Netherlands
The Journal of Medicine

Pancreatitis associated with the use of itraconazole

J.L.M. Passier[1]*, E.P. van Puijenbroek[1], G.J.P.M. Jonkers[2], A.C. van Grootheest[1]

[1]Netherlands Pharmacovigilance Centre Lareb, 's-Hertogenbosch, the Netherlands, [2]Rijnland Hospital, Department of Internal Medicine, Leiderdorp, the Netherlands, *corresponding author
tel.: +31 (0)73-646 97 18, fax: +31 (0)73-642 61 36, e-mail: a.passier@lareb.nl

ABSTRACT

Background: We call attention to the assumed association between itraconazole and pancreatitis by presentation of four Dutch case reports.

Methods and results: The Netherlands Pharmacovigilance Centre Lareb received four reports of pancreatitis associated with the use of itraconazole, all reported by health professionals. The diagnosis of pancreatitis was confirmed by diagnostic tests. All four patients had been using relatively high doses of itraconazole. In two of these cases, recurrent use of itraconazole resulted in recurrent symptoms. We describe these four cases and discuss the possible mechanism.

Conclusions: The presented cases suggest a causal relation between itraconazole and pancreatitis. Given the often mild indication for the use of itraconazole and the seriousness of this possible adverse drug reaction, it is essential that more data are obtained in order to strengthen the causality of this association. Physicians are invited to report their experiences on the subject.

KEYWORDS

Adverse drug reaction, itraconazole, pancreatitis

INTRODUCTION

Acute pancreatitis, pathophysiology

Acute pancreatitis is a relatively rare, but serious clinical disorder. 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. Acute pancreatitis arises when intracellular protective mechanisms to prevent trypsinogen activation or to reduce trypsin activity are overwhelmed. It is characterised by the presence of acute and constant pain in the epigastric area or the right upper quadrant. Pain might last for several days, radiate to the back, and be associated with nausea and vomiting. Amylase and lipase are released from acinar cells during acute pancreatitis, and their concentration in the serum is used to support the diagnosis. Serum amylase concentrations exceeding three times the normal upper limit confirm acute pancreatitis. Serum amylase rises within hours after the onset of symptoms and returns to normal values within three to five days. Serum lipase concentrations remain high for a longer period of time. Contrast-enhanced CT or MRI can be performed to confirm the diagnosis of pancreatitis.[1]

Possible causes

In developed countries, the most frequent causes of acute pancreatitis are alcohol abuse and cholelithiasis. In 10 to 30% of cases, the cause is unknown, although recent studies have suggested that up to 70% of cases of idiopathic pancreatitis are secondary to biliary microlithiasis. Other aetiologies include autoimmune diseases, inflammatory bowel diseases, infections, genetic disorders, toxins, trauma, postoperative complications, hyperlipidaemia, hypercalcaemia and exposure to specific drugs.[1-3] Overall, drugs are a rare cause of acute pancreatitis.[4]

Itraconazole-induced pancreatitis

Itraconazole is a triazole antifungal agent.[5] Gastrointestinal symptoms are the most commonly occurring adverse drug reactions (ADRs). To our knowledge, pancreatitis is not described as a possible ADR of itraconazole in the product information or in international literature, except for one single case report, which was based on one of the

Lareb cases included in this study.[6] It should be noted that pancreatitis is listed as an ADR in the official product information for two other antifungal triazole derivatives: posaconazole and voriconazole.[7,8]

The Netherlands Pharmacovigilance Centre Lareb has received four reports on pancreatitis in association with itraconazole. In this paper, we present a short overview of these reports.

MATERIALS AND METHODS

The Netherlands Pharmacovigilance Centre Lareb maintains the voluntary adverse drug reaction reporting system in the Netherlands on behalf of the Dutch Medicines Evaluation Board. Physicians and pharmacists have been reporting adverse drug reactions to Lareb since 1985. Patients may report ADRs since April 2003. The Lareb reports are sent to the European Medicines Agency (EMEA) and are included in the worldwide database of the World Health Organisation (WHO).

RESULTS

Dutch Lareb case reports

In the period from November 1999 to February 2010, the Netherlands Pharmacovigilance Centre Lareb received four reports of pancreatitis in association with the use of itraconazole. Details on these reports are summarised in *table 1*.

