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Case report

Recurrent venous thrombosis under rivaroxaban and carbamazepine for symptomatic epilepsy

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ABSTRACT

Background: The direct oral anticoagulant (DOAC) rivaroxaban, an oral Factor Xa inhibitor, is increasingly used as an alternative to vitamin-K-antagonists (VKAs). Absorption and elimination of DOACs are dependent on the permeability glycoprotein (P-gp) efflux transporter protein system, and DOACs are substrates of the hepatic cytochrome P 450 3A4 (CYP3A4) enzymes. Therefore, drug-interactions may occur when DOACs are administered with drugs affecting the activity of P-gp or CYP3A4 systems. Several antiepileptic drugs like carbamazepine are known to affect P-gp and CYP3A4-activity.

Case report: A 55-year-old male was admitted because of pain and swelling of his right leg spontaneously since 2 days. He was under a therapy with 20 mg rivaroxaban since 4 months because of an unprovoked venous thrombosis of his right leg. He had a history of poliomyelitis at age 6 months, structural epilepsy due to poly-microgyria with complex partial seizures with secondary generalization since age 6 years, why he was treated with carbamazepine (900 mg/d). He reported to be highly adherent to his anticoagulant and antiepileptic medication. Anti-Xa activity was <20 ng/ml according to a rivaroxaban calibrated anti-factor Xa assay. Therapy with rivaroxaban was stopped, and low-molecular-weight heparin, followed by phenprocoumon, was started.

Conclusion: The combination of DOACs with carbamazepine, an inducer of P-gp and CYP3A4-activity, should be avoided since the anticoagulant effect is decreased. There is an urgent need to increase our knowledge and physicians' awareness about the potential of drug–drug interactions of DOACs.

1. Introduction

The direct oral anticoagulant (DOAC) rivaroxaban, an oral Factor Xa inhibitor, is increasingly used as an alternative to vitamin K antagonists (VKAs) in patients with venous thromboembolism and atrial fibrillation [1,2]. DOACs are assumed to overcome some of the limitations of VKAs due to fewer food- and drug-interactions and a more predictable anticoagulant effect, thus allowing fixed dosing without the need for laboratory monitoring.

Intestinal absorption and renal elimination of DOACs are dependent on the intestinal and renal permeability glycopro-

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tein (P-gp) efflux transporter protein system [3]. Furthermore several DOACs like rivaroxaban are substrates of the hepatic cytochrome P 450 3A4 (CYP3A4) enzymes [4]. Thus, drug-interactions may occur when DOACs are administered concomitantly with drugs affecting the activity of P-gp or CYP3A4 systems. Coadministration with P-gp- or CYP3A4-inducing agents may lead to a decrease in the serum levels and thus, decrease anticoagulant activity of DOACs, whereas coadministration with P-gp- or CYP3A4-inhibiting agents may lead to an increase in the serum levels and thus, increase anticoagulant activity of DOACs. Several antiepileptic drugs are known to affect P-gp and CYP3A4-activity, however the clinical relevance of this drug–drug interaction with DOACs is largely unknown [5]. We recently observed a patient with recurrent venous thrombosis under a therapy with rivaroxaban and carbamazepine.

2. Case description

A 55-year-old Caucasian male was admitted because of increasing pain and swelling of his right leg starting spontaneously 2 days before admission. He was under a therapy with 20 mg rivaroxaban since 4 months because of an unprovoked venous thrombosis of his right leg. At that time neither abdominal sonography nor gastroscopy or colonoscopy had shown any signs of malignancy, and blood tests for carcinoembryonal antigen, carbohydrate antigen, alpha fetoprotein and prostate specific antigen were within normal range. Screening for thrombophilia including measurements of protein C, protein S, APC resistance and antiphospholipid antibodies had been negative, He had a history of poliomyelitis at age 6 months with residual spastic hemiparesis on the right side, structural epilepsy due to central and occipital polymicrogyria with complex partial seizures with secondary generalization since age 6 years, excision of a melanoma of the left upper extremity at age 53, recurrent lumbar spinal disc herniations since 10 years and a left-sided hemicastration because of a benign fibrosing testicular tumour at age 48 years. As an antiepileptic medication he took carbamazepine (900 mg/d). He was seizure-free during the last 11 years. He reported to be highly adherent to the prescription of his anticoagulant and antiepileptic medication. During several neurologic follow-up visits within the last 11 years, his serum carbamezepine-levels were within the therapeutic range at any time when they were measured. He reported not take any other medication or diet supplements, except carbamazepine and rivaroxaban. Regarding risk factors for thrombosis, he reported that an aunt had suffered from venous thrombosis. At clinical examination at admission he presented with a blood pressure of 130/80 mm Hg, pulse was 75/min and regular. His height was 180 cm, weight 113 kg and body mass index 34.9. Except for swelling of the right lower limb the remaining clinical examination was normal and no varices were detected. Duplex sonography showed a thrombosis of the right popliteal and femoral vein. Results of blood tests are listed in Table 1. The serum-carbamazepine level was within the therapeutic range. Anti-Xa activity was <20 ng/ml according to a rivaroxaban calibrated anti-factor Xa chromogenic assay 23 h after intake of the last 20 mg rivaroxaban [6].

