Clinical Biochemistry 118 (2023) 110613

Contents lists available at ScienceDirect

Clinical Biochemistry

journal homepage: www.elsevier.com/locate/clinbiochem

Altered plasma levels of apixaban in major gastrointestinal tract surgery: A case report and review of the literature

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ARTICLE INFO

Keywords:
Apixaban
DOACs
Drug monitoring
Stroke
Bleeding

ABSTRACT

Altered direct oral anticoagulant (DOAC) plasma levels can lead either to spontaneous hemorrhagic or thrombotic complications. We describe a case of suspected altered apixaban disposition in a patient with an upper gastrointestinal cancer resection treated with apixaban for non-valvular atrial fibrillation. Diagnosis of ischemic stroke for left hemiparesis was confirmed due to recent emergence of a hypodense area in the posterior capsular nucleus of ischemic reference in a context of binuclear capsular lacunar lesions. Thus, apixaban underexposure was suspected from anamnestic data and oral anticoagulation was switched to parenteral at the next scheduled dose for stroke recurrence. Before switching apixaban pharmacokinetic analysis was performed and unexpectedly showed apixaban plasma overexposure. After 3 days from the switch, the patient experienced spontaneous bleeding complications, for which the risk-benefit profile of continuing anticoagulant treatment for stroke recurrences warranted treatment discontinuation. Unexpected DOAC plasma exposure may present in special patient populations with thrombotic and bleeding complications. Though universally recognized therapeutic ranges have yet to be established for DOACs, periodic drug monitoring may aid in guiding optimization of DOAC therapy and reduce the risk of adverse events in special patient populations.

1. Introduction

Apixaban is an oral, selective, direct and reversible inhibitor of the coagulation factor Xa (FXaI) which is approved, among other indications, for reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF) [1].

Apixaban exhibits a pharmacokinetic (PK) profile characterized by oral bioavailability of ~50%, no clinically significant food effect, and dose-proportional increases in exposure over the clinical dose range [2,3]. With oral administration of apixaban, the maximum plasma concentration (C_{max}) appears after 3–4 h, with a biphasic decline. It is eliminated mainly by non-renal pathways, being a substrate for CYP3A4/5 and subject to various inhibitors and inducers [4]. Renal clearance accounts only for approximately 27% of total systemic clearance. Apixaban has a half-life of approximately 12 h, enabling a twice daily (BID) administration regimen [1].

Apixaban exhibits region-dependent absorption decreasing progressively along the gastrointestinal (GI) tract, indicating that absorption occurs primarily in the upper GI tract with a pH-independent reduction of ~60% when delivered to the distal small bowel and compared with oral administration [5]. Though direct oral anticoagulants (DOACs), particularly FXaI, seem to be adequately absorbed in cancer patients after gastrectomy [6] this evidence is scarce and limited to isolated case reports/series [7]. Moreover, assessing efficacy and safety of DOAC treatment after GI surgery is difficult due to possible erratic absorption, thus the Update on Guidelines for the Management of Cancer-Associated Thrombosis has recently expressed concerns regarding the use of DOACs in patients with proximal GI resection [8].

According to guidance from the International Council for Standardization in Haematology (ICSH), daily clinical practice does not require monitoring of DOAC plasma concentration [9,10], since all phase III randomized clinical trials (RCTs) comparing DOACs to vitamin K

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https://doi.org/10.1016/j.clinbiochem.2023.110613
Received 10 March 2023; Received in revised form 6 July 2023; Accepted 8 July 2023
Available online 13 July 2023

antagonists have been conducted without dose adjustments based on plasma level measurements [11]. However, these RCTs were conducted on healthy subjects with an intact GI tract, thus plasma level assessment may aid in clinical decision-making in special patient populations [8,11]. We describe a case of an upper-GI cancer-resected patient with unexpected apixaban plasma levels during treatment for non-valvular atrial fibrillation (NVAF).