CASE REPORT A

This case was reported to Lareb and published by the reporting internist in 2001.[6]

A 50-year-old woman, who neither smoked nor used alcohol, took itraconazole pulse therapy for onychomycosis. The patient used itraconazole 200 mg twice daily for a week. Seven days later she experienced abdominal pain, anorexia, vomiting and high fever. These symptoms disappeared spontaneously over time. After a medication-free interval of two weeks she took itraconazole for another two weeks. Nine days after starting this second course, the patient suffered from more severe abdominal pain, high fever and malaise. She was admitted to a hospital. The erythrocyte sedimentation rate (ESR) was 80 mm/h, leucocytes 10.1 x 10^9/l, serum amylase 438 U/l (normal (N) 50 to 220 U/l), and amylase in urine 4325 U/l (N 140 to 1500 U/l). Liver and kidney function were normal. Ultrasound showed a normal pancreas with normal biliary ducts, without gallstones. The patient was diagnosed with pancreatitis. Itraconazole use was discontinued and the patient recovered.

The dosage scheme for this patient was more intense than recommended for onychomycosis: the medication free

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 F,50**	Itraconazole for onychomycosis (pulse therapy)	2 dd 200 mg, pulse, 1 week + 2 weeks	None	Gastroenteritis Pancreatitis	7 days after start first week of treatment/ 9 days after start second course, recovered	Serum amylase 438 U/l Urine amylase 4325 U/l
B M,55	Itraconazole for tinea pedis	2 dd 200 mg, 17 days	Budesonide Betamethasone	Pancreatitis	Several days after start Not recovered (9 days after discontinuation)	Serum amylase 492 U/l Urine amylase 2173 U/l Lipase 531 U/l
C M,15	Itraconazole for tinea pedis	1 dd 100 mg, 7 weeks / 1 dd 250 g, 10 weeks	Ketoconazole cream	Recurrent pancreatitis	7 weeks after start of 100 mg treatment/10 weeks after start of 250 mg treatment No full recovery (5 months after discontinuation)	Serum amylase 2812 U/l Lipase 2925 U/l
D F,67	Ciprofibrate for hyperlipidaemia Itraconazole*** for onychomycosis (pulse therapy)	1 dd 100 mg 2 dd 200 mg, pulse 1 week	Simvastatin Psyllium seed 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

*Measurements were repeated in time; only peak values are presented here; **Published by reporting specialist in 2001;[6] ***Originally reported as concomitant medication.

period was two weeks instead of three, and the second treatment period was two weeks instead of one.

CASE REPORT B

A 50-year-old male used itraconazole 200 mg twice daily for tinea pedis. He experienced abdominal symptoms within days, leading to admission to the hospital. Laboratory values of 492 U/l serum amylase (N 70 to 300 U/l), 2173 U/l urine amylase (N 200 to 3500 U/l) and 531 U/l lipase (N 23 to 200 U/l) were measured. Based on these lab values in combination with his clinical presentation, the reporting internist diagnosed pancreatitis in this patient. The itraconazole was discontinued after 17 days of use. Nine days later, at the time of notification, the patient had not yet recovered. The daily dose of 400 mg was higher than the recommended dose (100 mg daily) for this indication.

CASE REPORT C

Patient C refers to a 15-year-old boy. After taking 100 mg itraconazole daily for seven weeks (for tinea pedis), he suffered from stomach ache. He restarted the itraconazole 1.5 months later: 250 mg daily for a period of ten weeks. He then experienced more severe symptoms of abdominal pain and vomiting and discontinued the itraconazole. He was admitted to hospital and was diagnosed with serious necrotising pancreatitis, complicated by pseudocyst formation (shown by MRI). Gallstones or an anatomic deviation of the pancreas or choledochal duct were excluded. Maximal serum amylase was 2812 U/l, and maximal lipase was 2925 U/l. Virology for hepatitis B and C, CMV, Epstein-Barr virus, parvo B19, enterovirus, herpes, varicella zoster and *Mycoplasma* was negative. The patient had no history of frequent alcohol use, hypercalcaemia or hypertriglyceridaemia. At the time of discharge, the patient had a PEG feeding tube. Five months after discontinuation of itraconazole he had not yet fully recovered.
The dosage of 100 mg for seven weeks and 250 mg daily for ten weeks was higher than recommended (100 mg daily during four weeks) for this indication.

