Author's response to reviews

Title: Rifampicin-warfarin interaction leading to macroscopic hematuria: a case report and review of the literature

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Author's response to reviews: see over
Prof. Dr Christopher Morrey  
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Dear Dr. Christopher Morrey,

We highly appreciated the suggestions and comments provided by the reviewers, which made substantial contribution to our paper. We have performed a revision throughout the paper to include the corrections suggested by the reviewers. In the following items, you can find our response with a point-by-point description of the changes made. Highlighted modifications can also be encountered in the revised manuscript. Additionally, we submitted the manuscript to American Journal of Experts for a professional language editing to help us copyedit the paper, as recommended. This service has performed a previous edit of our paper which was qualified for a re-edit under their editing guarantee.

Reviewer – Dr. Kathryn Momary

REVIEWER'S REPORT:

This case report detailing the drug-drug interaction between warfarin and rifampicin. The report details the efforts to get a therapeutic INR after starting rifampicin and after rifampicin. While the authors make it sound as though this is the first case of its kind, that is not true. This interaction has been well described in other literature. While this case may have more information included compared to previous reports, the information contained here is not new.

R.: Thanks for the comments. We agree that it’s not the first case of its kind. However, despite several reports of rifampicin-warfarin interaction, we have not found any paper describing a bleeding complication after a long-term follow-up. In Brazil, the access to anticoagulation clinics is not a reality in most cities. The number of warfarin users is increasing and their majority is monitored by primary care settings without
specific interventions for pharmacotherapy problems. We believe that this situation may occur in many other developing countries. Thus, even though this interaction has already been well described in the literature, our case provides elements to raise discussion on the risks of warfarin-bleedings associated with drug interactions and the need for weekly monitoring after stopping rifampicin. To improve the text, it was entirely revised to clarify sentences which could give the idea that our report is a new finding, as the changes below:

Abstract - Background: “(...) We report a bleeding episode after termination of the co-administration of rifampicin and warfarin and detail the challenges related to international normalized ratio (INR) monitoring. (...)” (1st paragraph, page 2)

Background – “However, there are no published long-term follow-up studies focused on bleeding events and INR values after termination of the co-administration of rifampicin and warfarin.” (3rd paragraph, page 3)

Discussion: “(...) The potential of rifampicin to induce warfarin metabolism has been well known for decades, although only a limited number of case reports have been published. In the current report, long-term INR monitoring helped demonstrate the effect that the concomitant use of rifampicin may have on the warfarin anticoagulant response and on the risk of adverse events, such as bleeding.” (3rd paragraph, page 5)

Major Compulsory Revisions
- This report is clouded by the patients previously documented non-compliance. It is unclear if the patient was taking warfarin during the time of potential "resistance", therefore the report of the interaction is complicated.

R.: Thanks for the comments. We would like to clarify that no consistent information to confirm non-compliance was detected. It was a hypothesis raised by our research group because of patient’s illiteracy and poor social situation. For these reasons we have prepared a patient care plan with regular visits to the anticoagulation clinic to help the patient to improve her knowledge on medical conditions and pharmacotherapy. After educational sessions, she gradually seemed to be more involved with her drug therapy and it was clearly verified by health professionals. The 3rd paragraph of the case presentation which gave details about these procedures was removed following a suggestion of another reviewer.

Regarding the potential warfarin resistance, the hypothesis of non-compliance was proposed and discussed by our research group. At the end, it was not considered as true because of other objective elements: i) after gradual increases of warfarin doses (45-80mg/week), INR 3.40 was obtained; ii) therapeutic INR results could be reached with 77.5mg/week; iii) timing aspects could be considered
because after rifampicin interruption there was an INR elevation (7.22), INR value showed reduction after prompt warfarin dose adjustments and it was stabilized in therapeutic range with doses of 35-37.5mg/week. Thus, we considered that at the beginning, if the patient had no compliance with 77.5mg/week, it would not be possible to stabilize INR in the therapeutic range for a while. Additionally, the stabilization of INR in therapeutic range with a significant warfarin dose reduction after rifampicin discontinuation weakens the possibility of patient’s non-compliance to warfarin therapy.

