Drug points

Serious interaction between warfarin and oral terbinafine

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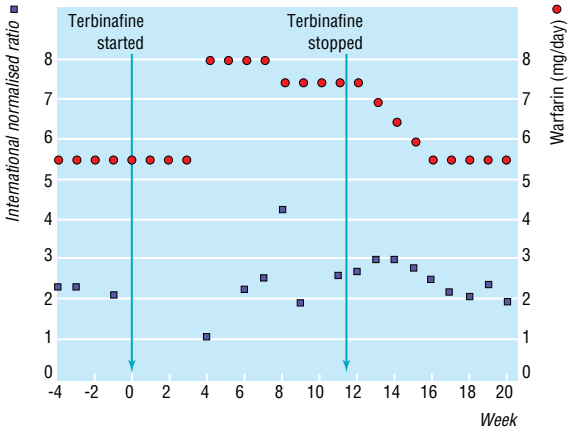
Drug interactions with warfarin are a common cause of loss of control of anticoagulation. Oral treatment with the antifungal drug griseofulvin decreases the anticoagulant effect of warfarin,[1] but, to our knowledge, ours is the first report of an interaction between warfarin and the oral antifungal terbinafine.

A 68 year old woman had taken warfarin for mitral valve disease since 1973. In the two years before November 1995 her daily maintenance dose was 5.5 mg. Monthly measurements of the international normalised ratio were stable at between 2 and 3. She also had non-insulin dependent diabetes mellitus. She took glibenclamide, metformin, frusemide, and spironolactone, the doses of which had not been changed in the previous 24 months. She reported drinking alcohol occasionally and was a non-smoker.

In November 1995 she started treatment with oral terbinafine hydrochloride 250 mg daily for three months for tinea unguium. Twenty eight days later her international normalised ratio decreased from 2.1 to 1.1 with her usual dose of 5.5 mg warfarin (figure). Over the next three weeks the warfarin dose was increased to 8.0 mg and then 7.5 mg daily to maintain the ratio between 2 and 3. Warfarin was continued for another five weeks at 7.5 mg. At week 12 terbinafine treatment was stopped. At week 13 warfarin was reduced to 7 mg, at week 14 to 6.5 mg, at week 15 to 6 mg, and at week 16 to 5.5 mg, which remains at the time of writing. She completed the three month course of terbinafine, with eradication of her tinea unguium.

Warfarin binds readily to albumin and can be displaced by several weakly acidic drugs, but this interaction does not typically result in clinically significant increases in the international normalised ratio. Drugs that induce hepatic microsomal enzymes, however, increase warfarin metabolism and hence the requirement for warfarin—for example, carbamazepine, phenobarbitone, rifampicin, and griseofulvin.[2]

Terbinafine is oxidised in the liver and excreted in urine, its metabolism requiring less than 5% of the total cytochrome *P*-450 capacity of the liver.[3] Terbinafine does, however, strongly inhibit the non-cytochrome *P*-450 enzyme squalene epoxidase.[4] In comparison with the azole antifungals (ketoconazole, itraconazole, and fluconazole), it has a low potential for interacting with other drugs because it is not extensively metabolised by cytochrome *P*-450, and, unlike griseofulvin, is not listed in the *British*



International normalised ratio and warfarin dose before, during, and after oral terbinafine treatment

National Formulary as a potential inducer of liver enzymes. In 20 normal subjects 250 mg terbinafine daily for six to seven days reduced the mean area under the curve of a single dose of cyclosporin by 12%, which was thought to be clinically unimportant.[5] In our patient the prolonged period of warfarin dose adjustment after the start and end of terbinafine treatment supports a mechanism of enzyme induction, in which onset and offset are gradual. Onset depends on the accumulation of the inducing agent and the synthesis of new enzyme and offset on the elimination of the enzyme inducing drug and decay of the increased enzyme concentrations.

Although warfarin and terbinafine are rarely prescribed together in clinical practice, their interaction could have catastrophic consequences in many of the conditions for which anticoagulant treatment is indicated. Caution should therefore be exercised whenever such combined treatment is prescribed.

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Parotid swelling and terbinafine

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Terbinafine is an effective antimycotic agent of the allylamine type which inhibits the enzyme squalene epoxidase.[1] It is generally well tolerated, although taste disturbance occurs in about 1 in 800 cases[2] and various skin reactions and hepatobiliary effects have been noted.[3]

A 38 year old man presented with a painful right ear 15 days after taking terbinafine 250 mg daily for tinea cruris. On examination a mild right otitis externa was noted, along with unrelated bilateral painless enlargement of the parotid glands. There was no associated hypersalivation or xerostomia. He had recently received booster immunisations for poliomyelitis and hepatitis B but was not receiving any other drug treatment. He gave a clear history of mumps as a child, and viral serology excluded active infection with either mumps or cytomegalovirus. A chest radiograph, a full blood count, the erythrocyte sedimentation rate, plasma viscosity, C reactive protein concentration, a biochemical profile, and an autoimmune screen were all normal. He was reviewed 12 days after stopping terbinafine treatment and the parotid swelling had significantly diminished. One month