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Drug-Induced Acute Pancreatitis Confirmed By Positive Re-challenge

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Abstract

Drug-induced pancreatitis is a rare but severe adverse drug reaction with an incidence of 0.1-2%. More recent reports have estimated an incidence of up to 5%. Over 500 medications have been associated with this disease. Recrudescence of pancreatotoxicity upon re-exposure to the suspicious drug is considered the more reliable evidence of drug-induced pancreatitis. A retrospective review of MEDLINE was conducted to assess clinical outcomes of positive drug re-challenge following possible drug-induced pancreatitis. A total number of 250 cases of drug-induced pancreatitis with positive re-challenge were identified, among which, 183 met inclusion criteria for analysis in our review. A broad spectrum of suspect drugs was identified. Analgesics and anti-inflammatory drugs were incriminated in 30% of all cases, antibacterials in 18.6%, and cardiovascular agents in 10.9% of cases, immunomodulators in 11% of cases and gastro-intestinal drugs in 4.9% of cases. Improved identification and communication of possible drug-induced pancreatitis is needed to avoid potentially serious and/or fatal drug re-challenges.

Keywords: Pancreatitis; Drug-induced; Positive re-challenge

Introduction

Acute pancreatitis is a severe disease with an overall mortality of nearly 5% [1]. The most common causes of pancreatitis are biliary tract disease and excessive alcohol use. Other less frequent aetiologies of acute pancreatitis are abdominal traumatism, autoimmune disease, inflammatory bowel disease, infections, neoplasm, metabolic disorders, drugs or idiopathic [2].

Drug-induced pancreatitis is rare with an estimated incidence of 0.1-2% [3]. In recent studies, an incidence of up to 5% has been reported [4]. Over 500 medications have been listed in the World Health Organization (WHO) database as suspected to induce acute pancreatitis as a side effect [5]. Currently, the diagnosis of drug-induced pancreatitis is challenging as clinical characteristics are various and non-specific. It is not standardized and it is made with varying levels of evidence. In fact, one of the major problems of the causality assessment of drug-induced pancreatitis is the lack of reliability in establishing whether the pancreatic disorder was caused by the drug or by another factor [6].

A relation between the incriminated drugs and pancreatitis may be assessed if there is a temporal correlation between drug ingestion and the signs of pancreatitis, the regression of symptoms on drug withdrawal, if other likely causes of pancreatitis are not present and on recurrence of symptoms of pancreatitis after re-exposure to the drug.

Main information about drug-induced pancreatitis is derived from isolated case reports and some reviews that tried to classify drugs with definite, probable or possible cause of drug-induced pancreatitis. To consider a drug-induced pancreatitis as definite, a re-challenge resulting in a second episode of pancreatitis is required. In this review, our purpose was to identify the main pharmaceutical agents that can be definitely linked to this adverse event.

Methodology

A MEDLINE search was conducted from January 1950 to June 2015, regardless of the language. The keywords used in the search were: "pancreatitis", "pancreatotoxicity", "positive re-challenge" and "drug-induced". Certain drugs were also inserted as keywords.

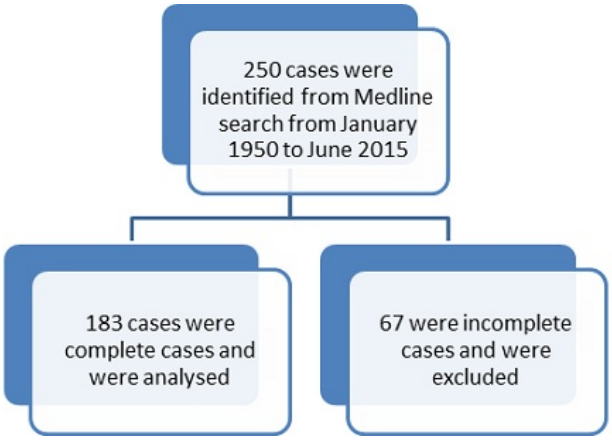

Figure 1: Consort diagram of methodology.

