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LETTER TO THE EDITORS

# Interaction between topical miconazole and coumarins

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The potential of miconazole to influence coumarin metabolism, which could result in overanticoagulation, has been well described for the oral and vaginal administration of this antifungal agent [1–6]. However, topical use of miconazole is thought not to be able to cause clinically relevant drug interactions because of limited systemic absorption [7]. We describe a series of cases where loss of coagulation control has occurred with simultaneous use of topical miconazole and a coumarin. These cases were reported to the Netherlands Pharmacovigilance Centre Lareb between April 2001 and July 2010. Lareb is responsible for the collection and analysis of reports of suspected adverse drug reactions in the Netherlands and covers a population of 16.5 million people [8]. In 2008, the defined daily doses (DDDs) in this population were 64,448,438 for coumarins and 230,070 for topical miconazole [9].

Patient A was an 80-year-old female who was treated with phenprocoumon for atrial fibrillation. She had a history of congestive heart failure and diabetes mellitus. She was prescribed miconazole 20 mg/g cream for a fungal infection around the anal region. Thirteen days later her INR increased to 10.8. In the previous 6 months her INR had varied from 1.7 to 4.8. The miconazole cream was withdrawn, and she was treated with a single dose of 5 mg vitamin K after which her INR dropped back again.

Patient B was a 77-year-old female with congestive heart failure and diabetes mellitus. She was treated with phenprocoumon, losartan, simvastatin, metformin, glimepiride, carvedilol and furosemide. For an intertrigo under and on her breasts, she was prescribed miconazole 20 mg/g cream. Normally her INR ranged between 2.5 and 4. Twelve days after the start of the miconazole cream her INR increased to 20. She recovered after withdrawal of the miconazole and treatment with a total dose of 15 mg vitamin K.

Patient C was a 69-year-old female with a history of dementia, cerebrovascular accident and diabetes mellitus. She was treated with acenocoumarol, metoprolol, bisacodyl suppositories, metformin, glimepiride, fosinopril and chlorothalidone. She was prescribed miconazole 20 mg/g cream for an extensive mycosis. One week later her INR increased to 12.1.

Patient D was a 59-year-old male with cardiac arrhythmia who was treated with acenocoumarol, sodium valproate, flecainide, sotalol and losartan. He was prescribed miconazole 20 mg/g cream for a fungal infection around the groin and in the armpits. Two weeks after initiation of miconazole cream his INR increased from his normal values, ranging between 3 and 4, to 5.9. His INR recovered after withdrawal of the miconazole and acenocoumarol dose reduction.

In the literature, we found one case report describing an interaction between topical miconazole and a coumarin. This report concerns the loss of coagulation control in a patient taking miconazole cream for flexural intertrigo. The patient had been stable for months on warfarin with an INR ranging between 2.2 and 3.1. After 2 weeks of applying topical miconazole to his right groin his INR increased to 21.4 [10]. Alexandra et al. [11] described six cases of overanticoagulation with coumarin therapy in patients treated with topical

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econazole or bifonazole. These patients applied the drugs to the vulva under a disposable diaper or to their buttocks, groin or trunk.

The pharmacological mechanism by which miconazole can interfere with the metabolism of coumarins—the inhibition of CYP2C9—is widely known. Systemic absorption of miconazole is necessary to initiate this interaction. However, in clinical trials in healthy people the biological availability of topical miconazole was less than 1% [7]. Higher systemic absorption has only been proven after repeated administration of the drug in children with diaper rash [7, 12]. Nevertheless, application of miconazole cream under occlusion, on large surfaces and close to mucous membranes could increase systemic absorption and therefore make patients more vulnerable to a systemic effect of miconazole [11]. As a matter of fact, all cases described in this letter were at risk for increased systemic absorption. Furthermore, in cases of dermatomycosis and intertrigo, skin lesions may occur, which may also enhance systemic concentrations. Other explanations that could explain the loss of anticoagulant control in these patients were absent.

In addition, genetic polymorphisms in the CYP2C9 gene might also increase susceptibility to this interaction. CYP2C9 poor metabolizers have a lower activity of this enzyme, therefore it can be expected that inhibition of CYP2C9 could occur at low miconazole plasma levels [13].

The described cases indicate that topical miconazole use can cause loss of coagulation control when simultaneously used with coumarins. Clinicians should be aware of this possible interaction to prevent serious consequences in vulnerable patients. When simultaneous use is necessary, close monitoring of the INR is indicated during topical miconazole therapy.

**Conflict of interest** None.

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The cases described in this study have been reported to the Netherlands Pharmacovigilance Centre Lareb (patient A: NL-LRB-43273; patient B: NL-LRB-44960; patient C: NL-LRB-59743; patient D: NL-LRB-70136).