Acute severe renal failure in a patient receiving apixaban: a case report

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ABSTRACT

Because there is little clinical experience with apixaban in patients with severe renal impairment and non-valvular atrial fibrillation, the European Medicines Agency does not advise using it to prevent strokes in these patients. However, only a small number of pharmacokinetic and pharmacodynamic investigations showed how crucially different elimination pathways contribute to the clearance of apixaban. A 74-year-old male patient who was receiving apixaban treatment for stroke prevention in atrial fibrillation was referred to our hospital because of acute severe renal failure brought on by dehydration and abnormally elevated apixaban plasma levels. The patient was treated only with intravenous fluid therapy; serum creatinine recovered slowly over the course of six days, but plasma apixaban levels recovered quickly. No bleeding events have been recorded. Our experience demonstrates the safety profile of apixaban in cases of severe renal failure, but it also emphasizes the need for more research to confirm this evidence.

Introduction

Apixaban is a direct factor Xa inhibitor approved in several countries for stroke prevention in patients with non-valvular atrial fibrillation (AF). Its elimination occurs via multiple pathways including metabolism, biliary excretion and direct intestinal excretion, with approximately 27% of total clearance occurring via renal excretion.[1]

Renal function is an important element for the prescription of apixaban in patients with AF since phase III clinical trials excluded patients with severe renal dysfunction, defined as a creatinine clearance of <25 ml/minute or a serum creatinine concentration >2.5 mg/dl, and patients receiving dialysis.[2,3] However, alternative and efficient elimination mechanisms, other than the renal one, are very important and often underestimated in clinical practice.

Case report

A 74-year-old man presented with acute diarrhea due to laxative abuse. He was on treatment with Apixaban 5 mg bid for stroke prevention in chronic AF and he underwent a scheduled laboratory control for direct oral anticoagulant (DOAC) prescription that documented very high serum creatinine (13.83 mg/dl, ref. value 0.5-1.2 mg/dl) and high through apixaban levels (300 ng/ml, ref. value 26-248 ng/ml; last drug assumption was ten hours earlier).

His past medical history included sinus node dysfunction treated with pacemaker implantation four years before, acquired hypothyroidism, previous Helicobacter Pylori positive duodenal ulcer, benign prostatic hyperplasia, and moderate chronic kidney disease. Six months before serum creatinine level was 1.14 mg/dl and creatinine clearance was 62 ml/min according to the Cockcroft-Gault (CG) equation.

Other medications included bisoprolol 2.5 mg, valsartan 80 mg, and L-thyroxine 75 mcgr.

The patient was admitted to our unit for medical treatment: at the admission the physical examination was unremarkable and the patient was asymptomatic. Glasgow Coma Scale was 15; the pulse was 60 bpm, blood pressure was 110/60 mm Hg, and oxygen saturation was 99%. Bedside echography disclosed no hydronephrosis or obstructive uropathy. Other significant laboratory data: white blood cell 15,850/ml, 80% neutrophils; alanine-aminotransferase (ALT)

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116 U/l (ref. value 0-41 U/l), aspartate aminotransferase (AST) 58 U/l (ref. value 0-50 U/l); thyroid-stimulating hormone 18.57 U/ml (ref. value 0.25-4.5 U/ml), free thyroxine 7.2 pg/ml (ref. value 5.5-12 pg/ml).

The patient was treated with intravenous fluids to reverse pre-renal azotemia. Twelve hours later, while renal function was still severely impaired, apixaban plasma levels had already entered a normal through value (100 ng/ml). Full recovery of apixaban's activity was reached 36 hours after the admission, while creatinine, albeit markedly reduced, was still indicative of severe renal failure (2.92 mg/dl; CG-Cr/Cl 29/ml/min). The clinical course was otherwise uneventful and the patient was discharged on day 6th when serum creatinine was 1.34 mg/dl, creatinine clearance (CG) was 60 ml and AST/ALT quite fully recovered. Apixaban 5 mg bid was then reintroduced and follow-up was regular: two months later, serum creatinine and AST/ALT were in the normal range with ongoing apixaban. Complete patient data and clinical features are reported in Table 1 and Figure 1.