All positive reports were selected according to the following criteria: abdominal pain clinically evident, amylasemia and lipasemia exceeding at least 3 fold upper limits normal and a positive drug re-challenge, defined by the recurrence of the abdominal pain with an

elevation of the level of amylases and lipases after restarting the suspect drug. Case analyses included age, sexe, suspected drug, dosage and length of drug exposure, associated medications, onset of pancreatitis, biology (amylasemia and lipasemia) and medical imaging.

Results

A total number of 250 cases of drug-induced pancreatitis with positive re-challenge was identified, among which, 183 cases were complete cases and were analysed in our review (Figure 1). The mean age was 40 years with a range from 8 to 81 years. 51% were females. The majority of patients (56.2%) had at least one concomitant medication in addition to the suspected drug (Table 1). All analysed cases had no lithiasis, dyslipidemia, hypercalcemia and alcohol use. The outcome was favourable except in one isolated case.

A large spectrum of drugs was associated with pancreatitis. Analgesics and anti-inflammatory drugs were incriminated in 30% of all cases, antimicrobials in 18.6%, and cardiovascular agents in 11.4% of cases, immunomodulator drugs in 10.9% of cases (the majority were azathioprine and 6-mercaptopurine) and gastro-intestinal drugs in 4.9% of cases (Table 2). The ten most reported drugs inducing pancreatitis with positive re-challenge are reported in Table 3. The leading single drug was azathioprine. The onset varied from few days to many years.

Variables	Positive re-challenge (n=183)
Age	20 (11%)
<20	42 (23%)
20-30	44 (24%)
31-40	24 (13.2%)
41-50	21 (11.4%)
51-60	32 (17.4%)
>60	
Gender	90 (49%)
Male	93 (51%)
Female	
Concomitant medications	80 (43.8%)
None	47 (25.7%)
1 medication	32 (17.4%)
2 medications	24 (13.1%)
> 3 medications	

Table 1: Demographic and clinical parameters of acute pancreatitis confirmed by positive re-challenge.

DRUGS	Number of cases (183)	(%)
Antimicrobials:	34	18.6
Antibacterials: Isoniazide, metronidazole, stibogluconate, ampicilline, erythromycin, imipenem, cotrimoxazole, dapsone, danazol, paromomycine, Pentamidine, Sulfafurazol, Sulfamethizol.	29	15.8
Antivirals: asparginase,didanosine, Nelfinavir, lamivudine.	5	2.8
Cardiovascular agents:	20	10.9
Beta-blockers: nadolol.	1	0.54
ACE: enalapril, ramipril, lisinopril.	4	2.2
Alpha 2 agonists: methyldopa, clonidine.	3	1.6
Diuretics: Furosemide, triamterene, chlorothiazide.	5	2.8
Anti-arrhythmics: Procainamide, amiodarone, aprindine.	3	1.6
Cholesterol lowering agents: Bezafibrate, simvastatine, fluvastatine, pravastatine.	4	2.1
Neuropsychiatric agents	19	10.3
Anticonvulsants: Valproic acid, vigabatrim, carbamazepine.	12	6.5
Antipsychotics: Clozapine, clothiapine, olanzapine, indalpine, mitrazapine.	7	3.8
Antineoplastic agents: Cytarabine, clomifene, bleomycine, cisplatine, vinblastine, diethylstilbestrol, sorafenib, purinethol, paclitaxel, mitoxantrone, ifosfamide, tamoxifen.	17	9.3
Analgesics and anti-inflammatory drugs: codeine, sulindac, piroxicam, phenacetine, oxyphenbutazone, mefenamic acid, morphine, dexamethasone, prednisolone, sulphapyrazone, mesalamine.	55	30
Gastrointestinal drugs: olsalazine, cimetidine, diphenoxylate, ranitidine.	9	4.9
Immunomodulator drugs: azathioprine, 6-mercaptopurine, anti-lymphocytaire, tacrolimus, interferon	20	11
Endocrine drugs: carbimazole, metimazole.	2	1.1

Others: isotritenoine, filgrastime, fenfluramine.	7	3.8

Table 2: Different classes of drugs incriminated in drug-induced pancreatitis followed by positive re-challenge.

Drugs	Number of cases of drug-induced pancreatitis
Azathioprine	13
Valproic acid	10
Codeine	8
Isoniazide	7
Mesalasine	7
Sulindac	7
Sulphapyrazone	6
Metronidazole	5
Octreotide	4
Stibogluconate	4

Table 3: The ten most implicated drugs in pancreatitis with positive re-challenge.