2. Case presentation

A Caucasian woman in her 80 s, with no comorbidity and family history of cancer underwent esophago-gastro-duodenoscopy for weight loss and microcytic sideropenic anemia, resulting in a diagnosis of infiltrative adenocarcinoma of the stomach. A computed tomography (CT) ruled out distant metastases. Thus, in April 2010 she underwent total gastrectomy with termino-lateral esophageal anastomosis with a jejunal loop at its III distal; the tumor was stage pT3N0M0, poorly differentiated G3 without metastasis to 18 regional lymph nodes (stage IIA as by 8th edition American Joint Committee on Cancer).

According to disease stage she was not a candidate for adjuvant therapy and underwent oncologic follow-up; there was no evidence of disease at 7 years (2017), hence follow-up was discontinued. In 2018 after a diagnosis of NVAF she was prescribed apixaban 2.5 mg orally twice daily for the following characteristics: age $\geq$80 years, body weight $\leq$60 kg as per the summary of product characteristics (SmPC) [1].

In July 2021 she was admitted to the Neurological Department of Galliera Hospital (Genoa, Italy) for left hemiparesis due to a recent hypodense area in the posterior capsular nucleus of ischemic reference in a context of binuclear capsular lacunar areas/lesions. Upon admission to the neurological ward clinical examination revealed, beside left hemilateral deficit, right eyelid ptosis due to herpes zoster ophthalmicus (occurred in June 2021, treated with local antiviral therapy). Blood tests, performed routinely, showed only chronic mild renal impairment (G1, creatinine clearance 78 ml/min/1.73 m^2) which was stable during hospitalization. Concomitant therapy at the time of admission included levothyroxine, doxazosin, bisoprolol, and sertraline. From the anamnestic data of upper GI tract surgery and the evidence of prior and recent onset of ischemic lesions, underexposure of apixaban due to malabsorption was then suspected. Therefore, in order to maintain adequate anticoagulation, the oral treatment with apixaban 2.5 mg BID was switched to subcutaneous enoxaparin 4000 IU daily at the next scheduled dose, as mandated by the SmPC [1,12].

Before switching, a clinical pharmacology consultation was requested to investigate under-absorption of the drug and establish its PK profile. Patient apixaban disposition was at steady state. Thus, blood samples for apixaban quantitation were collected before the next tablet intake (C_{trough}, minimum plasma concentration) and 3 h after intake (C_{max}).

After 3 days from the switch from oral to parenteral anticoagulation the patient developed a haemorrhagic complication with onset of a large spontaneous muscular hematoma in the left lower extremity, thus the risk–benefit profile of continuing anticoagulant treatment for stroke recurrences was for treatment discontinuation. In the following days brain CT documented a further extension of the recent ischemic right nucleobasal lesion, congruent with the worsening of the neurological clinical picture, in the absence of haemorrhagic complications.

Though stationary in the severe neurological picture, the patient experienced a worsening of her overall condition with infectious-inflammatory complications. Then, due to further general clinical worsening, palliative therapy with morphine was started. Despite best supportive care the patient's course was fatal.

3. Method of apixaban plasma quantitation

Apixaban plasma concentrations (shown in Table 1), were determined by an Ultimate 3000 UHPLC (Thermo Fisher Scientific, Milan, Italy) coupled to a TSQ Quantiva Triple Quadrupole system (Thermo Fisher Scientific, Milan, Italy). Plasma was separated from peripheral blood collected in EDTA K3 anticoagulant tubes by centrifugation at 4000×*g* for 5 min. The liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) method was validated according to European Medicines Agency (EMA) ICH M10 guidelines [13] in the concentration range 31.25–500.00 ng/mL. Calibrators and quality controls were obtained by adding apixaban and its deuterated internal standard to blank plasma. The precision and accuracy results obtained from within- and inter-run assays met the acceptance criteria of EMA ICH guideline M10 (±15%). Gradient separation chromatography was carried out using a Thermo Scientific™ Accucore™ Polar Premium column (50 mm × 2.1 mm, i.d. 2.6 m, Thermo Fisher Scientific, Milan, Italy) with mobile phase A consisting of formic acid 0.1% v/v in water and mobile phase B consisting of formic acid 0.1% v/v in acetonitrile. The specific transition of apixaban and IS were detected, with an electrospray ionization source operating in the positive ion mode (spray voltage at 3500 V), using multiple reaction monitoring (MRM): 460.236 → 184.719, 198.836, 443.213 for apixaban; 469.317 → 199.315 for [^{13}C,$^{2}H_8$]-apixaban, respectively.