- This report should include a much more extensive discussion of enzyme induction drug interactions. Specifically, the timing of such interactions.

R.: A new paragraph was included in the Discussion section to present an extensive discussion of enzyme induction drug interactions with a specific focus on the timing of such interactions. Please see Discussion, 1st paragraph, page 5, as follows:

"(...) The proposed mechanism for the rifampicin-warfarin interaction involves the induction of the isoenzymes CYP2C9, CYP3A4, CYP1A2 and CYP2C19 [25,26], accelerating the clearance of both the R and the S enantiomers of warfarin. Enzyme induction typically exhibits a slow onset and long-term recovery time. In particular, CYP induction depends on the synthesis of new drug-metabolizing enzymes, with the initial effects detectable within the first two days of concurrent therapy. However, it generally takes at least one week to observe the effects of maximal induction. The onset of CYP stimulation is also dependent on the half-life of the inducer. As rifampicin exhibits a relatively short half-life, steady-state serum concentrations are obtained faster when rifampicin is compared with other inducing drugs with longer half-lives [26,27]. The dissipation of CYP induction after the discontinuation of rifampicin occurs gradually, depending on the drug’s elimination and the gradual decay of the enhanced enzymatic activity in the liver [8,26]. The concurrent use of isoniazid may cause an opposite effect on the liver by inhibiting CYP3A4 [28-30], leading to the accumulation of the less potent R enantiomer. As an additional mechanism, an acquired inhibition of fibrin stabilization has been associated with isoniazid therapy [31]. In the present case, the stimulatory effect of rifampicin on the liver seemed to be clinically predominant over the effect of the concomitant use of isoniazid on the coagulation state, which is consistent with previous findings [12,14,15]. (...)"

The following references were included to support the information presented above:

(...)


(...)

(...)

- The review of warfarin metabolism is incomplete. Please state how each enantiomer is metabolized. This is especially important given the discussion of CYP3A4 with isoniazid.

R.: Information on how each warfarin enantiomer is metabolized was included in the Background section (2nd paragraph, page 3), as follows:

“(…) Warfarin is a coumarin derivative that is widely used to prevent and treat thromboembolic disorders. Racemic warfarin accumulates in the liver, in which both the R and the S enantiomers are metabolically transformed by different pathways [10]. The S enantiomer is approximately 90% oxidatively metabolized, primarily by the CYP2C9 enzyme of the CYP system and, to a lesser extent, by CYP3A4. The less potent R enantiomer is approximately 60% oxidatively metabolized, primarily by the two CYP enzymes CYP1A2 and CYP3A4 and, to a lesser extent, by CYP2C19 [11]. (…)”

- The authors mention several tools used to assess the causality of the drug interaction on the adverse event. Scores from these tools should be included in the manuscript.

R.: Scores from the tools used were included in the Discussion section (last paragraph, page 4), as presented:

“(…) The Naranjo algorithm [23] and the Drug Interaction Probability Scale (DIPS) [24] were also employed to evaluate the causality of the adverse event. The effect of each medication on the warfarin anticoagulant response was considered. Rifampicin showed a score of 8 (probable) for both methods, which was the highest score obtained for the medications in use. (…)”

- The authors make it sound as though warfarin is a p-gp substrate. I do not believe this is true. Please edit this an ensure that it is correct.

R.: We edited the text and removed the information on p-gp-substrate from the paragraph mentioning mechanisms of drug interactions to avoid any misunderstanding (see 1st paragraph, page 5, presented above). There was no consistent literature to sustain our hypothesis of any possible mechanism of warfarin-rifampicin interaction involving P-glycoprotein.
Minor Essential Revisions
- The first paragraph of the case presentation section is unclear. Please revise.

