ON DRUG-INDUCED PANCREATITIS AGAIN
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Key words: drug-induced pancreatitis, drug classes, pathogenesis, latent period, treatment

We have discussed the drug-induced pancreatitis in scientific publications three times [1, 2, 3], but in practice there are situations when this disease, which is an etiological variant of pancreatitis, is not properly interpreted by physicians, that is, the relationship between the possible progress of pancreatitis and administration of a particular drug is not taken into consideration. As a result, the treatment of pancreatitis may be faulty. For this reason, we decide once again to publish the up-to-date information on drug-induced pancreatitis and to extend the experience achieved in the treatment of this disease.

The drug-induced pancreatitis, that is, pancreatitis occurring due to drug administration, is infrequent among the diseases which are etiological variants of pancreatitis. The incidence of drug-induced pancreatitis is about 5 percent of all the cases of acute pancreatitis [149]. But considering the high rate of digestive apparatus diseases, including pancreatic gland diseases, in Ukraine [9], it is evident that these 5 percent of all the cases of acute pancreatitis correspond to the large number of particular patients. It is known that more than 70 drugs can induce pancreatitis.

The diagnosis of drug-induced pancreatitis is complicated, and to make the correct diagnosis, the following three basic requirements must be fulfilled. According to these requirements, it is necessary:

1. To have a well-defined criteria for confirming pancreatitis on the whole.
2. To exclude more frequent causes of pancreatitis, such as alcohol and microlithiasis.
3. To determine the relationship between pancreatitis and the drug administration.

As these requirements cannot be fulfilled in all cases, there are only about three hundreds of absolutely proved cases of drug-induced pancreatitis described in publications [149]. The diagnosis of drug-induced pancreatitis is complicated due to that this disease is rarely accompanied by symptoms of allergy (eosinophilia, urticaria fever, and other symptoms).

In cases of alcohol overindulgence or cholelithiasis (microlithiasis) with concurrent administration of pancreotoxic drugs, the cases of acute pancreatitis (pancreatic attacks) are considered as cases caused by more known etiological factors, and the relationship of the disease with the drug administration is ignored or, if such relationship is detected, this is considered as coincidence [149]. For such patients, the diagnosis of drug-induced pancreatitis is especially complicated, and as the cause of such pancreatitis is long-acting due to the further administration of the corresponding drug, the course of the disease will be severe, recurrent, and resistant even to intensive therapy.

The drugs causing drug-induced pancreatitis are divided into four groups depending on the pathogenesis of this disease. Such groups are the following:

1. True pancreotoxic drugs
2. Drugs inducing pancreatitis through idiosyncrasy
3. Drugs inducing pancreatitis through allergic reactions
4. Drugs inducing pancreatitis trough generation, during the usual metabolic process, of intermediate products which promote pancreatitis

True pancreotoxic drugs have a dose-dependent effect. Using such drugs, it is possible to experimentally induce pancreatitis in animals depending on the drug dose. The drug-induced pancreatitis is in progress within a short or close to short latent period (see Figure 1). In the
Pathogenesis of drug-induced pancreatitis caused by a true pancreototoxic drug, the sensitivity of a particular patient to the drug is of no importance. True pancreotoxic drugs include, for example, paracetamol and erythromycin, which cause pancreatitis at overdosage. In the pathogenesis of drug-induced pancreatitis caused by overdosage of erythromycin, additionally to the pancreotoxicity of this drug, the prokinetic action of the drug is of importance, with the possibility of Oddi's sphincter spasm and intraductal pancreatic hypertension [149].

**Fig. 1. Latent periods between the drug administration and the progress of pancreatitis (S.M. Tenner, W.M. Steinberg [149])**

The short latent period is 1-3 days, the medium latent period is 1-6 weeks, and the long latent period is more than 6 weeks.

