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.

- 1 Okino K, Weibert RT. Warfarin-griseofulvin interaction. *Drug Intelligence and Clinical Pharmacy* 1986;20:291-3.
- 2 Young LY, Koda-Kimble MA. *Applied therapeutics. The clinical use of drugs*. Vancouver: Applied Therapeutics, 1995.
- 3 Balfour J, Faulds D. Terbinafine. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in superficial mycoses. *Drugs* 1992;43:259-84.
- 4 Back DJ, Tjia JF. Comparative effects of the antimycotic drugs ketoconazole, fluconazole, itraconazole and terbinafine on the metabolism of cyclosporin by human liver microsomes. *Br J Clin Pharmacol* 1991; 32: 624-626.
- 5 Long CC, Hill SA, Thomas RC, Holt DW, Finlay AY. The effect of terbinafine on the pharmacokinetics of cyclosporin in vivo. *Skin Pharmacol* 1992;5:200-1.

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 cases² 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

later he was completely well with no evidence of any residual parotid enlargement.

Bilateral parotid swelling in association with hypersalivation has been reported in a 35 year old man with schizophrenia who had been treated with clonazepam and clozapine.⁴ Other drugs associated with parotitis include the butazones, bretylium, asparaginase, methyl dopa, and iodide preparations.⁵ The manufacturers of terbinafine are aware that a 65 year old woman developed parotid swelling and facial oedema after 12 days of terbinafine 250 mg and that this resolved 7 days after stopping treatment (Sandoz, personal communication). By April 1997 the Committee on Safety of Medicines had received three reports of parotid swelling associated with terbinafine, against a background of more than 500 000 patients

having been prescribed the drug (personal communication). We suspect that our case is an example of this rare but potentially alarming side effect. In view of the widespread use of terbinafine, general practitioners and hospital clinicians alike should be aware of this possible cause of parotid swelling.

- 1 Balfour JA, Faulds D. Terbinafine. A review of its pharmacodynamic properties and therapeutic potential in superficial mycoses. *Drugs* 1992;43:259-84.
- 2 Beutler M, Hartmann K, Kulm M, Gartmann J. Taste disorders and terbinafine. *BMJ* 1993;307:26.
- 3 Lowe G, Green C, Jennings P. Hepatitis associated with terbinafine treatment. *BMJ* 1993;306:248.
- 4 Martin SD. Drug-induced parotid swelling. *Br J Hosp Med* 1993;50:426.
- 5 Davies DM. *Textbook of adverse drug reactions*. 3rd ed. Oxford: Oxford University Press, 1985.

Nortriptyline intoxication induced by terbinafine

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We present a case of nortriptyline intoxication secondary to terbinafine treatment.

A 74 year old man with depression was treated with nortriptyline for several months (other drug treatment was cisapride, hydrochlorothiazide, and ranitidine). Serum nortriptyline concentration was maintained at 200 ng/ml for more than 3 months as his depression had recurred when the dose was lowered.

He complained of increasing fatigue, vertigo, loss of energy, and loss of appetite. A few days later he injured himself by falling down a flight of stairs. Nortriptyline concentration was 366 ng/ml and 7 days later was 450 ng/ml. All the symptoms observed could be explained by the increased nortriptyline concentration (therapeutic range 75-150 ng/ml). Terbinafine treatment, started 14 days earlier for onychomycosis, was suspected to be the cause of the increase and was consequently stopped. The nortriptyline dose was lowered from 125 mg to 75 mg a day. Nortriptyline concentration declined from 450 ng/ml to 320 ng/ml 1 week later and to 200 ng/ml 2 weeks later, stabilising at 125 ng/ml after 3 weeks (figure).

A rechallenge test was performed with terbinafine 250 mg daily. Nortriptyline concentration increased to 150 ng/ml on day 4 and to 200 ng/ml on day 7. On day 8 the patient complained of increasing fatigue, vertigo, drowsiness, and a heavy feeling in the head. This suggests that the serum concentration had risen well above 200 ng/ml as the patient had never before experienced such effects at similar concentrations. Terbinafine treatment was stopped and nortriptyline treatment was avoided for 1 day. Nortriptyline concentration decreased to 180 ng/ml on day 12 and to 150 ng/ml on day 15. No

Serum nortriptyline concentrations during first exposure to terbinafine and during rechallenge test

increases in concentrations of γ -glutamyl transferase, aspartate aminotransferase, or alanine aminotransferase were observed. Therefore, we postulate that the increased nortriptyline serum concentration was due to a pharmacokinetic interaction. To our knowledge, this is the first report of a potentially dangerous interaction between nortriptyline and terbinafine.

Correction

Intranasal chlorhexidine resulting in anaphylactic circulatory arrest

Peter Moul, consultant physician at the Whittington Hospital, London, was inadvertently omitted as an author of this drug point (27 September, p 785). He referred the patient whose case is discussed to the National Hospital for Neurology and Neurosurgery, and it was his history taking that pointed to chlorhexidine as a possible causative agent of the severe reaction while the patient was in intensive care there.

One hundred years ago Quackery in Germany

The Kingdom of Saxony is described by a German medical journal as an Eldorado for quacks. The annual report of the Saxon National Medical College for 1896 states that in that year no fewer than 745 quacks, naked and not ashamed, flourished in that happy land. This number was greater by 42 than that given for the previous year. The total number of legally qualified medical practitioners in Saxony for the corresponding period was 1,761, so that approximately there was one quack to every two regular doctors. In certain districts, however, such as Zittau,

Kamenitz, Rochlitz, Annaberg and Glachau, the quacks outnumbered the doctors. Of the 745 quacks, 163 were women. Of the special "lines" of quackery the most numerous represented was "nature healing," which was professed by 220 persons; then came "sympathy," with 106 exponents, homoeopathy with 97, massage with 72, "magnetism" with 46, and tapeworm-curing with 19. One enterprising gentleman makes a speciality of illumination of the cavities of the body with the electric light. (*BMJ* 1898;i:1222)