



International Journal of Case Reports (ISSN:2572-8776)



Major bleeding precipitated by interactions between antibiotics and warfarin: a case series

Luana Marchesan¹, Raíssa Londero Chemello¹, Vanessa Thomé¹, Diego Chemello^{1,2}

¹Department of Clinical Medicine, Health Science Center, Federal University of Santa Maria, Santa Maria, Brazil

²Postgraduate Program in Health Science, Federal University of Santa Maria, Santa Maria, Brazil

ABSTRACT

Warfarin is a widely used anticoagulant agent with a large spectrum of indications for prevention and treatment of thromboembolic complications. Despite its low cost, warfarin and all other vitamin K antagonist (VKA) use has several limitations, including narrow therapeutic index requiring frequent laboratory monitoring to prevent complications related to under- and over-anticoagulation. The concomitant use of medications may alter the metabolism of warfarin by inducing or inhibiting the cytochrome P450-2C9, resulting in a decrease or increase in anticoagulant effect. In this setting, interactions between warfarin and antibiotics have been described. These interactions represent one of the problems with VKA use in the clinical setting. We aimed to report four cases where the prescription of antibiotics without proper control of anticoagulation levels led to major hemorrhagic complications.

Keywords

Anticoagulants; warfarin; drug interactions; hemorrhage; anti-bacterial agents

Conflict of interest

None

*Correspondence to Author:

Diego Chemello, MD, ScD
Universidade Federal de Santa Maria (UFSM) Cento de Ciências da Saúde – Depto. de Clínica Médica
Av. Roraima, 1000. Prédio 26. Cidade Universitária. Bairro Camobi. Santa Maria, RS, Brazil. CEP: 97105-900

How to cite this article:

Luana Marchesan, Raíssa Londero Chemello, Vanessa Thomé, Diego Chemello. Major bleeding precipitated by interactions between antibiotics and warfarin: a case series. International Journal of Case Reports, 2018 2:22

 eSciPub
eSciPub LLC, Houston, TX USA.
Website: <http://escipub.com/>

Introduction

Warfarin is an anticoagulant agent that inhibits the synthesis of clotting factors II, VII, IX, and X, as well as the naturally occurring endogenous anticoagulant proteins C and S. Initiation and control of warfarin therapy is challenging, since pharmacodynamic response is delayed and difficult to predict. The safety and efficacy of warfarin therapy are dependent on maintaining the international normalized ratio (INR) within the target range for the indication, which is between 2.0 and 3.0 in most clinical scenarios, like atrial fibrillation (AF) and prevention or treatment of venous thromboembolism.¹ There are several challenges in providing optimal anticoagulation in patients on warfarin therapy. Among these challenges, the narrow therapeutic index is perhaps one of the most important. It demands frequent laboratory monitoring to prevent life-threatening complications due to under- and over-anticoagulation. Additionally, VKA has an extensive list of drug-drug interactions that can result in fluctuating INR values.²

Warfarin interactions with antibiotics are particularly problematic because of their intermittent use and short duration of exposure, which creates the potential for more INR variability and the need for additional INR monitoring.³ In addition to interacting with warfarin via cytochrome P450-2C9, these antibiotics also may eliminate vitamin K-producing bacteria from the intestines to further alter INR.⁴ Some antibiotic drug classes have been considered to be high risk for interactions with warfarin. Among these are cotrimoxazole, fluoroquinolones, macrolides, and azole antifungals. Some studies have also associated amoxicillin and cephalosporins with such interactions, particularly in elderly.⁴⁻⁶

We presented four cases of warfarin-related bleeding, in which antibiotic co-prescription probably affected INR control and contributed to serious adverse events.

Case 1

An 87-year-old man with persistent AF presented to the emergency department (ED) with a 20-day history of progressive lower abdominal pain. The patient was on chronic use of warfarin for prevention of thromboembolic complications (CHA₂DS₂-Vasc score of 4). The level of anticoagulation had been stable for the previous 3 months. Thirty days prior to admission the patient had developed chronic obstructive pulmonary disease (COPD) exacerbation and was treated with azithromycin for 5 days without further INR control. Physical examination revealed a tender mass in the hypogastric region and periumbilical ecchymosis. His hemoglobin level (Hb) was 9.7 g/dl and INR was > 10. An abdominal computed tomography (CT) revealed bilateral rectus sheath hematoma, from umbilicus to pubic symphysis (Figure 1). The clotting abnormality was treated with 5 mg vitamin K intravenously and 10 ml/Kg fresh frozen plasma. Patient remained hemodynamically stable. The INR was corrected to 2.01 on the third day of admission without further evidence of active bleeding. The hematoma was managed conservatively. Anticoagulation with warfarin was then restarted. Patient received instructions about concomitant use of warfarin and other medications. During the next 3 months, no complications were reported.

