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Acute Pancreatitis Induced by Drugs

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1. Introduction

Drug-induced acute pancreatitis (DIP) is generally considered to be a rare disease. Indeed, the incidence of cases caused by medication use is much lower than of those caused by biliary disorder or alcohol. On the other hand, the total incidence of acute pancreatitis in developed countries continues to rise as does the exposition of general population to medication. The disease was almost unknown before the 1960s. Probably the first two cases were reported in the late 1950s: by Zion *et al.* in 1955 and Johnston & Cornish in 1959. From that time, the number of reported cases has increased steadily until these days. A further increase in the incidence of drug-induced acute pancreatitis may be expected and seems to be actually present in recent scientific papers on the topic.

For a proper understanding of the disease, we must regard it not simply as one of many other types of acute pancreatitis, but primarily as an adverse drug reaction (ADR). A recent definition describes an ADR as “an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product” (Edwards & Aronson, 2000).

| Type of ADR | Mnemonic | Dose dependence / Predictability | Characteristics |
|-------------|------------|---------------------------------------|---|
| A | Augmented | Dose-related, predictable | Most usual; frequent |
| B | Bizarre | Dose-unrelated, unpredictable | Immunity-mediated reactions or idiosyncrasies; rare |
| C | Continuous | Related to a cumulative dose and time | Effect of chronic use, late toxicity |
| D | Delayed | Related to time | Long time from drug cessation |
| E | End of use | Related to drug withdrawal | Immediately after withdrawal |

Table 1. Types of adverse drug reactions

The vast majority of the reported DIP cases seem to have an idiosyncratic character (see Table 1). This also means that it is nearly impossible to obtain sufficiently large cohorts with similar patient characteristics. From that point of view, every case of drug-induced pancreatitis should be documented as well as possible, and also reported to a pharmacovigilance system for further evaluation.

2. Epidemiology

It is usually estimated that drug use accounts for 2% of all the causes of acute pancreatitis. It must be pointed out that the diagnosis might be underestimated, particularly for the difficulties in diagnosing this etiology. The overall incidence varies in different studies from 0.1 to 2% with a tendency to increase over time (Balani *et al.*, 2008).

There are three sources of information on the DIP incidence: data from clinical studies on acute pancreatitis, individual or serial case reports published in medical journals, and data on spontaneous reports from pharmacovigilance databases. Another possible source – data from clinical testing of new drugs – is not very useful because of an idiosyncratic character of DIP. The B-type of adverse drug reactions occurs with a frequency lower than 1:10,000, so their record in the first three phases of clinical drug investigation is almost impossible.

The number of cases reported to pharmacovigilance databases and of published case reports is increasing so rapidly that any number will be obsolete by the time it manages to be printed. According to Lancashire *et al.*, the WHO database of ADRs listed 2,479 episodes suspected of being caused by 529 different drugs from 1968 to 1993. An analysis of the DIP cases reported to the Danish Committee on Adverse Drug Reactions from 1968 to 1999 (Andersen *et al.*, 2001) showed an increasing number of reports in time and a predominance of women, but estimating the proportion of DIP in total acute pancreatitis incidence is clearly improper. The mortality of 9% among the cases analyzed shows a tendency to report the most severe cases, whilst the majority of mild-to-moderate cases remain unreported. On the other hand, an information bias, due to more frequent notification of a drug already known to cause a specific ADR, is limiting the validity of spontaneous reporting. A Medline search of the English literature revealed 1,214 case reports with 120 suspected drugs between 1955 and 2006 (Badalov *et al.*, 2007). The weakness of estimating DIP incidence from these sources is in preferential publication of the case reports describing ADRs of new – therefore more “attractive” – agents rather than of older ones in which the risk is considered to be well-known.

In a multicenter study by Gullo *et al.*, published 2002, in which the etiology and mortality of acute pancreatitis were studied, the proportion of drug injury was almost negligible: only 0.2% (2 patients) out of 1,068 cases. It is worth noting that three out of the seven centers involved in this study (providing 581 AP cases for the study) were surgical departments; moreover, 139 (13%) cases of acute pancreatitis in this study were classified as idiopathic. We believe that the incidence of DIP in this study may be somewhat underestimated. As will be discussed below, establishing the diagnosis of DIP often requires a re-evaluation and knowledge of the patient's post-episode history.

On the other hand, at least two published studies showed a significantly higher incidence of DIP in retrospective analysis. A study by Mennecier *et al.*, published 2007, found an incidence of drug-induced cases of 8.3 % among a total of 108 acute pancreatitis cases hospitalized in hepatogastroenterology and intensive care units of a French hospital over a 9-year period. Our study, published in 2010, included 170 acute pancreatitis cases

hospitalized in a tertiary hospital during a period of two years. The proportion of DIP in this cohort was 5.3% (Vinklerová *et al.*, 2010). Obviously, the incidence found in these studies is higher than in the general population. If DIP occurrence depends on the use of specific drugs, in tertiary hospitals as centers for the treatment of specific diseases (e.g. Crohn's disease or malignancies) it must be higher.

The discrepancy in the published results demonstrates, in particular, the fact that the importance of drug-induced pancreatic injury will be different in the general population than among the cases reported in surgical or medical departments. It is also clearly improper to suppose that this disease can have similar incidence in all countries because of its dependence on the consumption of causative drugs and, secondarily, the dependence on the incidence of diseases treated with these medications.

