Signal

Loperamide and acute pancreatitis in patients with a history of cholecystectomy: signal strengthening

Daniele Sartori, Uppsala Monitoring Centre

Summary

Loperamide is an over-the counter antidiarrhoeal with opioid receptor affinity. By virtue of their excitatory effects on the Sphincter of Oddi, opioids could increase the pressure of the pancreatic duct and lead to acute pancreatitis. In the wake of communications of acute pancreatitis induced by eluxadoline in patients without a gallbladder, some international medicines agencies have considered a mechanistically similar over the counter antidiarrhoeal, loperamide, as a potential factor in the onset of the same condition in patients with a similar clinical history. VigiBase, the WHO global individual case safety reports database, held 35 deduplicated case reports of loperamide and loperamide;simeticone with the MedDRA Preferred Terms "Pancreatitis" and "Pancreatitis acute" as of 26 January 2020. Of this patient sample, those without clear confounders (gallstones, infections, alcoholism) were mostly female, while eight of the 35 had a history of cholecystectomy; the time to onset ranged between one and five days (except an episode of two months) and there were at least 10 positive dechallenges. Of the patients with cholecystectomy, four had already been recorded in the published literature. This mmunication adds more information on the suspected relationship between loperamide and acute pancreatitis, and may be useful in the interim before scheduled PSURs emerge, or where relevant preceding regulatory decisions might be reconsidered in light of recent data. Precautionary measures may be necessary, as loperamide is an easily accessible alternative for patients who have experienced adverse effects to eluxadoline.

WHO Collaborating Centre for International Drug Monitoring
Box 1051, S-751 40 Uppsala, Sweden
Tel: +46 18 65 60 60, www.who-umc.org

Uppsala Monitoring Centre

Introduction

Loperamide is an over the counter agonist of μ-, κ-opioid receptors, with higher affinity for μ receptors, and an antagonist of δ-opioid receptors.[1, 2] It was originally approved in the United States in 1976[3] and was considered non-addictive, without evident clinical signs of long-term tolerance or interactions with barbiturates and alcohol.[4] Later analyses of spontaneous reports from the US Food and Drug Administration (FDA) database of adverse effects (FAERS) have suggested QT-prolonging effects in the context of abuse[5] that have resulted in the apposition of a boxed warning on the FDA's labels.[6] Loperamide's indications, as reported on the European Summary of Products Characteristics (SmPC) and FDA's drug labels, encompass short-term symptomatic relief of diarrhoea in patients above 12 years of age and extends to that induced by irritable bowel syndrome.[7, 8]

Cholecystectomy is a surgical procedure typically performed as an early response to acute cholecystitis (inflammation of the gallbladder), whether or not it is complicated by gallstones. A systematic review and meta-analysis of prospective randomised/non-randomised clinical trials and retrospective trials (10 studies in total) suggests laparoscopic are preferable over open procedures in terms of morbidity, mortality, post-operative length of stay and intra-operative blood loss.[9]

Acute pancreatitis is a transient inflammation of the pancreas and is distinct from its recurring counterpart: chronic pancreatitis. It is described as a common cause for hospitalisation, with an incidence of 14-45 cases per 100,000 persons, primarily induced by gallstones and alcohol abuse.[10] Specifically, biliary duct obstruction in the presence of gallstones is the aetiological explanation for acute pancreatitis, though formations of smaller biliary crystals (microlithiasis) without obstruction can also contribute to the onset of acute pancreatitis.[11]

Drug-induced pancreatitis is a complicated adverse effect difficult to ascertain; the mechanism varies according to the therapeutic class of the triggering drug, its dose, and the underlying conditions of the patient, and also varies in its time to onset: it may range from hours, to days, or even months.[12] There is at least one compendium of drugs "definitely" known to induce acute pancreatitis, primarily based on rechallenge information and time to onset.[12]

Finally, Oddi's Sphincter dysfunction has been described as a potential mechanistic explanation of (drug-induced) acute pancreatitis. This sphincter regulates the flow of pancreatic and biliary digestive secretions into the small intestines. In animal models and in humans its spasms may produce a reflux of secretions into the pancreas leading initially to increased ductal pressure and then to pancreatitis, though there may be idiosyncratic competing causes for the onset of acute pancreatitis.[13]

Reports in VigiBase

As of 26 January 2020, there were 39 case reports of loperamide, loperamide;simeticone and the MedDRA Preferred Terms (PT) "Pancreatitis" and "Pancreatitis acute" in VigiBase, the WHO global individual case safety reports database. The SMQ "Acute pancreatitis (narrow)" did not reveal additional case reports. Four case reports were identified as duplicates, leaving 35 in total. The cases were from France (13), Germany (4), United States (5), Spain (3), Canada (2), Italy (2), Switzerland (2), United Kingdom (2), Australia (1), Portugal (1). None of the drugs-adverse event combinations were disproportional.