Case 2

A 78-year-old female presented to the ED with a 2-week history of diffuse abdominal pain and distention, associated with pain in the right thigh. She also had nausea and vomiting. Her past medical history was characterized by a 60-day history of left lower limb fracture with immobilization. Rivaroxaban 10mg/day had been started for prophylaxis of venous thromboembolism (VTE) after lower limb immobilization, but it was switched to warfarin in the primary care setting due to financial reasons. The patient collected three INR levels after warfarin initiation, all showing therapeutic levels. Two weeks prior to the admission, the patient was started on ciprofloxacin 500mg/day for 7

days for urinary tract infection without further INR monitoring. At the ED, physical examination revealed tachycardia (106 bpm) and no signs of hypotension. There was reduction in bowel movements and a large hematoma in the right thigh. Laboratory showed Hb 9.0 mg/dl and INR > 10. Abdominal CT revealed a large retroperitoneal hematoma with extension to the right pararenal space and the right psoas and iliac muscles (Figure 2). The clotting abnormality was treated with 10 mg vitamin K intravenously and 15 ml/Kg fresh frozen plasma. After surgical consultation, the hematoma was managed conservatively with partial reabsorption and improvement of symptoms. Patient was discharged home after prolonged hospital stay without further anticoagulation. Mechanical compression stockings were recommended for VTE prophylaxis.

Case 3

A 41-year-old female with Marfan syndrome and a 10-year history of mechanical mitral valve replacement due to mitral regurgitation presented to the ED with a 10-day history of lower right abdominal pain. The patient was on chronic use of warfarin with maintenance of stable INR values over the last 5 years (55mg weekly dose, target INR 3,0). Recent medical history was characterized by urinary tract infection treated with nitrofurantoin for 7 days without further INR control. Physical examination revealed an abdominal pain under palpation in the right lower quadrant. There were no signs of hemodynamic instability. Her hemoglobin level (Hb) was 7,2 g/dl and INR was > 10. An abdominal computed tomography (CT) revealed retroperitoneal hematoma with extension to the right psoas muscle and no signs of active bleeding (Figure 3). The clotting abnormality was treated with 2 mg of vitamin K intravenously and fresh frozen plasma. The hematoma was managed conservatively. Anticoagulation was resumed with unfractionated heparin and warfarin without complications after 48 hours. Patient was discharged when INR reached 2.5. She was

posteriorly followed by the Anticoagulation Team and received instructions about concomitant use of warfarin and other medications.

Case 4

A 76-year-old man with permanent AF presented to the ED with rapid and progressive confusion and somnolence, associated with paraplegia. He also had a one-week history of macroscopic hematuria. The patient was on chronic use of warfarin for prevention of thromboembolic complications (CHA₂DS₂-Vasc score of 3). The level of anticoagulation had been stable for the previous 12 months, as indicated by his family physician. Medical history was characterized by recent use of ciprofloxacin for 10 days due to urinary tract infection without further INR control. Physical examination revealed hypotension (70/50 mmHg) and tachycardia (112 bpm). The neurologic evaluation showed paraplegia on the manual muscle testing scale, absence of position and vibration sense below the umbilicus, and hyporeflexia of the knee and ankle joint. There was also mild paraparesis rated as 3/5 on the manual muscle testing scale in the left upper arm. His Hb was 4.9 g/dl and INR was > 10. The clotting abnormality was treated with 10 mg of vitamin K intravenously and 15 ml/Kg fresh frozen plasma. Patient also received 4 units of red blood cells. Brain CT showed no abnormalities. A magnetic resonance imaging (MRI) of the spine revealed bone abnormalities suggestive of a myeloproliferative disorder, but no signs of bleeding. Neurological signs improved modestly with methylprednisolone. No further bleeding was observed. Complementary evaluation with bone marrow biopsy and lumbar puncture suggested a myeloproliferative disorder, but no definitive diagnosis was performed. The patient had a prolonged hospital stay due to several complications. He was then discharged for home care follow-up and ambulatory complementary investigation after partial recovery of the neurological status. Anticoagulation was not restarted due to refractory anemia. Patient presented several