R.: The first paragraph of the case presentation was revised to make it clearer:

"A 59-year-old, non-white woman was diagnosed with AF in May 2009, when warfarin therapy was initiated with a therapeutic INR range of 2.0-3.0. She was referred to the anticoagulation clinic of a university hospital in March 2010. Her typical warfarin dosage was nearly 52.5 mg/week. The patient’s medical history included systemic arterial hypertension, pulmonary arterial hypertension, rheumatic cardiopathy, asthma and chronic emphysema. She was also subjected to a biological mitral valve replacement in 2006. The patient denied any alcohol consumption and showed no evidence of hepatic or renal dysfunction. Her drug list included ferrous sulfate, hydrochlorothiazide and enalapril. (…)"

- Table 1 and figure 1 are highly repetitive. I do not believe that table 1 is necessary.

R.: Table 1 was deleted to avoid duplicate information and also to follow the same suggestion of another reviewer.

Reviewer – Dr. Michael Kostapanos

REVIEWER'S REPORT:

This paper by Auxilladora et al is a very interesting well-written and well-discussed case study on a drug-drug interaction between rifampicin and warfarin resulting in macroscopic hematuria. The authors also provide a review of the literature on this drug-drug interaction and a relevant discussion. Rifampicin and warfarin are commonly coadministered in the clinical setting, thus this paper is of high relevance. Despite numerous reports of this interaction, the present one is the first describing a bleeding complication in the long-term following rifampicin discontinuation. This highlights the importance of a close follow-up of all patients at risk for this drug-drug interaction. I have few discretionary comments for this paper:

1) Although generally well-written, this paper could benefit from some minor language editing.

R.: Thanks for the comments. As recommended, we submitted the manuscript to American Journal of Experts for a professional language editing to help us copyedit the paper.
2] I would like to know whether vitamin K or fresh frozen plasma was administered in the setting of macroscopic hematuria and increased INR.

R.: According to the hospital anticoagulation protocol, INR values between 6.00 and 8.00 without bleeding or with minor bleeding indicate the need for interruption of warfarin for two days and the reduction of 33% in the weekly dose, as implemented. Vitamin K administered orally is indicated when immediate reduction of INR is required within 24-48h. As the patient didn’t show signs of hemodynamic instability or other reason to justify immediate INR reduction (e.g. the need for invasive procedures), vitamin K or fresh frozen plasma was not administered. This information was included in the text (Case Presentation section) to make it more informative, as presented below:

“(…) The warfarin doses were interrupted for two days, and the weekly dose was reduced from 77.5 mg to 52.5 mg (33%), according to the hospital protocol. **Vitamin K or fresh frozen plasma was not administered due to the absence of hemodynamic instability or another reason justifying immediate INR reduction.** (…)” (3rd paragraph, page 4)

Reviewer – Dr. Sam Schulman

REVIEWER'S REPORT:

*Major Compulsory Revisions*

1. The authors talk about “aged” patients but the case is 59 y.o., which most of us would not consider elderly, and definitely not geriatric. Thus the discussion and conclusion should not be restricted to “aged patients”

R.: Thanks for the comments. Changes in the text were performed to make the text more general and not restricted to “aged patients”. Some of the modifications performed to follow this suggestion are copied below. The *Discussion* section was shortened, as recommended in another topic, and the modifications performed incorporated a general discussion to avoid the restriction to “aged patients”.

*Abstract - Background:* “Rifampicin remains one of the first-line drugs used in tuberculosis therapy. This drug’s potential to induce the hepatic cytochrome P450 oxidative enzyme system increases the risk of drug-drug interactions. Thus, although the presence of comorbidities typically necessitates the use of multiple drugs, the co-administration of rifampicin and warfarin may lead to adverse drug events. (…)” (1st paragraph, page 2)

*Abstract - Conclusions:* “(...) **In particular, patients with cardiovascular diseases** and active tuberculosis represent a group with a substantial risk of drug-drug interactions.” (3rd paragraph, page 2)
Background: “Rifampicin remains one of the first-line drugs used to treat tuberculosis (TB) [1,2]. This drug’s use is increasingly common due to the frequency of coinfection with TB and human immunodeficiency virus (HIV) [3,4] and the spread of TB within vulnerable populations [5,6]. (...)” (1st paragraph, page 3)

2. The report of the case is unnecessary long and should be concentrated. Also Table 1 contains duplicate information and details that are not required for this report and should be deleted. Just add in the case presentation that INR 5 days after the first dose reduction was 2.29.