The 16 cases that suggest a plausible relationship between the medicinal product and adverse event are summarised below and included in Table 1.

These case reports came from seven countries: France (8), United Kingdom (2), Italy (2), Canada, Switzerland, Germany and Portugal (1 each). Pancreatitis was diagnosed either by imaging (patients 1, 2, 3, 4, 5, 12) or blood amylase and lipase (6, 7, 10, 14). A positive dechallenge was recorded in ten case reports (patients 1, 4, 6, 7, 9, 10, 12, 13, 14, 15) with one positive rechallenge (patient 14) and one instance of recurrent pancreatitis on loperamide. Where reported, the time to onset was short: one to five days, except an outlier of two months. Eight patients had a history of cholecystectomy (patients 1-7, and 16). Of those who did not, one (patient 9) had a family history of pancreatitis. Females were far more prevalent (14 patients) than males (2) in the case series. Indication for use was diarrhoea of unclear aetiology where specified. Only one patient (number 16) had potential confounders, of Crohn's disease and a 'likely history of gallstones'. Since the latter was not ascertained, we saw fit to include this patient in this group.

The 19 cases that do not necessarily suggest a relationship between the medicinal product and adverse event are summarised below.

These case reports came from seven countries and are available upon reasonable request.

The time to onset was short but on the whole longer than those in the previous series; it ranged from 5 to 15 days, with 1 day, 2 days, and 1 month as outliers. Fewer case reports contained this information compared to the 16 case reports commented on above. Dechallenge and rechallenge fields were either incomplete or the role of other co-reported medicines could not be excluded. Where sex was reported, there were at least 8 male and 10 female patients. Imaging and other laboratory values were not specified to the same extent as in the previous group of reports.

Literature and labelling

Literature

There are six published literature cases for loperamide and pancreatitis or pancreatitis acute in patients who underwent cholecystectomy, with an additional one from a clinical trial whose cholecystectomy status is unknown.

Electronic databases

Four case reports in VigiBase were from the literature, and are summarised in Table 1.[14-16] Two additional case reports were found in PubMed and Embase when searching for "loperamide" AND "pancreatitis" in title and abstract.[17, 18] Both are discussed below:

Howaizi and colleagues describe a 57-year-old woman with concomitant dosulepine, alprazolam who experienced acute pancreatitis after two hours of loperamide intake, who had a positive history of cholecystectomy (21 years prior). Coproculture did not reveal pathogens. The patient had experienced four previous episodes in five years that rapidly improved and were described as "similar" by the patient. The two previous episodes coincided with intake of codeine;paracetamol fixed-dose combination, but for the other two episodes the cause was unclear.[17] This literature report presents strong similarities (dates of treatment and onset, patient age and gender) with case 5 in the table below. A 58-year-old woman with a history of hypertension, hypothyroidism, and cholecystectomy started taking loperamide due to diarrhoea, along with daily thyroxin, hydrochlorothiazide, and atenolol for her underlying conditions. She experienced abdominal pain, nausea, and vomiting after two days of loperamide, which went on for seven days before visiting the emergency room. She denied alcohol consumption or smoking. Her lipase, amylase, white blood cell-count and c-reactive protein were elevated. A CT scan showed post-cholecystectomy status and acute pancreatitis. Magnetic resonance cholangio-pancreatography confirmed post-cholecystectomy status, a common bile duct of 5 mm, and no signs of gallstones.[18]

Clinical trials

Consultation of the clinical trials registers in the United States (US) revealed one randomised controlled trial, later published as "Controlling faecal incontinence in women by performing anal exercises with biofeedback or loperamide: a randomised clinical trial", with one patient in the treated arm who experienced pancreatitis (PT). The comparison was placebo with or without biofeedback.[19, 20]

Labelling

Summaries of Product Characteristics

Pancreatitis is not labelled in the European SmPC available at the Electronic Medicines Compendium, nor on the US FDA's label.[3, 7]

Regulatory proceedings

Loperamide-induced pancreatitis was discussed by the Pharmacovigilance Risk Assessment Committee (PRAC) in January 2019, and the manufacturer was asked to review all the relevant cases of loperamide, and loperamide;simeticone, with pancreatitis in a PSUR (deadline: 28 August 2021).[21, 22] The same suspected adverse drug reaction has been partially touched upon by the Australian Therapeutic Goods Administration.[23] In 2011, FDA deemed that information available at that time on loperamide and pancreatitis was insufficient to take action.[24]