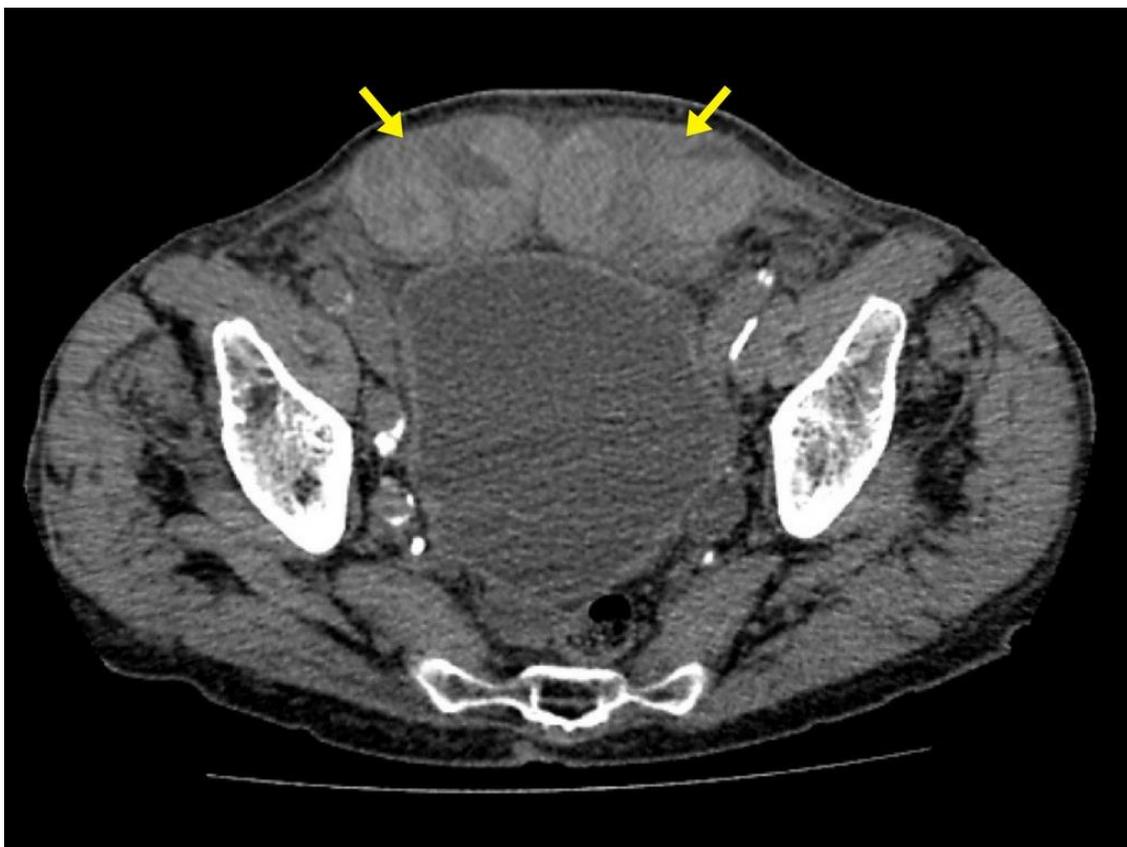


Figure 1. Noncontrast abdominal computed tomography. Arrows point to thickened rectus muscles and sheaths compatible with hematoma.

