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Drug-induced acute pancreatitis

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1. Introduction

Acute pancreatitis (AP) is a heterogeneous disease ranging from a clinically mild form to a more severe forms associated with high morbidity and mortality (78). A correct diagnosis of AP should be made within 48 h of admission. Understanding of the etiology and severity assessment are essential, as they may affect the acute management of the disease (8).

The most common etiology for AP are gallstones and alcohol abuse. Other causes include iatrogenic injury (i.e. post-ERCP), metabolic and autoimmune disorders, inherited disorders, neoplasia (even intraductal papillary mucinous neoplasia- IPMN), anatomical abnormalities, infections, ischaemia, trauma and drugs (87). Additional investigations after recovery from the acute episode are recommended in patients with an episode of AP classified as idiopathic (68).

Drugs may be considered a potential cause of the disease in patients who take medications that have been associated with AP.

Drug-induced pancreatitis (DIP) is assumed to be a relative rare entity, and its incidence is reported between 0.1 and 2% of AP cases (62). However, the true incidence of DIP is still unknown since little evidence has been obtained from clinical trials, and most incidences have been documented as case reports (62) generally limited by the absence or inadequacy of diagnostic criteria for AP, failure to rule out common etiologies of AP, and lack of a re-challenge test.

The main problem in the identification of DIP is the absence of a clear and largely accepted definition of the disease. The diagnosis of DIP is difficult to establish since it is rarely accompanied by clinical or laboratory evidence of a drug reaction and the large proportion of patients admitted for AP are already taking a medication. Therefore, criteria to diagnose DIP should include the evidence for drug intake shortly preceding AP, an increased risk for AP in patients taking the drug, direct correlation between increased risk and dose, presence of a plausible biological mechanism, evidence in clinical trials using the specific drug and a re-challenge test. However, we lack a definition for each of these potential diagnostic criteria for DIP (i.e. elapsed time between drug intake and AP).

Five-hundred and twenty-five different drugs suspected to cause acute pancreatitis are reported in the database of World Health Organization (WHO) (61). The majority of the data are derived from case reports, case series or summaries of them. Furthermore, the causality for many of these drugs remains elusive and for only about thirty of these 525 dugs has a definite causality been established (61). Another methodological problem is the evaluation of other potential cause of AP. Some definitions exclude the presence of other etiologies of AP, primarly biliary lithiasis and alcohol abuse. However, the

presence of other causes of AP do not exclude DIP but certainly decrease the probability of DIP.
The re-challenge test under the same conditions as in the first episode of suspected DIP is probably the best diagnostic criterion, but its use in clinical practice is limited particularly in patients with a severe attack of pancreatitis. The consequence is a dramatic decrease in the number of drugs shown to induce pancreatitis using the re-challange test. However, this test cannot be considered as a definitive criterion for the diagnosis since stopping and restarting a drug with a recurrence of pancreatitis may be a coincidence and not a demonstration of a cause and effect. This is probably the reason why Tenner in a recent review raised the question about the real existence of DIP (82).

A consequence of all these problems for the definition of DIP is its classification. Many classifications have been proposed. In the more recent critical review (62, 84), a classification system of the published case reports based on the level of evidence was used. A larger number of case reports and/or a consistent latency among the reports for a particular drug were evaluated. Badalov et al. (7) created a new classification of DIP based on the features of case reports and the presence or absence of a re-challenge test. However, a classification in definite, probable and possible association between drugs and pancreatitis is the most preferred (43, 61) **(Table 1)**, based on the evaluation of the rechallenge/dechallenge test, temporal sequence, exclusion of other causes of pancreatitis. A useful tool to establish the association of a drug with pancreatitis could be the Naranjo Score (58) **(Table 2)**.

A list of drugs classified in definitive and probable is listed on **Table 3** (61).

2. Drugs More Commonly Associated with AP

Azathioprine and 6-Mercaptopurine

Since 1980, azathioprine (AZA) and its metabolite 6-mercaptopurine (6-MP) were reported to be able to induce pancreatitis (33). The incidence is reported between 1% and 6% of exposed individuals. A Danish study (24) demonstrate a 7 to 8 fold increase in the risk to develop AP comparing ever- with never-takers. Despite the large size of the sample of study, the uniformly organized health care system and the use of appropriate population controls, the limit of the study was the incomplete registration of confounders (risk factors i.e. alcohol or gallstones), included potential association between inflammatory bowel disease (IBD) and autoimmune pancreatitis (25). Indeed, previous case reports have suggested that IBD is associated with a liability to develop pancreatitis, especially for Crohn's disease, because of common pathogenic mechanisms, diminished entero-hepatic circulation of bile acids in patients with ileal involvement or who underwent surgical ileal resection) (25), mechanic factors in duodenal localizations of disease (papilla of Oddi's disfunctionand coexistence of therapy with other drugs involved in DIP like mesalamine, glucocorticoids or metronidazole (35).