Idiosyncrasy, which occurs as the result of inherently deterministic alteration of the typical drug action, is the cause of drug-induced pancreatitis more frequently. Idiosyncrasy to drugs, including idiosyncrasy in connection with the drug-induced pancreatitis, is caused by inherent deficiency of certain enzymes (enzymopathy) which participate in the drug metabolism. It is important to note that these abnormalities are not specific, that is, not allergic. In this case, the disease is practically unpredictable, not dose-dependent, and cannot be reproduced experimentally, as well as the latent period is not constant. In the case of idiosyncrasy, pancreatitis is induced due to the accumulation of pancreototoxic metabolites of the drug when the inactivation or elimination of these metabolites in the specific patient's organism is inadequate. The latent period between the administration of the drug, which induces pancreatitis due to the inadequate metabolism and incomplete elimination of the metabolic products of the drug, that is, due to idiosyncrasy, and the start of the disease is medium or long (see Figure 1). The drugs inducing pancreatitis due to idiosyncrasy include, for example, thiazide diuretics and valerianic acid and its salts (acediprol and other salts) [149].
If pancreatitis is caused by hypersensitivity, that is, has the specific immune-associated (allergic) pathogenesis, the latent period upon each subsequent administration of the drug will be decreased, and the pancreatic attacks will be severer. The allergic drug-induced pancreatitis can be accompanied with urticaria fever, lymphadenopathy, joint pains, or eosinophilia. The drugs inducing allergic pancreatitis or inducing pancreatitis associated with other hypersensitivity reactions include, for example, azathioprine, 6-mercaptopurine, sulfanilamides, 5-aminosalicylates, tetracycline, metronidazole, and dideoxinozine [149].

The fourth variant of the pathogenesis of drug-induced pancreatitis is associated with the formation, at normal metabolism (without idiosyncrasy), of intermediate products which are dangerous for the pancreatic gland. For example, the cause of hypertriglyceridemia is the metabolism of estrogens and isotretinoin. Hypertriglyceridemia is the etiological agent of pancreatitis. If ceftriaxone is used for treatment, biliary sludge which can induce pancreatitis is generated [149].

At the present time, drugs are classified according to the probability for the drugs to induce pancreatitis (see Table 1) [149].

**Class 1 drugs (drugs which pertain to the high risk group)**
A drug pertains to Class 1 drugs if a relapse of pancreatitis after repeated administration of the drug is confirmed at least in one case.

**Class 2 drugs (drugs which pertain to the possible risk group)**
A drug pertains to Class 2 drugs if it is confirmed that pancreatitis is associated with the drug at least in three cases of pancreatitis, and a latent period with the duration characteristic for the drug is observed in more that 75 percent of cases.

**Class 3 drugs (drugs which pertain to the potential risk group)**
A drug pertains to Class 3 drugs if it is confirmed that pancreatitis is associated with the drug at least in two cases of pancreatitis, but without a latent period with the duration characteristic for the drug and without relationship between the administration of the drug and the relapse of pancreatitis.

**Class 4 drugs (drugs which pertain to the questionable risk group)**
A drug pertains to Class 4 drugs if it has the same characteristics as Class 3 drugs but the relationship between pancreatitis and the drug is confirmed in not more than one case or confirmed in more than one case but the corresponding information has not been published.

A drug can concurrently pertain to two or more classes, especially to Class 1 and Class 2.

The distribution of the drugs inducing pancreatitis according to the defined drug classes is presented in Table 1.

Physicians should take into account that one of the groups of drugs which can induce pancreatitis is a group of H2-blockers. For this reason, these drugs are not recommended for treating pancreatitis. It should be noted that omeprazole (Omez) does not pertain to the drugs inducing pancreatitis.

The severity of drug-induced pancreatitis does not depend on the class to which the corresponding drug pertains according to the probability for the drug to induce pancreatitis (see Table 1). In most cases, various drugs induce minor pancreatitis, excluding pentamidine, valerianic acid and its salts, and dideoxinozine. The latter three drugs induce severe acute pancreatitis with possible lethal outcome [149].
The methods of diagnosis and treatment of drug-induced pancreatitis are the same as the traditional methods. It is important to determine that the drug, acting as an etiological agent, can induce pancreatitis and timely to terminate the administration of the drug.

Table 1. Classification of the drugs that can induce acute pancreatitis (S.M. Tenner, W.M. Steinberg [149])

