



Letter to the Editor

Stroke and urosepsis after discontinuation of rivaroxaban[☆]Claudia Stöllberger^{a,*}, Josef Finsterer^{b,1}^a 2nd Medical Dept., Krankenanstalt Rudolfstiftung, Juchgasse 25, A-1030 Wien, Austria^b Krankenanstalt Rudolfstiftung, Juchgasse 25, A-1030 Wien, Austria

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Rivaroxaban, a factor Xa inhibitor, is a new oral anticoagulant (NOAC) which has been shown to be non-inferior to the vitamin-K-antagonist (VKA) warfarin for prevention of stroke or embolism in patients with atrial fibrillation (AF) in the ROCKET-AF trial [1]. It is unknown if this pretended advantage of rivaroxaban is also present outside clinical trials. Furthermore, concerns are emerging about an increase of thromboembolism when rivaroxaban is discontinued [1–3]. Additionally, there are indications that rivaroxaban might increase the risk of infection [4–6]. We report a patient with stroke shortly after discontinuation of rivaroxaban with a complicated course.

An 80-year old Caucasian man contacted his general practitioner in November 2012 because of increasing dyspnea and leg edema. He had a history of arterial hypertension, hyperlipidemia and benign prostatic hyperplasia necessitating transurethral resection of the prostate in 2008. AF was diagnosed for the first time in November 2012 and anticoagulant therapy with rivaroxaban 20 mg/d was initiated since it seemed more convenient for the patient in the eyes of the treating physician compared with VKA. The additional medication was furosemide, enalapril, allopurinol, hydrochlorothiazide, bisoprolol, simvastatin and amlodipine. In January 2013 he suffered from diarrhoea. Assuming that the diarrhoea was a side effect of rivaroxaban, the patient stopped the intake of rivaroxaban.

Five days later he was hospitalized because of an acute stroke. Clinical neurologic examination showed aphasia and a right-sided hemiparesis, and computed tomography a corresponding large ischemic lesion in the territory of the left cerebral medial artery. Duplex sonography showed no stenoses of the extracranial arteries. Under physiotherapy his symptoms improved, and after 4 weeks, rivaroxaban 20 mg/d was re-started since computed tomography did not show hemorrhagic transformation.

Because of his prostatic problems spontaneous micturition was not possible and he needed an indwelling catheter. Eight days after restarting rivaroxaban, a new catheter was inserted. After this procedure he developed fever, leukocytosis and *Pseudomonas aeruginosa* grew in the urine culture. Despite antibiotic therapy with ciprofloxacin he developed a right-sided epididymitis necessitating a scrotal semicastration after 4 days. He was transferred to a rehabilitation clinic.

Two months later, during change of the urinary catheter, a generalized seizure occurred for the first time. He was rehospitalized and an anticonvulsive therapy with carbamazepine 600 mg/d was started. Additionally, he suffered from urosepsis with *Proteus mirabilis* growing in urine and blood cultures. During antibiotic therapy with ceftazidime, signs of inflammation regressed. However, two weeks after cessation of antibiotic therapy, *Pseudomonas aeruginosa* and *Enterococcus faecalis* grew again in his urine culture. The neurological abnormalities remained unchanged and he was seizure-free under the antiepileptic treatment. Despite physiotherapeutic efforts his condition did not improve and he was transferred to a nursery home 5 months after stroke onset.

The story of the presented patient raises the question whether rivaroxaban might have contributed to the disastrous course. Rivaroxaban—in contrast to VKA—has a short half-life of 11–13 h, why discontinuation of the drug may lead to complete loss of antithrombotic efficacy within a short time [7]. An increased risk of stroke and non-CNS embolism was also observed in rivaroxaban-treated patients compared with warfarin-treated patients after the end of the ROCKET-AF-trial [2]. An in-vitro study has shown a rebound effect of rivaroxaban [3]. Although we have no evidence by laboratory testing of a rebound effect in our patient, this might have played a role. Additionally, dehydration due to fluid loss from the diarrhoea and intake of two different diuretic drugs might additionally have increased his thromboembolic risk.

Poststroke infections are frequent, and urinary tract infections are the most common infections among acute stroke patients. Urinary tract infections have been shown to be an independent predictor of poor functional outcome and death at discharge [8]. Epididymitis necessitating semicastration, however, has so far not been reported in stroke

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patients. Of interest, the patient had an indwelling urinary catheter since the admission whereas the urinary tract infection only started after 5 weeks.

It remains speculative if rivaroxaban might have contributed to the development of the infection. It is known from orthopaedic series that rivaroxaban, given for prevention of venous thromboembolism, leads to an increase in wound infections [4–6]. Thrombin is not only important for blood coagulation but also for defense against infections [9]. Theoretically, long-term delay in thrombin-generation by rivaroxaban could impair the immune system and mitigate the response to infections. So far it is unknown if rivaroxaban also favours infections in patients with atrial fibrillation. There are indications that thrombin is also involved in the pathogenesis of seizures in the brain, however the role of rivaroxaban in this situation has not been investigated [10].

We conclude from the presented case that there is a need for more research about a rebound effect of rivaroxaban. As long as these uncertainties exist, patients should be educated not to discontinue rivaroxaban without consulting their physicians since the risk of thromboembolism might be high due to the short half-life of the drug. Tapering down the dosage of rivaroxaban might prevent a potential rebound effect. There is a need to investigate the role of rivaroxaban and other thrombin generation inhibitors on the occurrence of infections as well as epileptic seizures in patients with atrial fibrillation.

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