World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.3748/wjg.v20.i44.16529

World J Gastroenterol 2014 November 28; 20(44): 16529-16534
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (18): Pancreatitis

Drug induced acute pancreatitis: Does it exist?

Scott Tenner

Scott Tenner, Division of Gastroenterology, Department of Medicine, State University of New York, Brooklyn, NY 11235, United States
Scott Tenner, Downstate Medical Center, State University of New York, Brooklyn, NY 11235, United States
Author contributions: Tenner S wrote the manuscript based on prior work with Nison Badalov and William Steinberg.
Correspondence to: Scott Tenner, MD, MPH, Division of Gastroenterology, Department of Medicine, State University of New York, 2211 Emmons Ave, Brooklyn, NY 11235, United States. drtenner@brooklyngi.com
Telephone: +1-51-63160830 Fax: +1-718-3682249
Received: March 10, 2014 Revised: May 8, 2014
Accepted: July 15, 2014
Published online: November 28, 2014

Abstract

As the incidence of acute pancreatitis continues to rise, establishing the etiology in order to prevent recurrence is important. Although the etiology of acute pancreatitis is not difficult in the majority of patients, almost a quarter of patients are initially labeled as having idiopathic acute pancreatitis. When confronted with a patient with acute pancreatitis and no clear etiology defined as an absence alcoholism, gallstones (ultrasound and/or MRI), a normal triglyceride level, and absence of tumor, it often appears reasonable to consider a drug as the cause of acute pancreatitis. Over 100 drugs have been implicated by case reports as causing acute pancreatitis. While some of these case reports are well written, many case reports represent poorly written experiences of the clinician simply implicating a drug without a careful evaluation. Over-reliance on case reports while ignoring randomized clinical trials and large pharmacoepidemiologic surveys has led to confusion about drug induced acute pancreatitis. This review will explain that drug induced acute pancreatitis does occur, but it is rare, and over diagnosis leads to misconceptions about the disease resulting in inappropriate patient care, increased litigation and a failure to address the true entity: idiopathic acute pancreatitis.

Key words: Drug induced acute pancreatitis; Idiopathic acute pancreatitis

Core tip: While the literature has reported over 130 drugs as causing acute pancreatitis, the evidence that these drugs have a true causal role is lacking in the vast majority of drugs. While idiopathic pancreatitis is common, accounting for almost a third of patients with acute pancreatitis, drug induced acute pancreatitis is probably an uncommon, perhaps a rare disease. Before a clinician blames a drug as causing acute pancreatitis, a thorough evaluation for more common causes should be made, even a consideration that the disease is merely idiopathic.

Tenner S. Drug induced acute pancreatitis: Does it exist? *World J Gastroenterol* 2014; 20(44): 16529-16534 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i44/16529.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i44.16529

PROBLEM OF IDIOPATHIC PANCREATITIS

Idiopathic Acute Pancreatitis accounts for 20-40 percent of patients with acute pancreatitis[1,2]. That is, normally, approximately a third of patients who present with acute pancreatitis defy the clinician's ability to determine what caused the disease. Idiopathic acute pancreatitis is defined as acute pancreatitis with no etiology established after initial laboratory (including lipid and calcium level) and imaging tests (trans-abdominal ultrasound, MRI and CT in the appropriate patient)[3]. These patients do not have gallstones, a significant history of alcohol use, hypertriglyceridemia and a tumor. Anatomic and physiologic anomalies of the pancreas occur in 10%-15% of the population, including pancreas divisum and sphincter of Oddi dysfunction[4]. However, it remains controversial if these disorders alone cause acute pancreatitis.

There may be a combination of factors, including anatomic and genetic, that predispose to the development of acute pancreatitis in susceptible individuals[5]. The influence of genetic defects, such as cationic trypsinogen mutation, SPINK, or CFTR mutations, in causing acute pancreatitis is being increasingly recognized. These defects, furthermore, may also increase the risk of acute pancreatitis in patients with anatomic anomalies, such as pancreas divisum[6]. The idea that acute pancreatitis may result from a combination of factors working together should not be a surprise when one considers that most patients with gallstones, hypertriglyceridemia, alcoholism and pancreas divisum will never develop acute pancreatitis.

