Reviewer's report

Title: UNEXPECTED EXCESSIVE APIXABAN EXPOSURE: CASE REPORT OF A PATIENT WITH POLYMORPHISMS OF MULTIPLE APIXABAN ELIMINATION PATHWAYS

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Reviewer: Stefanie Krick

Reviewer's report:

In the manuscript of Huppertz et al., the authors present a case report of an unexpected excessive apixaban exposure in a patient, who was found to have polymorphisms of multiple apixaban elimination pathways. The patient received apixaban for atrial fibrillation and was admitted for a presumed acute stroke, which turned out to be symptoms related to a sciatic nerve lesion. In addition, the patient was found to have acute kidney injury, rhabdomyolysis, a urinary tract infection and pneumonia. HPLC-MS showed that apixaban levels were extremely high and remained high. The patient underwent genotype analysis, which showed polymorphisms that are associated with functional impairments in multiple apixaban clearance pathways. The authors conclude that these genetic polymorphisms can impair apixaban clearance thereby increasing significantly exposure to it.

Overall, this is a very interesting case, but this case is quite complex and renal failure is most likely a major contributing factor. Therefore, the relevance of these polymorphisms has not been made clear enough.

Major concerns:

1. The relevance of increased apixaban levels in this case is not clear. The patient was admitted for an acute stroke, which turned out not to be a stroke and there were no bleeding complications, which would make it relevant here to assess these polymorphisms. In addition, wouldn't the renal impairment alone explain the increased levels and finally, is it relevant that the levels are increased or is it more important that the FX1 activity is assessed. The authors need to correlate apixaban concentrations with FXa activity in detail and have to make a case that assessing concentrations is superior or equally clinically relevant - why is measuring FXa activity not sufficient?

2. As stated above, the elevation could be explained by the renal failure. What was the baseline renal function of the patient? Once the renal function has improved, it seemed that apixaban levels are decreasing, too. If the authors want to make a case, they will need to include cases at least in their discussion, that these polymorphisms are clinically relevant in a case, where there are no concomitant contributing factors such as renal
failure. Or they could include cases that actually show an increased bleeding tendency with these polymorphisms.

3. The authors need to stress their importance for genetic analysis by strengthening their discussion.

4. Since the patient also has rhabdomyolysis, the authors should discuss contribution of it to the elevated apixaban levels as well.

5. Figure 1 and 2 legends are swapped. In addition to creatine kinase and anti-factor Xa, I recommend to add apixaban levels here, too.

Minor concerns:

1. Page 3 line 36/37: please specify "at the end of 2017".

2. Page 4 line 16, please unify font size.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript
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