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Supratherapeutic International Normalized Ratio with Concomitant Warfarin and Cupric Chloride (Copper) Therapy

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Abstract

We report a case of supratherapeutic international normalized ratio values in a hospitalized patient started on warfarin to prevent recurrent deep vein thrombosis. Her medical history showed a failed course of apixaban and so warfarin therapy was initiated during this admission but quickly stopped after sudden, significant increases in international normalized ratio for several days after termination of therapy. A review of any drug-drug interaction did not expose any reported interactions between warfarin and her current medications at that time. However, the concurrent administration of cupric chloride did raise the possibility of an undocumented interaction between these two entities. The pharmacokinetic/pharmacodynamic properties of both drugs provided a study into the consequences of a combination therapy, beyond the anticipated outcome, which is normally based on previously observed results.

Keywords

Warfarin, Copper, Supratherapeutic International Normalized Ratio

1. Introduction

Warfarin is a drug with multiple drug-drug interactions (DDIs) that require close monitoring and, in some instances, avoidance of co-administration if possible. The majority of these interactions involve elevation of the international normalized ratio (INR) due to interference with drug metabolism, drug protein-binding properties, fluctuating vitamin K exposure, or concurrent administration of drugs that affect platelet functionality. The vast number of interactions documented in medical literature and in drug databases is a testament to this observation. A recent inpatient encounter provided an opportunity to explore a potential, previously

unidentified, interaction between warfarin and cupric chloride (copper) therapy that resulted in a supratherapeutic INR within a short period of time after warfarin initiation.

2. Case Presentation

The patient was a 26-year-old female with an extensive medical history including congestive heart failure, hypertension, systemic lupus erythematosus (SLE), lupus nephritis, recurrent deep vein thrombosis (DVT), multiple miscarriages, depression, and thyroid disease. Her daily home medications reflected the various disease states reported in the patient history and included the following: lisinopril/hydrochlorothiazide, apixaban, metoprolol, docusate, and ibuprofen as needed. She was transferred to our facility from an outside hospital (OSH) for worsening myopathy/neuropathy and newly developed clonic-tonic seizures. The previous hospital performed a head scan by computerized tomography, which revealed multifocal cerebral calcifications. Follow-up magnetic resonance imaging (MRI) of the patient's head showed increased ventricular prominence, which was concerning for communicating hydrocephalus and symmetric, increased T2 signal, within the globus pallidus bilaterally. This could have suggested uremia versus striatal-dominant lupus encephalitis.

Labs on admission to our facility were consistent with mild abnormalities to be expected given her extensive medical history, and included the following results: serum creatinine of 2.0 mg/dl, alkaline phosphate 249 U/L, aspartate aminotransferase (AST) 112 U/L, and alanine transaminase (ALT) 142 U/L. In light of her anemia and progressive bilateral lower extremity weakness, a hematology workup was ordered. Lab values obtained from that workup included: copper (61.8 μg/ml, low), B12 (985 pg/ml, normal), folate (8.0 ng/ml, normal), and a reticulocyte count (7.80, high). Coagulation tests performed included: prothrombin time of 15.7 seconds (reference range 10.0 - 12.7 s), Anti Xa level of 0.11 IU/ml and an INR of 1.4 (reference range ≤ 1.1). Slight elevations of both INR and prothrombin time were to be expected while on apixaban therapy [1]. Intermittent hemodialysis was begun at the previous hospital for acute renal failure, which had led to volume overload. A renal biopsy performed there was positive for lupus nephritis. Immunosuppression was begun with methylprednisolone 500 mg IV daily for 3 days, followed by oral prednisone 40 mg daily along with hydroxychloroquine 200 mg by mouth daily, and mycophenolate mofetil 500 mg by mouth four times daily. Hemodialysis was continued three times weekly. A ventilation perfusion scan was ordered due to her history of recurrent DVTs, miscarriages, and possible antiphospholipid syndrome. This showed an intermediate probability of an acute pulmonary embolism (PE). SLE-related serositis was suspected after a thoracentesis at the OSH found exudative left pleural effusion, which re-occurred at our facility, requiring another thoracentesis with removal of 400 milliliters of exudate. An echocardiogram later identified a left ventricular apical thrombus. The patient had been diagnosed with Class 3 + 5 lupus nephritis previously and was dialysis-dependent when

she was admitted to our facility.