<table>
<thead>
<tr>
<th>Class 1 drugs</th>
<th>Class 2 drugs</th>
<th>Class 3 drugs</th>
<th>Class 4 drugs</th>
</tr>
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<tbody>
<tr>
<td>5-aminosalicylates [14, 15, 28, 32, 75, 123, 128]</td>
<td>Acetaminophen (paracetamol) [1, 43, 64, 72]</td>
<td>Clozapine [60, 81, 92]</td>
<td>Amiodarone [134]</td>
</tr>
<tr>
<td>Arabinosylyctosine [17, 140]</td>
<td>Cimetidine and other blockers of H₂-histamine receptors [20, 73, 77, 111]</td>
<td>Lisinopril and other inhibitors of angiotensin converting enzyme [44, 88, 143, 151]</td>
<td>Ceftriaxone [37]</td>
</tr>
<tr>
<td>Dexamethasone and other corticosteroids [22, 39, 82, 86, 107, 133, 144]</td>
<td>Dideoxinozine [48, 94]</td>
<td>Corticosteroids [22, 39, 82, 86, 107, 133, 144]</td>
<td>Citroheptydine [150]</td>
</tr>
<tr>
<td>Valerianic acid and its salts, for example, acediprol [12, 26, 27, 35, 42, 59, 121, 122, 131, 132, 154, 155, 162]</td>
<td>Valerianic acid and its</td>
<td>Valerianic acid and its</td>
<td>Valerianic acid and its</td>
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</tbody>
</table>

**Note**
In Table 1, the pharmacological names of the drugs are presented.

Earlier, we published information about the drug-induced pancreatitis [2]. But, as before, the methods of diagnosis and treatment of this disease are inadequate. Recently, for the treatment of drug-induced
pancreatitis, we began to use such a drug as omeprazole (Omez), which is the first proton pump inhibitor. The efficiency and safety of this drug were proved by the results of multiple demonstrative studies. At the present time, omeprazole is known as the standard and most studied drug among the drugs of the proton pump inhibitor group. Omeprazole is so effective that it is the most popular drug in the world, with an annual sales volume of about 6 billion US dollars [7].

The injection dosage form of omeprazole is justified in treatment of severe acid-dependent diseases. In practice, good results in treatment are achieved by using not only original but also some generic omeprazoles, such as Omez. For 20 years, this drug has been very popular in the pharmaceutical market of Ukraine. Omez is efficient at a reasonable price. The drug is supplied in capsules of 20mg and 40mg and in injection dosage form. These features allow the physician to use one or another dosage form of Omez depending on the severity of the disease and specific clinical conditions [7].

We have noticed publications with information on the use of double doses of proton pump inhibitors in some cases. For example, the results of the multicentric study of 602 patients with gastropathies associated with administration of antitumor drugs, which was performed when proton pump inhibitors were beginning to be used in the clinical practice, demonstrated that cicatrization in the 8th week of treatment was observed considerably scarcer after administration of 20mg than after administration of 40mg of the drug (61 % versus 81 %) [51]. The use of double doses of proton pump inhibitors is urgent for preventing peptic ulcer complications caused by administration of antitumor drugs [10].

A specifically reasonable method consists in assigning double doses of proton pump inhibitors to patients with low individual sensitivity to these drugs. This method was justified by Professor V.N. Chornobrovyi and his coauthors [10]. They demonstrated that, according to the results of express pH measurements, double doses of proton pump inhibitors in the treatment of erosive-ulcerous diseases of the stomach and duodenum reliably block gastric secretion only in 75 % of patients [4]. So, the situation with the deficiency of doses of proton pump inhibitors is sufficiently common, but in most cases this situation is not registered by physicians which cannot use pH measurements [10]. At the present time, double doses of proton pump inhibitors are used in eradication therapy [90]. The results of the cohort study demonstrate that 15 % of patients with peptic ulcer take not less than one and half standard dose of proton pump inhibitors, and 7 % of patients take not less than two standard doses of proton pump inhibitors [148].

Professor V.N. Chornobrovyi and his coauthors are of opinion that these values will be larger in Ukraine due to the wide propagation of Helicobacter pylori infection and, accordingly, there will be the necessity to provide eradication therapy more frequently. Moreover, the group of patients with high risk of gastropathies caused by antitumor drugs contains more patients due to the larger number of patients with peptic ulcer and gastrointestinal hemorrhage in anamnesis. Additionally, in the pharmaceutical market of Ukraine, there are some proton pump inhibitors whose efficiency does not confirmed by demonstrative studies, and the bioequivalence of which to original drugs is not proved. For this reason, there is the high probability that doses of proton pump inhibitors are not sufficiently efficient and should be increased [10].

