Coumarins and related drugs + Azoles; Miconazole

The anticoagulant effects of acenocoumarol, phenprocoumon, and warfarin can be greatly increased if miconazole is given orally as an oral (buccal) gel, and bleeding can occur. Oral miconazole has also been reported to interact with ethyl biscoumacetate, fluindione, phenindione and tioclomarol in a few reports. The interaction has also rarely been seen in some women using intravaginal miconazole, and in those using a miconazole cream on the skin.

Clinical evidence

(a) Oral gel

In one early report, a patient with a prosthetic heart valve and stabilised on **warfarin** developed blood blisters and bruised easily 12 days after starting miconazole gel 250 mg four times a day for a presumed fungal mouth infection. Her prothrombin time ratio had risen from less than 3 to about 16. She was subsequently restabilised in the absence of miconazole on her former dose of **warfarin**. [1]

Numerous other cases of this interaction with **warfarin** have been reported, and, where stated, often involved the use of 5 mL (125 mg) of the gel four times daily for oral candidiasis. [2-14] However, cases have occurred with lower doses; one case of an increase in INR to 11.4 with frank haematuria and spontaneous bruising was reported in a woman who had used 30 g of non-prescription miconazole (*Daktarin*) over 8 days (estimated daily dose of 75 mg), [7] and three other cases have occurred with non-prescription miconazole. [13-15] In another case, the interaction occurred with use of the miconazole gel locally around the corners of the lips for angular cheilitis. [11]

In 1996, the New Zealand Centre for Adverse Reactions Monitoring reported 5 patients taking **warfarin** whose INRs rose from normal values to between 7.5 and 18 within 7 to 15 days of starting to use miconazole oral gel. [5] In 2002, the Australian Adverse Drug Reactions Advisory

Committee (ADRAC) stated that they had received 18 reports of this interaction. In the 17 cases for which it was documented, the INR was above 7.5. Eight of the cases had bleeding complications, 9 required vitamin K, and 5 required fresh frozen plasma. [16] A small retrospective report found that in 32 patients stable taking warfarin and given miconazole oral gel the INR was increased from a mean of 2.44 (range of 1.92 to 3.18) to 8.8 (range of 4.9 to 16.9). The mean warfarin dose required by these patients was reduced (from 15.7 mg before to 10.8 mg after miconazole oral gel was started). Bleeding was reported in 15 patients. [17]

A few similar cases have also been reported for **acenocoumarol** [18-20] with miconazole oral gel. In addition, in one cohort study in patients taking **acenocoumarol** or **phenprocoumon**, the use of oral miconazole (form and doses not stated) greatly increased the risk of over-anticoagulation (INR greater than 6: adjusted relative risk 36.6; range 12.4 to 108). When analysed separately, the adjusted relative risk was higher for **acenocoumarol** than **phenprocoumon** (35.1 versus 16.5). [21]

A case has also been reported with the indanedione, **fluindione**. [22]

(b) Skin creams

An 80-year-old man stabilised on **warfarin** with an INR of 2.2 to 3.1 was found to have an INR of 21.4 at a routine check 2 weeks after starting to use miconazole cream for a fungal infection in his groin. He showed no evidence of bruising or bleeding. [23] In 2001, Health Canada reported that they had on record a case of an 80-year-old man taking **warfarin** and using topical miconazole who had a cerebral vascular accident, although this case was complicated by multiple medical conditions and medications. [24] In 2002, the Australian Adverse Drug Reactions Advisory Committee stated that they had received one report of an interaction involving topical miconazole cream. [16]

In one cohort study in patients taking **acenocoumarol** or **phenprocoumon**, the use of topical miconazole was associated with a

small increased risk of over-anticoagulation (INR greater than 6: adjusted relative risk 1.4) but this was not statistically significant. Note that this was much lower than the increased risk seen with oral miconazole (relative risk 36.6). [21]

(c) Tablets

In a study in 6 healthy subjects, miconazole 125 mg daily for 18 days (in the form of *tablets*) caused a fivefold increase in the prothrombin time response to a single dose of **warfarin** given on day 3. In addition, there was a threefold increase in the AUC of warfarin, with *S*-warfarin most affected (fourfold), and *R*-warfarin increased 1.7-fold. [25] In one early case report with warfarin, one patient with a prosthetic heart valve and stabilised on **warfarin** was found to have a prothrombin time ratio of 23.4 within 10 days of starting miconazole tablets 250 mg four times a day for a suspected fungal diarrhoea. He developed two haematomas soon after both drugs were withdrawn, and was subsequently restabilised, in the absence of miconazole, on his former dose of **warfarin**. [1]