The different classes of drugs incriminated in pancreatitis with positive re-challenge are the followings:

Analgesics and anti-inflammatory drugs

Analgesics and anti-inflammatory drugs are the most important class of drugs inducing acute pancreatitis confirmed by re-challenge. This may be due, at less in part, to the wide use of these drugs. Eight (8) cases of codeine-induced acute pancreatitis were reported. Five (5) of them were patients that have undergone cholecystectomy. The doses of codeine ranged from 40 to 60 mg daily. The mechanism of pancreatitis is likely a constriction of the sphincter of oddi as opiates are known to cause a transient spasm of the sphincter [7,8].

Sulindac is an anti-inflammatory drug that has been associated with 7 cases of acute pancreatitis [9, 10]. The doses varied from 200 to 400 mg daily occurred between a few days to two months after drug initiation. Mechanism of sulindac-induced pancreatitis is unclear. A possible absorption of the active metabolite of sulindac by the bile duct may be at the basis of acute pancreatitis.

Corticosteroids may also induce pancreatitis by stimulating both exocrine and endocrine pancreatic secretions. In fact, these drugs increase the viscosity of pancreatic secretions [11]. Sulphasalazine and mesalasine are both associated with a number of drug-induced pancreatitis [12,13]. Latency period varied from one day to one week. Pancreatitis reoccurs few days after re-challenge suggesting a hypersensitivity mechanism to drug-induced attacks.

Anti-infective drugs

The class of anti-infectives is very heterogeneous. Isoniazid-induced pancreatitis was reported in many cases. All of them had tuberculosis and two were suffering from chronic renal failure. The doses varied from 100 to 400 mg daily. The onset of pancreatitis occurs few hours to few days. The mechanism of isoniazid-induced pancreatitis is likely to be due to hypersensitivity [14]. Isoniazid was the only antituberculosis drug that has been reported with pancreatitis [15,16]. As antituberculosis medication is generally composed of at least two drugs, the imputability of isoniazid-induced pancreatitis may be challenging. A Re-challenge using each drug individually may assist diagnosis.

Metronidazole-induced pancreatitis has also been reported [17]. All cases were reported in females treated for vaginal discharge. The doses ranged from 750 to 1500 mg daily. Metronidazole is known to diffuse into the pancreas leading to a possible toxicity of free radicals on pancreatic cells [18]. Four cases of stibogluconate-induced pancreatitis with positive re-challenge are identified [19]. All patients were treated for cutaneous leishmanies. Doses were of 20 mg/kg/day, the onset of pancreatitis was about few hours to few days.

Cardiovascular Drugs

Antihypertensive agents such as alphamethyl dopa are reported to be responsible for (2) cases of pancreatitis with positive re-challenge [20]. Furosemide-induced pancreatitis is reported in (3) cases and angiotensin converting enzyme inhibitors (ACEI) are a cause of acute pancreatitis with positive re-challenge, in (2) cases with enalapril, in (1) case with ramipril and in (1) case with lisinopril [21-24]. ACEI may induce pancreatitis by causing angioedema of the pancreatic duct secondary to interference with kallikrein-kinin system, causing decreased degradation of kinins [25].

Lipid Lowering Agents

Lipid lowering agents may also induce acute pancreatitis. The mechanism of action of statin-induced pancreatitis is unclear. Drug interaction may play an important role in this adverse effect, e.g. association between ACEI and statins, as well as statins and fibrates are at higher risk. Clinicians should keep in mind that statin-induced pancreatitis may be a class effect. So, this adverse effect may reoccur despite switching statins [26].

Antineoplastic and Immunomodulating Agents

Azathioprine and its metabolite 6-mercaptopurine have been frequently associated with pancreatitis [27,28]. The majority of cases have been reported in patients with inflammatory bowel diseases. Re-challenge was reported in 15 cases. The doses varied from 50 to 200 mg daily. One case of death was reported in a 25-year old renal transplanted patient. The mechanism of toxicity of azathioprine and its metabolites is likely an idiosyncratic reaction, pancreatitis occurs probably by an inhibition of the intracellular mechanisms involved in acinar cell secretion [29].