Discussion

Of the 35 case reports, 16 may present evidence of pancreatitis-inducing effects of loperamide; the diagnosis of pancreatitis was based on medical history, upper abdominal pain, and laboratory

analyses in several patients. Eight in particular had a history of cholecystectomy, which raises the possibility that the surgical removal of the gallbladder may predispose patients taking loperamide to pancreatitis. In support of this hypothesis is the reported failure to detect cholelithiasis in patients with a history of cholecystectomy, a main cause of pancreatitis. Micro-crystalline formations at the common bile duct were ruled out in one case report (patient 5). Ten case reports suggested a positive dechallenge, with one positive rechallenge (though confounded by total colectomy). Other causes of pancreatitis were specifically excluded, for example history of alcohol abuse. Consistent with the literature, case reports in Table 1 have a time to onset compatible with the relatively short latency of drug-induced pancreatitis (e.g. in literature case reports describing patients on codeine and with a history of cholecystectomy).[12]

Another emerging finding is that women more frequently reported suspected pancreatitis with loperamide. Cholelithiasis is more common in women, which may explain the prevalence of female patients and, in particular, the original cause for cholecystectomy – for which the clinical rationale was never provided in the case reports.

Painful contractions of the Sphincter of Oddi in patients without gallbladder have been described as early as 1936, with morphine,[25] and later, following codeine, in 1941.[26] A recent claims-based nested case-control study of patients who had undergone laparoscopic cholecystectomy has found a four-fold risk of hospitalisation due to pancreatitis within the first 15 days of treatment with codeine.[27] In line with these findings, before the suspected pancreatitis due to loperamide, patient 5 had been hospitalised for pancreatitis due to codeine.

A substance similar to loperamide for its mixed agonist/antagonist-effect on μ-, κ-, and δ-opioid receptors, is eluxadoline[28]; it displays higher affinity for μ-receptors than for κ-receptors (although the affinity for κ-receptors was only determined in animal models).[29] Eluxadoline is indicated to treat diarrhoea due to irritable bowel syndrome, and has recently been under investigation by regulatory agencies, namely the FDA[30] and the Australian Therapeutic Goods Administration.[23] Among the 120 case reports in FAERS of eluxadoline and pancreatitis, 68 patients reported a gallbladder status and 56 had undergone cholecystectomy.

Both agencies concluded that plausible explanations for the causes of pancreatitis could include effects on the Sphincter of Oddi. This conclusion is warranted: sub-analgesic doses of morphine have been reported to have excitatory effects ('spasms') on Oddi's Sphincter by an increase in the frequency of its phasic pressure waves, phasic wave amplitude and basal pressure. The effects on the frequency of phasic pressure waves and basal pressure have been shown to be competitively antagonised by naloxone, which increases the possibility that Oddi's Sphincter could be partially regulated by opioids.[31] Indeed, morphine is a full agonist of μ-, κ- and δ-opioid receptors and naloxone a full antagonist, however, eluxadoline and loperamide are mixed agonists of μ-, κ-receptors but antagonists of δ-receptors. As mixed agonists/antagonists, eluxadoline and loperamide may have both excitatory and depressive effects on the Sphincter of Oddi mediated by their anti-δ-opioid receptor activity. A key distinction lies in their binding affinities for the δ-opioid receptors. Loperamide's inhibitory constant (Ki) is nearly ten times lower (meaning nearly ten times higher affinity) than eluxadoline's (48 nM[1] vs 430 nM[29]). A higher affinity for δ-receptors may suggest a higher inhibitory activity of loperamide's own excitatory potential when compared to eluxadoline.

Patient 9 was reported to have had a family history of pancreatitis. Howaizi and colleagues[17] suggest that Sphincter of Oddi's spasms caused by morphine derivatives could be explained by an individual's hereditary susceptibility. They support this claim with a reference to a series of three patients, one mother and her two children, who all experienced episodes of "biliary colic" after ethylmorphine or codeine phosphate for cough suppression. As negative controls, two other siblings had never had any episode of biliary colic but at the same time did not recall taking any opioid-based cough suppressant. Notably, the mother had experienced biliary spasms before undergoing cholecystectomy, and 13 years after the surgery.[32] These observations may suggest that family history may be a predisposing factor, rather than a confounding one.

