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CASE REPORT

Apixaban in a Morbid Obese Patient with Atrial Fibrillation: A Clinical Experience Using the Plasmatic Drug Evaluation

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Abstract: We present the case of a 45-year-old man with atrial fibrillation and morbid obesity (weight 128 kg, height 168 cm, BMI 45.4) who was switched from Warfarin 5 mg once daily to Apixaban 5 mg twice daily because he did not achieve at least 60% of the time in therapeutic range. We performed serial determinations of apixaban plasma concentration (at 2, 6, 12, 24 hrs after intake) showing drug levels within reference range, even when the patient lose weight.

Keywords: atrial fibrillation, obesity, non-vitamin k oral anticoagulant, plasma levels, apixaban, weight loss

Introduction

Obesity and Atrial Fibrillation (AF) are major risk factors for ischemic stroke.[1] The increased risk of cerebrovascular events in obese patients may be not only related to the accompanying co-morbidities, but it may also be explained by a low-grade chronic inflammation, which is associated with a prothrombotic/procoagulant state.[2] In obese patients, the glomerular filtration rate (GFR) and renal plasma flow (RPF) exceeded the control value by 51 and 31%, respectively. Consequently, the filtration fraction may increase, enhancing the renal clearance of oral anticoagulants (OACs).[3] Obese patients require greater doses of vitamin K oral anticoagulants (VKAs) and longer lead-in periods may be necessary for achieving therapeutic INR values.[4] Non-vitamin K oral anticoagulants (NOACs) should be preferred over VKAs for long-term stroke prevention in patients with non-valvular AF, according to the better clinical performance both in clinical trial[5–8] and in real-life setting.[9–14] However, based on the lack of clinical data about the efficacy and safety of NOACs in morbidly obese patients, both the International Society on Thrombosis and Hemostasis (ISTH) and the NOACs summary of product characteristics do not recommend the use of NOACs in patients with a body mass index (BMI) >40 kg/m^2 or a weight >120 kg, unless drug-specific peak or trough levels fall within the usual on-therapy range.[15]

Clinical Case

A 45-year-old man with dilated cardiomyopathy, morbid obesity (weight 128 kg, height 168 cm, BMI 45.4 kg/m^2), arterial hypertension, diabetes mellitus, moderate sleep apnea syndrome and paroxysmal atrial fibrillation was admitted to our

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department for implantable cardioverter-defibrillator (ICD) implantation in primary prevention of sudden cardiac death. The mean blood pressure (BP) was 145/90 mmHg over the last two weeks and the glycated hemoglobin (HbA1c) was 8.3%. Trans-thoracic echocardiography showed dilated cardiomyopathy with an ejection fraction (EF), calculated by the Simpson's biplane method, of 30% (n.v. >55%). The medical treatment included Bisoprolol 10 mg once daily (OD); Sacubitril/Valsartan 97/103 mg twice daily (TD), Canrenone 100 mg OD, Furosemide 25 mg TD, Amiodarone 200 mg OD, Metformin 1000 mg three times daily. For the high thromboembolic risk profile (CHA2DS2-VASc Score: 3), the patient was on anticoagulation therapy with Warfarin 5 mg OD; however, he did not achieve at least 60% of the time in therapeutic range (INR Target 2–3), assessed thought the Resendaal method (INR value range: 1.8–3.8). The serum creatinine level was 1.2 mg/dl and the estimated glomerular filtration rate, assessed by the Cockcroft-Gault equation, was 140.7 mL/min/1.73 m2. We switched the therapy from Warfarin to Apixaban (5 mg TD) and we performed serial determinations of apixaban plasma concentration (at 2, 6, 12.24 hrs after intake). The apixaban plasma level was detected by chromogenic anti-factor Xa assay according to the manufacturer's recommendations. The upper reference limit was 141 ng/mL. The clinical biochemistry laboratory of our institution has implemented and maintains a quality management system which fulfils the requirements of the standard ISO 9001:2008 (registration number: IT-74072). The apixaban plasma level at peak (2 hrs after the first intake) was 147 ng/mL, at 6th, 12th (at trough), 14th (2 hrs after the first intake), 18th and 24th hour (at trough) was 102 ng/mL, 83 ng/mL, 143 ng/mL, 110 ng/mL and 85 ng/mL, respectively (Figure 1). At three months from discharge the patient lost weight (weight 105 kg, height 168 cm, BMI 37.2), he showed well-controlled blood pressure (mean BP value 125/80 mmHg) and improved glycemic profile (HbA1c value <7.0%). The serum creatinine level was 1.1 mg/dl and the estimated glomerular filtration rate, assessed by the Cockcroft-Gault equation, was 125.9 mL/min/1.73 m2. The trans-thoracic echocardiography did not show a significant EF improvement (EF value of 33%). The effect of the weight loss, achieved by intragastric balloon procedure and strict diet, did not change the apixaban plasma level at peak (122 ng/mL) and at trough (87 ng/mL) (Figure 2). The patient did not report any thromboembolic or hemorrhagic events or other side effects at twelve months follow-up. The adherence to the apixaban therapy was 95%. The written informed consent has been provided by the patient to have the case details published. We received institutional approval from the University of Campania – Monaldi Hospital Ethical Committee to publish these details.

Discussion

The optimal anticoagulant treatment for stroke prevention in obese patients with atrial fibrillation is still a matter of debate.