Cytarabine is an antineoplastic agent associated with few cases of acute pancreatitis. All cases reported were patients who had leukemia [30,31]. Vemurafenib is a new kinase inhibitor associated with pancreatitis confirmed by positive re-challenge [32]. Tamoxifen was also associated with pancreatitis [33].

Neuropsychiatric Agents

Nervous system drugs are reported to induce pancreatitis with positive re-challenge. Valproic acid has been associated with pancreatitis since 1979. We identified 10 cases of valproic acid induced pancreatitis in epileptic patients. The majority were children. The doses varied from 1 to 2 g daily and long latency varying from one month to many years was reported. The drug-induced pancreatitis was resolved in all cases after cessation of the drug [34]. The mechanism of action from valpoic acid-induced pancreatitis is likely due to an accumulation of toxic metabolites of valproic acid. Vigabatrim and carbamazepine were also associated with acute pancreatitis confirmed by positive re-challenge [35,36].

Moreover, clozapine was reported in three cases of drug-induced pancreatitis with positive re-challenge [37].

Gastro-intestinal Drugs

Aminosalicylic acid drugs widely used in the treatment of inflammatory bowel disease are associated with pancreatitis occurs generally within hours after drug re-challenge [38]. And hypersensitivity was the suggested mechanism to drug-induced pancreatitis. Acid suppressants were all used in patients suffering from gastric or duodenal ulcers. Pancreatitis occurred one week after rechallenging the drug in two patients treated with cimetidine [39,40]. Acid suppressants may affect pancreatic secretory stimuli by reducing gastric and duodenal acidity [41].

Discussion

Drug-induced pancreatitis is rare. Approximately 2% of patients diagnosed with acute pancreatitis are drug-induced [42]. In Japan, a national survey carried out in 1999 reported that 1.2% of all cases of acute pancreatitis were drug-induced [43]. In Denmark, the incidence of drug-induced pancreatitis was of 1% [44]. Children, women, elderly and patients with concomitant diseases such as acquired immune deficiency syndrome, renal transplantation or inflammatory bowel disease are at higher risk of developing this condition.

Drug-induced pancreatitis must be diagnosed after excluding other aetiologies especially cholelithiasis, alcoholism, less likely abdominal traumatisms, tumor, hyperlipidemia, endoscopic retrograde cholangiopancreatography, infections and many other miscellaneous causes.

Drug-induced pancreatitis is a challenging diagnosis for clinicians because of many reasons. First, pancreatitis induced by drugs has no clinical features that can differentiate it from pancreatitis induced by other causes. Second, pancreatitis is often isolated; there are rarely clinical manifestations of drug reaction such as rash or lymphadenopathy or laboratory evidence of adverse drug reaction such as eosinophilia. Moreover, an ever expending list of drugs is associated with acute pancreatitis and several causality methods have been proposed in order to assess the causality of a drug in the occurrence of this adverse event.

Currently, classification system of drug-induced pancreatitis is widely used to assess causality in pancreatotoxicity in a uniform basis. In 1980, Mallory and Kern proposed a system in which a drug was classified as having either a definite, probable, or possible association with pancreatitis based on multiple criteria [45]. A group of drugs with a definite association with pancreatitis if the disease develops during treatment with the drug regresses after the drug is withdrawn and returns on drug re-challenge. A second group with a probable association if a relation between the drug and pancreatitis is thought to be likely and if some criteria of those with a definite association are met. If there is no evidence of association, drugs are classified as having a questionable association. Since that time, several review articles have used this 3-group classification system. However, Mallory and Kern do not clearly define the evidence for each group. In addition, the evidence for "definite" in their article is "usually" dependent on the presence of a re-challenge. In 2005, Trivedi and Pitchumoni introduced an adapted 3-group classification system and gave more weight to the number of reported cases and to the positive re-challenge [46]. These reviews describe the evidence of drugs causing pancreatitis in vague categories (definite, probable, and possible) with unclear inclusion criteria for which a drug becomes placed in the various categories. It briefly addresses the importance of a consistent latency, which might be important for providing evidence of causation.