With the patient's medical history of recurrent DVTs and miscarriages, and the VQ scan showing a probable PE, it was concluded that previous apixaban treatment had failed.

Anticoagulation therapy was switched from apixaban to a heparin infusion, following the guidelines of our heparin protocol for venous thromboembolism treatment. Oral anticoagulation was restarted with warfarin after 10 days, with heparin bridging therapy until the INR reached the therapeutic goal of 2.0 - 3.0. The starting dose was 5 mg of warfarin daily, with daily INR monitoring per our institution's warfarin management policy. Table 1 follows the warfarin doses and the subsequent INR values obtained for our patient. The course of her warfarin dosing regimen and resulting deviations from anticipated INR results prompted this investigation into the aberrant values. The warfarin dose fluctuated between 1 to 2.5 mg daily after the INR returned to below 2.0. The INRs values ranged from 2.1 to 2.5 while on an average dose of 2.5 mg of warfarin daily, leading to a warfarin dose of 2.5 mg daily upon discharge.

Table 1. INR values and warfarin doses.

Day of therapy	INR	Warfarin dose
1	1.5	5 mg
2	1.6	5 mg
3	2.7	3 mg
4	5.4	none
5	5.6	none
6	6.8	none
7	6.0	none
8	7.0	none
9	3.7	none
10	2.1	none
11	1.5	none
12	1.4	0.5 mg
13	1.3	0.5 mg
14	1.2	None, Pt refused
15	1.2	1 mg
16	1.4	2 mg
17	1.3	None, Pt refused
18	1.2	2.5 mg
29 days after start	1.5	Discharged on 2.5 mg daily

3. Discussion

This case provides an excellent study of what can transpire during warfarin ther-

apy, with multiple variables to consider when managing anticoagulation goals. The rapid increase in the patient's INR after only 3 doses, of which none would be considered overly aggressive based on the patient's age, medical history, or concurrent medications, raised questions as to what other factors may be contributing to the irregularity of the INR. Warfarin's pharmacological activity can be affected by factors that influence individual patient response, distribution, metabolism, and/or excretion.

3.1. Drug-Drug Interactions

When dealing with warfarin therapy, a major consideration that is prominent when formulating an initial starting dose is the presence of drugs and/or foods that may interact with the warfarin. The list of these items with documented warfarin interactions is extensive, resulting in both supratherapeutic and subtherapeutic INR values when concurrent administrations occur [2]. Supratherapeutic INRs can usually be avoided when the clinician prescribing the warfarin recognizes the potential interactions and adjusts the starting dose and subsequent dosage adjustments appropriately.

3.2. Drug-Protein Binding

Another consideration with warfarin is the possible effect of protein binding, or lack thereof. The effect occurs when a drug is known to be highly protein-bound and conditions exist that change the balance of bound to unbound drug. Protein binding can be a function of two or more drugs competing to bind with another drug, or a protein component in the blood, *i.e.* human serum albumin (HSA). This can result in the free, or unbound, drug concentration increasing, leading to increased drug activity. The degree to which this effect of more circulating free drug has consequences on drug distribution and dosing remains a topic of discussion, involving not only the physical consequences of protein binding but also the pharmacokinetic properties of the drug [3]. Warfarin is a highly protein-bound drug, with 99% of the drug bound by plasma proteins in normal physiological conditions. Warfarin pharmacokinetics can be significantly affected by changes that occur with decreased HSA levels [4]-[6]. A major consequence as a result of the protein-binding properties of drugs is the effect of a drug-drug interaction involving competition/displacement between 2 drug entities to bind to plasma proteins [7] [8].

3.3. Drug Hypersensitivity

Hypersensitivity to a drug can be an exaggerated pharmacological effect or an allergic reaction. Many factors can contribute to a reaction to a drug that falls outside the normal response(s) based on drug research and development. Hypersensitivity can be associated with an immune-mediated process, patient-specific demographics and polymorphisms, or concurrent drug therapy or state of health.