Table 1 – Results of blood tests at admission.

Parameter (reference)	Day 1
BUN, mg/dl (9–20)	10
Creatinine, mg/dl (<1.1)	0.94
Creatinine clearance (Cockcroft–Gault), ml/min (>90)	141
Glomerular filtration rate (modification of diet in renal disease), ml/min/1.73 m^2 (>90)	83
Haemoglobin, g/dl (14–17)	16.0
Thrombocytes/nl (150–450)	257
INR	1.24
Prothrombin time, % (70–130)	71.0
Activated partial thromboplastin time, s (25–36)	37.7
Thrombin time, s (10–17)	14.1
ALAT, U/l (10–50)	31
Bilirubin, mg/dl (<1.2)	0.22
Gamma-GT, U/l (0–60)	84
Carbamazepine level, μmol/l (therapeutic range 33.8–50.8)	41.7

Therapy with rivaroxaban was stopped, and low-molecular-weight heparin, followed by phenprocoumon, was started. The swelling and pain in his leg decreased and he was discharged with compression stockings after 5 days.

3. Discussion

Most likely, recurrence of venous thrombosis of the presented patient was the result of insufficient anticoagulation due to drug–drug interaction between rivaroxaban and carbamazepine, which is a known inducer of P-gp and CYP 3A4-activity [7,8]. This is supported by the missing serum anti-Xa activity in our patient, who was adherent and took the medication according to the prescription.

Whereas the drug–drug interaction between VKAs and carbamazepine are known for more than 20 years, and the mechanism is identified as CYP3A4 induction by carbamazepine, little is known about the influence of carbamazepine on DOAC-induced anticoagulation [9,10]. In the literature, a 53-year-old man is reported, who had just undergone partial knee arthroplasty and suffered from pulmonary embolism, diagnosed by computed tomography, one day after thrombosis prophylaxis was switched from dalteparin 5000 IU QD to rivaroxaban 10 mg QD. The patient also used carbamazepine 600 mg BID for epilepsy [11]. The authors hypothesized that carbamazepine, a CYP3A4 inducer, probably led to an increased clearance of rivaroxaban resulting in pulmonary embolism. No further reports about drug–drug interactions between carbamazepine and the DOACs apixaban, edoxaban or dabigatran are found in the literature. Since all DOACs, however, are substrates of the P-gp, and apixaban as well as edoxaban are also CYP3A4-substrates it can be expected that their anticoagulant effect might also be attenuated by carbamazepine [5].

According to the summary of product characteristics of rivaroxaban, as published by the European Medicines Agency (EMA), the concomitant use of rivaroxaban with strong CYP3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbital or St. John's Wort) may lead to reduced rivaroxaban plasma concentrations. Therefore, according to EMA, concomitant

administration of strong CYP3A4 inducers should be avoided unless the patient is closely observed for signs and symptoms of thrombosis [12].

Whereas interactions between VKAs and any other drug are easily detected because of deviations of the INR, in patients on DOAC, no laboratory test is easily available to detect the drug–drug interaction. Also in our patient, there was only a minimal prolongation of the activated partial thromboplastin time which might indicate an effect of rivaroxaban [13].

From our findings we conclude that the combination of DOACs with carbamazepine should be avoided since their anticoagulant effect may be decreased by a drug–drug interaction. There is an urgent need to increase our knowledge and physicians' awareness about the potential of drug–drug interactions of DOACs.

Conflict of interest

None declared.

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None declared.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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