Review

SIDE EFFECTS OF SYSTEMIC ANTIMYCOTIC TREATMENT

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SUMMARY

Fungal infections are common in humans and their prevalence is still growing. Most mycotic infections of skin, mucosae and their appendages are very appropriate for topical treatment, but for certain clinical manifestations (onychomycosis, tinea capitis, chronically recidivating vaginal infections and extensive or very resistant glabrous skin infections, especially in immunocompromized patients) systemic antimycotic therapy seems to be the reasonable choice. The mechanisms of action of oral antifungals that are currently most often prescribed in Slovenia and their most common side effects are discussed: adverse events, asymptomatic elevations of liver function tests, symptomatic liver injury, side effects connected with cytochrome P450 and drug interactions. Finally we describe the recommendations about oral antimycotics during pregnancy and lactation and their possible interference with the activity of oral contraceptives.

KEY WORDS

systemic antimycotics, griseofulvin, itraconazole, fluconazole, terbinafine, adverse events, asymptomatic and symptomatic hepatic injury, cytochrome P450 enzymes, drug interactions.

INTRODUCTION

On the phylogenetical tree there exists a strong branch of fungi, consisting of more than 100 000 species of dermatophytes, yeasts and moulds (1). Fungi are eukaryotes - they have a true nucleus with a nuclear membrane, cytoplasmatic membrane, and a special cell wall containing chitin.

Fungal infections are common in humans and their prevalence is even growing. Aging of the population and expansion of the immunocompromised population - either because of the underlying illness or caused iatrogenetically - are factors that contribute most to it. Certainly fungal infections of skin, mucosae and their appendages are appropriate for topical treatment, but in some situations systemic antimycotic therapy has advantages. Fungal infections of deep skin layers are often difficult to reache by local antimycotics in efficient concentrations. Topical agents can not - with few exceptions - penetrate hair or

Table 1. Laboratory monitoring: Suggested guidelines (6).

	Complete blood cell count	Liver function tests
Terbinafine Continuous therapy >4 weeks	Baseline, repeat monthly	Baseline, repeat monthly
Itraconazole Continuous therapy >4 weeks	-	Baseline, repeat monthly
Itraconazole Pulse therapy	-	One pulse not indicated; Two or three pulses – no specific recommendations
Fluconazole Pulse therapy	-	No specific recommendations

nails, often there are also problems with the vaginal wall. Not so rarely there is a problem of patient compliance: with awkwardly located lesions or prolonged topical treatment compliance is usually quite low, some patients even find topical treatment cosmetically unacceptable. It seems that oral therapy is a reasonable choice in the treatment of onychomycosis, tinea capitis, chronic recidivant vaginal infections, and prolonged, extensive, or very resistant fungal skin infections.

What do we expect from antiinfective agents? Ideally they should eradicate the infective organism without affecting the normal functioning of the host. But ideals are hard to reach and we speak of a good or successful drug when the balance is strongly against the infective organism and in favor of the host. This is usually achieved by exploiting differences in their structure and function. As already mentioned, fungi and humans are eukaryotes, which means they are quite similar at the cellular biochemical level. Although the precise structures of enzymes are species-, organ- and even membrane-specific, agents which react with some fungal enzyme, may at least minimally influence the related human enzymes, too.

MECHANISMS

In this article we will discuss the side effects of systemic antimycotics which are currently most often used in Slovenia in the treatment of fungal skin infections. These are griseofulvin as the representative of the older generation, the new azoles - itraconazole and fluconazole and oral allylamin compound - terbinafine. They have different sites of action (2): griseofulvin acts in the nucleus, it interferes with microtubule structure and function, and thus inhibits mitosis. The other three are active at the level of the cell membrane, they inhibit ergosterol biosynthesis at two different points: azoles disrupt cell membrane biosynthesis by inhibition of cytochrome P 450 activation of lanosterol demethylase; terbinafine inhibits the enzyme squalene epoxidase leading not only to ergosterol depletion but also to squalene accumulation which is supposed to act toxically on the cell.

SIDE EFFECTS

Systemic antimycotic drugs can, as any other drug, exert side effects either in a direct or indirect way. The drug itself may directly affect a physiological function or act indirectly - through its metabolites, haptens, or drug interactions. They can cause cell injury, suppress or induce different metabolic processes and/or immunological reactions (3). With oral antimycotics we most often observe the following:

a) different adverse effects
b) asymptomatic elevations of liver function tests and symptomatic hepatic injury
c) effects connected with mammalian cytochrome P 450 enzymes
d) drug interactions

Adverse events (AE)

AEs may occur with any antimycotic, the exact numbers differ in different studies and publications (griseofulvin from 13.0 - 20.3% (4), itraconazole 7.0 - 12.5%, fluconazole 12.6%, terbinafine 10.0 - 12.0% (5)). Oral antimycotics seem to induce similar types

of mainly minor adverse events.