Clinician's caring for a patient with acute pancreatitis yearn to find a diagnosis to prevent a recurrent attack. This is compounded by the patient's desire to understand what has happened to them to cause so much pain and suffering. In addition to endoscopic interventions, clinicians search the literature for possible causes. The profession demands it, the patient's deserve it, and the literature provides a plethora of possibilities.

DRUGS AS A CAUSE OF ACUTE PANCREATITIS

Most patients who are admitted to a hospital are already taking a medication. Nearly 240 million Americans take at least one prescription drug weekly, and pharmacies fill over ten million prescriptions each day[7]. Over 100 drugs have been reported to cause acute pancreatitis in the scientific literature. Most reviews claim that drug induced acute pancreatitis accounts for 3%-5% of all cases of acute pancreatitis[8]. The diagnosis of drug induced acute pancreatitis is difficult to establish since drug-induced pancreatitis rarely is accompanied by clinical or laboratory evidence of a drug reaction, such as rash, lymphadenopathy, and/or eosinophilia, few ancillary data are available to help with the diagnosis.

While a few medications have been reported to cause acute pancreatitis based on a large body of evidence, most of the drugs implicated are based on case reports that suffer from a combination of inadequate criteria for the diagnosis of acute pancreatitis, failure to rule out more common etiologies, and/or lack of a rechallenge with the medication[9]. A rechallenge is a case in which a patient who develops acute pancreatitis has the medication suspected as causing acute pancreatitis withheld. After the acute pancreatitis resolves, the medication is restarted (typically as the medication was not originally suspected of causing the acute pancreatitis). Within a period of time (typically shorter), after the medication is restarted, the patient has another attack of acute pancreatitis. A valid rechallenge case report should be considered when evaluating whether a particular drug causes acute pancreatitis; however, it is not proof of causation. For example, it is clear that many patients with idiopathic pancreatitis or microlithiasis have recurrent attacks of acute pancreatitis. Therefore, stopping and restarting a drug with recurrence of pancreatitis may be a coincidence and not cause and effect[10].

Table 1 Classification of drug induced pancreatitis

Class Ⅰa drugs
At least 1 case report with positive rechallenge, excluding all other causes, such as alcohol, hypertriglyceridemia, gallstones, and other drugs
Class Ⅰb drugs
At least 1 case report with positive rechallenge; however, other causes, such as alcohol, hypertriglyceridemia, gallstones, and other drugs were not ruled out
Class Ⅱ drugs
At least 4 cases in the literature
Consistent latency (75% of cases)
Class Ⅲ drugs
At least 2 cases in the literature
No consistent latency among cases
No rechallenge
Class Ⅳ drugs
Drugs not fitting into the earlier-described classes, single case report published in medical literature, without rechallenge

Badalov *et al*[9] published an extensive review of published case reports in the peer reviewed literature. Using criteria based on the presence of a rechallenge, latency, and the number of case reports (Table 1), a classification system "based on the evidence" was provided. Table 2 shows the medications from the published case reports with the "most evidence" of causing acute pancreatitis. At the time the authors published the paper, none of them were aware that the United States Food and Drug Administration ("FDA") and trial lawyers would use the classification as a partial basis for assigning blame to drugs as causing acute pancreatitis[11].

FDA ADVERSE EVENT REPORTING SYSTEM

Through the Federal Food, Drug, and Cosmetic Act ("FDCA"), the FDA is empowered to verify the safety of drugs on the market[12]. Although the FDA employs a rigorous review process to ascertain the safety and efficacy of drugs prior to approval, reports have consistently warned that pre-market research often fails to provide an accurate risk-benefit profile for marketed products[13]. Many drugs come to the market and subsequently are found to have significant side effects that pre-market trials did not reveal[14]. To rectify this problem, the FDA had developed the Adverse Event Reporting System (FAERS)[15].

