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Interaction between topical miconazole and coumarins

Nancy Broos MSc¹, Eugène P. van Puijenbroek MD, PhD¹

1. Netherlands Pharmacovigilance Centre Lareb, Goudsbloemvallei 7, 's-Hertogenbosch, the Netherlands

Corresponding author

Nancy Broos, telephone: 0031-736469700, fax: 0031-736426136, n.broos@lareb.nl

Informative title

Interaction topical miconazole and coumarins

Word count (excluding references)

768

Keywords

coumarin, cytochrome P450, interaction, INR, topical miconazole, cutaneous, topical

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5 The potential of miconazole to influence coumarin metabolism, which could result in
6 overanticoagulation, has been well described for the oral and vaginal administration of this
7 antifungal agent [1-6]. However, topical use of miconazole is thought not to be able to cause
8 clinically relevant drug interactions because of limited systemic absorption [7]. We describe a
9 series of cases where loss of coagulation control has occurred with simultaneous use of topical
10 miconazole and a coumarin. These cases were reported to the Netherlands Pharmacovigilance
11 Centre Lareb between April 2001 and July 2010. Lareb is responsible for the collection and
12 analysis of reports of suspected adverse drug reactions in the Netherlands and covers a population
13 of 16.5 million people [8]. In 2008, the defined daily doses (DDDs) in this population were
14 64,448,438 for coumarins and 230,070 for topical miconazole [9].

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19 cream was withdrawn and she was treated with a single dose of 5 mg vitamin K after which her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

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

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

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

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3 In literature, we found one case report describing an interaction between topical miconazole and a
4 coumarin. This report concerns the loss of coagulation control in a patient taking miconazole
5 cream for flexural intertrigo. The patient had been stable for months on warfarin with an INR
6 ranging between 2.2 and 3.1. After two weeks of applying topical miconazole in his right groin
7 his INR increased to 21.4 [10]. Besides, Alexandra et al [11] described six cases of
8 overanticoagulation with coumarin therapy in patients treated with topical econazole or
9 bifonazole. These patients applied the drugs to the vulva under a disposable diaper or to their
10 buttocks, groin or trunk.

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

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

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

Nothing to declare.

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Conflicts of interest

Nothing to declare

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