1.1. Topical imidazole derivatives and drug interactions

Introduction

The imidazole derivatives are potent antifungal agents. In the Netherlands the imidazole derivatives bifonazole, clotrimazole, econazole, ketoconazole, miconazole and sulconazole are registered for topical administration as creams, ointments, gels or sprays. They have all been registered between 1971 and 1986 [1-7]. When used topically, these drugs are indicated for *the treatment of mycotic infections of the skin, such as cutaneous candidosis, pityriasis versicolor and seborrheoic dermatitis caused by dermatophytes, candida and pitysporum spieces and yeasts* [1,2,4,7]. Currently, ketoconazole and bifonazole are prescription only drugs and econazole, miconazole, clotrimazole and sulconazole are available over the counter.
Imidazole derivatives inhibit the synthesis of ergosterol by competitive inhibition of the cytochrome (CYP) P450 enzyme lanosterol-14α-demethylase [8]. This enzyme is responsible for the transformation of lanosterol into ergosterol. The decreased ergosterol concentration causes an impairment of the fungal cellular membrane which leads to an altered cellular membrane permeability and the loss of essential cell contents. Besides, the imidazoles have some activity against gram-positive bacteria [1-7].
It is known that systemic administration of ketoconazole leads to inhibition of the hepatic enzyme CYP3A4 and systemic and vaginal administration of miconazole leads to inhibition of CYP3A4, CYP2C9 and CYP2C19 [8-13]. These inhibitions could lead to a decrease in the clearance of drugs which are metabolized through these systems, such as ciclosporin, phenytoin, coumarin anticoagulants and some statins. The systemic absorption of topical imidazole derivatives is thought to be low. All SmPCs of topical imidazoles, except for sulconazole, mention a systemic absorption of 2% or less [1-7]. The SmPCs of miconazole cream and miconazole/hydrocortisone cream and ointment state that considering the low systemic absorption after topical administration, clinical relevant interactions occur very rarely [4-5]. In the SmPCs of other topical imidazoles no possible interactions are mentioned [1-3,6,7]. This report describes the possible relation between the topical use of imidazole derivatives and the occurrence of drug interactions.

Reports

On April 8, 2009, the database of the Netherlands Pharmacovigilance Centrum Lareb contained 17 reports of possible drug interactions associated with the topical use of an imidazole derivative. 11 reports concerned an interaction between a topical imidazole and a coumarine derivative (table 1) which led to an increase in the international normalized ratio (INR), five reports concerned an interaction with a statin and one report showed an interaction with an anti-epileptic drug (table 2). Three reports originated from a general practitioner, one from the Federation of Dutch Thrombosis Services, five from a pharmacist, two from a nursing home practitioner, two from a consumer and four from a specialist doctor.
All patients used the coumarine, statin or anti-epileptic drug for months to years before the imidazole derivative was started. The times to onset in both tables concern the time from the start of the imidazole derivative to the beginning of the adverse drug reaction(s). The imidazole derivative was withdrawn in 13 patients, eight patients recovered and three patients were recovering at time of reporting. In one patient a positive rechallenge was reported. Ten reports concerned the use of miconazole cream, five reports ketoconazole cream, one econazole spray and one bifonazole cream.

Table 1. Reports of possible interaction of topical imidazole derivatives and a coumarine

Patient, Sex, Age, Reporter	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug Outcome Relevant clinical info

Patient, Sex, Age, Reporter	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug Outcome Relevant clinical info
A 70886 F, 77 Specialist doctor	miconazole cream 20mg/g dermatomycosis on and under breasts phenprocoumon	furosemide spironolactone simvastatin acetylcysteine losartan carvedilol	drug interaction potentiation, INR increased to 20	12 days unknown recovered
B 43273 F, 80 Fed. Dutch Thromb. Services	miconazole cream 20mg/g application around anus phenprocoumon		coagulation time increased, INR increased to 10.8	2 weeks discontinued recovered
C 53264 M, 57 Pharmacist	ketoconazole cream 20mg/g rash from tick bite acenocoumarol	doxycycline miconazole/ hydrocortisone cream (as needed)	drug interaction, INR increased	1 week discontinued recovered heterozygote for 2C19*2
D 60845 M, 68 Pharmacist	bifonazole cream 10mg/g onychomycosis (under occlusion), phenprocoumon	simvastatin	INR increased to 5.3	1 week discontinued recovering
E 44960 F, 77 Pharmacist	miconazole cream 20mg/g rash under and on the breast phenprocoumon	furosemide simvastatin carvedilol glimepiride metformin losartan	INR increased to 20	12 days no change unknown
F 22601 M, 74 General Practitioner	econazole dermal spray 10 mg/g fungal infection back acenocoumarol		prothrombin time prolonged, INR increased to 15.8	not reported unknown not reported
G 59743 F, 69 Nursing home practitioner	miconazole cream 20mg/g mycosis fungoides (large surface) acenocoumarol	chlortalidone fosinopril metoprolol bisacodyl glimepiride metformin	INR increased to 12.1	1 week no change unknown
H 70885 M, 73 Specialist doctor	miconazole cream 20mg/g doxycycline tablet 100mg respiratory tract infection phenprocoumon	vitamin B complex insulin flammazine levodopa/carbidopa lactulose paracetamol omeprazole motilin	drug interaction potentiation, INR increased to 7.4	1 day discontinued unknown