There are limitations to this assessment. First, a history of cholecystectomy was not given for most patients. Requests for original reports from national centres and corresponding authors revealed more information on gallbladder status and dates of surgery. Requests for additional information for the patient involved in

the clinical trial of loperamide and biofeedback for faecal incontinence were unsuccessful, so the dates of cholecystectomy were unknown for some patients without a gallbladder. These may have been useful in minimising confounding by "post-cholecystectomy syndrome".[34] Information on the surgical technique used to remove the gallbladder was not always given but would have been useful in understanding the individual risk of pancreatitis.[35]

The case reports that suggested a plausible relationship were more complete and had compatible times to onset, but they should be viewed together with the ones that did not. Moreover, the former cases were not without co-reported drugs (patients 1, 5, 7, 10, 13, 14) or underlying disorders (patient 16) that may have played a role in the onset of pancreatitis. Other case reports clearly indicated misuse of loperamide and overdoses in suicide attempts (these data are not shown, but available upon reasonable request), although there are two published case reports of pancreatitis following loperamide overdose.[36, 37]

Conclusion

The present communication strengthens earlier signals of loperamide-induced pancreatitis by providing evidence from case reports of, a) a subset of eight patients without a gallbladder, suggesting an at-risk-group; b) a time to onset compatible with drug-induced pancreatitis; c) ten instances of positive dechallenge and one positive rechallenge with minor significance (as it may have referred to the sporadic use of loperamide without diagnosis of pancreatitis). A further strength was that the same observations were consistent across seven countries (or 10, if one includes the reports that did not necessarily suggest a relationship).

With several published case reports, this association has already been discussed by different regulatory agencies, however, FDA's latest public update is from 2011 and the EU PSUR is due in 2021. This signal may prove sufficient to re-open previous decisions, or as an interim update before due PSUR dates. Finally, a loperamide-induced pancreatitis may suggest the need for action in view of the drug's over-the-counter availability and its status as proposed alternative for patients without gallbladder who have been treated with eluxadoline and experienced pancreatitis.

References

1. DeHaven-Hudkins DL, Burgos LC, Cassel JA, Daubert JD, DeHaven RN, Mansson E, et al. Loperamide (ADL 2-1294), an opioid antihyperalgesic agent with peripheral selectivity. The Journal of pharmacology and experimental therapeutics. 1999;289(1):494-502.

2. di Bosco AM, Grieco P, Diurno MV, Campiglia P, Novellino E, Mazzoni O. Binding site of loperamide: automated docking of loperamide in human mu- and delta-opioid receptors. Chemical biology & drug design. 2008;71(4):328-35.

3. Food and Drug Administration. Label for loperamide. [Accessed on 03/02/2020]. Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=017694].

4. Galambos JT. Loperamide, a new antidiarrheal agent in the treatment of chronic diarrhea. Schweizerische medizinische Wochenschrift. 1978;108(28):1080-1.

5. Swank KA, Wu E, Kortepeter C, McAninch J, Levin RL. Adverse event detection using the FDA post-marketing drug safety surveillance system: Cardiotoxicity associated with loperamide abuse and misuse. Journal of the American Pharmacists Association : JAPhA. 2017;57(2s):S63-s7.

6. Food and Drug Administration. FDA Drug Safety Communication: FDA warns about serious heart problems with high doses of the antidiarrheal medicine loperamide (Imodium), including from abuse and misuse. 2016 [Accessed on 27/01/2020]. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-warns-about-serious-heart-problems-high-doses-antidiarrheal].

7. Electronic Medicines Compendium. Summary of Products Characteristics for Imodium Original 2mg Capsules. 2020 [Accessed on 27/01/2020]. Available from: https://www.medicines.org.uk/emc/product/558/smpc].

8. Food and Drug Administration. Label for IMODIUM CAPSULES Rx. 2020 [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/017690s005lbl.pdf].

9. Coccolini F, Catena F, Pisano M, Gheza F, Fagiuoli S, Di Saverio S, et al. Open versus laparoscopic cholecystectomy in acute cholecystitis. Systematic review and meta-analysis. International Journal of Surgery. 2015;18:196-204.

10. Lankisch PG, Apte M, Banks PA. Acute pancreatitis. The Lancet. 2015;386(9988):85-96.

11. GERKE H, BAILLIE J. Biliary microlithiasis: A neglected cause of recurrent pancreatitis and biliary colic? Journal of Gastroenterology and Hepatology. 2005;20(4):499-501.

12. Badalov N, Baradarian R, Iswara K, Li J, Steinberg W, Tenner S. Drug-Induced Acute Pancreatitis: An Evidence-Based Review. Clinical Gastroenterology and Hepatology. 2007;5(6):648-61.e3.

13. Fazel A, Geenen JE, MoezArdalan K, Catalano MF. Intrapancreatic Ductal Pressure in Sphincter of Oddi Dysfunction. Pancreas. 2005;30(4):359-62.

14. Hastier P, Buckley MJ, Peten EP, Demuth N, Dumas R, Demarquay JF, et al. A new source of drug-induced acute pancreatitis: codeine. The American journal of gastroenterology. 2000;95(11):3295-8.

