1.1. Itraconazole and pancreatitis

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, pityriasis versicolor, lymphocutan sporotrichosis, paracoccidioidomycosis, dermatomycosis, onychomycosis, blastomycosis (in immunocompetent patients), histoplasmosis and systemic aspergillosis (in patients who are intolerant of or refractory to standard amphotericin therapy. Gastro-intestinal complaints are the most commonly occurring adverse drug reactions. Pancreatitis is not described in the SmPC of itraconazole. [1]

Reports

On August 5th 2008, the database of the Netherlands Pharmacovigilance Centre Lareb contained four reports of pancreatitis associated with the use of itraconazole (Table 1).

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

patient, sex, age	suspect drug, indication for use	dose, duration of treatment	concomitant medication	suspected adverse drug reaction	time to first symptoms, outcome	lab tests*
A 14341 F,67	ciprofibrate for hyperlipidemia itraconazole for onychomycosis (pulse therapy)	1 dd 100mg 2 dd 200mg, pulse, 1 week	simvastatin psylliumseed captopril chlortalidone beclometasone	necrotising pancreatitis, death	several days after start of ciprofibrate / 2 weeks after start of itracon, fatal	amylase 1728 U/l, lipase 13241 U/l, CT abdomen: picture fits necrotising pancreatitis
B 26427= 32195 F,50**	itraconazole for onychomycosis (pulse therapy)	2 dd 200mg, 1 week + 2 weeks	none	gastroenteritis pancreatitis	7 days after start first week of treatment / 9 days after start second course, recovered	serumamylase 438 U/l, urineamylase 4325 U/l
C 41019 M,55	itraconazole for tinea pedis	2 dd 200mg, 17 days	budesonide betamethasone	pancreatitis	several days after start, not recovered (9 days after discontinuation)	serumamylase 492 U/l urineamylase 2173 U/l lipase 531 U/l
D 72126= 73556 M,15	itraconazole for tinea pedis	1 dd 250mg, 6 months	ketoconazole cream	recurrent pancreatitis	6 months, no full recovery (5 months after discontinuation)	serumamylase 1420 U/l lipase 2149 U/l

* Measurements were repeated in time; only peak values are presented here
** Published by reporting specialist in 2001. [2]

Patient A suffered from hyperlipoproteinemia, which has been associated with acute pancreatitis. The use of ciprofibrate and simvastatin for this condition may have contributed to the symptoms as well. [3,4].
Patients A and B used itraconazole pulse therapy for onychomycosis: during the first, third and fifth week a dose of 2dd 200mg is being used, separated by medication free intervals. One week after the first week of treatment, patient A developed necrotising pancreatitis, with fatal outcome six weeks after start of itraconazole. Patient B experienced mild abdominal complaints after the first week, which disappeared spontaneously. After a medication free interval of two weeks she used itraconazole for another two weeks. Nine days after starting the second course, the patient experienced more severe abdominal symptoms and was diagnosed with pancreatitis. Although it was not objectified that the first abdominal symptoms could be ascribed to the pancreas as well, the course of the complaints is suggestive for a positive de- and rechallenge.

Patient C used itraconazole 2dd 200mg for tinea pedis and experienced symptoms within days. Patient D had a much longer latency time: he had been using itraconazole (1dd 250mg for tinea pedis) during six months before he experienced symptoms.
In all these cases the presence of acute pancreatitis was confirmed by diagnostic tests. Additional risk factors, like frequent alcohol use, have been excluded by the reporters.
The Lareb database does not contain any reports of pancreatitis associated with other systemic antifungal agents.

Other sources of information

Literature

Pancreatitis induced by different types of drugs is described in literature, mostly by case reports [4]. The association between itraconazole and pancreatitis was only described in one case report: the Dutch publication [2] based on report B in Table 1. Pancreatitis has not been associated with the use of other triazoles or imidazoles. [3,4]

Other databases

The database of the WHO Monitoring Centre contained 37 reports of pancreatitis on itraconazole, which supports a causal relationship (ROR=1.6; 95%CI: 1.1-2.2). Fifteen of these patients were male, 19 female, three unknown, the age ranged from 5 to 75 years.
Pancreatitis was the reported reaction in 33 cases, acute pancreatitis and haemorrhagic pancreatitis were both reported in two cases. The duration of treatment with itraconazole –if reported- varied from one day to three months. In 11 cases more suspected drugs were reported besides itraconazole. In nine patients itraconazole was the only suspect drug but (extensive) concomitant medication was reported as well. In the remaining 17 cases itraconazole was the only reported drug, with positive de- and rechallenge in seven of these cases. However, many patients with idiopathic pancreatitis or microlithiasis have recurrent attacks of acute pancreatitis. Therefore a positive re- and dechallenge may be due to coincidence: it is not considered indisputable evidence for a causal relationship between ADR and drug [4].
On September 8th 2008, the Eudravigilance database contained 15 reports of pancreatitis related to the use of itraconazole. Itraconazole was reported to be the sole medication used in six cases. The age of the patients ranged from 5 to 69 years (not specified in three patients). All reported reactions were rated serious. Once because of death following the reported reactions, in one case because of disability, hospitalization occurred nine times, a life threatening aspect was in one case reason to report as a serious reaction. CIOMS criterium 'other' was reported in five cases. In one case the reason to report as serious reaction was not specified. [1]

Prescription data

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

Table 2. Number of users of itraconazole in the Netherlands 2003-2007
(Source: GIP College voor Zorgverzekeringen, Diemen)

	2003	2004	2005	2006	2007
J02AC02 Itraconazol (*Trisporal* ®)	100,800	101,400	94,582	94,727	88,593

Mechanism

The acute inflammation of the pancreas is believed to be caused by inappropriate intra-pancreatic activation of digestive enzymes, which leads to subsequent auto-digestion. In 90% of the patients with acute pancreatitis the causes are reported to be alcohol or cholelithiasis. The remaining 10%

[1] In the Eudravigilance database, one case can be classified in multiple categories of serious adverse events.

are explained by various causes, like trauma, postoperative complications, hyperlipidemia and exposure to specific drugs. [3]
Various different drugs have been associated with pancreatitis. The cause of drug-induced pancreatic injury is unknown. Drugs associated with tissue-specific injury can be divided in those with intrinsic toxicity for the organ and those that cause injury as a result of an idiosyncratic reaction. Intrinsic toxicity is usually characterized by reproducibility, dose dependence and a short, consistent latency. Therefore, the idiosyncratic reaction; unpredictable, not dose dependent and with low incidence seems more plausible. [4]

Conclusion

Lareb received four well documented reports of pancreatitis in association with itraconazole, one of them with positive de- and rechallenge. This signal is supported by cases from the WHO and Eudravigilance.

References

1. Dutch SmPC Trisporal®. (version date: 14-9-2005, access date: 5-8-2008) http://db.cbg-meb.nl/IB-teksten/h13224.pdf.
2. Langers AM, Jonkers GJ. [Pancreatitis ascribed to the use of itraconazole]. Ned Tijdschr Geneeskd 2001;145(23):1127-8.
3. Bergholm U, Langman M, Rawlins M, Gaist D, Andersen M, Edwards IR, Wiholm B-E. Drug-induced acute pancreatitis. Pharmacoepidemiol Drug Saf 1995;4:329-34.
4. Badalov N, Baradarian R, Iswara K, Li J, Steinberg W, Tenner S. Drug-induced acute pancreatitis: an evidence-based review. Clin Gastroenterol Hepatol 2007;5(6):648-61.

This signal has been raised on December 2008. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbg-meb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).