Table 1
Monitoring of personal apixaban pharmacokinetics.

	Patient	ARISTOTLE trial*
C_{trough}	328 ng/mL	34–162 ng/mL
C_{max}	365 ng/mL	69–221 ng/mL

*ARISTOTLE trial PK ranges for apixaban 2.5 mg BID expressed as 5–95th percentile concentrations [1].

4. Literature review

The literature scoping strategy included PubMed, Scopus and Cochrane databases for inspection. The following search terms were used: apixaban, direct oral anticoagulants, DOACs, gastrectomy, intestinal resection, short bowel syndrome. Two domains ("DOACS" and "GASTRO") were defined by combining the previously reported MeSH terms and keywords using the Boolean operator "OR"; the consequent two domains were crossed with the Boolean operator "AND". The resulting records were checked for duplicates and screened according to PICo-based title-only screening [14]. We did not identify any case reports of unexpected excessive exposure to apixaban after major GI tract surgery, since possible apixaban under-absorption is consistent with proximal GI resection [5,7,8,15]. In fact, Pollak *et al.* [16] could overcome apixaban underexposure in a patient with short-bowel syndrome only with PK-guided dose titration.

However, Huppertz *et al.* [17] described a case of apixaban overexposure and prolongation of half-life in a 75 year-old patient affected by NVAF admitted for suspected stroke (later not confirmed). The patient was only affected by moderate renal impairment (creatinine clearance 40 ml/min) and further genotypic characterization showed that the patient was a CYP3A5*3/*3 non-expressor, a heterozygous carrier of the ABCG2 c.421C/A alleles, and a homozygous carrier of ABCB1 c.2677 T/T and ABCB1 c.3435 T/T. Thus, in the absence of known drug interactions, apixaban underexposure could be partially explained by erratic absorption in GI-resected patients and overexposure by a clearance deficit due to multiple genetic polymorphisms impacting known pathways of elimination.

5. Discussion

Various factors may alter apixaban disposition compromising the safety and efficacy of anticoagulation treatment. Although therapeutic ranges have not yet been established for apixaban and ICSH does not recommend routine therapeutic monitoring [9,10], thrombotic complications seem to occur mainly in patients with very low apixaban

C_{trough} plasma levels (22–145 ng/mL) [18], whereas bleeding ones tend to be more frequent in patients with higher C_{max} plasma levels [19]. DOACs may decrease the risk for stroke but not completely and causes of recurrences are yet to be defined. The RENO-EXTENDED study found that CHA_2DS_2-VASc score after the index event and hypertension are predictive factors of recurrent ischemic events, whereas age, history of major bleeding and the concomitant administration of an antiplatelet agent are predictive factors of bleeding events [20].

In our case, anamnestic history of major proximal GI-surgery coupled with evidence of ischemic stroke in a cerebral context of prior binuclear capsular lacunar lesions suggested erratic absorption of the drug with low plasma levels. Although, the clinical suspicion of apixaban underexposure was well founded and very likely, overexposure was then ascertained. In fact, on the basis of the clinical-anamnestic picture we expected a reduction in apixaban measurable plasma concentrations both at C_{trough} and at C_{max} but, in a totally unexpected manner, and nevertheless being regularly dosed with apixaban 2.5 mg BID to treat NVAF at the reduced strength corrected for age and body weight [1], our patient presented high plasma exposure (C_{trough} + 102.5%, C_{max} + 65.2% of the 95th percentile of concentrations measured in the ARISTOTLE trial) [1,11].