Gastrointestinal AEs mostly include nausea, abdominal pain, dyspepsia, rarely vomiting or diarrhoea. In connection with the nervous system, headaches, dizziness, and paraesthesias are mainly quoted. Skin symptoms vary from pruritus to maculopapular exanthemas or urticaria.

Asymptomatic elevations of liver function tests

Asymptomatic (pathologic) elevations of liver function tests (LFTs) do occur (from 0.1% with pulse itraconazole therapy, 3.0% with terbinafine, 3.3% with fluconazole and 4.0% with continuous itraconazole therapy and griseofulvin) but are usually reversible (6,7). However, when impairment is noted, LFTs should be repeated after a week, because the elevation may mirror an early onset of hepatotoxicity.

Symptomatic hepatic injury

Symptomatic hepatic injury may present as hepatocellular, cholestatic or mixed injury. The risk that it will develop is actually very low, but it is still a source of fear among physicians. It is important to know that it has been reported with every available antimycotic, but etiopathogenetically it is generally idiosyncratic and also not predictable. According to the WHO statistics most of the reported reactions developed between the second and the sixth week of treatment.

Only isolated cases connected to griseofulvin were reported and probably all were idiosyncratic. Association between ketoconazole and hepatobiliary dysfunction was only 1:15000 but it further accentuated concern. No hepatotoxicity was associated with one-week fluconazole pulse therapy. Severe hepatic reactions described in association with continuous therapy usually occurred in patients already affected by an underlying illness. Five cases of reversible idiosyncratic hepatitis were connected with itraconazole, in all instances with continuous therapy. For terbinafine, seven cases of idiosyncratic hepatobiliary disorders were reported, six were reversible and in one patient liver function tests remained persistently elevated.

Being aware of these facts a physician must differentiate when monitoring LFTs is necessary on scientific grounds and when it is performed mostly for medicolegal purposes. It is important however, to exclude pre-existing hepatic injury. For this reason an exact history and baseline LFTs are advisable, especially when starting a prolonged treatment with oral antimycotics (Table1) (6). Probably of the same importance is patient's education concerning self-observation. When a patient notices clinical signs of hepatobiliary dysfunction (malaise, nausea, vomiting, weakness, fatigue, anorexia, jaundice, dark urine, acholic stools, pruritus) he must visit his doctor immediately, the drug should be withdrawn and LFTs evaluated.

Side effects related to human cytochrome P 450

Cytochrome P 450 (CYP) enzymes are a very important group of enzymes in eukaryotes. In humans two of their most important functions are metabolism of different endogenous and exogenous agents and synthesis of steroid hormones. Any drug with an affinity for human CYP enzymes may be associated with a certain toxicity. For example when ketoconazole has been used, hypoadrenalism, decreased libido, impotence and gynecomastia have been observed.

Triazoles bind weakly and more selectively to the mammalian CYP enzymes and no side effects related to steroid hormones have been reported, but they may influence the metabolism of other drugs.

Drug interactions

Drug interactions are a very important part of systemic antimycotics' side effects. The manner in which a drug or its metabolites can interact with other drugs are of course manifold, concerning oral antimycotics there exist two main mechanisms: competition for plasma proteins and inhibition or induction of CYP enzymes. There is also a third mechanism worth mentioning - guilt by association, where side effects expressed with older agents are automatically (or speculatively) connected to newer drugs, even when there are only little or no scientific data for such interference (8).

Protein binding: most antifungals with the exception of fluconazole (only 12% bound) (9) bind strongly to plasma proteins (griseofulvin 84%, itraconazole 99.8%, terbinafine 99%), and therefore compete with other drugs, which may bind to the same protein receptors. This can lead to elevated plasma concentrations of either substance and possibly to stronger effects than expected. Because of rapid compensatory homeostatic mechanisms this is usually only a transient event, but one has to be careful

Table 2. Systemic antifungal (antimycotic) drugs and drug interactions (11).

Griseofulvin	Fluconazole	Ketoconazole	Itraconazole	Terbinafine
Drugs that may increase levels of listed antimycotic				
None	Hydrochlorothiazide	None	None	Cimetine
Drugs that may decrease levels of listed antimycotic				
Barbiturates	Rifampicin	Rifampicin Isoniazid Phenytoin H_2-antagonists (antacids and anticholinergics)	Rifampicin Isoniazid Phenytoin H_2-antagonists (antacids and anticholinergics) Phenobarbitona Carbamazepine	Rifampicin Phenobarbital
Drugs whose levels may be increased by listed antimycotic				
Alcohol	Warfarin Oral hypoglycaemics Phenytoin Cyclosporin ?H_1-antagonists (terfenadine and astemizole)	Phenytoin Warfarin Cyclosporin H_1-antagonists (terfenadine and astemizole) Oral hypoglycaemics Digoxin ?Insulin ?Corticosteroids ?Chlordiazepoxide	Phenytoin Warfarin Cyclosporin H_1-antagonists (terfenadine and astemizole) ?Oral hypoglycaemics Digoxin ?Insulin ?Corticosteroids ?Chlordiazepoxide Triazolam Felodipin Midazolam Cisapride	None
Drugs whose levels may be decreased by listed antimycotic				
Warfarin Oral contraceptives Cyclosporine	?Oral contraceptives	Antipyrine Oral contraceptives	Antipyrine ?Oral contraceptives	None

when administering drugs with narrow therapeutic index, small volume distributions, or rapid onset of action.