Based on "MedWatch Reports"[16] filed by interested clinicians, the FDA's reporting programs generate a "deluge of information. Annually the agency has received more than 200000 adverse event reports regarding drugs or biologic products. It is not surprising that the agency describes its analysis of this flood of data as triage[17]. The reports are typically incomplete and often, biased. Although more work on the database and system is need-

Table 2 Summary of drug-induced acute pancreatitis

Class 1a
Azodisalicylate; Bezafibrate; Cannabis; Carbimazole; Codeine; Cytosine; Arabinoside; Dapsone; Enalapril; Furosemide; Isoniazid; Mesalamine; Metronidazole; Pentamidine; Pravastatin; Procainamide; Pyritonol; Simvastatin; Stibogluconate; Sulfamethoxazole; Sulindac; Tetracycline; Valproic acid
Class 1b
All trans-retinoic acid; Amiodarone; Azathioprine; Clomiphene; Dexamethasone; Ifosfamide; Lamivudine; Losartan; Lynesterol/methoxyethinylestradiol; 6-MP; Meglumine; Methimazole; Nelfinavir; Norethindronate/mestranol; Omeprazole; Premarin; Sulfamethazole; Trimethoprimsulfamethazole
Class 2
Acetaminophen; Chlorthiazide; Clozapine; DDI; Erythromycin; Estrogen; L-asparaginase; Pegasparagase; Propofol; Tamoxifen

Table 3 Methods of causal inference

Randomized controlled trials
Controlled trials without randomization
Cohort studies
Case-control studies
Ecologic studies
Case reports and case series

ed to distinguish reliable findings from "variability and noise", more resources are necessary and lacking[18].

Despite incomplete data, the FDA often relying on the FAERS will issue warnings and require manufacturers to add "black box warnings" intended to alert physicians to the importance of the adverse information learned. However, with premature data causing unsubstantiated fears, the FDA has added, modified, and often removed black box warnings from the drugs in question. The addition of these black box warnings has fueled litigation[17].

AN ILLUSTRATION OF THE FALLACY OF DRUG INDUCED ACUTE PANCREATITIS: EXENATIDE (BYETTA®)

The claim that Byetta (exenatide and other GLP-1 agonists) cause acute pancreatitis exemplifies the problem with drug induced acute pancreatitis. Based on case reports, especially following the criteria set forth in the paper by Badalov *et al*[9] MedWatch reports, the FAERS, resultant black box warnings, and poor science, confusion and litigation resulted as "experts" claimed the exenatide caused acute pancreatitis.

Exenatide, an incretin mimetic, was approved as Byetta by the FDA on April 25, 2005. The drug is an adjunctive therapy to improve glycemic control in patients with type Ⅱ diabetes mellitus. The first published case reports of acute pancreatitis thought to be caused by exenatide appeared shortly after the drug was approved[19]. Additionally, by December 31, 2006, according to the FAERS database, there were 48 documented domestic cases of acute pancreatitis in patients taking exenatide[20]. Noting slightly more cases of acute pancreatitis than expected in the general population, the FDA asked the manufacturer, Lilly and Amylin Pharmaceuticals to strengthen the labeling of acute pancreatitis from the Adverse Reactions section to the Warnings and Precautions section of the exenatide label.

While the FDA was comparing the incidence of acute pancreatitis in the exenatide using diabetic population to the general population, it is not clear that they were aware that diabetic persons were at a significant increased risk of developing acute pancreatitis. For a variety of reasons, including increased incidence of gallstones and hypertriglyceridemia, the incidence of acute pancreatitis in patients with diabetes is higher than the general population[21]. Therefore, regardless of the drug used, if one simply compared the normal population incidence of acute pancreatitis with the diabetic population, one would find a higher incidence in the diabetics. This is a classic confounding variable rather than a drug effect.

The limitations to Medwatch reports cannot be over stated. In many reports the diagnosis of acute pancreatitis is not clearly established. Thus, there is no reason to proceed with considering the case as the adverse event suspected may be another pathology in the abdomen. Misdiagnosis of acute pancreatitis often occurs by clinicians who search for a reason for abdominal pain and merely rely on mild elevations in the amylase and lipase to reach a diagnosis. This is not appropriate, however, as any inflammatory process in the abdomen can cause a mild 2-3 fold elevation of the amylase and/or lipase[22]. Additionally, many patients with diabetes have been shown to have mild elevations, greater than three times the upper limit of normal, of amylase and/or lipase[23]. Thus, many patients with abdominal pain from other sources are falsely labeled as having acute pancreatitis. In the patients who truly have acute pancreatitis, many of the reports fail to identify if the patient has more likely causes of acute pancreatitis, such as gallstones, a history of alcoholism, hypertriglyceridemia[9].