The mechanism of how azathioprine causes pancreatitis is not well elucidated and the development of pancreatitis did not appear to be dose related (36). Therefore, it may be better classified as allergic or idiosyncratic. Although some authors have suggested the utility of thiopurine methyltransferase (TPMT) heterozygosity and enzyme activity as predictive tests for the development of azathioprine-related adverse events, the role in predicting acute pancreatitis has not been studied yet (34). Even if some authors have communicated that MP could safely be used after an AZA-induced episode of AP (1), most authors agree that a cross reaction after re- exposure of the related drug is probable.

Table 1: Classification of evidence according to Karch and Lasagna (43).

DEFINITIVE	Drug reaction that follows a reasonable temporal sequence from administration of the drug, that follows a known response pattern that is confirmed by stopping the drug (de-challenge), that is confirmed by reappearance of the symptoms upon repeated exposure to the drug (re-challenge).
PROBABLE	Drug reaction that follows a reasonable temporal sequence from administration of the drug, that follows a known response pattern, that is confirmed by de-challenge, that could not be explained by the known characteristics of the patient's clinical state.
POSSIBLE	Drug reaction that follows a reasonable temporal sequence from administration of the drug, that follows a known response pattern but that could have been produced by the patient's clinical state or other modes of therapy.

Table 2: Score of probability of association between drugs and adverse effect, modified from (58).

QUESTIONS	**Yes**	**No**	**Don't know**	**SCORE**
1. Are there previous conclusive reports on this reaction?	+ 1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+ 2	- 1	0	
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+ 1	0	0	
4. Did the adverse reaction reappear when the drug was readministered?	+ 2	- 1	0	
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	- 1	+ 2	0	
6. Did the reaction reappear when a placebo was given?	- 1	+1	0	
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+ 1	0	0	
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+ 1	0	0	
9. Did the patient have a similar reaction to the same or similar drug in any previous exposure?	+ 1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+ 1	0	0	
			Total score*	

***Total score is the sum of all subcategory scores**. The relationship is categorized as *definite* if the score is greater than 8, *probable* if the score is 5 to 8, *possible* if the score is 1 to 4, and *doubtful* if the score is 0.

Table 3: Drugs with definite or probable association to pancreatitis as reported in the summary of Nitsche (61) and other case reports until 2014.

CAUSALITY	MEDICATION	N°	RE-CHALLANGE
Definite	Acetaminophen	13	1
	Asparaginase	177	2
	Azathioprine	87	16
	Bortezomib	2	2
	Capecitabine	1	1
	Carbamazepine	15	1
	Cisplatin	11	1
	Cytarabine	26	4
	Didanosine	883	9
	Enalapril	12	2
	Erytrhromycin	11	1
	Oestrogenes	42	11
	Furosemide	22	3
	Hydrochlorothiazide	12	1
	Ifosphamid	2	1
	Interferon α2b	12	2
	Isoniazide	8	4
	Itroconazol	4	2
	Lamivudine	19	1
	Mercaptopurine	69	10
	Mesalamine/Olsalazine	60	12
	Metronidazole	15	3
	Octreotide	16	4
	Olanzepine	1	1
	Opiates	42	5
	Pentamidine	79	2
	Pentavalent anti-monials	80	14
	Phenformin	13	1
	Steroids	25	1
	Sulfasalazine	23	5
	Sulfmethaxazole/Tmp	24	1
	Sulindac	21	8
	Tamoxifen	1	1
	Tetracycline	36	2
	Valproic acid	82	11
	Vemurafenib	1	1
Probable	Atorvastatine	2	0
	Bezafibrate	1	1
	Carboplatin/docetaxel	1	0
	Ceftriaxon	1	0
	Cyclopenthiazide	11	0
	Liraglutide/DPP4-inhibitors	5	1
	Orlistat	9	0
	Rifampin	6	0
	Simvastatin	25	0
	Tyrosin kinase inhibitor	1	0

ACE Inhibitors

ACE inhibitors are one of the most commonly prescribed classes of medications, as they are used in hypertension, heart failure and proteinuria (32). The first reported case of ACE inhibitor-induced pancreatitis was seen with enalapril (15, 31, 54). Other case reports about pancreatitis induced by lisinopril (13, 28, 42, 53), captopril (38), ramipril (41) and perindopril (27) have been also published.