Discussion

Several analyses conducted in healthy subjects demonstrated the limited contribution of renal elimination to overall apixaban clearance.[4,5]

Consistent with this evidence, studies evaluating the effect of mild, moderate, and severe renal impairment on apixaban pharmacokinetic and pharmacodynamic, demonstrated that drug exposure increases with decreasing renal function, but the increase in exposure is modest compared with healthy subjects.[6-8] Furthermore, evidence in patients with end-stage kidney disease (ESKD) showed that plasma drug levels are only marginally increased in these patients, suggesting a good safety profile in such a frail population.[9]

In this context, alternative elimination pathways (cytochrome P450 metabolism, biliary excretion, direct intestinal excretion) play an essential role in drug clearance. These mechanisms are probably responsible for the clearance of apixaban in our patient, despite a temporarily knocked-out renal function.

In our patient, mild asymptomatic hypertransaminasemia (ALT>2 upper normal levels) spontaneously recovered. We speculate a possible drug liver injury (DILI) due to temporally elevated apixaban plasma level. The course of the coagulation test (prothrombin time/activated prothrombin time) matches ALT's peak/decrease, standing for a temporary stunned liver function. Hepatitis B/C and autoimmunity markers were negative; serum alkaline phosphatase was at the upper normal level; liver ultrasound was negative.

Table 1. Main patient's laboratory tests.

	6 Aug	7 Aug	8 Aug	9 Aug	10 Aug	11 Aug	13 Aug	16 Aug	24 Aug
Creatinine mg/dl	13.83	12.54	6.78	2.92	1.91	1.55	1.34	1.23	1.12
Creatinine clearence ml/min	6	7	12	28	43	53	62	67	74
PT ratio	1.65		1.31		1.32				
aPTT ratio	2.19		1.47		1.29				
Apixaban ng/ml	300	100	24	12					
AST U/L	58		48	52	51	51			35
ALT U/L	116		86	82	78	74			73

PT, prothrombin time; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; ALT, alanine-aminotransferase.

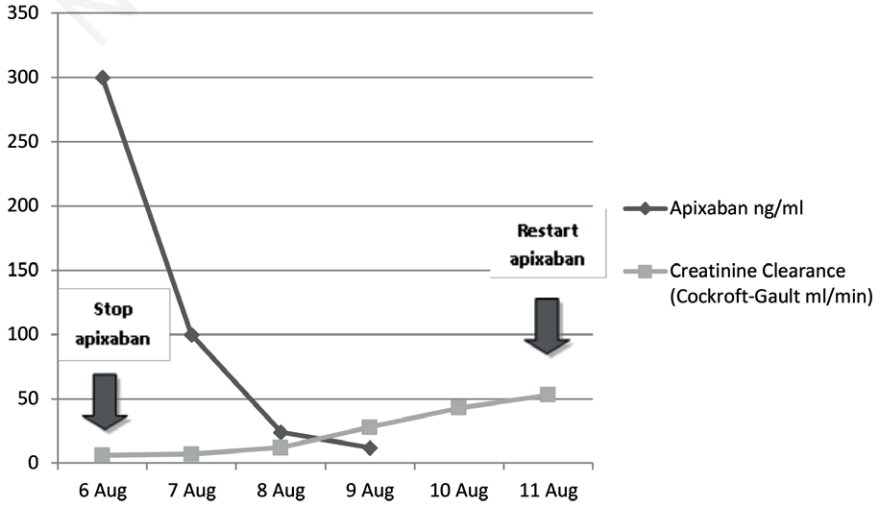

Figure 1. Combined trend of apixaban concentrations and creatinine clearance.

In phase-III clinical trials, an increased risk of hepatotoxicity was not reported.[2-3] An idiosyncratic mechanism is postulated for apixaban-DILI in the very few cases described in post-marketing studies.[10] This is not the case for our patient, because of normal ALT value in the follow-up with apixaban ongoing.

Conclusions

In the United States, the Food and Drug Administration approved the use of apixaban for stroke prevention in AF in patients with ESKD based only on pharmacokinetic data, while in Europe its use is not recommended due to the limited clinical experience.[11-12]

Because of such highly efficient alternative metabolic pathways, this case report from the real world further highlights the safety profile of apixaban, awaiting definitive data on its use in ESKD/hemodialysis.

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