Studies with very low report of DIP are usually characterized by a high number of idiopathic acute pancreatitis cases. Clinicians sometimes forget that there is no such thing as an "idiopathic" disease. The word "idiopathic" means that we are not able to establish the actual cause of the disease – and a not insignificant number of idiopathic cases of acute pancreatitis might be caused by xenobiotics, including medication. The only way how to determine the real incidence of drug-induced acute pancreatitis is to perform prospective multicenter studies targeted at the etiology of non-alcoholic, non-biliary acute pancreatitis.

3. Etiology

The pathogenesis of acute pancreatitis is probably very uniform differing only by the initial injury mechanism. It consists of three steps: (i) premature activation of trypsin in acinar cells; (ii) intrapancreatic inflammation; and (iii) extrapancreatic inflammation (Banks & Freeman, 2006). The mechanisms by which drugs initiate a cascade of damaging events remain shrouded in mystery. However, it should be borne in mind that the same is true for the vast majority of responses independent of drug dose.

3.1 Mechanisms of injury

Mechanism of medication's action against pancreas remains unknown. Two possible mechanisms of pancreatic injury caused by drugs are usually recognized, but in our opinion, at least three more possible mechanisms should be also mentioned:

- a. Direct toxic effect on pancreatic tissue;
- b. Idiosyncratic reaction;
- c. Influence of medication on the bile flow;
- d. Amplification of direct toxic effect of ethanol on pancreatic tissue;
- e. Secondary pancreatic damage.

Simple direct toxic injury of pancreatic tissue, similar to the hepatic injury caused by some drugs or their metabolites (e.g. paracetamol), seems very unlikely in the majority of reported DIP cases. This (A-type) pattern of ADR is dose-dependent, irrespective of the patient's response, reproducible and usually occurs in much higher numbers than usual in DIP. Although acute pancreatitis sometimes develops under the condition of an overdose of some drugs, its incidence remains so rare that an underlying predisposition must play a role in these cases. Genetic differences in metabolism are usually supposed to be the most probable predisposing factor here. Only several drugs are reported as causing DIP by overdose: paracetamol (or acetaminophen), erythromycin and carbamazepine. We had an

opportunity to describe DIP in a patient overdosed on mycophenolate (Vinklerová *et al.*, 2001). Some kind of cumulative dose-dependent effect of toxic metabolites is also sometimes hypothesized in drugs showing a consistent long latency (more than 30 days) at the onset of the first episode of DIP. It is supposed mainly in valproate, but possibly also in didanosine, tamoxifen, chlorothiazide and estrogens. This would correspond to the C-type (continuous) of ADR, but other mechanisms can also explain the late onset of DIP in these agents.

The definition of an idiosyncratic adverse drug reaction (B-type) best matches the actual characteristics of DIP. A strong correlation with some immune disorders (mainly Crohn's disease and HIV infections) implicates an immune-mediated reaction as a chief causative factor of the disease. Often, the latency between initiation of the drug and the onset of DIP is one week to one month, but later rechallenge led to a second episode in one to three days. The frequently mentioned lack of hypersensitivity symptoms (rash, fever, lymphadenopathy and eosinophilia) is of no major importance as it is rare in the majority of immune-mediated organ damage and cannot be considered pathognomic. An immune-mediated process is undoubtedly the pathogenetic nature of many rare ADRs also connected with the drugs mentioned here, such as drug-induced pericarditis, lupus-like syndrome and, moreover, some types of drug-induced liver injury. It is possible that all these reactions have a common immune-mediated nature and the specific organ is injured in fact "accidentally" as a current *locus minoris resistentiae*. Unfortunately, there is as little evidence available for this hypothesis as there is for the others. This should lead us to study these rare ADRs more in terms of patient characteristics than those of individual drugs.

The latter three mechanisms may not be as irrelevant as it might seem. Several drugs involved in acute pancreatitis have been implicated as causing cholestatic liver injury, e.g. azathioprine, cytarabine, estrogens and erythromycin. Codeine, morphine and possibly some other drugs can cause spasm of sphincter of Oddi. An interesting relationship between rofecoxib-induced cholestatic hepatitis and acute pancreatitis was observed (Sato *et al.*, 2006). Human leukocyte antigen haplotype HLA-A33/B44/DR6 is involved in both these reactions reported simultaneously in several patients. Cholestatic hepatitis caused by this haplotype may induce secondary pancreatitis. Also, the occurrence of drug-induced pancreatitis in alcoholic patients has been described, but this issue has not been given much attention. Secondary (off-target) injury of pancreatic tissue is also possible in some drugs. Known potential indirect effects of drugs on the pancreas comprise ischemia (azathioprine, diuretics), hypercalcemia (thiazide diuretics), thrombosis of pancreatic blood vessels (estrogens), and an increase in pancreatic juice viscosity (diuretics, pentamidine).

3.2 Predispositions

Several populations at higher risk have been identified during research in drug-induced pancreatitis. Predisposing demographic characteristics are female gender and younger age. The male-to-female ratio is inversed in comparison to other acute pancreatitis types, at least to 1:1.3. DIP is also more commonly reported in younger patients, not exceptionally in children. An increased risk in older patients with polypharmacy seems to be a bias: the risk is in the use of many drugs by a large segment of this population rather than old age itself.

Three types of diseases were recognized as the most frequent predisposing health factors: inflammatory bowel diseases, HIV infection and cancer treated by combined chemotherapy. In patients with advanced HIV infection (CD4 counts < 200 cells/mm³), treated with antiretroviral drugs, an incidence of 14% was found, but incidence of up to 40% is also

mentioned (Trivedi *et al.*, 2005). In an anticancer chemotherapy, the risk is also higher, but sometimes it is difficult to decide which of the multiple medications have caused the disease. The use of dexamethasone or cytarabine seems to be of the highest risk.