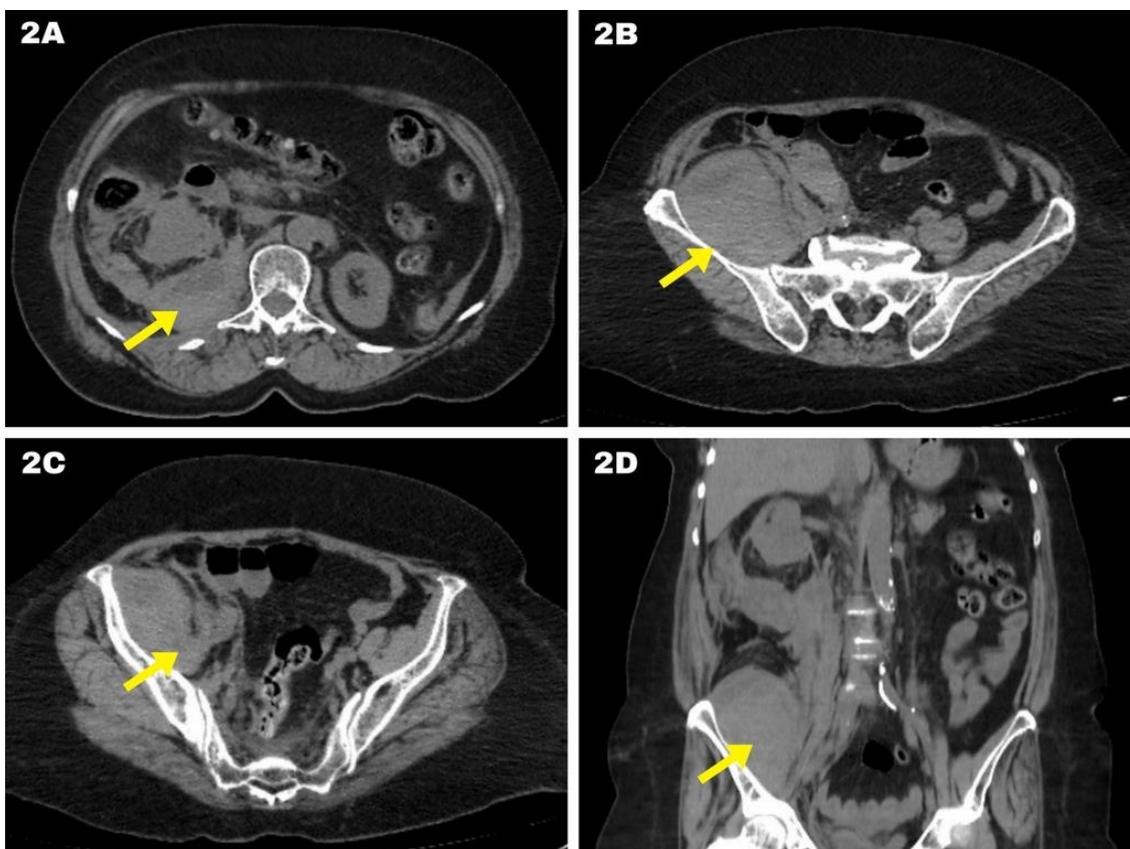


Figure 2. Noncontrast abdominal computed tomography showing large right sided retroperitoneal hematoma extending from the kidney (2A) to the pelvis (2C). The 2D image shows the hematoma in the longitudinal plain.



Figure 3. Contrast abdominal computed tomography showing large retroperitoneal hematoma (3A) with extension to the right psoas muscle. The 3B image highlights the hematoma size.

neurological and infectious complications, requiring urgent readmission. He died later from sepsis.

Discussion

Vitamin K antagonists remain a commonly prescribed anticoagulant therapy in patients with indications for thromboembolism prevention. A contemporary cohort showed that 42.8% of patients with atrial fibrillation (AF) were treated with VKA, despite the introduction to the new direct oral anticoagulant agents (DOAC).⁷

Among the risks related to VKA is major bleeding. This is defined by the International Society of Thrombosis and Haemostasis as clinically overt bleeding accompanied by a decrease in Hb level of at least 2 g/dl or transfusion of at least 2 units of packed red cells, occurring at a critical site (intracranial, intraocular, intraspinal, intra-articular, intramuscular with compartment syndrome, pericardial or retroperitoneal), or resulting in death.⁸ The safety and effectiveness of warfarin depends critically on the quality of anticoagulation control, often assessed using the percentage time in therapeutic range (TTR). In international guidelines, the cut-off of TTR varies between 60% and 70% as indications for INR controlling. Despite maximum benefits of

warfarin being observed when TTR is > 70%, real-world data indicate that TTR of at least 65% is often not achieved in routine clinical practice.^{7,9} Scores are currently used to assess the risk of thromboembolic events (CHA₂DS₂-VASC), as well as bleeding, (HAS-BLED). Those scores allow us to assess the indication for anticoagulation and its risks. However, they provide no information on how the patient will respond to treatment. Predicting which patients are good candidates for anticoagulation therapy would be very useful. In this setting, the SAME-TT₂R₂ Score has proven to be a good predictor of TTR for nonvalvular AF patients on oral anticoagulation with VKA.¹⁰

In the present case series, two patients with atrial fibrillation had high CHA₂DS₂-VASC. Another patient had mechanical mitral valve. They consequently have clear indication for anticoagulation. However, one patient was put on warfarin for VTE prevention after refusing to continue the use of DOAC for financial reasons. This is controversial at best. All anticoagulation statuses were followed by primary care physicians, which is reality in most places. Despite information of previous stable INR values, we could not have their laboratory recordings and consequently their TTR values.

Apparently, HAS-BLED and SAME-TT₂R₂ scores were not used in these cases to guide the choice of anticoagulation agent, as well as to highlight the risks of complications. One must emphasize the importance of using all clinical tools to optimize the use of VKA in the ambulatory setting.