15. Labgaa I, Uldry E, Doerig C, Schmidt S, Demartines N, Halkic N. Loperamide-induced recurrent acute pancreatitis. Clinics and Research in Hepatology and Gastroenterology. 2016;40(1):e13-e4.

16. Peserico G, Barbuscio I, Fantin A, Sturniolo GC. Drug-induced pancreatitis: loperamide and adverse event. Pancreatology. 2017;17(3, Supplement):S92.

17. Howaizi M, Sbai-Idrissi MS, Baillet P. [Loperamide-induced acute pancreatitis]. Gastroenterologie clinique et biologique. 2000;24(5):589-91.

18. Vidarsdottir H, Vidarsdottir H, Moller PH, Bjornsson ES. Loperamide-induced acute pancreatitis. Case reports in gastrointestinal medicine. 2013;2013:517414.

19. U.S. National Library of Medicine - Clinicaltrials.gov. Controlling Anal Incontinence by Performing Anal Exercises With Biofeedback or Loperamide (CAPABLe) (CAPABLe) - NCT02008565. 2018 [Accessed on 17/02/2020]. Available from: https://clinicaltrials.gov/ct2/show/results/NCT02008565?term=loperamide&rslt=With&draw=2&rank=2&view=results

20. Jelovsek JE, Markland AD, Whitehead WE, Barber MD, Newman DK, Rogers RG, et al. Controlling faecal incontinence in women by performing anal exercises with biofeedback or loperamide: a randomised clinical trial. The lancet Gastroenterology & hepatology. 2019;4(9):698-710.

21. Pharmacovigilance Risk Assessment Committee. Pharmacovigilance Risk Assessment Committee (PRAC), Minutes of meeting on 14-17 January. 2019 [Accessed on 24/02/2020]. Available from: https://www.ema.europa.eu/en/documents/minutes/minutes-prac-meeting-14-17-january-2019_en.pdf].

22. European Medicines Agency. EU reference dates list of Periodic Safety Update Reports. 2020 [Accessed on 04/03/2020]. Available from: https://www.ema.europa.eu/documents/other/list-european-union-reference-dates-frequency-submission-periodic-safety-update-reports_en.xls].

23. Therapeutic Goods Administration. Australian Public Assessment Report for Eluxadoline. 2018 [Accessed on 17/02/2020]. Available from: https://www.tga.gov.au/sites/default/files/auspar-eluxadoline-180516.docx.pdf].

24. Food and Drug Administration. Potential Signals of Serious Risks/New Safety Information Identified by the Adverse Event Reporting System (AERS). 2011 [Accessed on 24/02/2020]. Available from: https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/october-december-2011-potential-signals-serious-risksnew-safety-information-identified-adverse-event].

25. McGowan JM, Butsch WL, Walters W. PRESSURE IN THE COMMON BILE DUCT OF MAN: ITS RELATION TO PAIN FOLLOWING CHOLECYSTECTOMY. Journal of the American Medical Association. 1936;106(26):2227-30.

26. Williamson JB. Effect of Morphine after Cholecystectomy. British Medical Journal. 1941;1(4179):215-.

27. Kim J, Tabner AJ, Johnson GD, Brumback BA, Hartzema A. Increased Risk of Acute Pancreatitis with Codeine Use in Patients with a History of Cholecystectomy. Digestive Diseases and Sciences. 2020;65(1):292-300.

28. Fujita W, Gomes I, Dove LS, Prohaska D, McIntyre G, Devi LA. Molecular characterization of eluxadoline as a potential ligand targeting mu-delta opioid receptor heteromers. Biochemical pharmacology. 2014;92(3):448-56.

29. Food and Drug Administration. Label for Eluxadoline [Accessed on 03/02/2020]. Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process&ApplNo=206940].

30. Food and Drug Administration. FDA Drug Safety Communication: FDA warns about increased risk of serious pancreatitis with irritable bowel drug Viberzi (eluxadoline) in patients without a gallbladder. 2017 [Accessed on 03/02/2020]. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-warns-about-increased-risk-serious-pancreatitis-irritable-bowel].

31. Helm JF, Venu RP, Geenen JE, Hogan WJ, Dodds WJ, Toouli J, et al. Effects of morphine on the human sphincter of Oddi. Gut. 1988;29(10):1402-7.

32. Helene Ørstavik K. FAMILIAL OCCURRENCE OF OPIOID-INDUCED BILIARY COLIC. The Lancet. 1989;334(8667):874-5.

33. Wolfe D, Kanji S, Yazdi F, Skidmore B, Moher D, Hutton B. Methods for the early detection of drug-induced pancreatitis: a systematic review of the literature. BMJ Open. 2019;9(11):e027451-e.