The etiology of acute pancreatitis in patients with Crohn's disease was evaluated in a targeted study (Moolsintong *et al.*, 2005). Among the 48 patients treated for Crohn's disease who had acute pancreatitis between 1976 and 2001, an ADR was the cause in 17% of cases with the vast majority being caused by purine analogs – azathioprine and 6-mercaptopurine. The most common etiologies of AP – biliary and alcoholic – were found only in 21% and 15%, respectively. A higher risk of induction of AP in Crohn's disease was also proven by evidence in a study by Weersma *et al.* in which the risk was significantly higher in patients treated for Crohn's disease compared to the risk of those treated for autoimmune diseases or organ transplant. Also, a similar study performed by Bajaj *et al.* supports these findings. In ulcerative colitis, the risk is probably increased, but lower than in Crohn's disease. On the other hand, in a Danish population-based case-control study (1,590 incident cases of acute pancreatitis and 10 controls per case), a nearly four-fold increased risk of acute pancreatitis in patients with Crohn's disease and a 1.5-fold increased risk for ulcerative colitis were found, but the use of mesalazine or sulfasalazine was not associated with an increased risk (Munk *et al.*, 2004). We suppose that this can be explained by the low proportion of DIP in the etiology of acute pancreatitis. In the population with a significantly increased risk, the number of medication-associated cases cannot influence the total risk.

3.3 Experimental findings

The obvious aim of experimental models is to mimic as closely as possible the conditions in an organism suffering from acute pancreatitis. Some of those models were based on the systemic administration of an exogenous substance. They are not considered to be best available for many reasons, but they can help in further research on DIP pathophysiology.

Cerulein is a ten amino acid oligopeptide, similar to cholecystokinin, that stimulates gastric, biliary, and pancreatic secretion and also contraction of certain smooth muscles. It has been used by intravenous (as well as intraperitoneal or subcutaneous) route to cause acute pancreatitis in mice, rats, hamsters and dogs. Within one hour from application, cerulein causes pancreatic interstitial edema reaching a maximum in 12 hours. The supposed mechanism of action is the upregulation of NF- κ B (nuclear factor κ -light-chain-enhancer of activated B cells) leading to activation of ICAM-1 protein and promotion neutrophil adhesion onto pancreatic acinar cells. An increase in digestive enzyme production and activation of NADPH oxidase could be supporting mechanisms. Pancreatitis caused by cerulein is mild, with negligible mortality (Su *et al.*, 2006).

L-arginine is one of the most common natural amino acids. If administered intraperitoneally, it causes acute pancreatitis in mice and rats. Significantly increased plasma amylase levels, pancreatic MPO activity, trypsin activation, and histological changes including accumulation of fluid, disruption of histoarchitecture, acinar cell vacuolization, extensive acinar cell necrosis, and neutrophilic infiltration have been described. It is believed that nitric oxide synthase (NOS), present in acinar cells and metabolizing L-arginine, might play a role in the initiation of pancreatitis. Induction of NOS by L-arginine leads to an interaction of NO and superoxide radicals, which can generate peroxynitrite radicals causing cell injury (Dawra *et al.*, 2007). Effects are dose dependent and a higher dose can lead to acute pancreatitis within a few hours.

It is worth noting that some drugs known to cause human DIP (e.g. azathioprine) are able to successfully suppress the development of acute pancreatitis in various experimental models. This supports the opinion that host factors (most probably the immune system) are more important for the development of DIP than the pharmacodynamic properties of causative agents.

4. Causative drugs

Several hundreds of chemical substances have been reported to cause acute pancreatitis in humans. The majority of these reports remain single with a limited level of evidence. Drugs causing pancreatic injury more frequently have been listed in several reviews, some of which tried to quantify the risk of individual agents. A comparison of the ability to cause drug-induced pancreatitis is very difficult as the probability of an adverse effect is conditioned by many population or individual risk factors.

An interesting attempt to estimate the potential of individual drugs to cause DIP by pharmacoepidemiological methods was performed by Lancashire *et al.* in 2003. They examined the data held in the General Practitioner Research Database and compared the frequency of intake of different drugs by individuals with and without acute pancreatitis (3,673 cases of pancreatitis, 3 controls for each case). Odds ratios were calculated for recent (1–90 days before the episode), past (91–360 days before the episode) or continuing (prescription in both periods) use. A nine-fold increased risk in recent takers of mesalazine was found as well as a ten-fold increased risk in ever-takers of azathioprine in comparison to never-takers. Only a moderate risk was found for captopril and valproate. Strikingly increased odds ratios were found for recent takers of acid inhibitory drugs without having a peptic ulcer diagnosed. Although these drugs can certainly cause DIP, this is clearly a bias because their prescription is related to abdominal pain and other GIT symptoms preceding the diagnosis of acute pancreatitis. This result also shows the limitation of a study performed by using this method – no data on the etiology of acute pancreatitis were used. Estimating the risk of drugs to cause a rare ADR also requires a much greater population. There is no doubt that some diseases may predispose to the occurrence of acute pancreatitis in themselves. To distinguish the impact of this predisposition from the influence of medication, it will be necessary to carry out such studies in much larger cohorts. Therefore, a classification system based on the number of DIP reports appears to be the most appropriate way to assess the risk potential of a drug.

