Author's response to reviews

Title: Warfarin and boceprevir interaction causing subtherapeutic INR: a case report

Authors:

Andrew S Tsiattalos (atsiattalos@gmail.com)
Anita Patel (Anita.Patel@va.gov)

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Author's response to reviews: see over
Author’s response to reviews

Title: Warfarin and boceprevir interaction causing subtherapeutic INR: a case report

Authors:

Andrew Tsiattalos (atsiattalos@gmail.com)
Anita Patel (anita.patel@va.gov)

Version: 2 Date: 17 October 2014

Author’s response to reviews: see over
Reviewer's report

Title: Warfarin and boceprevir interaction causing subtherapeutic INR: a case report

Version: 1 Date: 5 August 2014

Reviewer: Ajantha Perera

Comments to authors:
I went through the case report. It is excellent, but I think the discussion is a little too long, it might be better if you can shorten it a little.

Discussion was shortened as much as possible. The following was deleted from the fourth paragraph, as well as other shorter segments:

In a pharmacokinetic, randomized open-label study with 39 healthy subjects, boceprevir decreased the exposure of ritonavir-boosted HIV protease inhibitors (PI/r) atazanavir, darunavir, and lopinavir.\(^\text{10}\) The area under the concentration-time curve was decreased by 0.65 (90% confidence interval [CI], 0.55-0.78) for atazanavir/r, 0.66 (90% CI, 0.6-0.72) for lopinavir/r, and 0.56 (90% CI, 0.51-0.61) for darunavir/r.

Overall, due to suggestions from our reviewers, the discussion has become longer.

Level of interest: An article of importance in its field

Declaration of competing interests:
I declare that I have no competing interests
Reviewer’s report

Title: Warfarin and boceprevir interaction causing subtherapeutic INR: a case report

Version: 1 Date: 30 August 2014

Reviewer: Sam Schulman

Which of the following best describes what type of case report this is?:
Unreported or unusual side effects or adverse interactions involving medications

Has the case been reported coherently?: Yes

Is the case report authentic?: Yes

Is the case report ethical?: Yes

Is there any missing information that you think must be added before publication?: Yes

Is this case worth reporting?: Yes

Is the case report persuasive?: No

Does the case report have explanatory value?: No

Does the case report have diagnostic value?: No

Will the case report make a difference to clinical practice?: Yes

Is the anonymity of the patient protected?: Yes

Comments to authors:

1. The authors report a case with suspected interaction between the protease inhibitor boceprevir and the oral anticoagulant warfarin, resulting in increased metabolism of warfarin and hypoprothrombinemia. The putative mechanism is induction of CYP1A2 and CYP2C9, although in vitro studies did not provide evidence for that. The authors should in the discussion use the Naranjo probability scale to support the probability of the interaction (Clin Pharmacol Ther 1981;30:239-45).

The Naranjo probability scale was added to the last paragraph of the discussion.

2. It is stated in the discussion that interferon and warfarin have no known significant interactions with warfarin, referring to the warfarin package insert, which surely is incomplete. A literature search should have been performed. It would show that ribavirin has been reported to have a similar inhibiting effect on warfarin (Ann Pharmacother 2002;36:72-4). The mechanism here seems to be via induction of factor VII mRNA (J Thromb Haemost 2006;4:469-70). This needs to be discussed and is it not possible that the mechanism for the boceprevir interaction could be of a similar nature in view of the conflicting information regarding cytochrome P450?
The following statements were added to the second to last paragraph of the discussion:

A literature review has shown evidence that interferon may potentiate the effect of warfarin, although this was not the effect seen in our case report. In the case of warfarin and ribavirin, a drug interaction search using Micromedex indicates there are no known drug interactions. Upon literature review, a case report by Schulman reports an inhibition of warfarin activity by ribavirin. In Schulman’s report, the interaction occurred immediately after initiation of the antiviral therapy. However, in our case report, the INR did not decline until 7 weeks after ribavirin was started. Furthermore, the dose of ribavirin was changed frequently in the patient due to his anemia. Despite ongoing ribavirin dose changes, his INR did not change significantly. See table 1 for details.

In an another study, ribavirin has been found to induce factor VII mRNA in patients with hemophilia resulting in a reduction in bleeding episodes. Due to the lack of clear evidence of boceprevir inducing CYP450 enzymes responsible for warfarin metabolism, it is possible that the inhibition of warfarin activity may be due to other unknown causes, such as in the case of ribavirin inducing factor VII mRNA.

3. The discussion regarding HIV protease inhibitors is superfluous and I suggest deleting “In a pharmacokinetic open-label randomized study ...for darunavir/r.”

This part of the discussion was deleted as suggested by the reviewer.

4. The data on INRs and warfarin doses in relation the events would have been more reader friendly in a graph rather than the table.

The utility of a graph is apparent although we decided to use a table since we have expanded it to include more information.

Minor comments
1. Case report, line 5: pulmonary embolism, for which ...
   Changes made as indicated by the reviewer.

2. Discussion, line 6 from the end: ... his 9/25/12 visit, at which ...
   Changes made as indicated by the reviewer.

3. Discussion, line 3 from the end: ... visits, at which times he stated that he did not ...
   Changes made as indicated by the reviewer.