CASE REPORT D

A 67-year-old woman, who neither smoked nor used alcohol, had a medical history of recurrent cystitis, hypertension, coronary artherosclerosis, combined hyperlipidaemia and diabetes. The patient was on ciprofibrate, simvastatin, psyllium seed, captopril, chlortalidone and beclometasone nasal spray and had recently taken itraconazole for a week. Two weeks after the start of itraconazole treatment, several days after starting ciprofibrate, the patient suffered from a swollen, hard and painful abdomen which aggravated over time. One month after the first symptoms the patient was admitted to ICU. Serum values of 1728 U/l amylase and 13241 U/l lipase were measured. CT scanning showed an oedematous pancreas and severe liver and spleen necrosis, reported as 'a picture fitting with acute necrotising pancreatitis'. The patient had severe liver failure and metabolic acidosis and died, two days after admittance. Autopsy was not performed.
The reporter indicated cipofibrate (100 mg once daily for hyperlipoproteinaemia) as suspect drug, because the symptoms appeared soon after starting this drug. However, in retrospect, she had used itraconazole 200 mg twice daily for a week (pulse therapy for onychomycosis), two weeks prior to the first symptoms. Moreover, from the medication history of this patient it appeared that she had taken itraconazole pulse therapy six months before as well: itraconazole 200 mg once daily for one week, followed by a medication free week and another two weeks of treatment with itraconazole 200 mg once daily. After both periods of treatment she complained of mild abdominal pain, treated with antacids. It cannot be excluded that these symptoms were caused by a mild pancreatitis as well. The close temporal relationship with the use of itraconazole for both the recent and the past episode is suggestive for a causal relationship between this drug and the occurrence of pancreatitis.
For this patient the medical history of hyperlipidaemia plus the use of simvastatin for this condition may have contributed to the development of acute pancreatitis.[2,9,10] Besides, a CYP3A4 interaction between itraconazole and simvastatin may have lead to increased risk of simvastatin-induced ADRs. There seems to be little support (from literature) for the role of ciprofibrate.
The dosage scheme used six months ago was more robust than the recommended scheme for onychomycosis: the medication free period was one week instead of three, while the treatment period was two weeks instead of one.

Case reports worldwide

The database of the World Health Organisation Collaborating Centre (accessed 22 February 2010) contained a total of 42 reports of pancreatitis in patients on itraconazole, including the four Dutch cases. In 33 of these cases itraconazole was reported to be the only suspect drug.

DISCUSSION

Drugs are a relatively rare cause of acute pancreatitis, with an estimated incidence of 0.1 to 2%. Certain subpopulations such as children, women, the elderly and patients with advanced HIV infection or inflammatory

bowel disease may be at higher risk.[2] In literature reviews e.g. Balani *et al*. Dhir *et al*., Badalov *et al*. and Bergholm *et al*. [2,4,9,10] various different drugs have been associated with pancreatitis. Literature on itraconazole-induced pancreatitis is as far as we know limited to only one Dutch case report, based on case A in *table 1*.[6]

Mechanism of drug-induced pancreatitis

Few data exist on the mechanism of drug-induced pancreatitis. Various mechanisms have been proposed, which differ for each individual drug.[4]

In general, 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 (type A) is usually characterised by reproducibility, dose dependence and a short, consistent latency.[9] With respect to drug-induced pancreatitis in general, there is little evidence for intrinsic toxicity of drugs being the causative factor: few drugs have been associated with acute pancreatitis in the setting of an overdose. An idiosyncratic reaction is considered more likely.[9]