4.1 Classification systems

Because the risk potential of individual drugs is difficult to establish, it is generally estimated from the absolute numbers of published cases. In earlier critical reviews, the potential of a drug to induce AP was evaluated as definite, probable or possible (Mallory & Kern, 1980; McArthur, 1996). The current knowledge has recently been summarized and used to propose classification systems in papers published by Trivedi and Pitchumoni in 2005 and Badalov *et al.* in 2007.

Trivedi & Pitchumoni classified risk drugs on the basis of the search of the reported cases in the National Library of Medicine/Pubmed from 1966 to 2004. Drugs were indexed into Classes I–III: Class I drugs were medications implicated in greater than 20 reported cases of acute pancreatitis with at least one documented case following re-exposure; Class II

involved medications implicated in more than ten cases of acute pancreatitis; and Class III drugs were all other medications reported to be associated with pancreatitis.

Also, Badalov *et al.* reviewed Medline reports of drug-induced AP from 1955 to 2006. The authors classified reported medications into four classes based on the published weight of evidence for each agent and the pattern of clinical presentation. Class I included medications in which at least one case was proven by a re-challenge with the drug. Class II included drugs with a consistent latency in 75% or more of the reported cases. Class III included drugs that had two or more case reports published, but neither a re-challenge nor a consistent latency period. Class IV drugs were similar to class III drugs, but only one case report had been found.

An apparent weakness of all existing drug classifications is the lack of the knowledge on the relationship between the incidence of drug-induced AP and population exposure to the causative drugs. Quantifying this relationship is a challenge for pharmacoepidemiology. In addition, regular updating of existing classifications appears necessary because every year new cases of DIP occur, which may result in a reclassification of the drugs included.

4.2 Drugs commonly associated with drug-induced pancreatitis

Among several hundreds of drugs reported as causative for drug-induced pancreatitis, only a few have a sufficiently strong evidence base to be clearly associated with this rare adverse drug reaction. These agents are listed in Table 2. At least some of them also deserve more detailed mention, which can be found in following sections..

4.2.1 Azathioprine

Azathioprine is a purine analog used in low doses as immunosuppressant. It is a pro-drug metabolized into the active 6-mercaptopurine, itself a purine synthesis inhibitor. Enzyme thiopurine S-methyltransferase (TPMT) deactivates 6-mercaptopurine. The most severe adverse effect of azathioprine is bone marrow suppression, especially in TPMT genetic polymorphism. Its adverse effects on the pancreas are well documented, so it is classified into class I according to the risk of induction of DIP by both classification systems. A significantly higher risk of azathioprine-induced acute pancreatitis was demonstrated in patients with Crohn's disease compared to all the others, including those with ulcerative colitis. Consistent latency of the DIP onset with an average of 25 days has been found. This adverse effect is neither dose related nor associated with myelotoxicity or the defect of TPMT. It is believed that the cause may be an immune-mediated response based on a genetic predisposition common to that predisposing to Crohn's disease.

4.2.2 Mesalazine

Mesalazine (mesalamine, 5-aminosalicylic acid) is an anti-inflammatory drug used to treat the inflammation of the digestive tract in ulcerative colitis and Crohn's disease. The mechanism of action remains unknown, but is limited to the intestine as the agent is not absorbed systemically in significant amounts. Therefore, systemic adverse reactions, e.g. interstitial nephritis and lupus-like syndrome, are uncommon and immune-mediated. Mesalazine belongs to drugs with the best documented association (Class I) with drug-induced acute pancreatitis. Acute pancreatitis induced by mesalazine usually occurs during the first days or weeks of treatment; however, an occurrence following prolonged use has

also been sporadically reported. No dose dependence has been observed and the symptoms usually disappear within 10 days after drug withdrawal.

| Drug class | Drug name | Risk class Trivedi | Risk class Badalov | Usual onset latency |
|------------------------|------------------|-----------------------|-----------------------|------------------------|
| Analgesics | codeine* | I | Ia | 1 day |
| | paracetamol | II | II | 1 day |
| | sulindac | I | Ia | > 30 days |
| Anesthetics | propofol | III | II | 1 day |
| Antidiabetics | exenatide* | - | - | |
| | sitagliptin* | - | - | |
| Anti-infectives | | | | |
| Antivirals | didanosine | I | II | > 30 days |
| | lamivudine | II | Ib | |
| Antibacterials | cotrimoxazole | I | Ia | 1 – 30 days |
| | erythromycin | II | II | 1 day |
| | tetracycline | I | Ia | |
| Antiparasitic agents | pentamidine | I | Ib | 1 – 30 days |
| | stibogluconate* | I | Ia | 1 – 30 days |
| Anticonvulsants | valproate | I | I and II | > 30 days |
| Antineoplastic agents | asparaginase | I | II | 1 – 30 days |
| | cytarabine | I | Ib | 1 – 30 days |
| Cardiovascular drugs | | | | |
| ACE inhibitors* | enalapril | II | Ia | > 30 days |
| Diuretics | furosemide | I | Ib | |
| Statins* | pravastatin | III | Ia | > 30 days |
| Gastrointestinal drugs | mesalazine | I | Ia | 1 – 30 days |
| | omeprazole | III | Ib | > 30 days |
| Steroid hormones | estrogens* | I | Ib | > 30 days |
| | glucocorticoids* | I | Ib | 1 – 30 days |
| Immunosuppressants | azathioprine | I | Ib and II | 1 – 30 days |
| | sulfasalazine | I | Ia | 1 – 30 days |

Table 2. Drugs commonly associated with drug-induced pancreatitis (* class effect probable)

4.2.3 Valproate

Valproic acid is an anticonvulsant, acting as an inhibitor of GABA transaminase in the CNS and blocking the neuronal voltage-gated sodium channels and T-type calcium channels. Tens of DIP cases caused by its use have been reported, with 75% of them being observed in children. There is a long latency of the first episode onset (3–17 months) and a short one in rechallenge (6–12 weeks). Although usually mild, valproate-induced pancreatitis may have a severe course with associated complications such as necrosis or even death.