34. Isherwood J, Oakland K, Khanna A. A systematic review of the aetiology and management of post cholecystectomy syndrome. The Surgeon. 2019;17(1):33-42.

35. Z'Graggen K, Aronsky D, Maurer CA, Klaiber C, Baer HU. Acute postoperative pancreatitis after laparoscopic cholecystectomy. Results of the Prospective Swiss Association of Laparoscopic and Thoracoscopic Surgery Study. Archives of surgery (Chicago, Ill : 1960). 1997;132(9):1026-30; discussion 31.

36. Epelde F, Boada L, Tost J. Pancreatitis caused by loperamide overdose. The Annals of pharmacotherapy. 1996;30(11):1339.

37. Lee HM, Villa AF, Caudrelier S, Garnier R. Can loperamide cause acute pancreatitis? Pancreas. 2011;40(5):780-1.

Table 1. Cases of pancreatitis and pancreatitis acute that suggest a plausible relationship with loperamide

Case	Age/ Sex	Other suspected (S), interacting (I) or concomitant (C) drugs	Reactions (MedDRA Preferred Term)	Time to onset	Action taken with drug (dechallenge and rechallenge)	Outcome	Comment
1	77/M	Metopimazine (S) Clopidogrel*, Rosuvastatin*, Serenoa repens, Lorazepam, Lansoprazole*, Sodium alginate, Paracetamol*, Verapamil, Glyceryl trinitrate, Macrogol (all C)	Pancreatitis	Within 1 day	Drug withdrawn/ Reaction abated	Recovered	Cholecystectomy 15 years before the event of pancreatitis Habitual treatment with concomitant drugs Lab values compatible with pancreatitis CT scan did not reveal cholelithiasis; alcoholic aetiology discarded
2	77/F	-	Pancreatitis	1 day	-	-	Literature case Peserico et al. 2017[16] History of remote cholecystectomy, at least 40 years before the date of the case report (personal communication) No alcohol consumption, smoking, or family history of pancreatitis Lab values compatible with pancreatitis Magnetic resonance-cholangio-pancreatography showed a well-defined pancreas without acute inflammation pancreatitis; common bile duct lithiasis excluded
3	46/F	-	Pancreatitis, Sphincter of Oddi dysfunction	1 day	-	-	Literature case Peserico et al. 2017[16] History of laparoscopic cholecystectomy confirmed by abdominal ultrasound, at least 10 years before the date of the case report (personal communication) Hepatic steatosis No fever, smoking, or alcohol consumption Magnetic resonance-cholangio-pancreatography: no inflammation of pancreas; no gallstones

* Known to be associated with pancreatitis on EU SmPC

Case	Age/ Sex	Other suspected (S), interacting (I) or concomitant (C) drugs	Reactions (MedDRA Preferred Term)	Time to onset	Action taken with drug (dechallenge and rechallenge)	Outcome	Comment
4	65/F	-	Pancreatitis acute	-	Drug withdrawn/ Reaction abated	Recovered	Literature case Labgaa et al 2015[15] Loperamide taken for 2 days, 6 mg/day History of laparoscopic cholecystectomy confirmed by abdominal ultrasound Recurrent pancreatitis after loperamide (previous occurrence 4 months before this report) Denies alcohol consumption, no family history for pancreatitis Lab values compatible with pancreatitis CT-scan (during prior admission): well-defined pancreas without interstitial or peripancreatic oedema Magnetic resonance-cholangio-pancreatography excluded inflammation of pancreas and common bile duct lithiasis Follow-up of 16 months, without loperamide and no recurrence of pancreatitis
5	57/F	Codeine* (S)	Oedematous pancreatitis, Product use in unapproved indication, Pancreatitis acute	-	-	Recovered	Literature case Hastier et al. 2000[14] presents strong similarities to literature report by Howaizi and colleagues[17] History of cholecystectomy 23 years before Denies "excessive" alcohol consumption, or risk factors for pancreatitis Recurrent "similar" abdominal pain after administration of loperamide and codeine, accompanied by "significant elevation of serum amylase on each occasion" Lab values compatible with pancreatitis Abdominal CT-scan: oedematous acute pancreatitis and normal common bile duct Biliary crystals not detected

