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Argatroban dosing in obesity☆

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ABSTRACT

Purpose: Obesity is associated with significant alterations in pharmacokinetic and pharmacodynamic properties. The use of weight based anticoagulants such as argatroban may put obese patients at an increased risk of hemorrhagic events. The purpose of this study was to evaluate argatroban dosing requirements in obese vs non-obese patients.

Methods: This single-center, retrospective cohort study included patients ≥18 years with suspected HIT, treated with argatroban for ≥12 h. Patients were stratified by body mass index (BMI) into obese (BMI > 30 kg/m^2) and non-obese (BMI ≤ 30 kg/m^2) groups. The primary outcome was the median maintenance dose required to achieve two consecutive therapeutic activated partial thromboplastin times.

Results: A total of 121 patients were included. The median BMI in the obese vs non-obese groups was 35.8 vs 24.05 kg/m^2 ($p < .0001$). Although statistically significant, there was no clinically significant difference in median maintenance argatroban dose in obese versus non-obese patients (1 vs 1 μg/kg/min; $p = .01$). In-hospital major bleeding and in-hospital thrombosis also did not differ between the two groups.

Conclusion: Obese patients require similar median argatroban maintenance doses when compared to non-obese patients. Based on these results argatroban should be dosed using actual body weight regardless of BMI.

1. Introduction

Heparin induced thrombocytopenia (HIT) is a potentially lethal immune mediated drug reaction, caused by heparin dependent IgG antibodies produced as a result of the binding of heparin and low molecular weight heparin to platelet factor 4 (PF4). Binding of these antibodies to the heparin-PF44 complex leads to platelet activation, platelet destruction (thrombocytopenia) and the release of pro-thrombotic microparticles. These effects on platelets can lead to thromboembolic complications, such as deep vein thrombosis, pulmonary embolism, stroke, and myocardial infarction. In an effort to reduce the complications associated with this hypercoagulable state, current guidelines recommend immediate discontinuation of all heparin based therapies and initiation of non-heparin anticoagulation upon suspicion of HIT [1].

Argatroban is a highly selective parenteral anticoagulant indicated for the treatment and prophylaxis of thrombosis in patients with HIT. Argatroban has demonstrated the ability to improve HIT associated morbidity and mortality, without significantly increasing bleeding risk [2,3]. Argatroban reversibly binds to the active thrombin site of free and clot-associated thrombin, without interacting with PF4, and thus has no cross reactivity in HIT. Argatroban exhibits linear pharmacokinetics with weight being the most significant predictor of dosing requirements. It is recommended to initiate argatroban at a dose of 2 μg/kg/min based on actual body weight, with dose adjustments to achieve an activated partial thromboplastin time (aPTT) within the therapeutic range of 1.5–3 times the baseline value [2,3]. However, as more than one third of adult Americans have obesity, the appropriate dosing of weight based medications such as argatroban in the obese population has been called into question [4].

Obese patients present several challenges when dosing medications, especially high risk agents such as anticoagulants. Pharmacokinetic and pharmacodynamic parameters including volume of distribution, tissue perfusion and drug clearance are often altered in this patient population [5]. Thus, the linear pharmacokinetics of argatroban may not hold true in obese patients. One of the greatest concerns surrounding the use of anticoagulants such as argatroban in this population is the potential risk of drug accumulation, leading to over anticoagulation and hemorrhagic complications. With the growing prevalence of obesity, clinicians are often faced with uncertainty surrounding the optimal dosing strategies for anticoagulants to balance achieving effective anticoagulation while minimizing bleeding complications [5].

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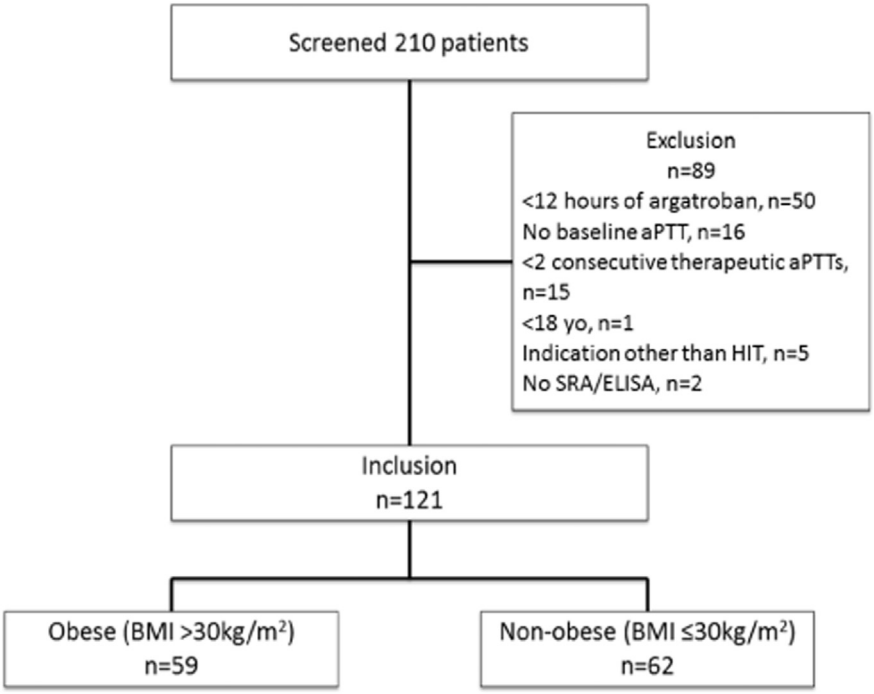

Fig. 1. Number of patients who were screened, assigned to a study group and included in primary analysis.
SRA: serotonin release assay.

