

## Cardiac failure and dyspnoea associated with the use of itraconazole

### Introduction

Itraconazole (Trisporal<sup>®</sup>, Sporanox<sup>®</sup>) is a synthetic antifungal agent approved for marketing in the Netherlands for the *treatment of vulvovaginal candidiasis, thrush, dermatomycosis, cutaneous sporotrichosis, paracoccidioidomycosis, blastomycosis, histoplasmosis, systemic aspergillosis and onychomycosis*[1]. Itraconazole is generally well tolerated. The most frequently reported adverse drug reactions are gastrointestinal reactions. More rarely a transient increase in liver enzymes has been reported[2].

In the first quarterly report of 1999 Lareb reported on the association between dyspnoea and the use of itraconazole[3]. It was suggested that dyspnoea might have been caused by a congestive heart failure. In June 2001 an article was published by Ahmad *et al.* [4] concerning 58 reports from the US Food and Drug Administration's Adverse Event Reporting System, which were suggestive of a possible association between the use of itraconazole and congestive heart failure. In 43 patients additional risk factors were present that may have confounded the association. The US Labelling of itraconazole has subsequently been changed, and the drug is now contraindicated for the treatment of onychomycosis in patients with evidence of ventricular dysfunction[5]. The most recent version of the Dutch Summary of Product Characteristics of Trisporal Oral Solution does mention this ADR in the section 'special warnings' but the SPC of Trisporal capsules and IV solution do not summarise congestive heart failure as a suspected ADR or as a warning yet[1]. Lareb received several reports of dyspnoea, which are sometimes associated with palpitations, oedema or other signs of congestive heart failure. A selection of these reports that may involve cardiac failure and similar reports in the WHO database will be described.

### Reports

An overview of the reports of dyspnoea submitted to the Netherlands Pharmacovigilance Foundation that may be indicative of congestive heart failure is provided in Table 1.

Table 1. Reports received by Lareb possibly related to congestive heart failure.

Sex, age	Drug, dosage Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset	Comments
I F,46	100mg od, Vulvovag. candidiasis	None	Pleural effusion, C/T ratio 19.5/29, ventricular extrasystoles	8 days	Recovered (valvular heart disease in history)
II M,67	100mg td, Dermatomycosis	Mesalazine	Exertion and nocturnal dyspnoea	Couple of weeks	Recovered
III F,57	200mg td, Tinea pedis	None	Dyspnoea, nausea, vomiting, palpitations, dizziness	1 day	Recovered Positive rechallenge
IV F,50	100mg td, Tinea pedis	Diclofenac Bromazepam Tiramconolon-cream	Dyspnoea, chest pain, nausea, vomiting, arrhythmia and rash	Couple of hours	Chest X ray: pleural & pericardial effusion, pulm oedema, cardiac enlargement after 9 weeks.
V M, 77	100mg td, Onychomycosis	'VSM Damiana'	Dyspnoea, chest pain, coughing	2 hours	Unknown
VI M,40	200 mg td, Onychomycosis	Atenolol Enalapril	Dyspnoea, oedema	Couple of days	Treated with hydrochlorothiaz, recovered

The mean age of the patients is 56.2 years, ranging from 40 to 77 years. Male- female ratio is 1. In two patients additional risk factors are present. (One patient had had a valvular heart disease

in the past, and one patient was known to have hypertension). Besides these reports Lareb received 5 reports on peripheral oedema (ROR 3.8, 95% CI 1,6-9,5). In these patients other possible signs indicative of heart failure were not reported. Patient III also reported palpitations in addition to dyspnoea, nausea and dizziness. This may point to the fact that arrhythmia may have caused heart failure.

## Other sources of information

### Literature

Apart from the article by Ahmad *et al.*[4], the association between itraconazole and congestive heart failure has not been reported in the literature earlier. The US product information of Sporanox<sup>®</sup> capsules mentions that congestive heart failure, peripheral oedema, and pulmonary oedema have been reported in post-market reports. Asymptomatic decreases in left ventricular ejection fraction, which resolved within 12 hours, were seen in healthy volunteers. The US product information states that for patients with ventricular dysfunction the treatment of onychomycosis with itraconazole is contraindicated. If signs and symptoms of CHF appear, itraconazole should be discontinued[6]. Hypertension and oedema have rarely been associated with the use of itraconazole[7-9].

### Databases

On April 11<sup>th</sup> 2002 10 reports on dyspnoea and 16 reports on oedema were filed in the Lareb database. Five of these reports are shown in Table 1. The other reports are not suggestive of congestive heart failure.

Reports sent to the WHO Collaborating Centre for Drug Monitoring concerning oedema, dyspnoea and heart failure (11 April 2002) are shown in Table 2. A comparison is made between itraconazole, terbinafine and griseofulvine since these drugs are frequently used for similar disorders.

Table 2. Overview of reports on itraconazole, terbinafine and griseofulvine in the WHO database.

	Itraconazole <i>n</i> (%)	Terbinafine <i>n</i> (%)	Griseofulvine <i>n</i> (%)
Dyspnoea	133 (1.2%)	75 (0.4%)	18 (0.4%)
Cardiac failure	36 (0.3%)	3 (0.0%)	0 (0.0%)
Oedema peripheral	216 (2.0%)	67 (0.3%)	23 (0.6%)
Total number of reports	10,749	17,325	3,720

Statistical data were only available until the end of the third quarter of 2001. At that time, the WHO contained 30 reports of cardiac failure associated with itraconazole. This association was disproportionally present in the database: Reporting Odds Ratio 1.7 (95% CI 1,2-2,4).

### Mechanism

The article by Ahmed *et al.* and the US product information on Sporanox<sup>®</sup> mention that unpublished studies of dogs and healthy human volunteers suggest negative inotropic effects with intravenous itraconazole. A Medline search revealed no additional information on the effects of itraconazole on the myocardium.

## Conclusion

Based on 58 cases of heart failure reported to the FDA the labelling of itraconazole was changed in the US. Congestive heart failure is presently not mentioned in the Dutch SPC. At present, the Lareb database contains five reports that may point to the existence of congestive heart failure. In the WHO database itraconazole is more strongly associated with oedema, dyspnoea and palpitations when compared to terbinafine and griseofulvine. Since the presence of congestive heart failure was suspected but not always diagnosed, additional observational studies should be conducted to confirm the association between itraconazole and congestive heart failure.

## References

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