Pancreatitis should be classified as an acid-dependent disease which requires therapy with the use of proton pump inhibitors. The reason for the use of proton pump inhibitors is that these drugs are required for the following [8]:

1. To provide the functionally comfortable state of the pancreatic gland.
2. To reduce the risk of gastropathy caused by antitumor drugs (at long-term administration of analgetics).
3. To compensate the insufficient efficiency of enzyme substitution therapy (the Italian Consensus for Diagnosis and Treatment of Chronic Pancreatitis and the Australian Recommendations...
on Treatment of Pancreatic Deficiency provide for the administration of double doses of proton pump inhibitors if steatorrhea is not monitored) [76, 91].

4. To prevent inactivation and intensify the action of enzymatic drugs (specifically skinless drugs) which are used for reducing pain syndrome.

The purpose of the study performed was to determine the efficiency of Omez in the treatment of drug-induced pancreatitis.

During the study, we were controlling 32 patients with drug-induced pancreatitis. The examination and treatment of the patients was accomplished in the gastroenterology section of the Donetsk Regional Clinical Territorial Medical Center. The group of patients consisted of 28 (87.5 %) women and 4 (12.5 %) of men. The patients were at the age of 36 through 64 years.

The control group consisted of 30 practically healthy women and men at the age of 35 through 62 years, with 26 (86.7 %) of women and 4 (13.3 %) of men, that is, the sex and age of the healthy women and men practically corresponded to the sex and age of the patients.

For all the patients, physical complaints and anamnesis were analyzed, and an objective laboratory and instrumental examination was provided. The patients were subjected to clinical blood analysis, clinical urine analysis, scatoscopy, and biochemical blood analysis.

All the biochemical studies were performed by using a Vitalab Flexor-2000 analyzer (the Netherlands). The activity of alpha-amylase and P-isoamylase in blood and urine was determined by using the same analyzer with materials supplied by Lachema (Czechia). The activity of hemolipase was determined by using the same analyzer with materials supplied by Sentinell (Italy). The content of pancreatic elastase-1 in faeces was determined by using an immunoenzyme analyzer Sanofi (France) with materials supplied by Schebo (Germany) [54, 56]. The ultrasonography of the pancreatic gland was performed by using ALOKA SSD-630 apparatus (Japan). The ultrasonography procedure consists in determining the dimensions of the pancreatic gland and its parts (head, body, and tail), sharpness of the gland outlines, uniformity of the gland structure, echogenicity, diameter of the Wirsung’s duct, and presence of pseudocysts and calcificates.

The statistical processing of the results obtained was performed by using a personal computer and a standard Microsoft Excel application program. For each of the parameters, an average value (M) and error (m) were calculated. The validity of the data obtained was estimated by the Student criterion, according to which the probability (p) of data validity was nor less than 95 %. To determine uniform groups according to specified parameters, cluster analysis was performed [5, 6].

Depending on the variant of medicinal treatment, the patients were divided into two groups, with 16 patients in each of the groups. The patients in the main group were subjected to the basic therapy with administration of Omez. At first, when a patient entered the clinic, the drug was administered intravenously, at the standard dose, two times per day for 5 Â 6 days. When the pain syndrome disappeared, Omez was administered per os by 40mg two times per day for 5 Â 6 days, and then by 20mg two times per day for 8 Â 10 days. The patients in the reference group were subjected only to the basic therapy. As an antisecretory agent, pirenzepine was administered at first parenterally and then per os by 50mg two times per day and later by 25mg two times per day. The patients in both the groups were matched by sex and age.

The results of the study are presented below.

We determined that the basic therapy provided distinct advantages in relation to the reduction of pain syndrome in the patients. The decrease or even disappearance of abdominal pain was more frequent in
the patients in the main group as compared with the patients in the reference group. This result was observed in 9 (56.3 %) patients in the main group and 4 (25.0 %) patients in the reference group.

After the treatment of the patients in the main group, normal results of faeces analysis for elastase were recorded for 12 (75 %) patients, light pancreatic insufficiency was detected in 2 (12.5 %) patients, moderate pancreatic insufficiency was detected in one (6.2 %) patient, and severe pancreatic insufficiency was detected in one (6.2 %) patient.

After the treatment of the patients in the reference group, normal results of faeces analysis for elastase were recorded for 10 (62.5 %) patients, moderate pancreatic insufficiency was detected in one (6.2 %) patient, and severe pancreatic insufficiency was detected in one (6.2 %) patient.

The results of studying the intrusion of enzymes into blood depending on the treatment variant used are presented in Table 2.

