Abstract

We present the case of an 80-year-old man with atrial fibrillation, morbid obesity (weight 123 kg, height 167 cm, BMI 44.1), high clearance of creatinine and pharmacological polytherapy, in which the serial determinations of edoxaban plasma levels help us to choose the appropriate dose.

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) usually exceeded the control value by 51 and 31%, respectively. Consequently, the filtration fraction may increase, enhancing the renal clearance of oral anticoagulants (OACs) [3]. For this reason, 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 showed both in clinical trial [5-8] and in real life setting [9-13]. 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/m² or a weight >120 kg, unless drug specific peak or trough levels fall within the usual on therapy range [14]. We report a case of an elderly AF patient with morbid obesity, in which the serial determinations of NOAC plasma levels help us to choose the appropriate dose.

Case Report

An 80-year-old man with hypertensive cardiomyopathy, morbid obesity (weight 123 kg, height 167 cm, BMI 44.1), diabetes mellitus, dyslipidemia, chronic obstructive pulmonary disease, severe sleep apnea syndrome, peripheral artery disease of the lower limbs and paroxysmal atrial fibrillation was admitted to our department for arrhythmogenic evaluation. The mean blood pressure (BP) was 135/85 mmHg over the last two weeks and the glycated hemoglobin (HbA1c) was 6.7%. Trans-thoracic echocardiography showed hypertensive cardiomyopathy, severe left ventricular systolic dysfunction, mild mitral and aortic regurgitation.

The medical treatment included Olmesartan 40 mg once daily (OD); Amlodipine 10 mg OD, Doxazosin 4 mg OD; Amiodaron
For the high thromboembolic risk profile (CHA2DS2-VASc Score: 5), 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 Rosendaal method (INR value range: 1.7-3.9). The serum creatinine level was 0.9 mg/dl and the estimated glomerular filtration rate, assessed by the Cockcroft-Gault equation, was 113.9 ml/min/1.73 m2. We switched the therapy from warfarin to edoxaban and we choose the dosage of 30 mg OD for the temporary concomitant use of acetylsalicylic acid 100 mg OD, due to recent angioplasty with stenting for lower extremity artery disease.

We performed serial determinations of edoxaban plasma concentration. The edoxaban plasma level was detected by chromogenic anti-factor Xa assay according to the manufacturer’s recommendations. The expected range of plasma levels at peak and trough for standard was 91-321 dose ng/mL and 31-230 ng/mL, respectively. The clinical biochemistry laboratory of our institution has implemented and maintains a quality management system which fulfills the requirements of the standard ISO 9001:2008 (registration number: IT-74072).

The edoxaban plasma level at peak (2 hours after first intake) was 165 ng/ml, at 4th, 6th and 24th hour (at trough) was 151 ng/ml, 129 ng/ml and 2.2 ng/ml, respectively (Figure 1). Given the low edoxaban plasma level at trough, we increased the dosage of edoxaban from 30 to 60 mg OD and we performed the serial determinations of edoxaban plasma concentration, according the previously used protocol. The edoxaban plasma level at peak (2 hours after first intake) was 343 ng/ml, at 4th, 6th and 24th hour (at trough) was 324 ng/ml, 285 ng/ml and 32.8 ng/ml, respectively (Figure 1).

At the three months follow-up, the hemoglobin value and the estimated glomerular filtration rate, assessed by the Cockcroft-Gault equation, were stable; the patient did not report any side effect. The adherence to the edoxaban therapy was 98%.

Discussion

The optimal anticoagulant treatment for stroke prevention in obese patients with atrial fibrillation is still a matter of debate. On one hand, VKAs required an increased starting dosage and more time for achieving the international normalized ratio (INR) values within the therapeutic range [15]; 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) [14]. Several recent studies (weight-based post-hoc analyses and retrospective cohort studies) investigated the clinical performance of NOACs in morbidly obese patients with AF [16-18].

Despite the recommendations of the ISTH guidelines, we switched the oral anticoagulation therapy from warfarin to edoxaban on the basis of our clinical experience that demonstrated a good clinical performance of edoxaban among elderly patients with AF [19]; moreover, a recent post-hoc analysis of ENGAGE AF TIMI 48 study showed that the efficacy and safety profiles of edoxaban vs warfarin were similar across BMI categories ranging from 18.5 to >40 [20].

The reduced edoxaban dose (30 mg OD) was empirically used for minimizing the bleeding risk related to the concomitant acetylsalicylic acid therapy; to date there are scarce evidence to support a specific antithrombotic regimen in patients with lower extremity artery disease and an indication for oral anticoagulation. The duration of combined therapy should be as limited as possible, depending on the clinical indication and bleeding risk.

We decide to evaluate the edoxaban serum level at peak and trough because the reduced dose was empirically prescribed, not according to the SmPC criteria for dose reduction, and because our patient showed high estimated clearance of creatinine (>95 mL/min); this condition is been related to a decreased efficacy of edoxaban compared with warfarin in the ENGAGE AF TIMI 48 study.

The evaluation of edoxaban serum level at peak and trough time demonstrated a low therapeutic drug levels of edoxaban when 30 mg OD was used, while the correct therapeutic drug levels were reached when edoxaban 60 mg was used. 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, or in special population in which the use of NOACs is still debated, or in case of not deferrable cardiac or non-cardiac interventional or surgical procedures, this approach may be considered.

Conclusions

The present clinical case suggests a possible role of edoxaban plasma levels evaluation for selecting the appropriate dose in elderly patient with morbid obesity and atrial fibrillation and suggests the edoxaban therapy could be as a valid alternative to VKA therapy in this special population.

References