Prolonged prothrombin time in a rare case of vitamin K deficiency: a case report and a narrative review

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ABSTRACT

Prolonged prothrombin time increases the risk of bleeding complications in proportion to prolongation severity. We reported the case of a 72-year-old woman with a recent hospitalization for methicillin-susceptible Staphylococcus aureus endocarditis complicated by spondylodiscitis who developed a severe prolongation of clotting time during treatment with cefazolin due to a vitamin K deficiency. Cefazolin is a first-generation cephalosporin active against gram-positive bacteria. Like other cephalosporins, it is potentially able to inhibit the enzymes involved in recycling vitamin K metabolites, leading to a fall in gamma-carboxylation of vitamin K-dependent clotting factors. Clinicians should be aware of the necessity of regular monitoring of clotting times for the duration of antimicrobial therapy, especially in those patients with several risk factors for a poor vitamin K nutritional status. Prompt detection of vitamin K deficiency should be recognized and adequately supplemented.

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Introduction

Vitamin K is a fat-soluble vitamin whose deficiency is primarily associated with hemorrhagic disorders.[1] Vitamin K deficiency is a fairly common condition in newborns where multiple risk factors coexist (*e.g.*, poor transfer through placental and breast milk, immature gut flora, and low intestinal absorption).[2] In contrast, it is a rarer condition in adults, primarily associated with liver diseases, malabsorption due to biliary-pancreatic or intestinal disorders, and medication intake. Among these, coumarin-like compounds and antibiotics are the more involved classes.[3] However, while for the former vitamin K deficiency resulting in prolonged prothrombin time is the therapeutic goal, for the latter it is a dangerous and often underestimated side effect.

Here, we report a case of endocarditis and spondylodiscitis treated with cefazolin that developed a severe prolongation of clotting time, and a narrative review aimed to summarize the knowledge about the association between cephalosporin and bleeding disorders.

Case report

A 72-year-old woman presented to the emergency department with hemodynamic instability due to persistent diarrhea caused by Clostridium difficilis. After fluid resuscitation, her vitals were stabilized and she was admitted to the Internal Medicine Unit. Her medical records were notable for arterial hypertension and hospitalization due to methicillin-susceptible Staphylococcus aureus endocarditis three months earlier, for which aortic valve replacement was performed and an-

timicrobial therapy with oxacillin started. Some days after cardiac surgery, she developed acute back pain. Magnetic resonance imaging was carried out showing an abnormal marrow signal lesion in D12-L1, compatible with spondylodiscitis. Positron emission tomography-computed tomography (PET-CT) confirmed the hypothesis proving an abnormal fluorodeoxyglucose (FDG) uptake at the dorso-lumbar vertebrae with a maximum standardized uptake value (SUV) of 10.3.

After a multidisciplinary discussion, antimicrobial therapy was switched from oxacillin to cefazolin (2gr tid) plus levofloxacin (750mg once daily). Nevertheless, on day 25 the patient started suffering from delirium and hallucination, so levofloxacin was stopped and cefazolin carried on as a single therapy.

On the day of admission at our unit, laboratory findings were: white blood cell 17.78 K/µL, Hb 8.6 g/dL, platelets 207 K/µL, prothrombin time international normalized ratio (PT INR) 2.77, activated partial thromboplastin time ratio 1.06, estimated glomerular filtration rate 50 ml/min, alanine transaminase 7 U/L, aspartate aminotransferase 8 U/L, c-reactive protein 253 mg/L.

She started vancomycin therapy orally with rapid clinical improvement and resolution of diarrhea on day 3. Due to the lack of recent imaging follow-up for spondylodiscitis cefazolin therapy was kept on and a PET-CT was scheduled.

During the following days, despite clinical improvement and the decrease of inflammatory markers a worsening of clotting time was observed with a PT INR's growing up on days 2 and 3 up to 3.28 and 3.69, respectively. On day 4, mixing text was performed with a starting PT INR of 5.5 and a PT INR after mixing of 1.27. An assay of clotting factors revealed a reduced activity of all Vitamin-K dependent factors [Factor (F) II 17.8%, FVII 4.7%, FIX 34.4%, FX 5.6%], and increased activity of non vitamin-K dependent factor (FV 110%). As the patient had no history of prolonged clotting times, was not taking any anticoagulant therapy at that time, and no impairment in the liver function was detected by laboratory and radiological tests, a diagnosis of acquired vitamin K deficiency was made.