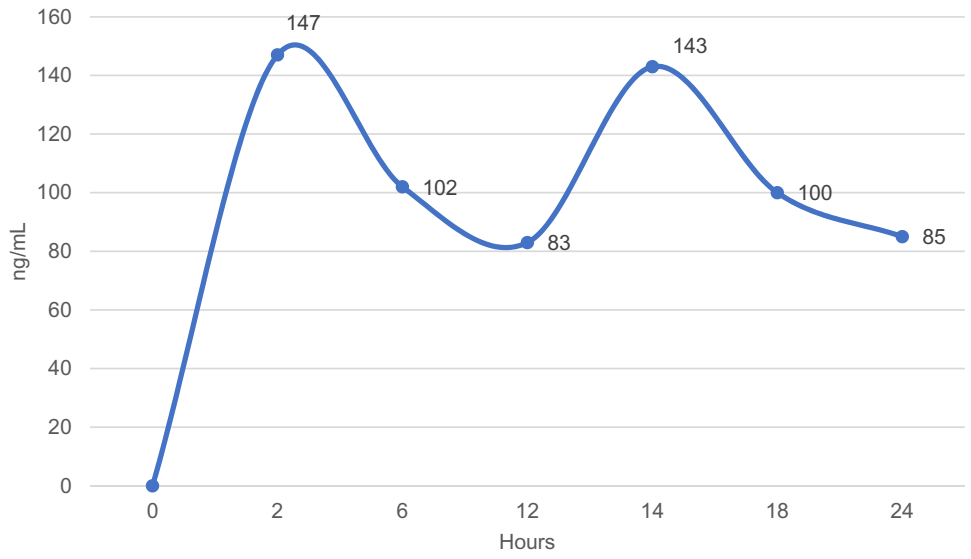

Figure 1 Apixaban plasma level at peak and at trough.

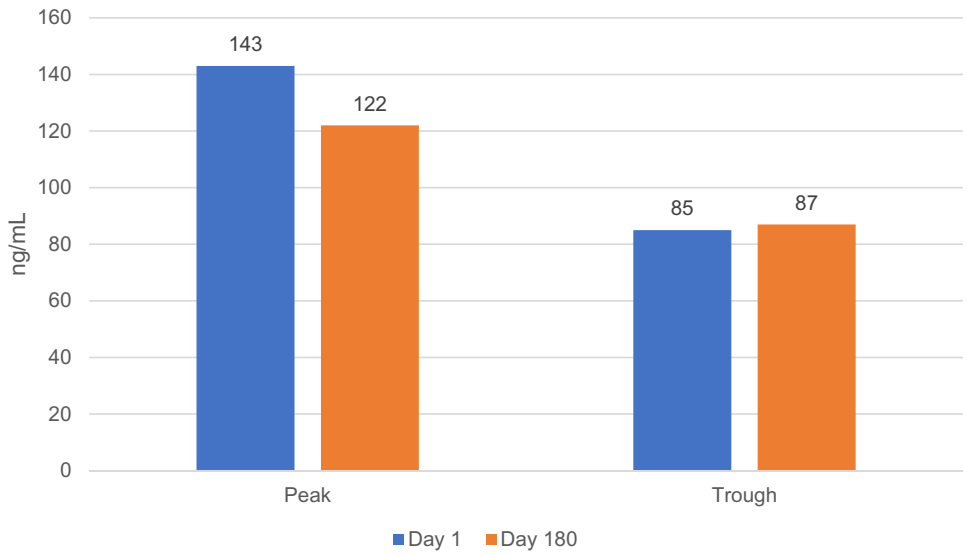

Figure 2 Comparison between apixaban plasma level (peak and trough) at Day 1 and Day 180.

On one hand, VKAs required an increased starting dosage and more time for achieving the international normalized ratio (INR) values within the therapeutic range;[16] on the other hand, no large randomized controlled trial has specifically investigated the efficacy and safety of NOACs in the obese population and the current guidelines recommends avoiding NOACs in morbidly obese patients (BMI >40 kg/m2 or weight >120 kg).[15] Several recent studies (weight-based post hoc analyses and retrospective cohort studies) investigated the clinical performance of NOACs in morbidly obese patients with AF.[17–22] Despite the recommendations of the ISTH guidelines, we switched the oral anticoagulation therapy from warfarin to apixaban (5 mg TD) because of its low volume of distribution[19] and on the basis of the results of a recent weight-based post hoc analysis of the ARISTOTLE trial that investigated the efficacy and safety of apixaban versus warfarin in 1035 obese patients (>120 kg).[16] This post hoc analysis demonstrated that apixaban treatment was associated with a non-significant lower risk for stroke/systemic embolism (0.4% vs 1.18%; 95% CI 0.111–1.063, *P* value= 0.063) and for major bleeding (1.67% vs 2%; 95% CI 0.422–1.636, *P* value= 0.6) respect to VKAs therapy. The evaluation of apixaban serum level at peak and trough time demonstrated the therapeutic drug levels in our morbid obese patient and the stability of apixaban plasma levels even when the patient has lost weight.

The use of plasma level monitoring for NOAC dose-adjustment is discouraged for the vast majority of patients due to the lack of outcome data to support such an approach; however, in rare cases of potentially substantial drug–drug interactions;[23,24] in special population in which the use of NOACs is still debated,[25,26] or in case of not deferrable cardiac or non-cardiac interventional or surgical procedures,[27] a "patient-centered approach", including the plasmatic drug evaluation, might be considered for choosing the more appropriate anticoagulant molecule.

Conclusions

The present clinical case describes a practice experience about the use of plasmatic drug evaluation to assess the apixaban therapeutic levels in morbid obese patients with atrial fibrillation, and suggests the apixaban therapy could be as a valid alternative to VKA therapy in this special population.

Ethics

Informed consent has been provided by the patient to have the case details published. The institutional approval was required to publish the case details by the University of Campania – Monaldi Hospital Ethical Committee.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final

approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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