4.2.4 Propofol

Propofol is an intravenously administered general anesthetic with several proposed mechanisms of action, mainly the potentiation of GABA_A receptor activity and blockade of neuronal sodium channels. The nature of an agent used as an anesthetic results in an immediate onset of drug-induced pancreatitis following a single use. At least 20 cases of propofol-associated acute pancreatitis have been reported in the literature with subsequent discussions on the possible role of drug formulation in the oil-in-water emulsion. Elevated serum lipids do not seem to be a reason for this ADR; the rarity of the ADR suggests an idiosyncratic nature (Jawaid *et al.*, 2002).

4.2.5 Enalapril and other ACE inhibitors

ACE inhibitors belong to the most widely used and most effective cardiovascular drugs. In contrast to their wide use, the occurrence of acute pancreatitis caused by these agents is rare. The number of reported cases clearly depends on the time from introduction of the specific agent and its widespread use; thus, enalapril is the most commonly reported agent (Class II, Trivedi; Class Ia, Badalov). Some cases of a second episode of DIP caused by another drug with a similar mechanism of action suggest the class effect. The risk of acute pancreatitis in patients using cardiovascular drugs has been extensively studied in the European study on drug-induced acute pancreatitis. The use of ACE inhibitors has been associated with an increased risk of acute pancreatitis (adjusted odds ratio 1.5). The risk increased with higher daily doses and was highest in the first six months of therapy (Eland *et al.*, 2006).

4.2.6 Statins

HMG-CoA reductase inhibitors are currently the most popular hypolipidemic agents. The number of DIP reports related to this drug class exceeded 50, most often concerning simvastatin and pravastatin. An odds ratio of 1.41 was found for the risk of acute pancreatitis in patients with a past history of exposure to statins (Singh & Loke, 2006). The risk appears to increase with the duration of treatment. The ability to cause pancreatitis is believed to be a class effect.

4.3 Controversial issues: Acid-suppressing drugs

The relationship between drugs suppressing the secretion of gastric acid and acute pancreatitis is a frequently discussed issue. Histamine H₂ receptor antagonists cimetidine and ranitidine have been reported to cause drug-induced pancreatitis in several case reports without an evidence of rechallenge or a consistent latency. Some experimental findings also indicate the possible causative relationship, whilst others deny it. Also, in much more effective drugs with a similar effect, the proton pump inhibitors (PPIs, namely omeprazole), the risk of inducing pancreatitis has been described. In the above-mentioned study by

Lancashire *et al.*, the odds ratios were extremely high for both H₂-receptor inhibitors and PPIs. On the other hand, a previous, much larger and better designed study brought no evidence for this suspicion (Eland *et al.*, 2000). We therefore believe that the relationship of these drugs with DIP is overestimated, perhaps with the exception of cimetidine.

4.4 Controversial issues: Incretin-related antidiabetics

Soon after the introduction of a new class of oral antidiabetic agents, stimulating receptors for glucagon-like peptide 1 (GLP-1), reports on acute pancreatitis caused by their use began to emerge. In a subgroup of direct GLP-1 receptor agonists, eight cases during clinical development and 36 cases in postmarketing surveillance were reported for exenatide (the first-of-class agent) and another four cases were reported for liraglutide (Anderson & Trujillo, 2010). This phenomenon was probably even more pronounced in a newer group of agents with similar effects, dipeptidyl peptidase-4 inhibitors. At least 88 cases of acute pancreatitis in patients using sitagliptin were reported to FDA until 2010 (Olansky, 2010).

A considerable effort has been made to refute this connection, which is, of course, in the interest of the manufacturers. It has been found that the risk of acute pancreatitis is significantly higher in the diabetic compared to the non-diabetic population and that the use of drugs affecting the GLP-1 system does not further increase this risk (Garg *et al.*, 2010). Here is yet another example of a negative result in a pharmacoepidemiological study. Again, the probable reason lies in an extremely small proportion of drug-induced cases in total numbers of acute pancreatitis, which of course cannot influence the overall risk in high-risk populations. Nevertheless, the number of DIP cases reported in these medications is exceptional and supports the hypothesis of an association between the use of these drugs and DIP. Only the future will reveal whether this new group of drugs will be more beneficial for the treatment of diabetes or for studying the pathogenesis of DIP.

4.5 Toxins and illicit agents

Acute pancreatitis caused by animal toxin poisoning has been sporadically described in the literature. Probably the best known are the effects of scorpion venom. Available clinical case reports or series are usually too outdated to rely on the information contained (Bartholomew, 1970), but experimental studies on the effects of scorpion toxin are very interesting. Concurrent stimulation of pancreatic secretion and contraction of the sphincter of Oddi have been demonstrated in the late 1970s. Recently, it has been proven that the venom from the Brazilian scorpion *Tityus serrulatus* and a purified fraction selectively cleave essential SNARE proteins within exocrine pancreatic tissue (Fletcher *et al.*, 2010). Rare reports on pancreatitis caused by adder bite (venom containing neurotoxic phospholipase A₂) or even blue-ringed octopus bite (venom containing tetrodotoxin) have been published.