In the meantime, as the risk of spontaneous hemorrhage was seriously increased, ten milligrams of fitomenadion intravenous were immediately provided with a PT INR of 1.68 six hours later.

On day 5, PET-CT was performed showing a significant reduction in FDG up-taking of note spondylodiscitis lesion (SUV max 6.6). Accordance to the infectious disease specialist, due to the clinical and radiological improvement, as well as the long-lasting therapy (12 weeks) and the onset of complications, cefazolin was stopped. On day 10, oral vancomycin therapy was also ended.

No other increase in clotting times was observed in the next two months of follow-up.

Discussion

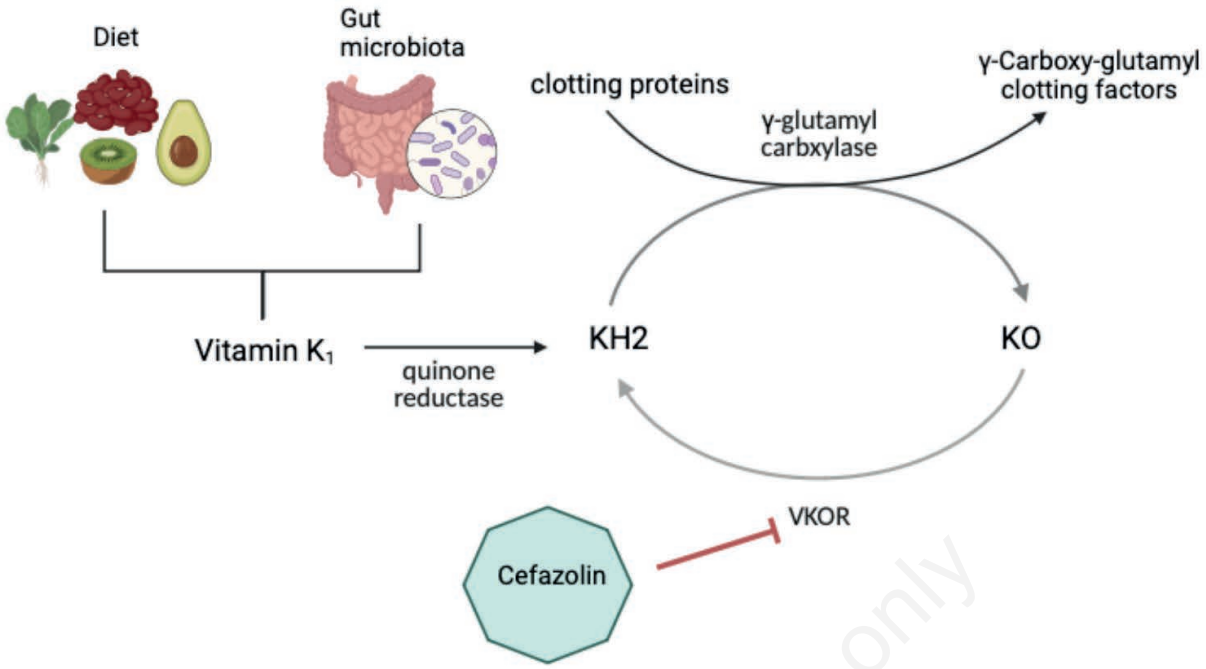
Vitamin K is naturally present in two different molecular forms, vitamin K_1, or phylloquinone, and vitamin K_2, also called menaquinones. The former is the predominant form of green leafy vegetables and fruits like spinach, cabbage, kiwi or avocado, whereas the latter are essentially synthesized by intestinal bacteria or can be found in food where bacteria are part of the production process.[4] Both forms can be taken up by enterocytes and delivered to the liver, where especially phylloquinone is involved in the pathway of clotting factors production.