* Known to be associated with pancreatitis on EU SmPC

Case	Age/ Sex	Other suspected (S), interacting (I) or concomitant (C) drugs	Reactions (MedDRA Preferred Term)	Time to onset	Action taken with drug (dechallenge and rechallenge)	Outcome	Comment
6	85/F	Lomefloxacin, Ibuprofen (all S) Levothyroxine, Metformin, Esomeprazole, Fenofibrate*, Irbesartan (all C)	Pancreatitis acute	5 days (15 days, 5 days for lomefloxacin and ibuprofen)	Drug withdrawn/ Reaction abated	Recovered	History of cholecystectomy Lab values compatible with pancreatitis. Negative for *C. difficile* Urinary infection treated with lomefloxacin, 10 days before onset of pancreatitis. Ibuprofen concomitant to start of therapy with loperamide Gout, urinary infection, sigmoid diverticulosis, hypertension arterial, gastritis, dyslipidaemia, hypothyroidism, type II diabetes mellitus
7	68/M	Tramadol*, Omeprazole (all S) Tamsulosin, Phloroglucinol, Trimethylphloroglucinol, Degarelix, Docetaxel, Parecetamol*, Tinzaparin (all C)	Pancreatitis acute	-	Drug withdrawn/ Reaction abated	Recovering	History of cholecystectomy and pancreatitis Prostate cancer Lab values compatible with pancreatitis
8	-/F	-	Pancreatitis acute	Within 1 day	-	-	-
9	23/F	-	Pancreatitis acute	Within 1 day	Drug withdrawn/ Reaction abated	Recovered	Lab values compatible with pancreatitis Family history of pancreatitis (grandmother) Viral load undetected No visible lithiasis "Occasional" alcohol intake
10	78/F	Paracetamol; Tramadol* (all S)	Pancreatitis acute	2 days (1 month for paracetamol; tramadol)	Drug withdrawn/ Reaction abated	Recovered	Lab values compatible with pancreatitis Hypertension arterial, diabetes No findings of dilation or obstacles of biliary ducts Paracetamol; tramadol reintroduced without recurrence of pancreatitis
11	30/F	Budesonide, Formoterol (all C)	Pancreatitis	1 day	-	Not recovered	Non-infectious gastroenteritis and colitis

* Known to be associated with pancreatitis on EU SmPC

Case	Age/ Sex	Other suspected (S), interacting (I) or concomitant (C) drugs	Reactions (MedDRA Preferred Term)	Time to onset	Action taken with drug (dechallenge and rechallenge)	Outcome	Comment
12	73/F	-	Pancreatitis acute	2 days	Drug withdrawn/ Reaction abated	Recovered	Lab values compatible with pancreatitis Abdominal scan without injection: intrahepatic tract aerobilia, slightly oedematous pancreas Abdominal scan with injection: G-lobe aerobilia, tumefied pancreatic tail Abdominal echography: Heterogeneous hepatic parenchyma without focal lesions, aerobilia
13	17/F	Ketoprofen*, Paracetamol*, Colchicine, Thiocolchicoside, Lansoprazole* (all S)	Pancreatitis	5 days	Drug withdrawn/ Reaction abated	Recovered	Lab values compatible with pancreatitis
14	50/F	Sulindac (C)*	Pancreatitis, Abdominal pain upper, Nausea, Vomiting	< 2 months	Drug withdrawn/ Reaction abated Rechallenge/ Reaction recurred	Recovered	Lab values compatible with pancreatitis, confirmed by echography Total colectomy due to familial polyposis Intermittent use of loperamide for the previous 2 years
15	50/F	Omeprazole, Ondansetron, Salbutamol (all C)	Pancreatitis	Within 1 day	Drug withdrawn/ Reaction abated	Recovering	-
16	53/F	-	Pancreatitis	-	-	-	History of cholecystectomy age 19 History of C. difficile infection (2 years before date of report) Concurrent conditions: hypothyroidism, fibromyalgia Hysterectomy (7 years prior to date of report) Potential confounders: Crohn's disease, 'likely history of gallstones'

* Known to be associated with pancreatitis on EU SmPC

SIGNAL

WHO defines a signal as:

"Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously". An additional note states: "Usually more than one report is required to generate a signal, depending on the seriousness of the event and the quality of the information".*

A signal is therefore a hypothesis together with supporting data and arguments. A signal is not only uncertain but also preliminary in nature: the situation may change substantially over time one way or another as more information is gathered. A signal may also provide further documentation of a known association of a drug with an ADR, for example: information on the range of severity of the reaction; the outcome; postulating a mechanism; indicating an "at risk" group; a dose range which might be more suspect; or suggesting a pharmaceutical group effect or a lack of such an effect by a particular drug.

Signals communicated by UMC are derived from VigiBase, the WHO global database of individual case safety reports. This database contains summaries of individual case safety reports of suspected adverse drug reactions, submitted by national pharmacovigilance centres (NCs) that are members of the WHO Programme for International Drug Monitoring. More information regarding the status of this data, its limitations and proper use, is provided in the Caveat on the last page of this document.