Influence on human cytochrome P 450 enzymes: CYP enzymes are a big family of heme-containing enzymes which catalyse reactions in the first phase of biotransformation of endogenous and exogenous agents, including various drugs. There are over hundred different, genetically determined enzymes located on the membrane of the reticular endoplasmatic system, which are classified into families (Arabic numbers) and subfamilies (capital letters), the most important being CYP 1A, CYP 2C, CYP 2D and CYP 3A. Metabolism of many drugs starts with CYP enzymes, there may be activated only one or a few subfamilies. On the other hand there are many drugs that influence the cytochrome P 450 activity. Metabolism of antimycotics is usually not problematic and only

stronger CYP inducers can increase or decrease their plasma levels (for example the influence of cimetidin, rifampin and phenobarbital on terbinafine biotransformation or influence of rifampin, phenitoin and phenobarbital on itraconazole metabolism). Table 2.

More important is the fact that systemic antimycotics substantially interfere with CYP enzymes. The most important are azoles, which is understandable considering their mechanism of action. But again it should be stressed that newer agents act much more specifically and influence only specific subfamilies. Itraconazole for example is a strong inducer of CYP 3A enzyme subfamily (therefore it diminishes biotransformation of cisapride, astemizole, cyclosporin, terfenadin) and does not influence CYP 2C or CYP 1A subfamilies, which are for example connected with metabolism of sulfonylureas (10). Fluconazole in usual doses inhibits only CYP 2C subfamily but in larger doses also CYP 3A subfamily. Griseofulvin is an inducer of CYP 3A subfamily and can decrease plasma concentration of some drugs; most noteworthy are warfarin, cyclosporin and oral contraceptives. Terbinafine has practically no influence on the metabolism of other drugs (Table 2) (11).

Special side effects of quoted oral antimycotics

Griseofulvin is derived from a fungus Penicillium griseofulvum and may as such crossreact with penicillin. Disulfiram-like reaction with alcohol ingestion, rare cases of neutropenia and splinter subungual haemorrhages were also reported. It was also connected with exacerbation of systemic lupus erythematosus and is contraindicated in porphyrias, especially in porphyria cutanea tarda, as it may increase the concentration of porphyrins in the liver and urine. Because of its antimitotic action it is strongly contraindicated during pregnancy and lactation.

Itraconazole: animal studies on rats showed embryotoxicity, skeletal malformations and maternal toxicity so it is contraindicated during pregnancy, and contraceptive precautions are advised during itraconazole treatment (12). There is no information about excretion in breast milk, but because of its lipid solubility it is contraindicated during breast-feeding too.

Fluconazole: there is not much information about fluconazole and most side effects were reported in critically ill patients with many medicaments where it is hard to relate the side effect to a specific drug.

Terbinafine: unusual but mostly reversible taste (0.7%) and smell (0.02%) disturbances were reported (13). Although animal studies showed no risk, it is contraindicated during pregnancy because no clinical experience in pregnant women is available. As it is excreted in breast milk it is also contraindicated during breast-feeding.

All aforementioned systemic antimycotics are contraindicated during pregnancy; but as these agents in general cause some important drug interactions, concern arose about possible influence of oral antimycotics on the oral contraceptive agents. The basic question is, whether oral contraceptives are efficient enough when taken together with a systemic antimycotic. At the 19th World Congress of Dermatology Del Rosso and al. (14) gave a review on available case reports and clinical studies.

Griseofulvin: fifteen cases of breakthrough bleeding, five unexplained amenorrhoeas and two unintended pregnancies were reported in United Kingdom and the Netherlands. In a special study menstrual irregularities have been reported and reproduced after rechallenge. Because of that combination, a combined treatment with griseofulvin and oral contraceptives is best to avoid.

Fluconazole is supposed to be probably safe in the usual doses, but some anecdotal reports of intermenstrual bleedings exist and minor fluctuations in ethinyl oestradiol and levonorgestrel (increased hormonal levels) were reported.

Itraconazole is considered to be most probably safe; no changes in ethinyl oestradiol and even increased bioavailability of norethisterone were noticed (15). There is one report of unintended pregnancy.

Terbinafine is also said to be probably safe, but caution is recommended because nine reports on breakthrough bleeding and one unintended pregnancy are available and no in vivo studies are known.

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