The Centres de Pharmacovigilance Hospitalière in Bordeaux have on record 5 cases where miconazole (oral doses of 500 mg daily, where stated; form not mentioned) was responsible for a large increase in prothrombin times and/or bleeding (haematomas, haematuria, gastrointestinal bleeding) in patients taking the coumarins **acenocoumarol** (2 cases), **ethyl biscoumacetate** (1 case) and **tioclomarol** (1 case) and the indanedione **phenindione** (1 case). [26] Other cases and reports of this interaction involving **acenocoumarol** have been described elsewhere. [27-29]

(d) Vaginal dose forms

In 1999, the Netherlands Pharmacovigilance Foundation LAREB reported two elderly women patients taking **acenocoumarol** whose INRs rose sharply and rapidly when they were given miconazole pessaries 400 mg daily for 3 days. [30] Another report describes the development of bruising and an INR of almost 10 in a 55-year-old woman taking **warfarin** on the

third day of using 200-mg miconazole pessaries. For a subsequent course of intravaginal miconazole 100 mg daily for 7 days, the dose of warfarin was decreased by 28%, and her INR was 3.27. [31] Yet another report describes haemorrhage of the kidney in a 52-year old woman taking **warfarin** after she used vaginal miconazole for 12 days. [24] In one cohort study in patients taking **acenocoumarol** or **phenprocoumon**, the use of vaginal miconazole was associated with a small increased risk of over-anticoagulation (INR greater than 6: adjusted relative risk 4.3) but this was not statistically significant. Note that this was much lower than the increased risk seen with oral miconazole (relative risk 36.6). [21] A small retrospective case study found that in 3 patients stable taking warfarin and given intravaginal miconazole pessaries, the INR was increased from a mean of 3 to 4.9. The mean warfarin dose required by these patients was reduced (from 14.5 mg before, to 12 mg after, intravaginal miconazole was used). [17]

Mechanism

Miconazole is a moderate inhibitor of the metabolism of *S*-warfarin by CYP2C9, and, to a lesser extent, it also inhibits the metabolism of *R*-warfarin, probably by inhibiting CYP3A4. Even low oral doses of miconazole (125 mg daily) greatly inhibit warfarin metabolism, so it is not surprising that prescription doses of miconazole oral gel (480 to 960 mg daily) interact, as the gel is swallowed after retaining in the mouth. Very unusually, the low absorption of miconazole from the vagina and even exceptionally through the skin, can result in increased anticoagulant effects. Acenocoumarol would be expected to be similarly affected.

Importance and management

The interaction of **miconazole oral gel** and **miconazole tablets** with the coumarins is a very well established and potentially serious interaction. Most of the reports are about warfarin or acenocoumarol, but many other coumarins and indanediones, have been implicated. In some cases the bleeding has taken 7 to 15 days to develop, [1,3,26] whereas others

have bled within only 3 days. [28,31] Raised INRs have been seen even sooner. Given the extent of the interaction, usual prescription doses of miconazole oral gel (5 to 10 mL (120 to 240 mg) four times daily) should generally be avoided in patients taking any oral anticoagulant. Should concurrent use be necessary, prothrombin times should be closely monitored and suitable dose reductions made. The interaction has also been seen with non-prescription miconazole (one 30 g tube given over 8 days, or about 75 mg daily), which is not surprising in the context of the pharmacokinetic study, and suggests that patients taking coumarins and indanediones should also avoid using non-prescription miconazole. Nevertheless, the UK patient information leaflet for non-prescription *Daktarin* oral gel simply advises patients taking oral anticoagulants to talk to their doctor, and does not advise avoiding the product. [32] Nystatin and amphotericin are possible alternative antifungals to miconazole for mouth infections. However, note that one report suggests that nystatin might also interact with warfarin, see 'Coumarins + Nystatin'.

An interaction with **intravaginal miconazole** would not normally be expected because its systemic absorption is usually very low (less than 2%) in healthy women of child-bearing age. [33] However, the reports cited above show that sufficient absorption to provoke an interaction can apparently occur in a few patients, particularly in those with conditions that allow increased absorption to occur (for example, in postmenopausal women with inflamed vaginal tissue). Appropriate monitoring is therefore needed even with this route of administration in potentially at-risk women taking coumarins.

Topical (cutaneous) miconazole would also not be expected to interact, but the few reports cited shows that some caution might be warranted.

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