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EDITORIAL COMMENT
Other

Response to editorial comment 'Direct oral anticoagulant failure in TIA/stroke: neurologic and pharmacokinetic considerations'

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This editorial refers to 'DOAC failure in TIA/stroke: neurologic and pharmacokinetic considerations', by D.S. Rose and W.S. Burgin *et al.*, doi:10.1093/ehjcr/ytaa178.

We appreciate the interest in our case report from Drs Rose and Burgin in their editorial comment entitled 'DOAC failure in TIA/Stroke: neurologic and pharmacokinetic considerations'[1] and thank the editor for facilitating this discussion. Drs Rose and Burgin raise two main concerns regarding our case report: the first is the accuracy of the patient's diagnosis of transient ischaemic attacks (TIAs), the second issue is our explanation for the sub-therapeutic dabigatran levels.

Rose and Burgin eloquently describe the signs and symptoms of cerebral ischaemia with reference to those experienced by our patient. We agree that clinical differentiation of cases such as ours are not straightforward and certainly not the subspecialty of the authors. However, our patient was admitted under the neurology stroke service. The treating neurologist was confident in diagnosing both TIA and migraines in this patient after comprehensive review. We (the authors) assisted management of atrial fibrillation and anticoagulation choice as consultative services and thus investigated the question of dabigatran efficacy in this patient. We thank Drs Rose and Burgin in highlighting these points to remind clinicians of the complexities of neurological presentations.

The second issue raised was in relation to 'more likely explanations than an unconfirmed polymorphism' for the sub-therapeutic dabigatran levels found in our patient. We detail potential reasons for failing to achieve adequate dabigatran levels in Table 1 of our report and addressed each of these individually in our patient. Drs Rose and Burgin rightly point out that the correct storage of the agent is required for optimal efficacy of dabigatran: one of our first hypotheses was inadequate anticoagulation related to the patient's practice of removal of dabigatran from original packaging and transfer into a medication blister packet. However, incorrect storage is unlikely to have resulted in extremely low levels of dabigatran as seen in this patient. This was confirmed when we subsequently tested the dabigatran levels after the patient received drug correctly dispensed by hospital pharmacy directly from packaging as an inpatient. The failure to achieve detectable levels after direct observation of four doses of dabigatran in this supervised setting indicated that, in this case, incorrect storage was not the sole reason for the sub-therapeutic dabigatran levels. Furthermore, one recent case study reassuringly shows that drug levels in pharmacy blister packs were stable out to 120 days.[2]

The half-life of dabigatran in young patients with normal renal function is 12–14 h. Previous pharmacokinetic studies demonstrated a t-max at 1.5 h indicating that even after a single dose, dabigatran levels should be detectable if active drug is absorbed. Steady state is achieved in 2–3 days (five half-lives) with twice-daily dosing.[3] Our patient had his dabigatran level taken 1 h and 55 min after his 4th directly observed therapy dose. The level (<40 ng/mL) should represent a peak level near steady state with the hospital supply of dabigatran and well beyond steady state for drug taken outside the hospital setting.

The objective of our case report was to discuss potential causes of anticoagulant failure with dabigatran and to highlight the dangers of assuming that direct-acting oral anticoagulants (DOACs) always provide therapeutic anticoagulation. Apparent failure should prompt

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further investigations including consideration for measurement of DOAC levels. Our patient presented with symptoms consistent with acute cerebral ischaemia and was diagnosed with TIAs by a neurologist whilst reporting compliance with therapeutic dabigatran. This prompted us to evaluate the efficacy of this patient's anticoagulation, which revealed undetectable levels of dabigatran. Treatment with apixaban led to therapeutic anticoagulant levels and he has not developed neurological symptoms since. We completely agree with the adage that 'common things occur commonly' and in most cases, there will be more common explanations for failure of anticoagulant therapy. However, as each of the items on our suggested list was sequentially ruled out, we continue to support our original hypothesis of a polymorphism to explain dabigatran failure in this patient.

Lead author biography

Ronald Huynh completed his medical studies at the University of Notre Dame in Sydney Australia in 2013. He completed his Basic Physician's Training in 2017 and is currently a Cardiology Advanced Trainee at Concord Repatriation General Hospital in Sydney Australia.

Conflict of interest: none declared.

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