Several clinical conditions may lead to high apixaban plasma concentrations. Interacting drugs in concomitant therapy may increase the overall risk of bleeding [21], whereas renal impairment prolongs apixaban elimination half-life albeit without significantly altering C_{max} [22]. Our patient was affected only by chronic mild renal impairment that was stable during hospitalization, with no concomitant drug interaction impact on apixaban plasma concentration. This prompted us to investigate other causes of the ischemic event beside unexpected apixaban plasma levels, since sources of venous (i.e. deep vein thrombosis with patent foramen ovale) or arterial (i.e. carotid arteriopathy) embolism were ruled-out. Considerable evidence reports that zoster ophthalmicus may be related to an increased risk of cerebral ischemic stroke, manifesting often in the following week or month after onset [23]. In this instance, patient's ischemic event occurred a month apart from diagnosis of zoster infection. Indeed, herpes zoster virus reactivation enhances a vasculitis process in adjacent vessels [24]. Hence, we hypothesize zoster infection might have been additive to the patient's cerebrovascular risk.

In this context a more accurate definition of DOAC optimal therapeutic windows in high-risk patients should be issued to guarantee effective protection from both thrombotic and bleeding cardiovascular complications through periodic therapeutic drug monitoring (TDM) assessment of target concentrations. The availability of a robust and validated assay for clinical use that accurately measures apixaban in biological fluids (e.g., plasma) is then highly desirable to improve the current clinical management of high-risk patients through TDM. There are two main categories of methods for determining DOACs in biological fluids: quantitative methods, which directly assess the blood concentration of DOACs (using HPLC or LC-MS/MS methods), and functional methods (chromogenic anti-Xa assays), which indirectly assess DOAC activity [25–27]. Functional assays are characterized by lower specificity than quantitative methods. In particular, chromogenic anti-Xa (C-FXa) assays are based on p-nitroaniline release from a specific chromogenic FXa substrate. The optical density generated per minute is inversely proportional to the amount of direct FXaI in the sample [9], hence the indirect assessment of DOAC concentration by these assays. LC-MS/MS is considered the gold standard technique for the determination of small molecules in biological fluids due to its high specificity and selectivity [25,28,29]. However, the need for rapid assessment of apixaban concentration in some clinical circumstances could be decisive in the choice of the quantification method. Indeed, one limitation of LC-MS/MS is the prolonged turnaround time relative to other more automated methods. The overall turnaround time of our LC-MS/MS assay was about 4 h. The lack of laboratories performing routine TDM analysis and expensive shipping costs also hinder the use of LC-MS/MS in daily routine clinical practice. In the absence of LC-MS/MS (the considered gold-standard), the ICSH recommends C-FXa assays with apixaban-specific calibrators to be used for the quantification of apixaban levels [9]. Therefore, in institutions that are unable to rapidly measure apixaban by LC-MS/MS, the use of C-FXa assays calibrated for apixaban quantitation could play the main role [30]. One solution is to correlate the anti-Xa assay used to quantify apixaban with LC/MS-MS during assay validation, as reported by Isabelle Gouin-Thibault et al. [31]. Nevertheless, routine use, skill and expertise of the LC-MS/MS center reduces costs and improves performance of the drug quantitation technique.

In this context, accurate quantitation of drugs allows personalized anticoagulation which could benefit special patient populations in achieving normal therapeutic concentrations through PK-guided dose adjustments.

6. Conclusions

Unexpected DOAC plasma exposure may present in special patient populations with both thrombotic and bleeding complications. Though universally recognized therapeutic ranges have yet to be established for DOACs, periodic drug monitoring may aid in guiding optimization of DOAC therapy and reduce the risk of adverse events in special patient populations.

Funding

This research received no external funding.

Ethical statement

The study was conducted in accordance with the ethical standards of the institutional and national research committee and with the 1975 Helsinki Declaration and revised in 2013. Because of the retrospective nature of the study ethical review and approval were waived.

9. Consent statement for publication

Written informed consent has been obtained from the patient at the time of admission to the Hospital to use clinical data for research purposes, following E.O. Ospedali Galliera, Genoa, Italy, Privacy Policy.

CRediT authorship contribution statement

Giammarco Baiardi: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Alessia Cafaro:** Data curation, Validation, Writing – original draft. **Manuela Stella:** Conceptualization, Writing – review & editing. **Michela Cameran Caviglia:** Data curation. **Maria Gabriella Poeta:** Data curation. **Giuliana Cangemi:** Validation, Writing – review & editing. **Francesca Mattioli:** Conceptualization, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors are sincerely grateful to the patient for his participation to the present study and the precious help of the nursing staff.

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