Despite the limitations to the reports and the FDA's position that the FAERS is for hypothesis testing, Elashoff and colleagues[24] examined the FAERS database from 2004-2009 for reported adverse events for exenatide and other medications (which served as controls) in order to determine if patients were at an increased risk of developing pancreatitis. The authors found that the risk of developing pancreatitis from exenatide was higher compared to from other therapies, but importantly the issue of reporting bias could not be entirely ruled out.

Although the FDA agreed to study the issue further, in the meantime it required Amylin and Lilly to alert health care professionals in several ways - including *via* industry letters, published articles, and reports of these cases in the FDA Newsletter[25]. The result was a surge of FAERS cases involving exenatide as a cause of acute pancreatitis immediately followed the FDA notification requirement. Despite the obvious reporting bias induced by the FDA notification, and the failure of the FDA to

Table 4 Bradford Hill criteria for causation

Temporality - causal factor must precede effect
Strength of association - magnitude of the relative risk estimates observed
Consistency of the association - extent to which scientific results are similar across the entire body of evidence
Biologic gradient (dose-response) - the extent to which the relative risk estimates increase in magnitude as the dose of the exposure increases
Biologic plausibility - the extent to which a mechanism of action has been proposed, studied and demonstrated in toxicological or other laboratory based studies
Specificity - refers to the precision with which the exposure and the outcome can be defined
Coherence - the extent to which the evidence and hypotheses for the results fit together into a reasonable and well-tested explanation
Experimentation - the extent to which a randomized clinical trials or cohort studies are available
Analogy - the extent that the purported exposure-disease relationship under consideration is similar to other relationships

note that the population using exenatide-diabetics-inherently had a predisposition for acute pancreatitis, the FDA subsequently added a black box warning to the drug's labeling. The black box warning stated that exenatide could cause acute pancreatitis[26].

Immediately thereafter, thousands of persons who had developed acute pancreatitis while taking exenatide initiated multiparty litigation suits. They relied on the FAERS database and resultant black box warning. The plaintiffs, diabetics already at risk for developing acute pancreatitis, claimed that the defendants Lilly and Amylin Corporations knew or should have known of the hazards associated with exenatide in causing acute pancreatitis. In addition, by claiming that the defendants actively concealed information that demonstrated the dangers of their drug and thus misled the public and prescribing physicians, the plaintiffs were granted broad access to company documents during discovery[27]. The costs of litigation skyrocketed.

Despite the persistent litigation occurring, over the last year, the FDA independently evaluated the post marketing reports that exenatide was a cause of acute pancreatitis. After an exhaustive evaluation of more than 250 toxicology studies conducted in nearly 18000 live animals, no evidence of pancreatic disease was found[28]. In addition to the laboratory data, the FDA reviewed data from 200 trials (including other GLP-1 agonists), involving 41000 patients, and found no evidence of an increased risk of pancreatic disease. The FDA has promulgated that "assertions concerning a causal relationship between incretin drugs are inconsistent with the scientific literature. Simply, despite case reports and MedWatch reports, exenatide does not cause acute pancreatitis.

RETHINKING CAUSATION

It is important to use the general scientific method in making causal claims about human health and disease[29]. The basic structure of the scientific method to determine causation includes: hypothesis generation, observable predictions, alternatives, and tests to distinguish between the causal hypothesis of interest and its alternatives. There could be competing explanations for any scientific observation. Epidemiologic methods involving human subjects are the most important means for identifying and testing hypotheses involving human disease causation. Randomized controlled trials are the strongest means and case reports are the lowest means[30] (Table 3). The use of the scientific method avoids falsely claiming causation when the truth is mere chance. Chance is not the only alternative to causation, but must be considered strongly.

The criteria of causation is best understood by the Hill criteria[31]. An "association" in this methodology is not satisfied by the existence of individuals with exposure to the putative cause and the disease of concern. Rather, an "association" from a causal perspective would only exist if a statistically-significant relationship (*e.g.*, between the rate of acute pancreatitis in patients with diabetes mellitus patients exposed to exenatide and the rate of acute pancreatitis in similar diabetic patients not exposed to exenatide) was demonstrated in analytical epidemiological studies. Those studies should be well-designed, with careful attention to diagnostic criteria, adherence to medication, control of confounders, and avoidance (or correction) of important sources of bias. Case reports would never meet this level of evidentiary need to determine causation.