More recently, in 2007, Badalov et al. have proposed a new classification of drug-induced pancreatitis in which number of reports is less important and more weight is given to a positive re-challenge, the exclusion of other causes, and the time relation between drug use and the onset of acute pancreatitis [47]. This classification system is composed of five classes. Class Ia includes drugs with at least one case report with positive re-challenge excluding all other causes of acute pancreatitis. Class Ib includes drugs having at least one published case showing a positive re-challenge, but the case failed to rule out other common causes of acute pancreatitis. Class II includes drugs having at least 4 case reports published and in which there is a consistent latency in 75% or more of the reported cases. Class III includes drugs having at least two case reports but no re-challenge performed and no consistent latency period among cases was reported. Class IV drugs have only one case report without re-challenge.

Definite proof for causality is defined by the WHO classification if symptoms reoccur upon re-challenge. Despite these different classifications of drug-induced pancreatitis and in front of the lack of specific markers of the disease, recrudescence of the pancreas injury upon re-exposure to the suspicious drug is considered the more reliable evidence of drug-induced pancreatitis. For causality assessment, a positive re-challenge test carries the strongest value.

In fact, the majority of drug-induced pancreatitis classifications consider the positive re-challenge as determinant criteria in the causality assessment. A positive re-challenge is a recrudescence of features of pancreatitis upon the intentional or inadvertent administration of the suspicious drug. Theoretically, re-challenge may confirm the putative involvement of a drug and it is considered the most powerful single piece of evidence pointing to drug-induced pancreatitis. Although re-challenge is dangerous, it should be carried out if the diagnosis of drug-induced pancreatitis was highly doubtful. It should also be carried out if there are no other drugs available to treat a serious disease while the patient has improved remarkably from the incriminated drug. Re-challenge reinforces the presumptive diagnosis of drug-induced pancreatitis. However, drug re-challenge is not performed in the majority of cases. It is thought that in drug-induced pancreatitis, patients should never be re-challenged with any drug that has caused at least one episode of pancreatitis [48]. There are a general belief that re-challenge in adverse drug reaction is typically met with a more severe reaction regardless of whether the initial reaction was severe or mild. The research does not support this view. It was found that death, the delay of hospitalisation and the delay of

regression was not increased when the drug was re-challenged. Indeed, only one case of death was noticed with an overall mortality rate of 0.006%. Drug-induced pancreatitis has a good prognosis and there are rare cases of fatalities reported in the literature.

As drug-induced pancreatitis has no distinguishing clinical features, the clinical diagnosis is based on the patient's characteristic abdominal pain and nausea associated with elevated pancreatic enzyme serum levels. Ranson's criteria have been used to reflect the severity of an episode of drug-induced pancreatitis and to predict mortality. In fact, the presence of three or more of criteria is correlated to a more severe pancreatitis with a higher risk of mortality [49]. If drug-induced pancreatitis is suspected, careful review of current medications and their duration of use are crucial for making the diagnosis. All drugs reported in our review may be classified among class IA of classification system of Badalov et al. For patient's benefit, it is important to suspect precociously drug etiology especially when there is a high evidence of association between the drug and pancreatitis in the literature. A rapid withdrawal of the suspected drug and an appropriate management of pancreatitis are important factors.

Moreover, patients taking drugs known to induce pancreatitis should be informed and instructed of the risk of occurrence of this adverse effect. Further publications and studies are needed to enlarge the list of drugs causing acute pancreatitis.