Aside from alcohol, another addictive substance often mentioned in association with acute pancreatitis is marijuana, abused by smoking. A smaller series of marijuana-induced pancreatitis cases was reported by Wargo *et al.* in 2007. The authors suggest a dose-related mechanism of pancreatic injury. Cannabinoid receptors CB1 and CB2 were found in the pancreas, so their stimulation might be a trigger of the proinflammatory cascade there. Interestingly, stimulation of cannabinoid receptors was found to be a protective mechanism during experimental pancreatitis. This is yet another example of ambivalent behavior of some xenobiotics towards the pancreatic tissue. The importance of smoking, as a route of THC administration, for the initiation of pancreatitis has not yet been reviewed.

5. Diagnostics, disease course and management

Among the reasons why the real incidence of drug-induced acute pancreatitis is still not known, the difficulties in diagnosis are probably most important. Milder cases of pancreatic injury are often missed because serum amylase and lipase estimations are not part of the metabolic profile obtained during a routine health checkup and abdominal pain is often attributed to underlying diseases. Many cases of DIP are also erroneously classified as alcoholic or biliary in etiology often by default, whether they are causal or innocent bystanders. If acute pancreatitis is diagnosed, the treatment invariably includes exclusion of oral intake and, thus, also abolishment of causative oral medication and thereby the opportunity to diagnose DIP is missed (Trivedi & Pitchumoni, 2005).

5.1 Diagnosis

As is usual with the vast majority of idiosyncratic adverse drug reactions, no specific test for establishing the diagnosis of drug-induced pancreatitis is available. Therefore, the diagnosis is usually based on the following criteria:

- a. Acute pancreatitis occurs during the administration of a drug;
- b. All other common causes are excluded;
- c. Symptoms of acute pancreatitis disappear after drug withdrawal;
- d. Symptoms recur after a re-challenge of the suspected drug.

These criteria bring some problems in all ADRs, not only in such a difficult one as DIP. The first criterion seems to be easy to achieve until we remember that monotherapy in our patients becomes more and more scarce. If DIP occurs in the later course of the pharmacotherapy, the decision which drug is most suspicious is not easy. Use of the classification systems mentioned above may be very useful for that purpose.

Excluding all other causes of the disease is also not so straightforward in many cases of acute pancreatitis. However, modern diagnostic methods have led to a great progress in this area. The validity of diagnosis may depend on the equipment available and even more on the experience of the medical staff. From this point of view, previously published DIP case reports should also be considered since the possibilities of excluding other causes of acute pancreatitis are quite different now than they were in the 1970s.

Disappearance of symptoms following drug withdrawal is also sometimes misleading. Discontinuation of oral therapy is a natural part of any management of acute pancreatitis. In patients treated by multiple pharmacotherapy, it is impossible to decide which medication withdrawal led to a resolution of the symptoms and laboratory findings. A similar problem occurs in drugs administered at once, e.g. general anesthetics or anticancer chemotherapeutics. In these cases, acute pancreatitis is usually diagnosed within several days from drug administration.

Due to the character of the disease and ethical considerations, deliberate, repeated administration of suspect drug to induce a new episode of acute pancreatitis is not possible. Re-challenge is usually unintended, mainly if the cause of the first AP episode was not properly recognized. An exception is the use of essential drugs in cases where the benefits outweigh the risks. In such cases, the patient's written informed consent should be obtained. A simplified algorithm for diagnosing drug-induced pancreatitis is given in Figure 1. The suspected drug etiology should be considered after the exclusion of more common causes of illness. For the above reasons, it seems obvious that it is not always possible to establish a definitive diagnosis of drug-induced AP immediately. A "second-look" with the knowledge

of the subsequent patient's history may often be necessary. For that purpose, a proper documentation of each case is needed. A detailed medication history documentation is obvious as well as the determination of suspicious substances. We strongly recommend the use of scoring system of ADR probability and classification of suspicious drugs according to the DIP risk in the patient's files.