Hill's 9 criteria evaluate the totality of evidence for causation evaluating for temporality, strength of association, consistency of the association, the presence of a biologic gradient (dose-response), biologic plausibility, specificity, coherence, experimentation and analogy (Table 4). In applying the 9 criteria to a drug like exenatide, the evidence shows no causal association. There is no temporality as the latency for exenatide causing acute pancreatitis varies among the reports. As to strength, large epidemiologic studies show no causal relationship of exenatide to acute pancreatitis. There is no consistency of the data. Results from clinical trials, epidemiology, case reports, and animal studies are inconsistent. Based on animal and clinical trial data there is no biologic plausibility (no established mechanism) or gradient. There is no evidence that increase in dosage and/or increase in time results in a linear increase in episodes of acute pancreatitis. Experimental data, in both animals and humans, do not establish that exenatide is a cause of acute pancreatitis. There is also a coherence that exenatide does not cause acute pancreatitis from laboratory, clinical, case report, and epidemiologic studies. Analogy to other anti-diabetic drugs does not strengthen the causal hypothesis as other GLP-1 agonists have also been shown not to cause acute pancreatitis from clinical trials.

Making reliable causal claims in pharmacovigilance is difficult if not impossible when case reports and case series are used as the primary evidentiary source[15]. While the case reports and series generate hypothesis testing, as was shown for exenatide, it is irresponsible to assign causation based on causal hypothesis[32].

DRUG INDUCED ACUTE PANCREATITIS AND IDIOPATHIC ACUTE PANCREATITIS

Although the vast majority of drugs that have been purported to cause acute pancreatitis probably do not, drug induced acute pancreatitis does exist! When evaluating drugs for causation on the basis of the evidence as described by Hill, two drugs meet the evidence of causation: Azathioprine (and its metabolite 6-mercaptopurine) and 2'3'-dideozyinosine (DDI). The strong evidence comes not from case reports but a consideration of the totality of the evidence, including randomized prospective trials, cohort trials, case reports and a molecular basis[33,34]. For example, in the National Cooperative Crohn's Disease study, almost 6% of the 116 patients treated with 6-MP developed acute pancreatitis[35]. Similarly, Haber *et al*[36] treated 400 patients with inflammatory bowel disease with 6-MP and 3.25% developed acute pancreatitis. There are many more randomized trials that support the simplistic case reports.

More recently, Floyd *et al*[34] performed a large population based study including 1388 patients taking azathioprine and 13836 controls in a single county. The incidence rate for acute pancreatitis among all users of azathioprine was one per 659 treatment year. The crude odds ratio (OR) of having redeemed prescriptions for azathioprine within 90 d before admission for acute pancreatitis was 7.5 (95%CI: 2.6-21.6). After adjustment for gallstone disease, alcohol-related diseases, inflammatory bowel disease, and use of glucocorticoids, the OR increased to 8.4 (95%CI: 2.4-29.4). Although there was a significant risk of persons on azathioprine in developing acute pancreatitis, the population-attributable risk, which measures the proportion of all cases of pancreatitis that are attributable to the use of azathioprine in this study population, was 0.4%.

This finding of less than a half percent attributable risk of azathioprine as a cause of acute pancreatitis is extremely important when considering the claims that drug induced acute pancreatitis accounts for 3%-5% of all cases[37-39]. In the absence of data from controlled clinical trials and large pharmacoepidemiologic trials, there is little to no evidence that other drugs cause acute pancreatitis. Although similar data exists for DDI, the drug is not widely used at this time[40,41]. Therefore, drug induced acute pancreatitis probably accounts for less than 1% of cases, and maybe extremely rare in patients who are not taking obvious drugs.

Premarket approval and post-marketing surveillance has become sensitive to determining complications of drugs such as acute pancreatitis. Randomized controlled trials that evaluate for other complications, such as cardiac complications, would detect significant risks of drugs causing acute pancreatitis[42]. In addition, large pharmacoepidemiologic databasis and meta-analyses are often searched for signals to determine whether drugs cause acute pancreatitis[43].