R.: The report of the case was revised to simplify the text and to concentrate on essential information. Thus, the third paragraph of this section was removed. Table 1 was deleted to avoid duplicate information and also to follow the suggestion of another reviewer. Moreover, the information about INR (2.29) 5 days after the dose reduction was included in the text. Another reviewer suggested the inclusion of information about the use vitamin K or fresh frozen plasma which was added in the 3rd paragraph of the Case Presentation section.

Case presentation: “A 59-year-old, non-white woman was diagnosed with AF in May 2009, when warfarin therapy was initiated with a therapeutic INR range of 2.0-3.0. She was referred to the anticoagulation clinic of a university hospital in March 2010. Her typical warfarin dosage was nearly 52.5 mg/week. The patient’s medical history included systemic arterial hypertension, pulmonary arterial hypertension, rheumatic cardiopathy, asthma and chronic emphysema. She was also subjected to a biological mitral valve replacement in 2006. The patient denied any alcohol consumption and showed no evidence of hepatic or renal dysfunction. Her drug list included ferrous sulfate, hydrochlorothiazide and enalapril.

By the time the patient was sent for outpatient anticoagulation control, she had been diagnosed with pleural TB and had begun treatment with isoniazid (400 mg/day), rifampicin (600 mg/day) and pyrazinamide (2 g/day). The pyrazinamide was discontinued after two months. Subtherapeutic INR values were obtained for several weeks after initiating TB therapy. Routine reevaluations were necessary for INR monitoring and warfarin dosage adjustments. Thus, the warfarin dosage was gradually increased from 45 mg/week to 80 mg/week. Three months were necessary to reach a stable INR, which was maintained for an additional three months.

On October 15th, 2010, the patient’s rifampicin and isoniazid use was discontinued by an infectious disease specialist. One week later, a therapeutic INR of 2.02 was obtained. On November 11th, 2010, the patient noticed significant macroscopic hematuria that lasted for three days and a supratherapeutic INR (7.22) was measured on the same day. The warfarin doses were interrupted for two days, and the weekly dose was reduced from 77.5 mg to 52.5 mg (33%), according to the hospital protocol. Vitamin K or
fresh frozen plasma was not administered due to the absence of hemodynamic instability or another reason justifying immediate INR reduction. Five days after the dose reduction, the patient’s INR was 2.29. The patient had no history of bleedings, and there were no reported dosing errors or changes in drug therapy, vitamin K intake or medical status. A urinalysis performed five days after the first bleeding episode showed no significant presence of erythrocytes. Afterward, INR control was reached at a weekly warfarin dose of 37.5 mg. Sequential INR values and related warfarin weekly doses for the 35-month follow-up are presented in Figure 1. (last paragraph, page 3, continuing on 1st and 2nd paragraphs, page 4)

3. Figure 1: I can't see the bar that is supposed to indicate the duration of rifampicin therapy. Please clarify.

R.: The Figure 1 was modified to include the bar that indicates the duration of rifampicin therapy, as follows:

![Duratin of Rifampicin Therapy](image)

4. The increased need for warfarin after initiation of rifampicin is well known and the description of details in all studies that have demonstrated that in the past is superfluous. I suggest shortening the Figure 2 – which in my opinion is a Table – to contain only the last 3 studies. These also reported the increased sensitivity after stopping rifampicin. A comment in the text or another column should be added whether the supratherapeutic INRs in those studies were associated with bleeding.