Idiosyncratic drug reactions, also known as type B reactions, are drug reactions which occur rarely and unpredictably amongst the population. Idiosyncratic drug reactions do not appear to be directly dose related. Clinical symptoms of idiosyncratic drug reactions are different than the pharmacological effect of the drug. The proposed mechanism of idiosyncratic drug reactions is not certain, but may involve a reactive metabolite of the drug binding to proteins, thereby causing a response from the immune system (hapten hypothesis). This response may be triggered by cell injury or cell stress (danger hypothesis). Stressed cells produce danger signals that stimulate an immune response, by co-stimulation of T cells. In the absence of this second signal, the response would be tolerance.[11,12] An alternative theory is the pharmacological interaction hypothesis, which suggests a direct binding of the drug (not the metabolite) to the MHC-T cell receptor complex, causing an immune response. In practice, it appears that a clear separation between an immune and a nonimmune mechanism may not be possible: a cytotoxic agent may well cause cell damage that provokes an immune response and the immune response may contribute to the damage caused by a cytotoxic agent.[12]

Mechanism of itraconazole-induced pancreatitis

With respect to the Lareb cases on itraconazole and pancreatitis, the low incidence and poor predictability make an idiosyncratic reaction a plausible cause. The relatively short time period for the onset of pancreatitis in cases A, B and D and the rapid recurrence of symptoms after recurrent use of itraconazole in patients A and D are in line with an immune response.

On the other hand, relatively high doses of itraconazole were used in all four cases, which would be in favour of an accumulation of a toxic metabolite.[4]

FINAL REMARKS

The diagnosis of acute pancreatitis was medically confirmed by the treating internist in all four cases, based on diagnostic tests in combination with the clinical presentation of the patient.

In general, acute pancreatitis is seldom caused by drugs, which makes it important to rule out more common causes.[4] The cases we have presented here do not provide conclusive evidence for the causative role of itraconazole. However, the reporting internists of cases A, B and C specifically indicated that there were no other possible causes involved besides the use of itraconazole.

The recurrence of symptoms in patient C, despite discontinuation of itraconazole, may be explained by the fact that many patients with idiopathic pancreatitis experience spontaneous recurrent attacks of acute pancreatitis.[9]

Confounding by indication is considered unlikely for these four patients, given the indication for use (onychomycosis and tinea pedis).

CONCLUSION

The presented cases suggest a causal relation between itraconazole and pancreatitis. Given the often mild indication for the use of itraconazole and the seriousness of this possible adverse drug reaction, it is essential that more data are obtained in order to strengthen the causality of this association. Physicians are invited to report their experience on the subject.

REFERENCES

1. Frossard JL, Steer ML, Pastor CM. Acute pancreatitis. Lancet 2008;371(9607):143-52.
2. Balani AR, Grendell JH. Drug-induced pancreatitis : incidence, management and prevention. Drug Saf. 2008;31(10):823-37.
3. Gardner TB, Berk BS, Yakse P. Pancreatitis, acute. http://emedicine medscape com/article/181364-overview 2008 June 10 [cited 2009 Jul 6].
4. Dhir R, Brown DK, Olden KW. Drug-induced pancreatitis: a practical review. Drugs Today (Barc). 2007;43(7):499-507.
5. Dutch SmPC Trisporal®. http://db cbg-meb nl/IB-teksten/h13224 pdf 2005 September 14 [cited 2008 Aug 5].
6. Langers AM, Jonkers GJ. [Pancreatitis ascribed to the use of itraconazole]. Ned Tijdschr Geneeskd. 2001;145(23):1127-8.
7. EPAR Vfend®. http://www emea europa eu/humandocs/PDFs/EPAR/vfend/H-387-PI-en pdf 2007 March 21 [cited 2009 Jul 6].
8. EPAR Noxafil®. http://www emea europa eu/humandocs/PDFs/EPAR/noxafil/H-610-PI-en pdf 2005 October 25 [cited 2009 Jul 6].

9. 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.

10. Bergholm U, Langman M, Rawlins M, Gaist D, Andersen M, Edwards IR, et al. Drug-induced acute pancreatitis. Pharmacoepidemiol Drug Saf. 1995;4:329-34.

11. Knowles SR, Uetrecht J, Shear NH. Idiosyncratic drug reactions: the reactive metabolite syndromes. Lancet. 2000;356(9241):1587-91.

12. Uetrecht J. Idiosyncratic drug reactions: current understanding. Annu Rev Pharmacol Toxicol. 2007;47:513-39.~