Regarding VKA narrow therapeutic range, several studies have proved the interactions between warfarin and antibiotics in the clinical practice. Lane et al. showed that warfarin users who received high risk antibiotics (azithromycin, cotrimoxazole, ciprofloxacin, levofloxacin and clarithromycin) had an increased risk of hospitalization for serious bleeding events compared with those receiving low-risk antibiotics. Azithromycin nearly doubled the risk of serious bleeding events.⁴ Baillargeon et al. reported similar findings. They showed increased risk of bleeding in older patients with exposure to antibiotic agents within 15 days of the event/index date. This risk was particularly high with azole antifungals.⁵ In a retrospective cohort, Ghaswalla et al. demonstrated that the use of antibiotics may lead to an increase in INR in older patients on stable warfarin therapy. Although this increase did not result in significant outcomes of bleeding or hospitalization, this study highlights that INR should be routinely monitored in patients taking antibiotics.⁶

In the present case series, all patients shared the similar history of major bleeding related to over anticoagulation. The temporal relationship between antibiotic prescription and the initiation of bleeding indicated that these medications are the potential agents associated within INR disruption. In clinical practice, several strategies can be implemented to avoid the consequences of such interactions. First, whenever possible, it is useful to prefer using antibiotics with low-risk of interactions, like clindamycin and cephalexin. Another strategy is to closely follow-up with patients after antibiotic prescriptions to detect early signs of INR disruption. Finally, it has recently been shown that a multifaceted and multilevel intervention resulted in a significant

increase in the proportion of patients with AF treated with anticoagulation, which also reduced the incidence of thromboembolic events.¹¹ Perhaps a similar strategy could anticipate situations where VKA interactions are a potential threat, minimizing the risk of hemorrhagic complications.

Conclusion

The major bleeding outcomes presented in the current case series reinforces the potential threatening interaction between VKA and antibiotics, with a clear tendency of INR increase after antibiotic use. In such cases, clinicians should consider using antibiotics with low-risk profiles, if appropriate, based on the patient's clinical situation. If such therapeutic options are not possible, close INR monitoring is imperative to reduce the risk of bleeding and perhaps hospitalization.

References

1. Kuruvilla M, Gurk-Turner C. A review of warfarin dosing and monitoring. *Proc (Bayl Univ Med Cent)*. 2001;14(3):305-306.
2. Schulman S, Beyth RJ, Kearon C, Levine MN. Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*. 2008;133(6 Suppl):257S-298S.
3. Clark NP, Delate T, Riggs CS, et al. Warfarin interactions with antibiotics in the ambulatory care setting. *JAMA Intern Med*. 2014;174(3):409-416.
4. Lane MA, Zeringue A, McDonald JR. Serious bleeding events due to warfarin and antibiotic co-prescription in a cohort of veterans. *Am J Med*. 2014;127(7):657-663.e652.
5. Baillargeon J, Holmes HM, Lin YL, Raji MA, Sharma G, Kuo YF. Concurrent use of warfarin and antibiotics and the risk of bleeding in older adults. *Am J Med*. 2012;125(2):183-189.
6. Ghaswalla PK, Harpe SE, Tassone D, Slattum PW. Warfarin-antibiotic interactions in older adults of an outpatient anticoagulation clinic. *Am J Geriatr Pharmacother*. 2012;10(6):352-360.
7. Haas S, Ten Cate H, Accetta G, et al. Quality of Vitamin K Antagonist Control and 1-Year Outcomes in Patients with Atrial Fibrillation: A Global Perspective from the GARFIELD-AF Registry. *PLoS One*. 2016;11(10):e0164076.
8. Hylek EM, Held C, Alexander JH, et al. Major bleeding in patients with atrial fibrillation receiving

apixaban or warfarin: The ARISTOTLE Trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation): Predictors, Characteristics, and Clinical Outcomes. *J Am Coll Cardiol.* 2014;63(20):2141-2147.

9. Wan Y, Heneghan C, Perera R, et al. Anticoagulation control and prediction of adverse events in patients with atrial fibrillation: a systematic review. *Circ Cardiovasc Qual Outcomes.* 2008;1(2):84-91.
10. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J.* 2016;37(38):2893-2962.
11. Vinereanu D, Lopes RD, Bahit MC, et al. A multifaceted intervention to improve treatment with oral anticoagulants in atrial fibrillation (IMPACT-AF): an international, cluster-randomised trial. *Lancet.* 2017;390(10104):1737-1746.

