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DISCUSSION FORUM

Levetiracetam and non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation and epilepsy: a reasonable combination

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This commentary refers to 'The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation', by J. Steffel *et al.*, *Eur Heart J* 2018;39:1330–1393.

We have read with great interest 'the 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants (NOACs) in patients with atrial fibrillation'.[1] Table 5 lists interactions with antiepileptic drugs (AEDs). Levetiracetam is according to the expert opinion contraindicated with NOAC because of potential P-gp interference. Since, it was highlighted that there is no evidence for levetiracetam to cause P-gp mediated drug–drug interaction with NOACs in humans.[2] In reply, the guidance authors argued that caution needs to be applied in order to have effective NOAC therapy.[3]

We are concerned about the expert advice given, classifying levetiracetam as contraindicated due to concerns over potentially reduced plasma levels of NOACs. We are arguing against such advice for the following reasons:

(1) The rate of post-stroke epilepsy (PSE) is expected in 8% of stroke patients after 5 years. Predictors include severity of stroke, cortical involvement, and territory of middle cerebral artery involvement,[4] indicating a high proportion of patients with AF as stroke aetiology and the need of life-long oral anticoagulant and antiepileptic therapy.
(2) So far, there are no clinically relevant drug–drug interactions known with levetiracetam. Additional characteristics such as linear pharmacokinetics, renal clearance, and little risk for cognitive impairment are particular useful features for AED treatment with levetiracetam in the elderly with multimorbidity and polypharmacotherapy.
(3) Levetiracetam was shown to be superior to extended release carbamazepine in a randomized controlled trial in the elderly, mostly suffering from PSE. Superiority in AED trials is rarely reached, so this result is highly respected.[5]
(4) PSE is a serious condition with increased mortality and reduced functional outcome. Withholding or switching a well-established therapy with levetiracetam according to the advice given in the guidance, puts patients on significant risk of break through seizures and status epilepticus including an additional risk for injuries including intracranial haemorrhage under NOAC therapy.

We strongly believe that these risks are much more clinically relevant than concerns about potential P-gp interference, which was only apparent in a mice model and was not replicated in humans. We agree with the authors that caution should be applied. Therapeutic drug monitoring for levetiracetam and NOAC levels should be sufficient to indicate if subtherapeutic NOAC therapy might increase risk for recurrent stroke of embolic cardiac aetiology.

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