Drug–drug interaction between levetiracetam and non-vitamin K antagonist anticoagulants

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Online publish-ahead-of-print 29 November 2018


In the updated guide on NOAC use in patients with non-valvular atrial fibrillation, the European Heart Rhythm Association recommends against the use of the antiepileptic drug, levetiracetam, due to potential P-glycoprotein-mediated drug–drug interaction (DDI).\(^1\)

While the summary of product characteristics of apixaban, and edoxaban list phenytoin, carbamazepine, and phenobarbital, and dabigatran’s lists phenytoin and carbamazepine, none lists levetiracetam as a P-gp inducer.

In a Phase I trial, healthy volunteers received concomitant levetiracetam and digoxin, a P-gp substrate.\(^2\) Administration of a P-gp inducer with digoxin would be expected to decrease digoxin plasma concentrations; however, repeated levetiracetam exposure had no effect on digoxin steady-state pharmacokinetics.\(^2\) Absence of effect on digoxin pharmacodynamics, as measured by ECG parameters, supports this lack of interaction.\(^2\) P-gp and CYP450 enzyme expression induction by xenobiotics is primarily mediated by the pregnane X receptor (PXR). Since levetiracetam does not induce CYP450 enzyme expression, as supported by clinical data,\(^3\) it is unlikely to activate PXR, and therefore, induce P-gp expression. Finally, levetiracetam has no effect on the expression, or function of the products of the ABC transporter genes, ABCB1 (coding for P-gp), ABCC1, ABCC2, and ABCC2, in human cell lines.\(^4\) Importantly, P-gp function is species-specific; levetiracetam is a substrate of mouse, but not of rat or human P-gp.\(^5\) Data obtained in non-human models may not be relevant to humans.

The recommendation appears to be solely based on results from in vivo animal models. However, clinical data, which supersede animal model data, demonstrate that levetiracetam is not a P-gp inducer. Evidence presented here support the absence of any clinically relevant DDI between levetiracetam and NOACs. The recommendation could potentially constitute a serious safety risk for patients treated concomitantly with levetiracetam and a NOAC, if levetiracetam is substituted.

Conflict of interest: All authors are employees of UCB-Pharma, marketing holder of Keppra (levetiracetam). Azita Tofighy provided writing support, funded by UCB-Pharma.

References