31. A patient taking Flovent, glyburide, metformin, and warfarin was started on fluconazole 200 mg daily x 21 days for oral thrush. Two weeks into treatment, the patient began feeling lightheaded, and noticed his stools were darker.

Case #31 Warfarin & Fluconazole

This case focuses on a patient whose maintenance medication list includes flovent, glyburide, metformin, and warfarin. The patient was recently diagnosed with oral thrush and started on a 21 day therapy of fluconazole 200 mg by mouth once daily. After 14 days of treatment the patient presents with lightheadedness and visibly darker stools than normal. These symptoms are indicators of blood loss and upper GI bleeding.

Taking into consideration the timing of symptom onset, as well as the patient's maintenance medications, it is clear that the newly added fluconazole is the precipitating drug and that the symptoms are caused by an interaction between the fluconazole and the warfarin. The mechanism behind this reaction includes fluconazole's inhibition of CYP2C9 and CYP3A4[1]. Fluconazole is a potent inhibitor of CYP2CP and a moderate inhibitor of CYP3A4. CYP2C9 is the major enzyme responsible for warfarin's metabolism and acts on the S-enantiomer of warfarin, which is the more potent isomer. CYP3A4 is a minor enzyme responsible for warfarin's metabolism, acting upon the R-enantiomer. The inhibition of these CYP enzymes, especially the inhibition of CYP2C9, leads to a dramatic increase in active warfarin concentration in the body by preventing warfarin from being metabolized into an inactive substrate. This increase in active warfarin concentration leads to an elevated INR and an increased risk of bleeding events.

In our patient of interest, they were on a modest dose of fluconazole for an extended period of time, resulting in a longer duration of warfarin metabolism being inhibited and a greater window of supratherapeutic INR for the patient to experience a bleeding event in. Warfarin itself has a very narrow therapeutic index, with an increase in INR leading to increased bleeding risk. Based on the patient's maintenance medications, namely metformin and glyburide, it is also a safe assumption that they are diabetic, which is potentially linked to increased rates of serious bleeding events and increased recovery times from such events. Diabetes is also linked to renal dysfunction, although it is unknown whether our patient has any renal disease at this moment in time. If our patient did have renal dysfunction, it would be significant due to the fact that fluconazole is primarily renally eliminated[1]. A decrease in renal function could increase the concentration of fluconazole in the body by decreasing the amount excreted, in turn providing a higher concentration of fluconazole to interact with the

warfarin. Factors such as medication adherence, alcohol consumption, and any dietary changes that could impact INR are unknown at this time.

Several studies have been conducted demonstrating that the addition of fluconazole therapy to patients on warfarin therapy results in an elevated INR, in turn leading to increased incidences of serious bleeding events[1-3]. A retrospective cohort study conducted by Lane et al.[2] looked at 22,272 patients who were stable on warfarin for at least 30 days with target INRs between 2 and 3, and were started on antibiotic or antifungal drug therapy. INR was measured after treatment, and rates of elevated INR were measured for each added drug. For fluconazole, 13.9% of patients experienced an elevated INR of between 4 and 6, and 9.7% experienced an INR greater than 6. Of note, 2.3% of patients on fluconazole therapy experienced a serious bleeding event. Our patient stated that he had darker than normal stools, which indicates an upper GI bleed. Our patient also reports lightheadedness, which is a symptom of internal bleeding and blood loss, which would line up with our patient in terms of potential causes and other concomitant symptomology.

An additional study conducted by Schelleman et al.[3] focused specifically on rates of gastrointestinal bleeding in patients taking both warfarin and antifungal therapy. This was a case-control, case-crossover study that pulled information from the US Medicaid database with 35 patients who were on both warfarin and fluconazole. The results of this study showed an odds ratio of 1.55 for patients who took 5 days of fluconazole therapy or less, and odds ratio of 1.89 for patients who took 6-10 days of fluconazole therapy, and an odds ratio of 2.32 for patients who took 11-15 days of fluconazole therapy to experience a serious GI bleed requiring hospitalization compared against patients on warfarin but not fluconazole therapy. Our patient presented with symptoms after 14 days of treatment, which puts him in the group of having a 2.32 odds ratio of experiencing a serious GI bleeding event, or nearly two and one-half times more likely to experience a GI bleed than someone on warfarin but not on fluconazole. This lines up with what could be predicted with our patient based on risk profile.

Our current plan is to discontinue the fluconazole and reassess the need for further treatment of oral thrush as well as determine if our patient's bleeding is severe enough to require warfarin reversal agents. It is likely that the oral thrush was caused by use of the Flovent inhaler without the patient rinsing their mouth out after use[4]. The patient should be counseled on rinsing their mouth out to avoid future recurrence of thrush. The drug interaction could have been prevented with use of different antifungal treatments that do not interact with warfarin. Nystatin, 5 mL by mouth 4 times daily for 1 week, would be a safe and effective choice of treatment. Nystatin does not undergo any appreciable metabolism in the body and has no documented interactions with other medications as it does not interfere with

any CYP450 enzymes[5]. This lack of metabolism and resulting lack of drug interactions would make nystatin our best possible choice for treatment of oral thrush in our patient. A retrospective cohort study conducted by Hellfritzsch et al.[5] compared INRs of warfarin patients with an INR goal of 2-3 who were treated with either miconazole or nystatin. In the nystatin cohort, the mean INR before treatment was 2.7 and mean INR after treatment was 2.5, demonstrating that nystatin does not have a risk of increased INR in patients taking warfarin.

A second potential alternative would be clotrimazole troches, 10 mg dissolved in the mouth 5 times daily for 14 days. These troches do not provide enough systemic absorption to significantly impact metabolism of other medications, including warfarin, and it does not interact with CYP2C9, making this a safe option to be considered as well[4,5]. INR should be monitored closely in the future when any drug changes are made and the patient should be educated about signs and symptoms of bleeding. In the cohort study by Hellfritzsch et al,[5] they did not specifically report INRs of patients on concomitant warfarin and topical clotrimazole treatment, but did note that the lack of 2C9 metabolism of clotrimazole would make it a theoretically safe option. A meta-analysis conducted by Quintiliani et al.[6] demonstrated good local effectiveness of clotrimazole troches with minimal systemic effects, making it a generally safe choice in terms of preventing drug interactions.

If it is determined that our patient's bleeding is severe enough to warrant treatment to reverse the effects of the warfarin, warfarin should be held and vitamin K could be administered for a slow reversal, as warfarin works by inhibiting VKORC1 in the body, decreasing the amount of vitamin K available to synthesize clotting factors[7]. For more rapid reversal, fresh frozen plasma could be used to immediately replenish the diminished clotting factors. This option is typically used for severe, life-threatening bleeding events. At this time, more information is needed before initiating a reversal agent, such as the patient's current INR value.

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