



# General aspects of drug interactions with systemic antifungals in a retrospective study sample\*

Aspectos gerais de interações medicamentosas com antifúngicos sistêmicos em um estudo amostral retrospectivo

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**Abstract:** A retrospective study evaluating hepatic laboratory alterations and potential drug interactions in patients treated for onychomycosis. We evaluated 202 patients, 82% female. In 273 liver enzyme tests, there were changes in only 6%. Potential drug interactions were identified in 28% of patients for imidazole and 14% for terbinafine. The risk of potential interactions increased with the patient's age and use of multiple drugs.

**Keywords:** Drug interactions; Fluconazole; Liver diseases; Onychomycosis

**Resumo:** Estudo retrospectivo avaliando alterações laboratoriais hepáticas e potenciais interações medicamentosas em pacientes tratados para onicomicose. Foram avaliados 202 pacientes, sendo 82% do sexo feminino. Em 273 exames de enzimas hepáticas, houve alterações em apenas 6%. Potenciais interações medicamentosas foram identificadas em 28% dos pacientes para imidazólicos e 14% para terbinafina. O risco de interações potenciais aumentou com a idade do paciente e o uso de múltiplas medicações.

**Palavras-chave:** Fluconazol; Hepatopatias; Interações de medicamentos; Onicomicose

Onychomycosis is a nail infection caused by dermatophytes, yeasts and filamentous fungi non-dermatophytes. It is a common nail problem, accounting for 15-40% of nail diseases: however, some studies show that onychomycosis is responsible for 40-60% of nail aspect abnormalities. The diagnosis can be done by direct mycological examination and culture, but there are diagnostic accuracy limitations ranging from 40 to 70%.<sup>1,2,3</sup>

Concerning onychomycosis treatment, the use of systemic drugs acting on cytochrome P-450 may interact with other medications. Systemic drugs are more effective, however there are liver toxicity risks.<sup>1,3,4,5</sup>

This study aims to trace the demographic and clinical profile of patients with onychomycosis treated in a dermatology clinic in Curitiba, emphasizing risks of drug interactions and laboratory abnormalities.

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It is a retrospective study, which analyzed medical records of dermatology outpatients of a public clinic in the region of Curitiba / PR treated between 2008 and 2010, who had received a clinical diagnosis of onychomycosis. Patients were evaluated by graduated dermatologists and residents in dermatology. Patients who did not maintain clinical follow up for more than six months were excluded. Data were collected on a standardized form.

Liver enzyme tests (aminotransferase, gamma glutamyl transferase, alkaline phosphatase) with values above the normal limit stipulated by the performing laboratory were considered abnormal (Municipal Laboratory of Curitiba).

Categorical variables were represented by percentages and associations by the "odds ratio" and a confidence interval of 95%. The continuous variables were represented by medians [interquartile deviations]. Data were compared by chi-square, Fisher's exact test, G Williams test or Mann-Whitney U test. The correlations were determined by Spearman's test, and normality of distributions was determined by the Shapiro-Wilk test.

We evaluated 202 patients, 82% were female. Women were significantly younger at the beginning of treatment (56 [19] x 65 [12] years old,  $p < 0.01$  - Mann-Whitney test).

Eighty-seven percent had involvement of the foot, but only 40% had involvement of other toenails than the hallux. This involvement was associated with males (OR = 2.17 [1.04 to 4.50],  $p = 0.04$  - chi-square). The hand was affected in 28%.

After a median follow-up period of 22 [30] months, only 12% were considered clinically cured.

One hundred and twenty-one patients underwent serum liver tests, totaling 273 evaluations. In only 6% of these there was any laboratory abnormality and all were not prominent and without clinical significance during follow-up (Chart 1). Concomitant use of other medications and age were not associated with risk of laboratory alterations.

Forty-four percent of patients were taking some systemic medication. There is significant correlation between age at diagnosis and number of medications. (Spearman = 0.36,  $p < 0.01$ ). Fifty-four different medications were recorded, and the 25 most commonly used are shown on chart 2. Sixty-three percent of patients taking other medications had potential interaction with imidazole and 31% with terbinafine ( $p < 0.01$  - chi-square), whereas for those using three or more drugs, the potential rose to 87% and 36% respectively ( $p < 0.01$  - Test G).