In one case-control study, the use of ACE inhibitor was associated with an increased risk of acute pancreatitis, with an odds ratio of 1.5. The risk increased with higher daily doses and was highest during the first 6 months of therapy (22).

Pancreatitis associated with ACE inhibitors is thought to reflect localized angioedema of the gland, linked probably to an increase of bradykinin secondary to its decreased degradation. Angiotensin II receptors regulate pancreatic secretion and microcirculation, and these effects may be contribute to the pathogenesis of ACE inhibitors induced pancreatitis (73). However, ACE inhibitors, in particular captopril, showed an important role in attenuating vascular permeability in experimental severe acute pancreatitis in rats, reducing expression of matrix metalloproteinase 9. No human studies are available yet to confirm this experimental evidence and to develop a target therapy. In summary, there are controversies on the role of ACE inhibitors in DIP, since they may induce mild pancreatitis in humans, but may reduce the severity of experimental AP in animals.

Antidiabetic Drugs

Metformin, a biguanide commonly used in type 2 diabetes, is considered to be a safe drug with minimal side effects and only few papers (case report) data suggest metformin as associated with DIP. Among these published case reports, the mechanisms postulated are drug overdose, drug accumulation, and acute renal failure triggered by vomiting (12, 23, 52). Therefore, metformin has been classified as possible DIP.

Incretin-based therapies such as glucagon-like peptide-1 agonists (GLP-1) and di-peptidyl peptidase-4 (DPP-4) inhibitors have become important therapeutic options for treatment of type 2 diabetes. Proposed mechanisms of action include enhanced glucose-dependent insulin secretion from pancreatic-cells, restoration of first phase insulin response, suppression of glucagon secretion, and delay of gastric emptying. Acute pancreatitis has been reported with both GLP-1 agonist (5, 44, 48, 75, 83) and DPP-4 inhibitor (30, 46). Over the last several years post-marketing reporting of this adverse events to FDA resulted in manufacturers emphasizing for acute pancreatitis and, later, in controindications for incretin-based therapies in patients with a history of pancreatitis (37).

Recently, several metanalysis and cohort studies demonstrated that the incidence of pancreatitis in patients taking incretins is low and that these drugs do not increase the risk of pancreatitis (3, 20, 21, 26, 29, 39, 50, 56). Li et al. found no association between the use of GLP-1-based therapies and pancreatitis in a self-controlled case series analysis in a large observational database from dispensing data on 1.2 million patients (50). Even animal research demonstrated no evidence of acute pancreatitis in GLP-1 agonist/DPP-4 inhibitors (6, 45, 80, 81, 86). A recent meta-analysis of randomised and non randomised studies confirmed that the risk of AP under incretin-based therapy is not increased (49).

Statins

While statins are generally well tolerated they have been known to be associated with pancreatitis.

DIP is a rare adverse effect of statin therapy, but it has been documented mainly in case reports involving atorvastatin (11, 77), fluvastatin (85), rosuvastatin (17, 47), simvastatin (40, 67, 69), and

pravastatin (4, 10), leading to the conclusion that statins induced pancreatitis may be a class-effect (74). An immune-mediated inflammatory response, direct cellular toxicity and metabolic effect have all been postulated, even though the mechanism of action remains ill-defined. Statin-induced pancreatitis can occur at any time but seems to be very uncommon early in treatment and more likely to occur after months of therapy. Singh and Loke have postulated that differences exist in the safety profiles of the various statins that may correlate with the degree to which they inhibit cytochrome P450 CYPA4 as well as the degree of their lipophilicity (76).

Recently, larger studies have challenged the correlations made by earlier case reports, and demonstrate instead a mild protective effect in statin users, as previously shown in animal models of acute pancreatitis (18), where statins appear to reduce inflammatory cytokines and pulmonary neutrophilic activation in a severe acute pancreatitis model (2).