Currently only one study exists evaluating argatroban dosing in obese versus non-obese patients [6]. Rice and colleagues [6] found no significant difference in initial or maintenance argatroban infusion rates required to achieve the first therapeutic aPTT between the two groups. However, the study included a total of 83 patients of which only 32 were defined as obese. Given the lack of evidence available in the literature for dosing argatroban in obese patients, the results of the study by Rice and colleagues must be further evaluated. The goal of this study was to compare dosing requirements and outcomes in obese versus non-obese patients treated with argatroban for historical, suspected or confirmed HIT.

2. Methods

This was an institutional review board approved single center retrospective cohort study. The study population was assembled from a pharmacy database query of all consecutive patients treated with argatroban from February 2013 through July 2016 at Ochsner Medical Center, a tertiary academic medical center in New Orleans, Louisiana. Potential cases were identified and retrieved from hospital electronic medical records. The study included patients at least 18 years of age with a diagnosis or suspicion of HIT, or a history of HIT, subsequently treated with argatroban for at least 12 h. Only those patients with a documented weight and height available for the calculation of body mass index (BMI) were included for analysis. BMI was calculated as the patient's actual body weight in kilograms, divided by the square of the patient's height in meters. Patients were stratified according to their BMI: $> 30\,kg/m^2$ (obese group) or $\leq 30\,kg/m^2$ (non-obese group). Patients were excluded if they were pregnant, lacked a baseline activated partial thromboplastin time (aPTT) prior to the start of argatroban, and/or had fewer than 2 consecutive therapeutic aPTTs while on argatroban.

Baseline demographics and laboratory values were collected for all patients. Pertinent characteristics that could alter dosing requirements including level of care and the presence of hepatic or multi-organ dysfunction were also collected. The primary outcome of the study was the median infusion rate required to obtain two consecutive therapeutic aPTTs (therapeutic aPTT defined as 1.5 to 2.5 times the initial baseline value per institution guidelines). Secondary outcomes included time to achieve two consecutive therapeutic aPTT values, in-hospital thrombosis and in-hospital major bleeding following initiation of argatroban. In-hospital thrombosis was defined as a deep vein thrombosis (DVT), pulmonary embolism (PE) or stroke confirmed via ultrasound, or computed tomography imaging. In-hospital major bleeding was defined as overt major bleeding associated with a hemoglobin decrease of ≥ 2 g/dL or leading to a transfusion of ≥ 2 units of packed red blood cells (PRBCs), symptomatic bleeding from a critical organ, or fatal bleeding [7]. Bleeding was further categorized into gastrointestinal, non-gastrointestinal, or intracranial. Both in-hospital thrombosis and major bleeding were identified via manual chart review.

Statistical analysis was performed via Statistical Analysis Software (SAS). Continuous variables were analyzed using the Wilcoxan rank sum test. Chi square or Fisher's exact tests were performed to assess categorical variables. A multivariable analysis was performed a priori to determine if age, gender, weight, BMI, liver failure or multi-organ dysfunction were significant predictors of maintenance dose. Values of $p < .05$ were regarded as significant. Prior literature suggests that patients with multi-organ dysfunction and liver dysfunction require lower doses of argatroban; hence a subgroup analysis excluding these patients was performed to evaluate the effect on the primary outcome [8,9]. Liver failure was defined as history of liver disease documented in the electronic medical record or an aspartate aminotransferase (AST)/alanine aminotransferase (ALT) $\geq 3\times$ the upper limit of normal. Multi-organ dysfunction was defined as a sequential organ failure assessment (SOFA) score of ≥ 2 in ≥ 2 different organ systems [10].

3. Results

A total of 210 consecutive patients received argatroban from February 2013 through July 2016 (Fig. 1). One hundred twenty-one patents met the specified inclusion criteria; 59 patients in the obese group and 62 patients in the non-obese group. Baseline characteristics comparing the obese and non-obese groups are shown in Table 1. Median actual body weights in the obese and non-obese groups were 105 kg and 70.7 kg ($p < .0001$), while BMI was $35.8\,kg/m^2$ and $24.1\,kg/m^2$ ($p < .0001$). There was a predominance of liver dysfunction in the obese group (44.1% vs. 25.8% $p = .03$). Roughly one-third of the study population was admitted to the Intensive Care Unit (ICU).