1.1. Itraconazole and dyspnoea

Introduction

Itraconazole (Trisporal®) is a triazole antifungal agent which was registered in the Netherlands in 1990. It is indicated *for treatment of vulvovaginal candidiasis, oropharyngeal candidiasis, lymphocutan sporotrichosis, paracoccidioidomycosis, dermatomycosis, onychomycosis, pityriasis versicolor, blastomycosis (in immunocompetent patients), histoplasmosis and systemic aspergillosis (in patients who are intolerant of or refractory to standard amphotericin therapy)* [1]. In 2002 Lareb called attention to the association between itraconazole and dyspnoea, most probably due to congestive heart failure [2]. By now, congestive heart failure is mentioned as a possible adverse drug reaction in the SmPC. Pulmonary oedema is also mentioned in the SmPC. Lareb received several reports of dyspnoe, in which congestive heart failure or pulmonary oedema is less likely. Dyspnoea as a separate symptom is not described in any of the SmPCs on Trisporal® [1] or other itraconazole containing products.

Reports

On April 8, 2010, the database of the Netherlands Pharmacovigilance Centre Lareb contained 20 reports of dyspnoea associated with the use of itraconazole. Fourteen of these reports referred to dyspnoea as a separate symptom; the other six were likely to be due to cardiac failure, since palpitations, oedema or other signs of cardiac failure were mentioned as adverse drug reactions as well.
The 14 reports where dyspnoea was reported as a separate symptom in association with the use of itraconazole are listed in Table 1. It should be noted that dyspnoea is a rather subjective symptom which was not objectified in all cases.

Table 1. Reports of dyspnoea associated with the use of itraconazole

Patient, Number, Sex, Age	Drug (daily dose) Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 20917 F, 30	itraconazole 2dd 100mg dermatophytosis	propranolol	dyspnoea	several hours discontinued not reported
B 21867 F, 67	itraconazole 2dd 100mg tinea unguium	-	dyspnoea	1 day discontinued recovered
C 22587 F, 44 I	itraconazole 1dd 100mg dermatophytosis	-	dizziness, paraesthesia, micturition frequency, dyspnoea	1 day discontinued recovered
D 34366 F, 28	itraconazole 1dd 200mg dermatitis fungal	dexamethason/ framycetine/ gramicidine eardrops clemastine	dyspnoea	several hours discontinued recovering
F 47880 F, 31	itraconazole 2dd 100mg candida		dyspnoea	unknown discontinued recovered
G 52196 F, 22	itraconazole 2dd 100mg vaginal mycosis	cyproteron/ethinyl estradiol	agitation, hypoaesthesia, fatigue, dyspnoea, cramps	10 hour discontinued recovered
H 87864 F, 55	itraconazole 2dd 200mg onychomycosis	amiloride/hydrochlorothiazide	dyspnoea, myalgia	several hours discontinued unknown

Patient, Number, Sex, Age	Drug (daily dose) Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
I 89146 F, 25	itraconazole 1dd 100mg onychomycosis	montelukast, ethinylestradiol/ levonorgestrel, budesonide, formoterol/ budesonide, fexofenadine	pruritus, dyspnoea	1 day unknown unknown
J 15063 F, 39	itraconazole 2dd 200mg	lynestrenol	breath shortness	1 week dose reduction recovered
K 16691 M, 67	itraconazole 2dd 100mg dermatophytosis	mesalazine	dyspnoea	several weeks discontinued recovering
L 17989 F, 57	itraconazole 2dd 200mg tinea pedis		palpitation, dizziness, vomiting, dyspnoea	1 day recovered after continuation of first course, recurrence of complaints during second course
M 20942 F, 49	itraconazole 2dd 100mg tinea pedis	bromazepam, diclofenac	chest pain, arrhythmia, vomiting, dyspnoea	several hours discontinued recovered
N 34054 M, 40	itraconazole 2dd 200mg	enalapril, atenolol	oedema, dyspnoea (cardial and renal exam: no abnorm)	several days discontinued recovered
O 66498 F, 40	itraconazole 1dd 200mg	coal tar shampoo, naproxen	chest pressure sensation of, dyspnoea, fluid retention	6 hour discontinued recovering

The time to onset varied from several hours to several weeks, with a median of one day. In 11 cases a positive dechallenge was reported. Twelve of these patients were younger than 60, eight of them even younger than 40 years of age, which is supportive of a non-cardiac underlying cause.
It should be noted that patient F has a medical history of asthma, and patient I uses concomitant medication indicating an asthmatic condition.
Furthermore, in patient L, M and O some symptoms are mentioned that may suggest a possible cardiac involvement. However in none of these patients a clear diagnosis of a possible cardiac cause was made.

Other sources of information

Literature

In June 2001 an article by *Ahmed et al*. was published about the possible association between itraconazole and congestive heart failure (by negative inotropic effects of itraconazole), a condition which can be accompanied by dyspnoea [3]. There is no information in the literature concerning a direct association between use of itraconazole and isolated dyspnoea.

