

The Summaries of Product Characteristics (SPCs) states that topiramate should not be used during nursing since there is no documentation on safety in nursing children. In the literature, we found only eight cases describing topiramate and breastfeeding.^[1-4] Topiramate has been shown to be present in breast milk and has been found in the plasma of nursing children, without apparent clinical effects.

Conclusion: Topiramate may cause diarrhea as an adverse drug reaction and the prolonged diarrhea may have been caused by topiramate in the mother's milk. A continuing situation with untreated diarrhea may put children at risk for dehydration and electrolyte disturbances. Withdrawal of breast milk was associated with rapid clinical improvement of the child's diarrhea. The safety profile and pharmacokinetics of topiramate in children have not been not assessed.

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39. Pancreatitis Associated with the Use of Itraconazole

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Introduction: Acute pancreatitis is a relatively rare, but serious clinical disorder with high mortality. 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. Clinical symptoms are acute and constant pain in the epigastric area or the right upper quadrant. The most frequent causes of acute pancreatitis are alcohol abuse and cholelithiasis, comprising 70–80% of all cases.^[1] Drugs are a relatively rare cause of acute pancreatitis, with an estimated incidence of 0.1–2%.^[2] In literature reviews 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.^[3]

Aim: To call attention to the assumed association between itraconazole and pancreatitis by presentation of four cases.

Methods and Results: The Netherlands Pharmacovigilance Centre Lareb, maintaining the voluntary adverse drug reaction reporting system in the Netherlands received four case reports of pancreatitis associated with use of itraconazole. Indication for use was onychomycosis for two female patients, 50/67 years old, and tinea pedis for two male patients, 55/15 years old. Time to onset varied from 3 days to 7 weeks after start of the medication. The diagnosis pancreatitis was confirmed by lab tests. In two of these cases, recurrent use of itraconazole resulted in recurrent symptoms. All four patients had been using relatively high doses of itraconazole. The database of the WHO Collaborating Centre contains 34 additional reports of pancreatitis on itraconazole.

Mechanism of itraconazole-induced pancreatitis: Given the low incidence and poor predictability of this adverse drug reaction, an idiosyncratic cause seems plausible. The relatively short time period to onset and the rapid de- and rechallenge that were reported are in line with an immune response.^[4] However, relatively high doses of itraconazole were used in all four cases, which would be in favor of an accumulation of a toxic metabolite.^[5]

Conclusions: The presented cases suggest a causal relation between itraconazole and pancreatitis. More data on this association are needed. We intend to stimulate awareness of this association among physicians, so they can inquire about the possible use of itraconazole while diagnosing patients with unexplained abdominal complaints. Given the mild indication for the use of itraconazole and the seriousness of this possible adverse drug reaction, physicians may wish to reconsider the prescription of itraconazole to patients with risk factors for drug-induced pancreatitis.

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40. The Development Safety Update Report: A New Challenge for Academic Sponsors?

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Introduction: Periodic reporting to Competent Authorities concerning the safety of marketed drugs is mandatory in the ICH regions and the reports are standardized in the form of the Periodic Safety Update Report (PSUR) defined by ICH E2C.^[1] Concerning periodic reports for clinical trials there is no standard throughout the ICH regions and differences in content, periodicity and format between countries exist, bringing to light the need for a standardized report. The Development Safety Update Report (DSUR) was initiated by the CIOMS VI working group^[2] in 2005. The purpose of DSUR would be to inform appropriate stakeholders of new safety data and the evolving safety profiles of drugs, vaccines, and therapeutic biological products before they are marketed, and also when new indications or formulations are being studied for already marketed products.^[3] Periodic safety reports on clinical trials already exist in the US (Investigational New Drug Annual Report), in the EU (Annual Safety Report). In Japan, there is no standard concerning clinical trial safety reporting. As the DSUR fits mainly for clinical trials conducted by the pharmaceutical industries it would concern only one investigational medicinal product (IMP) whereas for non commercial sponsors it would concern one or more IMPs in only one trial, therefore it appears that there is a need for developing a DSUR that suits for one single trial with several IMPs.

Methods: In respect of ICH E2F recommendations, we have worked on different DSUR templates for clinical trials with several IMPs that are mainly conducted by non commercial sponsors.

Results: We established 2 templates both in French and English for academic sponsors that incorporate at least some items from the Clinical Trial Application, aggregated tables for both serious adverse events and reactions and templates for Suspected Unexpected Serious Adverse Reaction narratives. The adapted DSUR was already sent to Competent Authorities and Ethics Committees for 3 clinical trials with several IMPs.

Conclusion: The adapted DSUR appears to increase the visibility in terms of safety and to facilitate the analysis and detection of safety