Patient, Sex, Age, Reporter	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug Outcome Relevant clinical info
I 81519 F, 98 Nursing home practitioner	miconazole cream 20mg/g miconazole/hydrocortisone ointment dermatitis fungal under breasts acenocoumarol	esomeprazole movicolon paracetamol oxazepam prednisolone sodium phosphate, spironolactone estriole epoetine alpha alfacalcidol ferro sulphate cipramil bumetanide acebutolol nitroglycerin	drug interaction potentiation, INR increased to > 8	12 days discontinued unknown
J 70136 M, 59 Consumer	miconazole cream 20mg/g dermatomycosis groins and armpits acenocoumarol	valproic acid sotalol losartan flecainide	drug interaction potentiation, INR increased to 5.9	2 weeks dose discontinued not recovered
K 82897 F, 88 General Practitioner	vascular occlusion, miconazole cream 20mg/g erythema acenocoumarol	simvastatin nitrendipine alendronic acid tolbutamide irbesartan/ hydrochlorothiazide	drug interaction potentiation, epistaxis, INR increased to 5.5	1 month discontinued unknown

All patients in table 1 were using a coumarine when the topical imidazole derivative was introduced. The time between the start of the imidazole and the increase of the INR was 1-2 weeks. In one patient a latency of one month was reported. The difference in latency might be explained by differences in the interval of regular INR controls. The INR of patients A, B and C normalized after discontinuation of the topical imidazole derivative. Patients D and J were recovering at the time of reporting after withdrawal of the imidazole derivative. The absorption of the topical used imidazoles could have been influenced by the application site of the drug. In patient F the cream was applied on a large surface, patient B used the cream around the anus which could have led to absorption through the mucous membranes and in patients A, D, E, I and J the cream was (partly) used under occlusion (for example application under the breasts in women). The maximum INR after application of the imidazole creams varied from 5.3 to 20.

Table 2. Reports of possible interaction of topical imidazole derivatives and statins and anti-epileptic drugs

Patient, Sex, Age, Reporter	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
L 83697 F, 49 Specialist doctor	ketoconazole cream 20mg/g atorvastatin 20mg hypercholesterolemia	acetylsalicylic acid losartan	drug interaction, rhabdomyolysis (CK>8000)	unknown discontinued atorvastatin recovering
M 55882 M, 53 Pharmacist	miconazole cream 20mg/g dermatitis fungal large surface trunk simvastatin 20mg hypercholesterolaemia	mesalazine	drug interaction, myalgia	2 days discontinued miconazole recovered + rechallenge reported

Patient, Sex, Age, Reporter	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
N 29492 M, 46 General Practitioner	ketoconazole cream 20mg/g seborrhoeic dermatitis atorvastatin 20mg pure hypercholesterolaemia	colestipol aspirine	tiredness, muscle weakness	1 day discontinued ketoconazole recovered
O 62101 F, 70 Pharmacist	ketoconazole cream 20mg/g eczema armpits, simvastatin 20mg	acetylsalicylic acid metoprolol	drug interaction, myalgia	2 weeks discontinued ketoconazole recovered
P 65620 M, 66 Consumer	ketoconazole cream 20mg/g dermatomycosis armpits, simvastatin 40mg		drug interaction, myalgia	week discontinued ketoconazole not recovered
Q 85713 M, 7 Specialist doctor	miconazole cream 20mg/g mycoses behind both ears clobazam tablet 10mg epilepsy	levetiracetam movicolon carbamazepine	drug interaction intoxication	months discontinued recovered

The patients in table 2 were all using a statin when a topical imidazole derivative was started. The time to onset of the adverse drug reaction of the statin was reported in four of the five patients and varied from one day to two weeks. In patient M a positive rechallenge was reported. The absorption of the imidazole derivative could have been influenced by application on a large surface in patient M and under occlusion by using the cream in the armpits in patients O and P. Patients M, N and O recovered after withdrawal of the imidazole derivative, one patient (P) did not recover after withdrawal of the ketoconazole and patient L was recovering at the time of reporting after discontinuation of atorvastatin.
Patient Q presented with symptoms of fatigue a couple of months after the start of miconazole cream. Clobazam had been used for more than two years. A blood test showed a major increase in plasma level of the clobazam metabolite desmethylclobazam with a normal clobazam plasma level. Normally the proportion clobazam:desmethylclobazam is one to eight [14]. In this patient the proportion was one to fifty. The patient recovered after discontinuation of both miconazole and clobazam.