VigiBase is periodically screened to identify drug-ADR combinations that are unknown or incompletely documented. Combinations of such interest that they should be further reviewed clinically are sent to members of the Signal Review Panel for in-depth assessment. The Signal Review Panel consists of experienced international scientists and clinicians, usually affiliated with a governmental or an academic institution. The expert investigates the clinical evidence for the reaction being related to the suspected drug.

The topics discussed in the signals represent varying levels of suspicion. Signals contains hypotheses, primarily intended as information for the national regulatory authorities. They may consider the need for possible action, such as further evaluation of source data, or conducting a study for testing a hypothesis.

The distribution of signals is currently restricted to NCs, regulatory authority staff and their advisers, participating in the WHO Programme. Signals are sent to the pharmaceutical companies when they can be identified as uniquely responsible for the drug concerned. UMC does not take responsibility for contacting all market authorisation holders. As a step towards increased transparency, since 2012 UMC signals are subsequently published in the WHO Pharmaceuticals Newsletter.

National regulatory authorities and NCs are responsible for deciding on action in their countries, including communicating the information to health professionals, and the responsible market authorisation holders, within their jurisdiction.

In order to further debate, we encourage all readers of signals to comment on individual topics.

* Edwards I.R, Biriell C. Harmonisation in pharmacovigilance. Drug Safety 1994;10:93-102.

Responses from industry

Signals on products under patent are submitted to patent holders for comments. Responses from industry are unedited. The calculations, analysis and conclusions are theirs, and should be given serious but critical consideration in the same way as any scientific document. The WHO and UMC are not responsible for their findings, but may occasionally comment on them.

WHO Collaborating Centre for International Drug Monitoring
Box 1051, S-751 40 Uppsala, Sweden
Tel: +46 18 65 60 60, www.who-umc.org

Uppsala Monitoring Centre

Caveat Document

Statement of reservations, limitations and conditions relating to data released from VigiBase, the WHO global database of individual case safety reports (ICSRs). Understanding and accepting the content of this document are formal conditions for the use of VigiBase data.

Uppsala Monitoring Centre (UMC) in its role as the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring receives reports of suspected adverse reactions to medicinal products from National Centres in countries participating in the WHO Programme for International Drug Monitoring. The information is stored in VigiBase, the WHO global database of individual case safety reports (ICSRs). It is important to understand the limitations and qualifications that apply to this information and its use.

Tentative and variable nature of the data

Uncertainty: The reports submitted to UMC generally describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. In most instances it cannot be proven that a specific medicinal product is the cause of an event, rather than, for example, underlying illness or other concomitant medication.

Variability of source: Reports submitted to national centres come from both regulated and voluntary sources. Practice varies: some national centres accept reports only from medical practitioners; others from a broader range of reporters, including patients, some include reports from pharmaceutical companies.

Contingent influences: The volume of reports for a particular medicinal product may be influenced by the extent of use of the product, publicity, the nature of the adverse effects and other factors.

No prevalence data: No information is provided on the number of patients exposed to the product, and only a small part of the reactions occurring are reported.

Time to VigiBase: Some national centres make an assessment of the likelihood that a medicinal product caused the suspected reaction, while others do not. Time from receipt of an ICSR by a national centre until submission to UMC varies from country to country. Information obtained from UMC may therefore differ from that obtained directly from national centres.

For these reasons, interpretations of adverse effect data, and particularly those based on comparisons between medicinal products, may be misleading. The data comes from a variety of sources and the likelihood of a causal relationship varies across reports. Any use of VigiBase data must take these significant variables into account.

Prohibited use of VigiBase Data includes, but is not limited to:

- patient identification or patient targeting
- identification, profiling or targeting of general practitioners or practice

Any publication, in whole or in part, of information obtained from VigiBase must include a statement:

(i) recording 'VigiBase, the WHO global database of individual case safety reports (ICSRs)' as the source of the information

(ii) explaining that the information comes from a variety of sources, and the probability that the suspected adverse effect is drug-related is not the same in all cases

(iii) affirming that the information does not represent the opinion of the UMC or the World Health Organization.

Omission of this statement may exclude the responsible person or organization from receiving further information from VigiBase.

UMC may, in its sole discretion, provide further instructions to the user, responsible person and/or organization in addition to those specified in this statement and the user, responsible person and/or organization undertakes to comply with all such instructions.

WHO Collaborating Centre for International Drug Monitoring
Box 1051, S-751 40 Uppsala, Sweden
Tel: +46 18 65 60 60, www.who-umc.org

Uppsala Monitoring Centre