Azathioprine (and 6-MP) and exenatide represent the two extremes of the data demonstrating a causal association for a drug and acute pancreatitis. While there are case reports in the literature and Medwatch reports on the FARS that both drugs cause acute pancreatitis, only for azathioprine (and 6-MP) have multiple randomized controlled trials and large pharmicoepidemiologic studies showing a statistically significant association. For exenatide (and the other GLP-1 agonists), the opposite is true. Multiple controlled trials, pharmacoepidemiologic databases fail to show any causal association with acute pancreatitis.

While clinicians continue to publish case reports blaming drugs as causing acute pancreatitis, it is important to consider the ideas discussed in this paper. Be critical, cynical and remember that idiopathic pancreatitis is common. Clinicians should perform a thorough workup as described to verify the absence of gallstones, alcoholism, hypertriglyceridemia, tumors. However, the struggle to identify a cause, especially in assigning blame to a drug should be done with extreme caution. When a patient asks "what caused my acute pancreatitis?" Clinicians must remember that almost a third of cases will not be clear and are labeled as idiopathic. As clinicians do not have trouble explaining to patients that "bad luck" is the cause of appendicitis, diverticulitis, cholecystitis, telling a patient that it appears simply "idiopathic" may be correct.

REFERENCES

1 **van Brummelen SE**, Venneman NG, van Erpecum KJ, Van-Berge-Henegouwen GP. Acute idiopathic pancreatitis: does it really exist or is it a myth? *Scand J Gastroenterol Suppl* 2003; (**239**): 117-122 [PMID: 14743894]

2 **Frossard JL**, Steer ML, Pastor CM. Acute pancreatitis. *Lancet* 2008; **371**: 143-152 [PMID: 18191686 DOI: 10.1016/S0140-6736(08)60107-5]

3 **Al-Haddad M**, Wallace MB. Diagnostic approach to patients with acute idiopathic and recurrent pancreatitis, what should be done? *World J Gastroenterol* 2008; **14**: 1007-1010 [PMID: 18286679 DOI: 10.3748/wjg.14.1007]

4 **DiMagno MJ**, Dimagno EP. Pancreas divisum does not cause pancreatitis, but associates with CFTR mutations. *Am J Gastroenterol* 2012; **107**: 318-320 [PMID: 22306946 DOI: 10.1038/ajg.2011.430]

5 **Steinberg WM**, Chari ST, Forsmark CE, Sherman S, Reber HA, Bradley EL, DiMagno E. Controversies in clinical pancreatology: management of acute idiopathic recurrent pancreatitis. *Pancreas* 2003; **27**: 103-117 [PMID: 12883257 DOI: 10.1097/00006676-200308000-00001]

6 **Tenner S**, Baillie J, DeWitt J, Vege SS. American College of Gastroenterology guideline: management of acute pancreatitis. *Am J Gastroenterol* 2013; **108**: 1400-115; 1416 [PMID: 23896955 DOI: 10.1038/ajg.2013.218]

7 **Jain V**, Pitchumoni CS. Gastrointestinal side effects of prescription medications in the older adult. *J Clin Gastroenterol* 2009; **43**: 103-110 [PMID: 19142171 DOI: 10.1097/MCG.0b013e31818f9227]