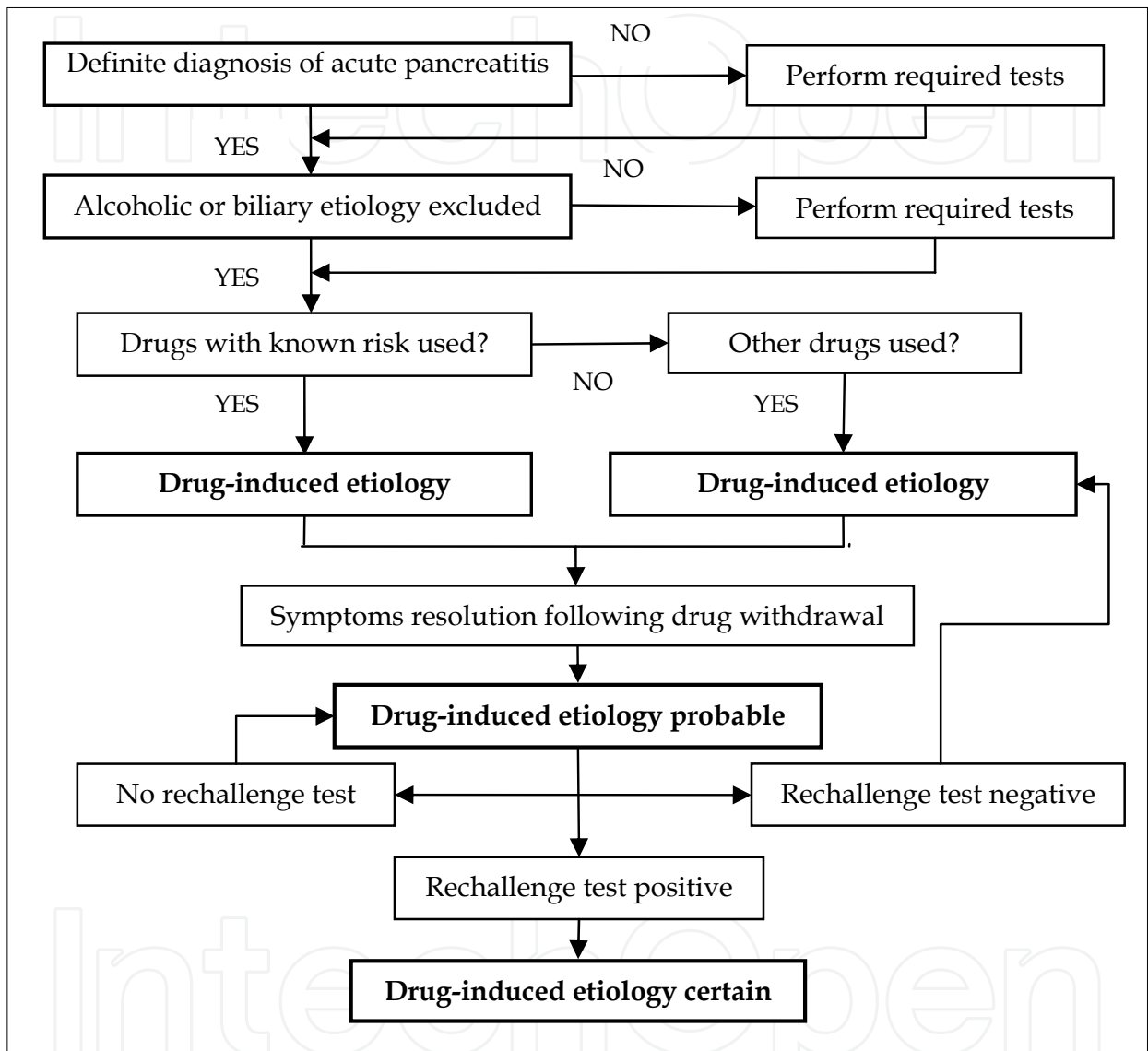


Fig. 1. Algorithm for diagnosing drug-induced acute pancreatitis

5.2 Probability scoring

For the purposes of future re-evaluation of each DIP case, it is very useful to classify drugs involved in the event by the above classification systems. There is no evidence for preferring one of these systems, so it is possible to use both, mainly if there is a difference between them in classifying a specific suspicious agent. Assigning probability of causation to a suspected adverse drug reaction can be best done by using the WHO scoring system (see Table 3). Of course, the diagnosis of DIP comes into consideration only in the first three degrees of probability: certain, probable or possible.

It is therefore appropriate that a record of the event in the patient's documentation should be written as follows: “Acute pancreatitis, drug induced; probability level: probable according to WHO scoring system; causative agent: azathioprine, class I according to Badalov”. Using these classification systems may improve the quality of information for further patient treatment and further processing of the event for scientific or pharmacovigilance purposes.

| Level of probability | Characteristics |
|-------------------------------|--|
| Certain | A clinical event, including a laboratory test abnormality, that occurs in a plausible time relation to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals The response to withdrawal of the drug (dechallenge) should be clinically plausible The event must be definitive pharmacologically or phenomenologically using a satisfactory rechallenge procedure if necessary |
| Probable | A clinical event, including a laboratory test abnormality, with a reasonable time relation to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge) Rechallenge information is not required to fulfill this definition |
| Possible | A clinical event, including a laboratory test abnormality, with a reasonable time relation to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals Information on drug withdrawal may be lacking or unclear |
| Unlikely | A clinical event, including a laboratory test abnormality, with a temporal relation to administration of the drug, which makes a causal relation improbable, and in which other drugs, chemicals, or underlying disease provide plausible explanations |
| Conditional / unclassified | A clinical event, including a laboratory test abnormality, reported as an adverse reaction, about which more data are essential for a proper assessment or the additional data are being examined |
| Unassessable / unclassifiable | A report suggesting an adverse reaction that cannot be judged, because information is insufficient or contradictory and cannot be supplemented or verified |

Table 3. Causality assessment of suspected ADRs (Edwards & Aronson, 2000)

5.3 Disease severity, management and secondary prevention

It is believed that drug-induced pancreatitis usually has a mild course. Lankisch *et al.* in 1995 showed that the disease course was usually favorable in patients with drug-induced AP, but more recent greater studies strongly suggest that the etiology of acute pancreatitis generally does not determine the severity (Gullo *et al.*, 2002). Also, a number of deaths from DIP were reported, for example, in a Danish analysis of spontaneous reports, four (9%) out of 47 DIP episodes led to death (Andersen *et al.*, 2001). Of course, severe cases tend to be more often

reported both in the literature and in spontaneous pharmacovigilance reports. Sometimes it may be rather difficult to decide to what extent DIP contributed to the death, especially in the presence of a severe, often end-stage underlying disease such as HIV infection or disseminated tuberculosis (Książczyńska, 2001).

In the disease management, there are no specific issues concerning drug-induced pancreatitis, with an exception of an immediate withdrawal of the suspected drug. The treatment does not differ from other types of acute pancreatitis. A difficult question is how to reintroduce medication if the causative agent is not unambiguously identified. We recommend not introducing all withdrawn drugs at the same time to distinguish the cause of a possible flare-up. An agent with the lowest risk should be reintroduced first. The most suspected drugs should be substituted by their analogs with a different chemical structure. Secondary prevention consists of avoiding the drug which caused the episode of acute pancreatitis. Rechallenge of such an agent is justified only if its benefits outweigh the risks, as discussed above.

