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Title

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Journal

Proceedings of UCLA Health, 20(1)

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Publication Date

2015-11-18

CLINICAL VIGNETTE

Cautions with Warfarin

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A 51-year-old male on warfarin was admitted to the hospital with an international normalized ratio (INR) was greater than eight. Repeat lab testing in the emergency room confirmed the value to be greater than nine. He started warfarin after a history of thromboembolic stroke in 2006. Given his young age and no comorbidities, an extensive hypercoaguable work-up was performed at several outside institutions but was unremarkable. The final theory was that given a history of significant pectus excavatum, bony protuberances irritated the pericardium leading to arrhythmias and development of subsequent emboli. Since his anatomical issues were not reversible, it was determined he required lifelong anticoagulation. He had some residual aphasia from his prior stroke but was otherwise active and healthy. His only outpatient medications included warfarin, lorazepam, and recent use of topical econazole. For the nine years, the patient had been on warfarin and never had such a supratherapeutic INR. Over the last six months, his numbers had been very stable in the therapeutic range of 2 to 3. He had no dietary changes and no recent oral antibiotics or medications had been added. He currently had no bleeding or bruising or other complaints. Physical exam and laboratory workup beyond the INR were unremarkable.

He was given Vitamin K 5mg orally in the emergency room. As the patient was not bleeding and was stable, no additional treatment was given for his elevated INR. About 24 hours later, labs confirmed his INR to be down to 1.6. Further questioning determined that the patient had started the topical econazole about 3 weeks prior for extensive tinea cruris. The patient was very generous in his application, coating thick layers along his scrotal, perianal, and bilateral thigh areas multiple times per day.

It was presumed that the patient had significant systemic absorption of the econazole due to his overzealous use. Furthermore, the area of application was quite vascular and increased the likelihood of systemic levels of the antifungal. He was instructed upon discharge to resume his usual warfarin dosing and terminate use of the topical medication. Outpatient follow up demonstrated that his INR quickly returned to his therapeutic levels by remaining off of the antifungal medication.

Review of the literature confirmed a very similar report of supratherapeutic anticoagulation after use of econazole.¹ The patient in that case had a similar history of stable INRs on

warfarin for years but presented with worsening ecchymoses after one week of econazole use.¹ Other accounts describe similar problems after miconazole application in the setting of warfarin administration.^{2,3} A prior retrospective study indicated that even topical nystatin can potentiate warfarin effects with lower doses of the anticoagulant needed in order to maintain therapeutic INR levels.⁴ Inhibition of the CYP liver enzymes by the antifungals leads to decreased metabolism of warfarin and consequently higher levels of warfarin in the blood.⁵

Other classes of topical medications can also alter warfarin levels as well. Methylsalicylate is a common offender in the literature. In one paper, patients using this topical salicylate while on warfarin presented with hematomas and bleeding.⁵ Like the patient presented here, their application was generally extensive. The report documented serum levels of the salicylate, confirming the systemic uptake from the skin.⁵ Similar potentiation of warfarin effects have been noted with use of topical testosterone as well.⁶ Furthermore, it is well known that many oral antibiotics can influence warfarin levels, and thus, therapeutic levels must be monitored closely when treatment for an infection is necessary. The data on the effects of other forms of antibiotics, such as topical or vaginal applications, are limited and guidelines are not clear. Regardless given the risks with oral metronidazole, the literature recommends similar close surveillance for the smaller but still potential risks of topical forms of the drug.⁷

While most physicians are aware of the effects of certain oral medications or food groups on warfarin dosing, we often minimize the extent of systemic absorption and the precautions needed with topical medications particularly in the setting of warfarin use. Unfortunately, there is minimal information regarding most topical medications and their potentiation of warfarin. Lang *et al*¹ does outline certain factors that can increase the risk of systemic toxicity from topical drugs, including extremes of age, renal/hepatic impairment, percentage of body surface area where medication is applied, condition of the area involved, etc. The above case and the few previous reports in the literature certainly highlight the need for caution even with topical medications. Systemic absorption can be extensive particularly with large and frequent applications of any medication. We need to caution patients on use given the life-threatening complications that occur with anticoagulation.

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