8 **Tenner S**. Drug-induced acute pancreatitis: underdiagnosis and overdiagnosis. *Dig Dis Sci* 2010; **55**: 2706-2708 [PMID: 20686844 DOI: 10.1007/s10620-010-1367-2]
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**: 648-61; quiz 644 [PMID: 17395548 DOI: 10.1016/j.cgh.2006.11.023]
10 **Girard M**. Conclusiveness of rechallenge in the interpretation of adverse drug reactions. *Br J Clin Pharmacol* 1987; **23**: 73-79 [PMID: 3814464 DOI: 10.1111/j.1365-2125.1987.tb03011.x]
11 **Tenner S**. Isotretinoin and inflammatory bowel disease: trial lawyer misuse of science and FDA warnings. *Am J Gastroenterol* 2014; **109**: 570-571 [PMID: 24698863]
12 Federal Food, Drug, and Cosmetic Act, 21 U.S.C.A. 301-399f (West 2013). Available from: URL: http://web2.westlaw.com/signon/default.wl?vr=2.0&fn=_top&rs=WLW14.10&bhcp=1
13 **Irey NS**. Diagnostic problems in drug-induced diseases. *Ann Clin Lab Sci* 1976; **6**: 272-277 [PMID: 942185]
14 **Stricker BH**, Psaty BM. Detection, verification, and quantification of adverse drug reactions. *BMJ* 2004; **329**: 44-47 [PMID: 15231627 DOI: 10.1136/bmj.329.7456.44]
15 **Venning GR**. Identification of adverse reactions to new drugs. III: Alerting processes and early warning systems. *Br Med J (Clin Res Ed)* 1983; **286**: 458-460 [PMID: 6401562 DOI: 10.1136/bmj.286.6363.458]
16 MedWatch: The FDA Safety Information and Adverse Event Reporting Program. Available from: URL: http://www.fda.gov/Safety/MedWatch/default.htm
17 **Struve CT**. The FDA and the tort system: postmarketing surveillance, compensation, and the role of litigation. *Yale J Health Policy Law Ethics* 2005; **5**: 587-669 [PMID: 16052895]
18 Food and Drug Administration Amendments Act of 2007, PL 110–85, September 27, 2007, 121 Stat. 823. Available from: URL: http://web2.westlaw.com/signon/default.wl?vr=2.0&fn=_top&rs=WLW14.10&bhcp=1
19 **Denker P**, DiMarco P. Exenatide as a cause of acute pancreatitis. *Diabetes Care* 2008; **29**: 471-472 [DOI: 10.2337/diacare.29.02.06.dc05-2043]
20 **Drug Evaluation and Research**. Division Director's Memo, Pancreatitis (June 18, 2009). Available from: URL: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021919s000SumR.pdf at 13
21 **Girman CJ**, Kou TD, Cai B, Alexander CM, O'Neill EA, Williams-Herman DE, Katz L. Patients with type 2 diabetes mellitus have higher risk for acute pancreatitis compared with those without diabetes. *Diabetes Obes Metab* 2010; **12**: 766-771 [PMID: 20649628 DOI: 10.1111/j.1463-1326.2010.01231.x]
22 **Smotkin J**, Tenner S. Laboratory diagnostic tests in acute pancreatitis. *J Clin Gastroenterol* 2002; **34**: 459-462 [PMID: 11907364 DOI: 10.1097/00004836-200204000-00018]
23 **Steinberg WM**. Comment: acute pancreatitis associated with liraglutide. *Ann Pharmacother* 2011; **45**: 1169 [PMID: 21811002 DOI: 10.1345/aph.1P714a]
24 **Elashoff M**, Matveyenko AV, Gier B, Elashoff R, Butler PC. Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies. *Gastroenterology* 2011; **141**: 150-156 [PMID: 21334333 DOI: 10.1053/j.gastro.2011.02.018]
25 Amylin, Lilly and Alkermes Submit Reply to FDA Complete Response Letter for BYDUREON™ (April 22, 2010). Available from: URL: http://newsroom.lilly.com/releasedetail.cfm?releaseid=462639
26 FDA, Amylin Pharmaceuticals, Inc., Bydureon, Highlights of Prescribing Information (Jan 2012). Available from: URL: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022200s000lbl.pdf at 5, 12, 27
27 Complaint for Damages, Johnson v. Amylin Pharmaceuticals, 13CV1346 DMS NLS (S.D. Cal. filed June 10, 2013). Available from: URL: http://web2.westlaw.com/signon/default.wl?vr=2.0&fn=_top&rs=WLW14.10&bhcp=1