Other sources of information

SmPC

The SmPCs of miconazole cream and miconazole/hydrocortisone ointment and cream state that considering the low systemic absorption after topical administration, clinical relevant interactions occur very rarely [4-5]. In the SmPCs of other topical imidazoles no possible interactions are mentioned [1-3,6,7].
The SmPCs are not consistent about the bioavailability of the topical creams. The SmPC of ketoconazole cream states that after topical application no detectable plasma levels were found, which means a concentration of lower than five microgram per liter. In babies from one to five months with seborrheic dermatitis plasma levels up tot 133 microgram per liter were measured [1]. The SmPC of clotrimazole cream mentions a systemic absorption of less than 2% of the applied dose [6]. The SmPCs of both miconazole and econazole cream state that the bioavailability after topical application is less than 1% [4,7]. The SmPC of miconazole adds that systemic absorption has been detected after repeated topical administration in children with nappy rash [4]. The product information of sulconazole cream mentions a bioavailability of 10% after application of the cream on normal skin [3]. The SmPC of bifonazole does not give any information about bioavailability [2].

Literature

Only one article was published about the biological availability of topical administration of the in the Netherlands registered imidazole derivatives. In 1996 an analytical method using high-performance liquid chromatography for the determination of miconazole in human plasma was published [15]. Pershing *et al.* investigated the in vivo pharmacokinetics and pharmacodynamics of topical ketoconazole and miconazole in six people. They detected a systemic concentration for both drugs. Unfortunately the exact percentage or concentration was not mentioned [16].

Despite this limited information about the absorption and bioavailability of topical imidazoles, a couple of case reports have been published about the use of topical imidazole derivatives and drug interactions. In 1992, the effect of topical ketoconazole on the metabolism of oral ciclosporin was investigated in five patients with allergic contact dermatitis. They were given a six-day course of ciclosporin 1 mg/kg/day and applied ketoconazole 2% cream to an area of one arm and an inert base on the other. No significant difference in response was found between the two sites which indicates that topical ketoconazole does not potentiate oral ciclosporin [17]. The British Medical Journal published in 2002 a case report about the loss of control of anticoagulation in a patient taking over the counter 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 two weeks of applying topical miconazole in his right groin his INR increased to 21.4 [18]. Lang *et al*. reported in 2006 a 79-year-old man, taking long-term warfarin, who was given econazole cream for a fungal groin infection. Within one week of starting to apply the cream, he noticed bruising. His INR was increased from 2.2 to 12 [19]. Another case report concerns an 84-year-old woman who had been receiving acenocoumarol 4 mg per day for ten years for episodes of atrial fibrillation and recurrent deep venous thrombosis. Seventeen days after she started using econazole lotion 1% for a dermatitis affecting 12% of the body surface she suffered from overanticoagulation and a life-threatening laryngeal hematoma [20]. Alexandra *et al.* described in 2008 six cases of overanticoagulation with coumarin therapy in patients treated with a topical azole. Four of the patients had an INR greater than 9.0. Three of the patients were heterozygous for a CYP2C9 variant allele, all with INR values greater than 11.0 (highest INR>20). Three patients applied econazole (lotion, cream or powder) to the vulva under a disposable diaper. The other three patients applied econazole cream to their buttocks, groin and trunk. The authors conclude that cutaneous application of azole to large and/or relatively penetrable areas increases the risk for systemic absorption, thereby leading to marked systemic effects, especially when applied under occlusive diapers [21]. No case reports with a possible interaction between a topical imidazole derivate and a statin or an anti-epileptic drug were found.

Databases

In April 2009, the database of the Netherlands Pharmacovigilance Centre Lareb contained 17 reports of a possible interaction between topical imidazole derivatives and other drugs. Due to varieties in encoding the interactions and/or adverse drug reactions in the system and the different drugs concerned, it is not possible to determine a reporting odds ratio for this association.
Unfortunately it is also not possible to extract information about possible interactions related to the use of topical imidazole derivatives from the database of the World Health Organization (WHO) and the Eudravigilance database.

Mechanism

Imidazole derivatives can interfere with the metabolism of other drugs by influencing the cytochrome P450 system. Some imidazole derivatives can inhibit certain enzymes from the cytochrome P450 system. Inhibition of these enzymes leads to an increased plasma level of drugs metabolized by these enzymes. Concomitant use of an imidazole derivative and a drug which metabolism could be influenced by this antifungal agent, could lead to an increased plasma level of the drug concerned, more adverse drug reactions and even intoxication.