The relationship between acute DIP and chronic pancreatitis is not known. Trivedi & Pitchumoni in their above cited paper hypothesized – on the basis of a known sequence in the pathogenesis of chronic pancreatitis – that prolonged use of a causative drug in a patient who experienced an episode of DIP may lead to chronic pancreatitis by causing repeated clinical or subclinical episodes of DIP but no evidence is available for this suggestion to date.

6. Future research

Given how inadequate the current state of knowledge on drug-induced pancreatic injury is, the area for further research in this field is remarkably wide. The majority of the knowledge on the topic has been obtained from case reports or their series. These will remain a major source of information, so it is necessary to improve their informative value substantially. The following recommendations for processing case reports on DIP were proposed by Balani & Grendell in 2008. Published case reports should:

- a. Provide the age and sex of the patient, along with the indication for treatment with a drug; provide the dose and frequency of medication;
- b. Document a definite case of pancreatitis based on current diagnostic guidelines;
- c. Provide information on the time course between initiation of drug and onset of pancreatitis;
- d. Exclude the most common causes of pancreatitis; document a positive response to withdrawal of medication;
- e. Provide the response to a rechallenge, if available.

Higher level of knowledge may be obtained by performing multicenter studies targeted at the etiology of non-alcoholic, non-biliary pancreatitis. Several thousands of acute pancreatitis cases must be involved in these studies to reveal the actual occurrence of drug-induced pancreatitis. Better cooperation between gastroenterologists and pharmacoepidemiologists is also needed to assess the actual risk of DIP for individual drugs. Any new pharmacoepidemiological study on this topic would be useful, but to improve the validity of its outcomes, substantially better input data are required. For this purpose, it would be optimal that each single case of acute pancreatitis included in such a study be documented according to the above principles.

Integration of the research in different disciplines would also be very useful for studying the causes of DIP. An obvious field for this research is the issue of diseases with a high

incidence of this disorder. Identifying the genetic differences predisposing to pancreatic injury caused by medication in patients suffering from Crohn's disease or AIDS would be the most axiomatic target. Another issue is the experimental pharmacological research of mechanisms by which xenobiotics can damage the pancreatic tissue as well as the common mechanisms of immune-mediated tissue injury caused by drugs. Any substantial progress in this research can contribute to a progress in two scientific challenges: recognizing the nature of more frequent causes of acute pancreatitis and also recognizing the cause and pathogenesis of idiosyncratic adverse drug reaction.

7. Conclusion

Drug-induced injury is a rare cause of acute pancreatitis. Epidemiological studies show a very wide range of its incidence, but at least the absolute number of its cases is undoubtedly increasing. We are able to identify the drugs with the greatest risk and populations at risk, but the absolute risk for medication users is still very low. On the other hand, the pathogenesis of the disease remains completely unknown. A better understanding of drug-mediated pancreatic injury can also help to understand the etiology of more common types of acute pancreatitis. Research in drug-induced acute pancreatitis is both a challenge and an opportunity to improve the collaboration of gastroenterology and clinical pharmacology.

8. Acknowledgment

Supported by grants IGA UPOL LF_2011_005 and MSM 6198959216.

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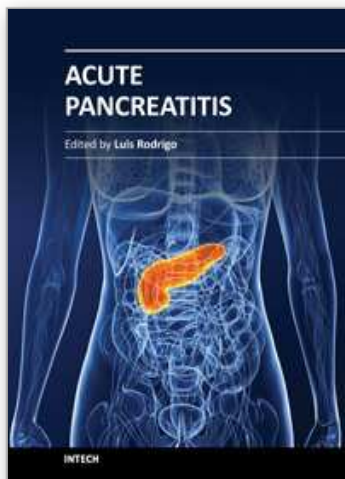
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Acute Pancreatitis

Edited by Prof. Luis Rodrigo

ISBN 978-953-307-984-4

Hard cover, 300 pages

Publisher InTech

Published online 18, January, 2012

Published in print edition January, 2012

Acute Pancreatitis (AP) in approximately 80% of cases, occurs as a secondary complication related to gallstone disease and alcohol misuse. However there are several other different causes that produce it such as metabolism, genetics, autoimmunity, post-ERCP, and trauma for example... This disease is commonly associated with the sudden onset of upper abdominal pain that is usually severe enough to warrant the patient seeking urgent medical attention. Overall, 10-25% of AP episodes are classified as severe. This leads to an associated mortality rate of 7-30% that has not changed in recent years. Treatment is conservative and generally performed by experienced teams often in ICUs. Although most cases of acute pancreatitis are uncomplicated and resolve spontaneously, the presence of complications has a significant prognostic importance. Necrosis, hemorrhage, and infection convey up to 25%, 50%, and 80% mortality, respectively. Other complications such as pseudocyst formation, pseudo-aneurysm formation, or venous thrombosis, increase morbidity and mortality to a lesser degree. The presence of pancreatic infection must be avoided.

How to reference

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Karel Urbánek, Ilona Vinklerová, Ondřej Krystyník and Vlastimil Procházka (2012). Acute Pancreatitis Induced by Drugs, Acute Pancreatitis, Prof. Luis Rodrigo (Ed.), ISBN: 978-953-307-984-4, InTech, Available from: <http://www.intechopen.com/books/acute-pancreatitis/acute-pancreatitis-induced-by-drugs>

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