Databases

The database of the Netherlands Pharmacovigilance Centre Lareb contained 20 reports of dyspnoea associated with the use of itraconazole. However, in six cases the dyspnoea could be

attributed to other conditions, like cardiac failure. The ROR for the association itraconazole - dyspnoea includes these reports and is therefore not mentioned here. In three of the cases presented in table 1 (L, M and O) cardiac involvement cannot be excluded either.
In addition, the Netherlands Pharmacovigilance centre received one report (14689) concerning a 45-year-old female who had been using itraconazole 100 mg once daily for moniliasis. Eight days after the start of this drug she developed pleural effusion. This case has been described in one of the previous quarterly reports [4].
With respect to other triazoles, Lareb received only two reports of dyspnoea in association with fluconazole.

The WHO database of the Uppsala Monitoring Centre contained 185 reports of dyspnoea on itraconazole. It concerns 103 female and 79 males. In three cases, the gender of the patient involved has not been reported. The average age was 54.6 years (range 6-86 years). The most frequently reported other adverse drug reactions where: (peripheral) oedema (36 cases), chest pain (22 cases), fatigue (22 cases) and dizziness (24 cases). Rash and fever each were reported 13 times. In only nine cases cardiac failure was reported. Among the respiratory symptoms, pulmonary oedema was mentioned five times, pleural effusion six times and pneumonia five times.

On April 6th, the Eudravigilance database contained 69 reports of dyspnoea associated with itraconazole use. Nineteen reports concern dyspnoea in which cardiac failure seems likely to be contributive. Of the 50 remaining cases, 46 were rated serious, affecting 17 male and 27 female patients. Ages of patients involved in dyspnoea not due to cardiac failure, ranged form 19 to 82 years. In five cases the reaction reported resulted in death of the patient. The cause of death was aspiration pneumonia in one patient, circulatory failure in one patient, sepsis in one patient and a suspected hypersensitivity in two patients.
Exact diagnoses are difficult to assess. However in seven cases, out of the 69 reports of dyspnoea, many more ADRs were reported, in eight cases there were clear indications for alternative causes (e.g. adrenal insufficiency or aspiration), in 19 cases cardiac insufficiency may be assumed, immunologic causes may have been causative in at least 16 cases, in 19 cases no clear cause could be assessed.
Among the respiratory symptoms, pleural effusion was mentioned in 20 reports.

Prescription data

The number of patients using itraconazole in the Netherlands is shown in Table 2.

Table 2. Number of itraconazole users in the Netherlands between 2005 and 2008 [5]

Drug	2005	2006	2007	2008
Itraconazole	101,400	94,582	91,983	88,046

Mechanism

Itraconazole prevents growth of several types of fungi by preventing the fungi from producing the membranes that surround the fungal cells. It inhibits the fungal synthesis of ergosterol [6].
Since the concentration of itraconazole in pulmonary tissue (as well as in kidney, liver, bone, stomach, spleen and muscle tissue) is two to three times higher than the plasma concentration [1], it may be relatively vulnerable for ADRs.
There is no clear mechanism to explain how itraconazole can induce dyspnoea.
Dyspnoea associated with itraconazole use, not associated with cardiac failure, may be due to for instance bronchospasm or an asthma attack in susceptible patients (case D, F, I). Anxiety or a panic attack (as in patient G) may be induced by the dyspnoea itself, and may aggravate the symptoms. Upper respiratory tract infections are actually mentioned as a possible ADR in - only

two of the 17 available - SmPCs (Apothecon and Actavis) [7,8], possibly in an attempt to explain the symptoms of dyspnoea.

Discussion

These Lareb reports of dyspnoea in association with itraconazole cannot simply be explained by co-morbidity in older patients such as COPD or (asymptomatic) heart failure. Confounding by indication is unlikely, considering the relatively mild indication and its local character in many cases. The recovery after discontinuation of itraconazole in 14 cases supports the association with this drug. The relatively high dose of itraconazole in pulmonary tissue may cause this reaction in pulmonary susceptible patients.
Also based on the data of the Eudravigilance and WHO databases, it is likely that dyspnoea does not have its origin in cardiac failure only. Possible related mechanisms are allergic causes (case I) or pleural effusion, which might also explain the occurrence of cardiac failure in relatively young patients.

Conclusion

Dyspnoea should be mentioned as a separate adverse drug reaction in the SmPC of itraconazole.

- Dyspnoea should be mentioned in the SmPC of itraconazole.

References
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8. Dutch SmPC Itraconazol Actavis 100 mg. (version date: 20-2-2007, access date: 12-4-2010) http://db.cbg-meb.nl/IB-teksten/h31569.pdf.

This signal has been raised on September 2010. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbgmeb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).