Table 2. The effect of treatment on the results of the tubeless analysis of the exocrine function of the pancreatic gland

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Main group (n = 16)</th>
<th>Reference group (n = 16)</th>
<th>Control group (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood alpha amylase (cat/l)</td>
<td>Before treatment</td>
<td>After treatment</td>
<td>Before treatment</td>
</tr>
<tr>
<td></td>
<td>1.52 ± 0.30</td>
<td>1.31 ± 0.26</td>
<td>1.54 ± 0.33</td>
</tr>
<tr>
<td>Urine alpha amylase (cat/l)</td>
<td>6.32 ± 0.58</td>
<td>5.64 ± 0.52</td>
<td>6.41 ± 0.53</td>
</tr>
<tr>
<td>Blood isoamylase (cat/l)</td>
<td>2.64 ± 0.23</td>
<td>0.91 ± 0.11</td>
<td>2.67 ± 0.14</td>
</tr>
<tr>
<td>Urine isoamylase (cat/l)</td>
<td>6.58 ± 0.36</td>
<td>3.46 ± 0.24</td>
<td>6.55 ± 0.39</td>
</tr>
<tr>
<td>Hemolipase (unit/l)</td>
<td>76.0 ± 4.0</td>
<td>31.0 ± 4.0</td>
<td>75.0 ± 7.0</td>
</tr>
</tbody>
</table>

* The difference between the parameters before and after treatment is statistically reliable.
** The difference between the parameters for the main group and the reference group is statistically reliable.

The activity of alpha-amylase in blood and urine of the patients in both the groups after the treatment was as normal as before the treatment. Only in one (6.2 %) patient from the reference group, the parameters of activity of alpha-amylase in both biological fluids were enhanced after the treatment. In all the patients in the main group, which at first had hyperamylasemia and hyperamylasuria, the parameters characterizing the activity of alpha-amylase were normalized due to the treatment.

The activity of P- isoamylase in blood and urine of the patients in the main group was reliably reduced in the process of treatment, and after the treatment, did not differ reliably from the parameters characteristic for the patients in the control group. In the reference group, only the activity of P- isoamylase in blood was reliably reduced, and the activity of P- isoamylase in urine had an unreliable tendency to decrease and considerably exceeded the normal value (the activity of P- isoamylase in urine of the patients after the treatment did not differ from that of the practically healthy persons) (see Table 2).

The activity of hemolipase of the patients in the main group was reliably reduced and normalized. In the reference group, there was only tendency to such reduction, and the value of this parameter exceeded the normal value (see Table 2).

After the treatment, the head of the pancreatic gland was enlarged in one (6.2 %) patient in the main group and in two (12.5 %) patients in the reference group. The increase of the body and head of the pancreatic gland was not detected in the patients in the main group, and was detected in one (6.2 %)
patient in the reference group. The increase of the whole pancreatic gland or only the tail of the pancreatic gland after the treatment was not detected in the patients in both the groups. Blurring of the pancreatic gland outline was detected in 8 (50 %) patients in the main group and 11 (68.8 %) patients in the reference group. The enhanced echogenicity of the pancreatic gland tissue after the treatment according to the basic variant was unchanged in 9 (56.3 %) patients in the main group and 11 (68.8 %) patients in the reference group. The reduced echogenicity was detected in one (6.2 %) patient in the main group and 4 (25 %) patients in the reference group. The nonuniformity of the parenchymatous tissue of the pancreatic gland after the treatment was detected in the patients in both the groups.

The widening of the Wirsung’s duct after the treatment was detected in 5 (31.3 %) patients in the main group and 6 (37.5 %) patients in the reference group.

Pseudocysts were detected in 2 (12.5 %) patients in each of the groups.

Conclusions

The drug-induced pancreatitis is characterized by four variants of pathogenesis. More than 70 drugs which cause drug-induced pancreatitis are classified according to four classes depending on the probability of occurrence of this disease. Additionally, three types of latent periods between the administration of the drug and the manifestation of the disease are defined. Most of drugs induce light forms of pancreatitis. For treatment of pancreatitis, it is necessary to use conventional methods of therapy and drugs, including antisecretory drugs. But it is necessary to take into account that H2-blockers can cause drug-induced pancreatitis, so such drugs are nor recommended for treatment of pancreatitis. Omez is considered as an efficient drug for the therapy of pancreatitis, as this drug does not cause drug-induced pancreatitis and allows specified results to be obtained by using various dosage forms in specific clinical conditions.


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