



Clinical letter

Clinically relevant interaction of rivaroxaban and valproic acid – A case report

Lisa Langenbruch^{a,*}, Sven G. Meuth^a, Heinz Wiendl^a, Rolf Mesters^b, Gabriel Möddel^a^a University Hospital Münster, Department of Neurology with Institute of Translational Neurology, Albert-Schweitzer-Campus 1, Gebäude A1, 48149 Münster, Germany^b University Hospital Münster, Department of Medicine A, Hematology and Oncology, Albert-Schweitzer-Campus 1, Gebäude A1, 48149 Münster, Germany

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1. Introduction

During the past years, the use of non-vitamin K oral anticoagulants (NOAC) has become more and more widespread. One of the major advantages compared to vitamin K-antagonists is the easy administration without frequent therapeutic drug monitoring. Nevertheless, interactions with other substances must be kept in mind, as NOAC efficacy may change upon co-administration of inducers or inhibitors of cytochrome P450 3A4 (CYP3A4) or P-glycoprotein (P-gp). With epilepsy being a frequent comorbidity, especially in the setting of post-ischemic epilepsy, the number of patients who require oral anticoagulation as well as antiseizure drugs has been reported as high as 15.3% [1]. A recent study showed an increased risk of major bleeding events for the combination of NOAC and valproic acid, levetiracetam or phenytoin [1]. Otherwise, knowledge about interactions of NOAC and antiseizure drugs is scarce despite the marked clinical relevance (see additional reading material online). We here present a patient case with recurrent deep vein thrombosis (DVT) upon combination of valproic acid and rivaroxaban.

2. Case report

A 30 years old male patient had suffered bacterial meningococcal meningitis in his first year of life. He developed severe cognitive disability and refractory focal epilepsy. The patient's legal representative gave

consent for publication. For the previous seven years, his anticonvulsive treatment consisted of valproic acid and lamotrigine. One year before presentation, seizures recurred after a seizure-free period of six years. The recurring seizures led to an increase in valproic acid dose to 2000 mg daily in combination with 200 mg lamotrigine daily.

The patient had developed DVT three times (13, 12 and 5 years previously). Upon the third DVT, rivaroxaban 15 mg daily was started and increased to 20 mg after another suspected DVT, one year before presentation. The thrombophilia work-up revealed protein S-deficiency, hyperhomocysteinemia and elevated lipoprotein(a).

The patient now presented with yet another DVT despite correct medication intake. An infectious disease was excluded. Therapeutic drug monitoring results are shown in Table 1. Rivaroxaban trough and peak levels were well below the 5th percentile of the levels reported in previous literature [2]. Because of the suspected interaction of valproic acid and rivaroxaban, valproic acid was gradually tapered and ultimately replaced by perampanel. Lamotrigine and rivaroxaban were continued and the patient was started on pipamperone for severe sleep disturbances. Although pipamperone as many other non-benzodiazepine hypnotic drugs may lower the seizure threshold, an increased risk of seizures due to sleep disruption was deemed potentially more hazardous. Pipamperone treatment was induced without negative consequences on seizure frequency. On follow-up, rivaroxaban trough and peak levels increased significantly.

Abbreviations: AED, antiepileptic drug; CYP, cytochrome P450; DVT, deep vein thrombosis; MDR1, multidrug resistance 1; NOAC, non-vitamin K oral anticoagulant; P-gp, P-glycoprotein

* Corresponding author.

E-mail addresses: lisamarie.langenbruch@ukmuenster.de (L. Langenbruch), sven.meuth@ukmuenster.de (S.G. Meuth), heinz.wiendl@ukmuenster.de (H. Wiendl), rolf.mesters@ukmuenster.de (R. Mesters), gabriel.moeddel@ukmuenster.de (G. Möddel).

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Table 1
Medication and therapeutic drug monitoring.

	Baseline	Follow-up	Therapeutic reference range
Daily dose			
- rivaroxaban	20 mg	20 mg	
- valproic acid	2000 mg	–	
- lamotrigine	200 mg	400 mg	
- perampanel	–	8 mg	
- pipamperone	–	20 mg	
AED trough level			
- valproic acid	87.9 mg/l	NA	50-100 mg/l ^b
- lamotrigine	12.3 mg/l	7.2 mg/l	3-15 mg/l ^b
- perampanel	NA	615 µg/l	180-980 µg/l ^b
Rivaroxaban trough level	8.6 ng/ml	16.02 ng/ml	12-137 ng/ml ^a
Rivaroxaban peak level	53.9 ng/ml	130.7 ng/ml	184-343 ng/ml ^a

^a 5th to 95th percentile [2].

^b Internal laboratory reference range.

3. Discussion

This case suggests a relevant interaction of valproic acid and rivaroxaban with a decrease in rivaroxaban plasma levels and recurrence of DVT. The most likely mechanism is an induction of CYP3A4 or P-gp as the two main effectors of NOAC plasma levels. Valproic acid is known for its inhibitory influence on lamotrigine metabolism via UDP-glucuronyl-transferase. Data on effects of valproic acid on other metabolic pathways or drug transporters is inconclusive. In vitro data showed induction of multidrug resistance 1 (MDR1, encoding P-gp) gene expression in different human and rat cell types, and increased or decreased P-gp function depending on cell type [3,4]. CYP3A4 expression was increased in vitro in human cell lines [3]. Valproic acid may also have contributed to the patient's hyperhomocysteinemia. An elevated total serum homocysteine is a risk factor for stroke and atherosclerosis and found more frequently in epilepsy patients than in the general population, especially with concomitant intake of enzyme-inducing antiseizure drugs.

In vitro data also suggest an influence of many other commonly used antiseizure drugs on P-gp and CYP3A4, which may be cell or tissue specific, so in vivo effects remain unclear. Current recommendations of the European Heart Rhythm Association based on limited data advise to avoid levetiracetam, carbamazepine, valproic acid, phenobarbital, phenytoin and, depending on the NOAC of choice, oxcarbazepine and topiramate [2]. According to these recommendations, the preferred drugs would be lamotrigine, zonisamide, pregabalin, gabapentin, and ethosuximide. With the exception of lamotrigine as a widely used and effective antiseizure drug, this does not reflect the reality of epilepsy treatment. Newer antiseizure drugs such as lacosamide, perampanel or brivaracetam were not mentioned.

Considering the widespread use especially of levetiracetam, carbamazepine and valproic acid, a relevant number of patients may be at risk of potentially harmful decrease of their NOAC plasma levels. On the other hand, valproic acid, levetiracetam and phenytoin have been shown to increase the risk of major bleeding events when coadministered with a NOAC [1]. Laboratory data on pharmacokinetics was not reported in that study, so an explanation for the increased bleeding risk is still lacking. In the case of valproic acid, thrombocytopenia, acquired von Willebrand disease, impaired platelet function or pharmacokinetic interactions may serve as explanations.

As almost all evidence regarding the risk of recurrent thromboembolic events so far stems from single case reports, larger studies are warranted to address this issue and provide solid evidence. Until then,

caution should be used in combining antiseizure drugs and NOAC. This may be one of the few situations in which therapeutic drug monitoring of NOAC could be advisable.

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Declaration of Competing Interest

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.seizure.2020.05.024>.

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