In the population studied, clinically diagnosed onychomycosis proved to require prolonged treatment with low rates of clinical cure, which may be related to several factors.

Among these factors we highlight possible misdiagnosis, associated onychodystrophy, correct use of medications and effectiveness of medications from compounding pharmacy.

The time of treatment, medication used, age and comorbidities such as diabetes and immunodeficiency may be factors that alter the clinical cure rates, but our study failed to identify such factors.

Despite continuous use of itraconazole or terbinafine having similar effectiveness in up to one year follow-up, there have been more long-term cures with terbinafine.<sup>4</sup>

**CHART 1:** Laboratory abnormalities observed during the use of systemic antifungal agents\*

Patient	Abnormalities **	Antifungal used	Other systemic medications being used
1	GGT	Terbinafine	Captopril, Methyl dopa, Hydrochlorothiazide, Glibenclamide, Metformin, Simvastatin
2	GGT	Fluconazole	No
3	AP, GGT	Fluconazole	Omeprazole, Ketoprofen, Hydrochlorothiazide, Amiloride, Amitriptyline
4	AP	Fluconazole	No
5	GGT, AST	Fluconazole	No
6	GGT, AST, ALT	Terbinafine	Hydrochlorothiazide, Nifedipine
7	AST, ALT	Fluconazole	No
8	ALT	Fluconazole	Atenolol

\* Two hundred and seventy-three laboratory evaluations were performed in 121 patients under systemic treatment for onychomycosis.

\*\* GGT: Gamma Glutamyl Transferase; AP: Alkaline Phosphatase; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase

**CHART 2:** Most frequently used medications and potential interactions with systemic antifungals\*

Drug	Number of patients	Interaction with imidazole	Interaction with terbinafine
Captopril	33		
Hydrochlorothiazide	26		
Acetylsalicylic acid	19		
Metformin	14		
Simvastatin	13	X	
Propranolol	11	X	X
Amitriptyline	10	X	X
Enalapril	9		
Glibenclamide	9	X	
Atenolol	6		
Furosemide	6		
Levothyroxine	6		
Nifedipine	4	X	
Omeprazole	4		
Prednisone	4		
Amlodipine	3	X	
Digoxin	3		
Fluoxetine	3	X	X
Amiodarone	2		
Carvedilol	2		X
Imipramine	2		X
Losartan	2	X	
Methyldopa	2		
Sertraline	2		

\* Two hundred and two patients were evaluated; 89 of them used some systemic medication.

In our study, women were the majority, starting treatment at younger ages than men. Other studies in Brazil also found a higher prevalence of disease in women - 80%, 71%, 66%. Moreover, the clinical profile appears to be different between genders, with men having more extensive involvement of the feet, which may be due to delay in seeking treatment or even a different mode of contagion.<sup>4,6,7</sup>

Our data showed very uncommon liver changes, with rates close to those observed in the population considered healthy. Other studies found that terbinafine, fluconazole and itraconazole can cause liver toxicity, but low rates of elevated liver enzymes, suggesting that severe reactions are very rare and idiosyncratic.<sup>5,8</sup>

Fluconazole and itraconazole are considered strong inhibitors of some cytochrome p450 enzymes (iso-

forms 2C9 and 3A4,5,7), many of which operate in the metabolism of drugs commonly used in prevalent chronic diseases. Terbinafine is a moderate inhibitor of less common pathways of cytochrome P450 (isoform 2D6).<sup>5,8,9</sup>

There was frequent potential drug interaction between oral antifungal used and medication used regularly in this population, such as antihypertensive, hypoglycemic and medications used for dyslipidemia (Chart 2). In the meantime, oral terbinafine appears to be a safer medication, especially in older patients using multiple systemic medications.

Because this was a retrospective study, we have limitations regarding irregularity of medical records, which may lead to underestimation of some variables and selection biases. However, we consider the results important by presenting data on laboratory findings and potential drug interactions in this population. □

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