is not sensitive to UFH and detects only direct thrombin inhibition. The ecarin clotting time (Haemosys®-ECA, ECA-T, HaemoSys GmbH, Jena, Germany, normal range 48–52 s) was determined on ACL® 7000.

2.5.2. Prothrombinase-induced clotting time (PiCT)

PiCT is a plasma clotting assay based on the activation of coagulation using a combination of a defined amount of Factor Xa (FXa), phospholipids mimicking platelet membranes or other negatively charged surfaces, and an enzyme, which specifically activates Factor V (FV; FV activator from the Russel's Viper venom). Time to clotting is measured on ACL® 7000. All reagents used in this test were provided by Pentapharm Ltd, Basel, Switzerland (Pefakit PiCT®). The results are given in seconds (normal range 21–24 s).

2.5.3. Endogenous Thrombin Generation (ETP) assay

Thrombin generation was measured using a microtiter plate fluorometer (Fluoroskan Ascent Type 374, Lab-systems; Finland). The first derivative of the fluorescence–time curve reflects the course of thrombin activity in the sample. The parameter of interest in our study was the maximal generation rate, which is the peak of the first derivative (ETP-peak) of the thrombin generation curve.

2.6. Statistics

Demographic and baseline characteristics were compared between groups by means of the analysis of variance (age) or the χ^2 test (gender). Values for ACT, aPTT, PiCT and ETP between the argatroban groups and the heparin group were compared by the Wilcoxon test. The χ^2 test was used to compare the patient proportions among the argatroban groups and the heparin group, which reached a minimum target ACT of ≥250 s after initial bolus. The proportions of patients not requiring additional bolus injections as well as the incidences of clinical endpoints were compared with the Fisher's exact test. No adjustments were made for multiple comparisons. Results were considered statistically significant when p was <0.05. All analyses were calculated with SAS version 8.02 or higher (SAS institute Inc., Cary, NC).

3. Results

Between August 2005 and October 2006, 140 patients (age 42 to 86 years) with defined coronary anatomy were enrolled. Table 1 summarizes patient demographic and baseline data. There were no clinically or statistically relevant differences among treatment groups for any of these characteristics. Patients received concomitant medication in addition to study drug according to their risk factors or the presence of coronary artery disease, and no significant differences were detected among study groups. Three patients, one in each of the ARG250, ARG300, and UFH additionally received GPIIb/

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