28 **Egan AG**, Blind E, Dunder K, de Graeff PA, Hummer BT, Bourcier T, Rosebraugh C. Pancreatic safety of incretin-based drugs--FDA and EMA assessment. *N Engl J Med* 2014; **370**: 794-797 [PMID: 24571751 DOI: 10.1056/NEJMp1314078]
29 **Weed DL**, Gorelic LS. The practice of causal inference in cancer epidemiology. *Cancer Epidemiol Biomarkers Prev* 1996; **5**: 303-311 [PMID: 8722223]
30 **Weed DL**. Causal and Preventive Inference.In: Greenwald P, Kramer BS, Weed DL. Cancer Prevention and Control. Chapter 17. New York: Marcel Dekker, 1995: 285-302
31 **Hill AB**. The environment and disease: association or causation? *Proc R Soc Med* 1965; **58**: 295-300 [PMID: 14283879]
32 **Goldman SA**. Limitations and strengths of spontaneous reports data. *Clin Ther* 1998; **20** Suppl C: C40-C44 [PMID: 9915089 DOI: 10.1016/S0149-2918(98)80007-6]
33 **Van Dieren JM**, Hansen BE, Kuipers EJ, Nieuwenhuis EE, Van der Woude CJ. Meta-analysis: Inosine triphosphate pyrophosphatase polymorphisms and thiopurine toxicity in the treatment of inflammatory bowel disease. *Aliment Pharmacol Ther* 2007; **26**: 643-652 [PMID: 17697198 DOI: 10.1111/j.1365-2036.2007.03412.x]
34 **Floyd A**, Pedersen L, Nielsen GL, Thorlacius-Ussing O, Sorensen HT. Risk of acute pancreatitis in users of azathioprine: a population-based case-control study. *Am J Gastroenterol* 2003; **98**: 1305-1308 [PMID: 12818274 DOI: 10.1111/j.1572-0241.2003.07459.x]
35 **Present DH**, Korelitz BI, Wisch N, Glass JL, Sachar DB, Pasternack BS. Treatment of Crohn's disease with 6-mercaptopurine. A long-term, randomized, double-blind study. *N Engl J Med* 1980; **302**: 981-987 [PMID: 6102739]
36 **Haber CJ**, Meltzer SJ, Present DH, Korelitz BI. Nature and course of pancreatitis caused by 6-mercaptopurine in the treatment of inflammatory bowel disease. *Gastroenterology* 1986; **91**: 982-986 [PMID: 2427386]
37 **Grendell JH**. Editorial: drug-induced acute pancreatitis: uncommon or commonplace? *Am J Gastroenterol* 2011; **106**: 2189-2191 [PMID: 22138943 DOI: 10.1038/ajg.2011.307]
38 **Mallory A**, Kern F. Drug-induced pancreatitis: a critical review. *Gastroenterology* 1980; **78**: 813-820 [PMID: 6986321]
39 **Lowenfels AB**, Maisonneuve P, Sullivan T. The changing character of acute pancreatitis: epidemiology, etiology, and prognosis. *Curr Gastroenterol Rep* 2009; **11**: 97-103 [PMID: 19281696 DOI: 10.1007/s11894-009-0016-4]
40 **Lambert JS**, Seidlin M, Reichman RC, Plank CS, Laverty M, Morse GD, Knupp C, McLaren C, Pettinelli C, Valentine FT. 2′,3′-dideoxyinosine (ddI) in patients with the acquired immunodeficiency syndrome or AIDS-related complex. A phase I trial. *N Engl J Med* 1990; **322**: 1333-1340 [PMID: 2139173 DOI: 10.1056/NEJM199005103221901]
41 **Maxson CJ**, Greenfield SM, Turner JL. Acute pancreatitis as a common complication of 2′,3′-dideoxyinosine therapy in the acquired immunodeficiency syndrome. *Am J Gastroenterol* 1992; **87**: 708-713 [PMID: 1590305]
42 **Scirica BM**, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, Ohman P, Frederich R, Wiviott SD, Hoffman EB, Cavender MA, Udell JA, Desai NR, Mosenzon O, McGuire DK, Ray KK, Leiter LA, Raz I. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med* 2013; **369**: 1317-1326 [PMID: 23992601 DOI: 10.1056/NEJMoa1307684]
43 **Alves C**, Batel-Marques F, Macedo AF. A meta-analysis of serious adverse events reported with exenatide and liraglutide: acute pancreatitis and cancer. *Diabetes Res Clin Pract* 2012; **98**: 271-284 [PMID: 23010561 DOI: 10.1016/j.diabres.2012.09.008]

P- Reviewer: Matsuo Y, Olah A, Streba LAM **S- Editor**: Qi Y
L- Editor: A **E- Editor**: Zhang DN

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

ISSN 1007-9327