Indeed, after absorption vitamin K_1 is reduced by a quinone reductase to hydroquinone (KH2). KH2 is an essential co-factor of gamma-glutamyl-carboxylase that catalyzes the gamma-carboxylation of glutamate residues of vitamin K-dependent clotting factors (II, VII, IX, and X). Gamma-carboxylation is a crucial step for the capability of these factors to bind calcium and phospholipids of membrane cells when the coagulation cascade is started.[5] At the end of the reaction, KH2 is converted into vitamin K 2,3-epoxide (KO) which in turn is recycled into KH2 by vitamin K epoxide reductase (VKOR).[6] (Figure 1)

Antibiotics can lead to a vitamin K deficiency by affecting intestinal bacteria activity or, rarely, by inhibiting KO recycling by VKOR. This mechanism was hypothesized for the first time in the 1980s after an increased incidence of hypoprothrombinemia associated with cephalosporins use.[7] Cephalosporins, like other beta-lactam antibiotics, act by inhibiting the bacterial synthesis of the cell wall. They are widely used for uncomplicated and complicated infections with a different spectrum of activity among the five generations class available.[8] The association with hemostatic disorders is mainly reported for those containing a methyl-tetrazole (MTT) side chain, such as some of those of second and third generations (*i.e.*, cefamandole, cefmetazole, cefotetan, cefoperazone). A meta-analysis including thirteen studies reported a 2-fold increased risk of prolonged PT with MTT-cephalosporins *vs*. other types of antibiotics, including non-MTT-cephalosporins, penicillins, and aminoglycosides (OR 2.05, 95% CI 1.39-3.01). The corresponding increased risk of bleeding was around 30%, even though not statistically significant (OR 1.36; 95% CI 0.92-2.10).[9]

Rarer, prolonged PT has been observed also for cephalosporins with a methyl-thiadiazol (MTD) side chain, like cefazolin. Indeed, the MTD group is probably less frequently released and more rapidly inactivated by methylation than the MTT group.[6]

MTT and MTD groups can inhibit VKOR provoking an increase in KO plasma concentration similar to that observed in patients treated with coumarin drugs,



Legend: KH2: hydroquinone, KO: vitamin K 2,3-epoxide, VKOR: vitamin K epoxide reductase

Figure 1. Vitamin K metabolism and possible underlying mechanism for cephalosporins interference.

as reported by Shearer *et al*.[10] However, they are weak VKOR inhibitors and this probably confines the association between the use of cephalosporins and PT prolongation to those patients with a poor nutritional vitamin K status for other reasons. Indeed, Strazzulla *et al.,* in their observational study including 132 patients, most of whom had no clinical features of a severe disease or a malnutrition status, did not find any association between PT prolongation and cefazolin use.[11]

Our patient suffered from vitamin K deficiency probably due to the presence of several risk factors. She had been hospitalized for three months and even though fed orally her daily intake was not optimal. She had concomitant colitis due to Clostridium difficilis that although not directly involved in vitamin K absorption testified a severe intestinal dysmicrobism and an impaired gut microbiota activity. Finally, due to the severe dehydration consequence of diarrhea, the plasma concentration of cefazolin was probably increased.

Therefore, in a predisposing condition, the administration of cefazolin led to the development of a clinically relevant vitamin K deficiency. The normalization of clotting time after its withdrawal evidenced how crucial its role was in the physiopathologic mechanism.

Conclusions

Multi-morbidity stands as a common clinical condition within Internal Medical units, substantially contributing to the complexity inherent in daily clinical activities. We reported a noteworthy prolongation of prothrombin time, potentially able to provoke a bleeding disorder, in a patient undergoing a twelve-week course of cefazolin therapy due to endocarditis complicated by spondylodiscitis.

Cefazolin is a first-generation cephalosporin generally well-tolerated and widely used for gram-positive infection. Its potential capability to inhibit the recycling cycle of vitamin K, especially in those patients with several risk factors for poor nutritional vitamin K status, should be taken into account by clinicians. In these patients, we recommend regular monitoring of clotting times and prompt supplementation of vitamin K if deficiency is suspected.

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