3.4. Drug-Coagulation Cascade Effect

Attenuation of the coagulation cascade by various drugs, chemicals, and plant extracts is a documented cause of hypercoagulability in patients taking anticoagulants. The effects of medicinal plants on both the intrinsic and extrinsic coagulation pathways have provided insight into the impact of various compounds on oral anticoagulants, blood coagulation, and hypercoagulable results [9].

3.5. Clinical Implications

For this patient's response to warfarin, the rapid and prolonged increase in the INR despite the drug being held for 8 days after the third dose, indicated some underlying condition or process contributing to the irregularity in the patient's response to the drug. The possibility of hypersensitivity to warfarin was considered to explain the immediate rise in INR on Day 3 of therapy. Warfarin hypersensitivity can be mediated by patient age, comorbidities, ethnicity, concurrent medications, and genetic variants in two genes, CYP2CP and VKORC1, that can affect warfarin requirements. Li *et al.* (2009) studied the time to over-anticoagulation in patients who were determined to be "very sensitive" to warfarin, based on the above criteria, age, comorbidities, etc. In their study of 214 patients, 1.9 % of their subjects, or 4 patients, had an INR greater than 4 after 3 days of warfarin 5 mg daily dosing. An early response was considered achieved in 200 of 214 patients after a median time of 8.5 days [10]. These findings support the expectation that if hypersensitivity were involved, the time to a supratherapeutic INR would have been farther out than the 3 days in which our patient reached supratherapeutic range.

Drug interactions when dealing with warfarin therapy are common and require close monitoring to avoid aberrant INR results. Concurrent medications at the time the warfarin was initiated included carvedilol, empagliflozin, guaifenesin, hydralazine, hydroxychloroquine, isosorbide mononitrate, **mirtazapine**, mycophenolate, nifedipine, pantoprazole, **prednisone**, sevelamer, **sertraline**, thiamine, and valacyclovir. Of these medications, it was noted that those in bold lettering carry a drug-drug interaction warning with warfarin, classified as interactions that could increase, or with prednisone also decrease, warfarin's anticoagulant effect. Initial dosing of the warfarin started at 5 mg daily, with no loading dose. This followed our pharmacy department policy for a HAS-BLED scoring tool of > or = 3, designating an elevated risk of bleeding and the need for close monitoring of warfarin therapy.

Review of the supratherapeutic INR result on Day 3 of warfarin led to investigation into one drug-drug interaction that represented an uncommon medication given at our institution, an outlier when reviewing concurrent medications given with her warfarin. The copper therapy touches upon two of the points highlighted in the earlier discussion. Looking into the protein binding aspect of this drug-drug interaction, we find that copper, like warfarin, is highly protein-bound. Displacement of warfarin by copper could have increased unbound, free warfarin in the blood and increased its pharmacological effect. The significance of an increase in

free drug has been questioned when the pharmacokinetic properties of warfarin are put under general pharmacokinetic scrutiny. The displacement of warfarin by copper would cause a transient increase in circulating free drug. This effect is inherently transient, because of a concomitant increase in drug clearance, as the liver would increase metabolism of the free drug presented to the hepatic receptor sites [11]. However, when working with warfarin, the consequence of dealing with a drug with an active metabolite, 3'-hydroxywarfarin, must be considered. A study by Gemmati *et al.* discovered anticoagulant activity of the active metabolite, which acted in conjunction with the anticoagulant activity of the parent drug [12].

The second prospect of how copper played a role in this case involves copper's effect on the coagulation cascade, with fibrinogen dysfunction noted. Research into the impact of copper on coagulation studies has demonstrated that an anticoagulant effect exists and would represent an additive effect when combined with an anticoagulant, such as warfarin [13] [14].

4. Conclusion

When prescribing warfarin for anticoagulation therapy, drug and food interactions must be considered as they pertain to dosing recommendations and adjustments. While we use the knowledge that we have accumulated on warfarin dosing to guide the patient to a safe, therapeutic INR goal, the introduction of a drug or medicinal agent that represents an uncommon combination with warfarin can expose a previously unrecognized interaction. Our case report is prompted by such an abnormal result in the INR for our patient that researching the underlying elements made this an interesting study of what has not been previously reported in the literature.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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