5-ASA and Derivatives

Since 1989 mesalamine induced pancreatitis has been described (71). Several mesalamine preparations have been implicated in causing pancreatitis, both orally and via enema, and sulfasalazine. A hypersensitivity mechanism seems to be involved and pancreatitis occurs usually after few days or weeks (short latency).

A higher frequency of pancreatitis has been proposed for new mesalamine formulations, included MMX. However, a recent pharmaco-epidemiological study showed a similar incidence compared to delayed or controlled release, warranting a formal postmarketing safety assessment. It has been well established that newer drugs are monitored more closely for adverse effects (AEs) and that those AEs are more likely to be reported than for medications that have been in long-term use (70).

Antibiotics

Metronidazole has been reported as having a probable association with acute pancreatitis (16, 19, 60, 63, 64, 79), although the mechanism of DIP is still unknown. Speculative mechanism may be free radical production, immune-mediated inflammatory response, and metabolic effects (79). The association is based on case reports, 3 of them with positive rechallenge test (latency time 1-7 days) (16, 19, 64). In a population-based case-control study, Nørgaard et al. showed that metronidazole was associated to a threefold increased risk of acute pancreatitis (63). Furthermore, the use of metronidazole in combination with other drugs used for H. pylori (PPI, antibiotics) within 30 days before admission was associated with an eightfold increased risk of acute pancreatitis.

Tetracyclines have been implicated as a causative agent for acute pancreatitis. Early reports of acute pancreatitis after tetracycline administration were associated with liver dysfunction attributed to the drug's ability to induce fatty degeneration of this organ (59). In the following years, case reports about tetracycline induced pancreatitis even in patients without evidence of liver abnormalities have been described. A large Swedish pharmaco-epidemiological study reported a 1.6 odds ratio among current users of tetracycline after adjustment for potential confounders (51).

Regards the new drug tygecicline, an analogue of the semi-synthetic tetracycline minocycline, in Phase 3 and 4 clinical studies McGovern et al. defined the pancreatitis as uncommon in treated patients, with an occurrence of <1%. Caution should be exercised with close monitoring in patients with past acute or chronic pancreatitis, although there is documented safety even in these patients (55).

Valproic acid (VPA)

Since the introduction of VPA in 1979, a drug commonly prescribed for generalized and focal epilepsy, migraine, neuropathic pain, and bipolar

disorder, cases of coincident pancreatitis have been reported (9, 14, 57, 65, 72), often involving children. Acute pancreatitis is rarely seen in children, and, in contrast to cases in adults, it is more commonly associated with drugs. The common side effects associated with VPA are typically benign, but more serious adverse effects may occur. These include hepatotoxicity, hyperammonemic encephalopathy, coagulation disorders, and pancreatitis. The possible association between VPA and pancreatitis led the US Food and Drug Association to issue a box warning for all VPA products in 2000. In a recent systematic review Pellock et al.(66) reported that there were several confounding elements and possible alternative etiologies in many of the trials and case reports, leading to the conclusion that VPA-coincident acute pancreatitis is an uncommon but definite and idiosyncratic event. It is most common during the first year of therapy and during dosage increases.

3. Conclusions

Drug-induced pancreatitis is a rare entity and difficult to diagnose. Only a minority of cases associated with acute pancreatitis are linked to drugs and clinical presentation and mechanisms of injury to the pancreas are not well understood or controversial. The diagnosis of DIP remains possible or probable in many patients. Several of these drugs are used for diseases associated with pancreatitis (i.e. inflammatory bowel diseases, dyslipidemia). The resolution of pancreatitis after drug discontinuation (de-challange test), could improve the diagnosis of DIP. However, it is difficult to establish the direct correlation between resolution of symptoms and drug withdrawal. Re-challenge tests may be performed in some cases, but it is strictly dependant on the severity of the index pancreatitis.

Clinically, it is important to exclude any alternative possible etiology to avoid unnecessary drug withdrawal. However, drugs suspected to induce pancreatitis should be discontinued or exchanged with an alternative drug, when possible. Drugs even probably associated to pancreatitis should be avoided in patients with previous episode(s) of pancreatitis. The knowledge of drugs commonly linked to acute pancreatitis **(Table 3)** may lead to earlier suspicion of the diagnosis of DIP and to more quickly discontinue drug administration in patients where a cause of AP cannot be found.

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