Level of interest: An article of limited interest

Quality of written English: Needs some language corrections before being published

Declaration of competing interests: No competing interests
Reviewer's report

Title: Warfarin and boceprevir interaction causing subtherapeutic INR: a case report

Version: 1 Date: 6 September 2014

Reviewer: Danielle C Gatti

Which of the following best describes what type of case report this is?: Unreported or unusual side effects or adverse interactions involving medications

Has the case been reported coherently?: Yes

Is the case report authentic?: Yes

Is the case report ethical?: Yes

Is there any missing information that you think must be added before publication?: Yes

Is this case worth reporting?: Yes

Is the case report persuasive?: No

Does the case report have explanatory value?: Yes

Does the case report have diagnostic value?: No

Will the case report make a difference to clinical practice?: Yes

Is the anonymity of the patient protected?: Yes

Comments to authors:
This is a very well written case report which further looks at the potential for possible induction of warfarin metabolism by protease inhibitors. However, there are some concerns that I would like the authors to further address.

First, throughout the patient's course of therapy, the patient was admitted to the hospital due to thrombocytopenia and was also treated for two suprapubic abscesses. However, there is no mention of any other medications that the patient may have received while in care for these two separate incidences. As we know, many medications, especially antibiotics can affect the patient's INR.

For the patient's suprapubic abscess, he was given a course of amoxicillin/clavulanic acid. For his facial abscess he was given a course of clindamycin. This information is now included in the case presentation in the second to last paragraph, and table 1. Neither antibiotic is known to significantly affect INR, although amoxicillin/clavulanic acid can increase the risk of bleeding while on warfarin. Regarding his thrombocytopenia, the patient's Hepatitis C medications were discontinued and he did not require hospitalization. One month after discontinuing his HCV medications, he was admitted to an outside hospital for urinary tract infection and bacteremia,
which is noted in table 1. This information was not included in the case report since it occurred after his HCV medications were stopped. It is being included in the table to account for possible confounding factors for changes in INR after his HCV meds were discontinued.

Also, because the patient was admitted for thrombocytopenia and suffered from anemia, was the dose of ribavirin decreased at any point during his course of therapy?

Yes, his ribavirin dose was continuously being adjusted. The ribavirin dose adjustments are now included in the second to last paragraph of the case presentation, as well as in table 1.

The author states that there is no known drug interaction with warfarin and ribavirin or peginterferon. However, there are articles, which suggest possible interactions with these medications, which should be mentioned and ruled out.

In an article by Schulman, after the initiation of interferon and ribavirin, the dosage requirement of warfarin progressively increased over the course of a month. After the discontinuation of these agents, the patient’s warfarin requirement fell to a level similar to the baseline. Schulman S. Inhibition of warfarin activity by ribavirin. Ann Pharmacother. 2002; 36:72-4. If the dose of these agents were ever decrease, this could also potentially cause variations in the INR.

An article which suggests an interaction with warfarin and peginterferon resulting in an increase in INR has been included in the second to last paragraph of the discussion. However, we found the opposite to occur in our case.

It is possible that ribavirin changes could have caused variations in the INRs of the patient. Of note, the INR did not drop until 3 weeks after boceprevir was started, and 7 weeks after ribavirin was started. In Schulman's report, the variation in INR was seen immediately after ribavirin was started, which was not the case in our report. Also, it is important to note that the ribavirin dose in our patient was continuously being adjusted with the lowest dose at 200mg/day, significantly less than the dose of 1600mg/day used in Schulman's report. Therefore, we continue to believe the drop in INR was due to boceprevir, although ribavirin may have played some role.

What is also interesting is that when the boceprevir was discontinued, the patient’s weekly warfarin requirements did not return to baseline. In fact, it remained about 50% higher (23.75mg) than the patient’s initial weekly dose of 15mg. Additionally, the INR did not increase when the boceprevir was discontinued, which was thought to be causing the induction of the warfarin metabolism.

The warfarin dose was prophylactically decreased when the patient’s HCV medications were stopped in anticipation of the INR increasing. A few weeks after the HCV medications were stopped, the INR did increase at which point, the warfarin dose was lowered.

Was there a Drug Interaction Probability Scale score calculated for this case report? Could this interaction be concluded as probable?
A Naranjo probability score was calculated indicating the interaction as possible, and is included in the last paragraph of the discussion.

Lastly, it is also worth mentioning if the patient’s INR was being checked via a lab drawn venous puncture or through a point of care (POC) INR device. POC INR devices list anemia as a potential limiting factor in INR accuracy.

Comments about the methodology used for measuring the patient’s INR is now included in the third paragraph of the case presentation. The table now also indicates which methodology was used for each INR. The POC instrument our clinic uses is the CoaguChek XS Plus. According to their manufacturer, Roche’s manual, “Hematocrit results between 25-55% do not significantly affect results”. The patient in our case never had his hematocrit below this range. In addition, there were 2 days where both a POC and LAB INR were taken and their results correlated; this information further confirms INR accuracy from the POC device.

I agree that the protease inhibitors may cause some induction of warfarin metabolism and this needs to be further investigated. We also need to keep this potential interaction in mind while adjusting warfarin therapy in our patients that are undergoing Hep C treatment. However, this patient does have many variables during his course of therapy, which may have contributed somewhat to his variances in his INR, and the author should address.

We feel with the addition of the above revisions, other variables which may have contributed to the variance in INR are now addressed.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Declaration of competing interests:**
None of the above

Thank you for your reviews. We appreciate the feedback and suggestions for improvement.