References

1. Banks PA, Freeman ML; Practice Parameters Committee of the American College of Gastroenterology (2006) Practice guidelines in acute pancreatitis. Am J Gastroenterol 101: 2379-2400.
2. Pandol SJ, Saluja AK, Imrie CW, Banks PA (2007) Acute pancreatitis: bench to the bedside. Gastroenterology 132: 1127-1151.
3. Nitsche CJ, Jamieson N, Lerch MM, Mayerle JV (2010) Drug induced pancreatitis. Best Prac Res Clin Gastroenterol 24: 143-155.
4. Vinklerová I, Procházka M, Procházka V, Urbánek K (2010) Incidence, severity, and etiology of drug-induced acute pancreatitis. Dig Dis Sci 55: 2977-2981.
5. Lancashire RJ, Cheng K, Langman MJ (2003) Discrepancies between population-based data and adverse reaction reports in assessing drugs as causes of acute pancreatitis. Aliment Pharmacol Ther 17: 887-893.
6. Balani AR, Grendell JH (2008) Drug-induced pancreatitis: incidence, management and prevention. Drug Saf 31: 823-837.
7. Hastier P, Buckley MJ, Peten EP, Demuth N, Dumas R, et al. (2000) A new source of drug-induced acute pancreatitis: codeine. Am J Gastroenterol 95: 3295-3298.
8. Gross JB, Comfort MW, Mathieson DR, Power MH (1951) Elevated values for serum amylase and lipase following the administration of opiates: a preliminary report. Proc Staff Meet Mayo Clin 26: 81-87.
9. Memon AN (1982) Pancreatitis and sulindac. Ann Intern Med 97: 139.
10. Zygmunt DJ, Williams HJ, Bienz SR (1986) Acute pancreatitis associated with long-term sulindac therapy. West J Med 144: 461-462.
11. Dreiling DA, Janowitz HD, Rolbin H (1958) Effect of ACTH and adrenocortical steroids on external pancreatic secretion in man. N Engl J Med 258: 603-605.
12. Anderson JR, Johnstopn GW, Kennedy TL (1985) Drug-associated recurrent pancreatitis. Dig Surg 2: 24-26.
13. Besseau M, Delchier J C, Blazquez M, Soule J C (1991) Pancreatite aigue due a la mesalazine (Pentasa*). Gastroenterol Clin Biol 15: 174-175.
14. Stephenson I, Wiselka MJ, Qualie MJ (2001) Acute pancreatitis induced by isoniazid in the treatment of tuberculosis. Am J Gastroenterol 96: 2271-2272.
15. Chow KM, Szeto CC, Leung CB, Li PK (2004) Recurrent acute pancreatitis after isoniazid. Neth J Med 62: 172-174.
16. Chan KL, Chan HS, Lui SF, Lai KN (1994) Recurrent acute pancreatitis induced by isoniazid. Tuber Lung Dis 75: 383-385.
17. Feola DJ, Thornton AC (2002) Metronidazole-induced pancreatitis in a patient with recurrent vaginal trichomoniasis. Pharmacotherapy 22: 1508-1510.
18. Sura ME, Heinrich KA, Suseno M (2000) Metronidazole-associated pancreatitis. Ann Pharmacother 34: 1152-1155.
19. Gasser RA Jr, Magill AJ, Oster CN, Franke ED, Grögl M, et al. (1994) Pancreatitis induced by pentavalent antimonial agents during treatment of leishmaniasis. Clin Infect Dis 18: 83-90.
20. Van der Heide H, Ten Haaft MA, Stricker BH (1981) Pancreatitis caused by methyldopa. Br Med J (Clin Res Ed) 282: 1930-1931.
21. Juang P, Page RL, Zolty R (2006) Probable loop diuretic-induced pancreatitis in a sulfonamide-allergic patient. Ann Pharmacother 40: 128-134.
22. Maringhini A, Termini A, Patti R, Ciambra M, Biffarella P, et al. (1997) Enalapril-associated acute pancreatitis: recurrence after re-challenge. Am J Gastroenterol 92: 166-167.
23. Carnovale A, Esposito P, Bassano P, Russo L, Uomo G (2003) Enalapril-induced acute recurrent pancreatitis. Dig Liver Dis 35: 55-57.
24. Kanbay M, Selcuk H, Yilmaz U, Boyacioglu S (2006) Recurrent acute pancreatitis probably secondary to lisinopril. South Med J 99: 1388-1389.
25. Csajka C, Buclin T, Brunner HR, Biollaz J (1997) Pharmacokinetic-pharmacodynamic profile of angiotensin II receptor antagonists. Clin Pharmacokinet 32: 1-29.
26. Singh S, Nautiyal A, Dolan JG (2004) Recurrent acute pancreatitis-induced by atorvastatin and rosuvastatin: is statin-induced pancreatitis a class effect? JOP 5: 502-504.
27. Paloyan D, Levin B, Simonowitz D (1977) Azathioprine-associated acute pancreatitis. Am J Dig Dis 22: 839-840.
28. Tragnone A, Bazzocchi G, Aversa G, Pecorelli MG, Elmi G, et al. (1996) Acute pancreatitis after azathioprine treatment for ulcerative colitis. Ital J Gastroenterol 28: 102-104.
29. Haber CJ, Meltzer SJ, Present DH, Korelitz BI (1986) Nature and course of pancreatitis caused by 6-mercaptopurine in the treatment of inflammatory bowel disease. Gastroenterology 91: 982-986.
30. McGrail LH, Sehn LH, Weiss RB, Robson MR, Antin JH, et al. (1999) Pancreatitis during therapy of acute myeloid leukemia: cytarabine related? Ann Oncol 10: 1373-1376.
31. Houde LL, Sehn LH, RobsonMR, Antin JH, Strickland WR, et al. (1996) Pancreatitis during therapy of acute myeloid leukaemia: cytarabine related? Blood 88: 217.
32. Muluneh B, Buie LW, Collichio F (2013) Vemurafenib-associated pancreatitis: case report. Pharmacotherapy 33: e43-44.
33. Sakhri J, Ben Salem C, Harbi H, Fathallah N, Ltaief R (2010) Severe acute pancreatitis due to tamoxifen-induced hypertriglyceridemia with positive re-challenge. JOP 11: 382-4.
34. Parker PH, Helinek GL, Ghishan FK, Greene HL (1981) Recurrent pancreatitis induced by valproic acid. A case report and review of the literature. Gastroenterology 80: 826-828.
35. Jadresic D (1994) Acute pancreatitis associated with dual vigabatrin and lamotrigine therapy. Seizure 3: 319.
36. Laczek JT, Shrestha M, Kortan ND, Lake JM (2010) Carbamazepine-induced pancreatitis with positive re-challenge. J Clin Gastroenterol 44: 153-154.
37. Chengappa KN, Pelucio M, Baker RW, Cole D (1995) Recurrent pancreatitis on clozapine re-challenge. J Psychopharmacol 9: 381-382.
38. Poldermans D, van Blankenstein M (1988) Pancreatitis induced by disodium azodisalicylate. Am J Gastroenterol 83: 578-580.
39. Wilkinson ML, O'Driscoll R, Kiernan TJ (1981) Cimetidine and pancreatitis. Lancet 1: 610-611.
40. Hainaut P, Schapira M, Mugabo P, Cerulus G, Coche E (1987) [Acute pancreatitis induced by cimetidine]. Rev Med Interne 8: 516-518.
41. Banerjee AK, Patel KJ, Grainger SL (1989) Drug-induced acute pancreatitis. A critical review. Med Toxicol Adverse Drug Exp 4: 186-198.