R.: The discussion was focused on the results of recent case reports, as presented below. The Figure 2 was converted into Table 1 and simplified to contain only the last three studies. The title was adapted to “Summary of recent studies reporting drug-drug interactions involving rifampicin and warfarin in humans”.
The corrected table can be verified in the current version of the paper. Additionally, a comment was included in the text to emphasize that supratherapeutic INR values were not associated with bleeding in these studies.

“(…) Other recent case reports have demonstrated an increased sensitivity to warfarin after stopping rifampicin therapy and the need for more than four weeks to achieve a therapeutic INR, until the drug-drug interaction dissipated [16-18]. However, supratherapeutic INR values were not associated with bleeding in these studies (Table 1). (…)” (2nd paragraph, page 5)

5. The Discussion also needs shortening to focus on the case. The third paragraph should be deleted. Also other paragraphs should be shortened and the text ought to be better organized. The emphasis should be on the need for weekly monitoring after stopping rifampicin, until the maintenance dose of warfarin has decreased to what it was before rifampicin.

R.: A revision throughout the paper was performed, especially in the discussion, to shorten the text and to focus on the case. The third paragraph was deleted. Specific information about the need for warfarin weekly monitoring after stopping rifampicin was included in the text, as follows:

Abstract - Conclusions: “(…) Additionally, this case highlights the need for warfarin weekly monitoring after stopping rifampicin until the maintenance dose of warfarin has decreased to the amount administered before rifampicin use. (…)” (3rd paragraph, page 2)

Minor Essential Revisions
1. ABSTRACT, background: Suggest shortening “The co-administration of rifampicin and warfarin in older patients with atrial fibrillation may lead to adverse drug events. We aimed at reporting, for the first time” to “The co-administration of rifampicin and warfarin may lead to adverse drug events. We report for the first time”

R.: The text was shortened as suggested (see below). We would like to clarify that, following the suggestion of another reviewer, the same sentence was corrected to remove the idea of reporting this adverse event for the first time.

Background: “(…) Thus, although the presence of comorbidities typically necessitates the use of multiple drugs, the co-administration of rifampicin and warfarin may lead to adverse drug events. We report a bleeding episode after termination of the co-administration of rifampicin and warfarin and detail the challenges related to international normalized ratio (INR) monitoring.” (1st paragraph, page 2)
2. **ABSTRACT, Case presentation:** (therapeutic range, INR 2.0-3.0) (and also later in the manuscript, because the target INR is 2.5 but 2.0-3.0 is a range)

R.: The corrections were made in the Abstract and later in the manuscript, as follows:

*Abstract – Case presentation:* “(…) A 59-year-old Brazilian woman chronically treated with warfarin for atrial fibrillation *(therapeutic INR range: 2.0-3.0)* was referred to a multidisciplinary anticoagulation clinic at a university hospital. (…)” *(2nd paragraph, page 2)*

*Case presentation:* “A 59-year-old, non-white woman was diagnosed with AF in May 2009, when warfarin therapy was initiated *with a therapeutic INR range of 2.0-3.0.* (…)” *(last paragraph, page 3)*

3. **BACKGROUND, end of 2nd para:** The sentence “bleeding events and INR values during co-administration of rifampicin and warfarin” should be modified since the event occurred after the treatment with rifampicin had been concluded. Write instead “bleeding events and INR values after termination of co-administration …”

R.: The text was modified, as recommended. To be consistent with this modification, *Background* in the *Abstract* was also corrected.

*Abstract – Background:* “(…) **We report a bleeding episode after termination of the co-administration of rifampicin and warfarin** and detail the challenges related to international normalized ratio (INR) monitoring. (…)” *(1st paragraph, page 2)*

*Background:* “(…) However, there are no published long-term follow-up studies *focused on bleeding events and INR values after termination of the co-administration of rifampicin and warfarin.* (…)” *(3rd paragraph, page 3)*

On behalf of all authors, once more, we would like to thank the reviewers for the important contribution to this manuscript, and we hope you will find it suitable for publication now.

Yours sincerely,

Maria Auxiliadora Parreiras Martins

Antonio Luiz Pinho Ribeiro