Ketoconazole is a potent inhibitor of CYP3A4. Miconazole is a potent inhibitor of CYP2C9 and a less potent inhibitor of CYP3A4 [22]. In the literature it has been prescribed that miconazole is also a potent inhibitor of CYP2C19 [13]. Econazole is structurally similar to miconazole and inhibits CYP2C9 and CYP3A4 [22]. No information is available about the possible influence of bifonazole and sulconazole on the cytochrome P450 system, although influence is expected due to chemical structure similarities of the imidazole derivatives.
Warfarin, phenprocoumon and acenocoumarol are racemic mixtures of S- and R- enantiomers. These enantiomers are metabolized by different cytochrome P450 isoenzymes. The S-enantiomers of all three coumarines are mainly metabolizes by CYP2C9. The R-enantiomers are metabolized by different other cytochrome P450 isoenzymes such as CYP2C19, CYP3A4 and CYP1A2. Inhibition of these enzymes can lead to an increased plasma concentration and systemic effect of coumarines (increased international normalized ratio) [22]. The Federation of Dutch Thrombosis Services mentions in their protocol that the effect of application of topical miconazole on a large surface or under occlusion on this possible interaction is not yet known [23].
Simvastatin and atorvastatin are metabolized by CYP3A4. Atorvastatin is less sensitive to CYP3A4 inhibition than simvastatin, because AUC and Cmax increase to a lesser extent with strong CYP3A4 inhibitors [24]. Combined use of systemic ketoconazole, miconazole or econazole and simvastatin or atorvastatin could therefore lead to increased plasma levels of these cholesterol synthesis inhibitors and to an increased risk for (serious) adverse drug reactions [25].
Clobazam is metabolized by CYP3A4 and in a lesser extent CYP2C19 to the active metabolite desmethylclobazam. Desmethylclobazam is metabolized by mainly CYP2C19 to a pharmacologically inactive product [26]. Miconazole can influence the metabolism of clobazam by inhibition of CYP3A4 and CYP2C19. Concomitant use could lead to accumulation of clobazam and desmethylclobazam. In the case reported to Lareb (patient Q) miconazole also caused inhibition of the metabolism of carbamazepine by CYP3A4 as carbamazepine is metabolized by this enzyme. Carbamazepine also induces CYP3A4 which could have let to an increased convertion of clobazam in desmethylclobazam. This could explain the extreme increase in the plasma level of desmethylclobazam with a normal clobazam level in this patient.

Discussion

Topical imidazole derivatives are used quite regularly. The number of patients prescribed a topical imidazole derivative in 2007 can be seen in table 3. The actual number of users is higher as econazole, miconazole, clotrimazole and sulconazole are also available over the counter.

Table 3. Number of patients that were prescribed a topical imidazole derivative in 2007 [27].

Drug	Number of patients
Clotrimazole	15
Miconazole	4,831
Econazole	0
Ketoconazole	287,350
Sulconazole	34,237
Bifonazole	1,186
Miconazole / Hydrocortisone	999

The interaction between systemically used imidazole derivatives and drugs metabolized by the cytochrome P450 system is well known. However, the possible effect of topical administered imidazole derivatives on these enzymes has only been published a couple of times and is not recognized in protocols of doctors and pharmacists. The Federation of Dutch Thrombosis Services is currently implementing the possibility of interactions of topically used imidazole derivatives and coumarines in their protocol.
On top of that little is known about the systemic absorption of topical administered imidazole derivatives. In most of the 17 reports received by the Netherlands Pharmacovigilance Centre Lareb, the application site could be an explanation for systemic absorption as application under

occlusion, on large surfaces and close to mucous membranes were reported. The influence of application site on the risk of these interactions was confirmed in the literature [21]. As the systemic absorption in clinical trials for topical imidazoles was either below detectable levels or under 2%, except for sulconazole with an absorption of 10%, the influence of application site and surface must be taken into account when determining the risk of an interaction between an imidazole derivative and a drug metabolized by CYP3A4, CYP2C9 and/or CYP2C19 in an individual patient.

Besides, genetic differences could influence the risk of developing a clinically relevant drug interaction when using a topical imidazole derivative. Genetic variabilities have been described for CYP2C9 [22]. Poor metabolizers have a lower activity of certain enzymes of the cytochrome P450 system. Therefore poor metabolizers have a higher risk for drug interactions with a low systemic concentration of an imidazole derivative than normal metabolizers do.

Conclusion

Lareb received 17 reports of drug interactions associated with the use of a topical imidazole derivative. These reports concerned the topical imidazoles miconazole (n=10), ketoconazole (n=5), econazole (n=1) and bifonazole (n=1). Systemic absorption and therefore the risk for interactions on the cytochrome P450 system could have been influenced by application under occlusion, on a large surface and close to mucous membranes. Genetic differences could influence the susceptibility for this interaction.

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