42. Thomson SR, Hendry WS, McFarlane GA, Davidson AI (1987) Epidemiology and outcome of acute pancreatitis. Br J Surg 74: 398-401.
43. Sekimoto M, Takada T, Kawarada Y, Hirata K, Mayumi T, et al. (2006) JPN guidelines for the management of acute pancreatitis: epidemiology, etiology, natural history, and outcome predictors in acute pancreatitis. J Hepatobiliary Pancreat Surg 13: 10-24.
44. McBride CE, Yavorski RT, Moses FM (2001) Acute pancreatitis drug-induced pancreatitis in Denmark from 1968 to 1999. J Clin Pharmacol 57: 517-521.
45. Mallory A, Kern F Jr (1980) Drug-induced pancreatitis: a critical review. Gastroenterology 78: 813-820.
46. Trivedi CD, Pitchumoni CS (2005) Drug-induced pancreatitis: an update. J Clin Gastroenterol 39: 709-716.
47. Badalov N, Baradarian R, Iswara K, Li J, Steinberg W, et al. (2007) Drug-induced acute pancreatitis: an evidence-based review. Clin Gastroenterol Hepatol 5: 648-661.
48. Tisdale JE, Miller DA (2005) Drug-Induced Diseases. Prevention, Detection and Management. Bethesda, Maryland: American Society of Health-System Pharmacists Press.
49. Ranson JH, Rifkind KM, Roses DF, Fink SD, Eng K, et al. (1974) Prognostic signs and the role of operative management in acute pancreatitis. Surg Gynecol Obstet 139: 69-81.

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