Drug induced acute pancreatitis: incidence and severity

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Abstract
To determine the incidence and severity of drug induced acute pancreatitis, data from 45 German centres of gastroenterology were evaluated. Among 1613 patients treated for acute pancreatitis in 1993, drug induced acute pancreatitis was diagnosed in 22 patients (incidence 1.4%). Drugs held responsible were azathioprine, mesalazine/sulfasalazine, 2',3'-dideoxyinosine (ddI), oestrogens, frusemide, hydrochlorothiazide, and rifampicin. Pancreatic necrosis not exceeding 33% of the organ was found on ultrasonography or computed tomography, or both, in three patients (14%). Pancreatic pseudo-cysts did not occur. A decrease of arterial Po₂, reflecting respiratory insufficiency, and an increase of serum creatinine, reflecting renal insufficiency as complications of acute pancreatitis were seen in two (9%) and four (18%) patients, respectively. Artificial ventilation was not needed, and dialysis was necessary in only one (5%) case. Two patients (9%) died of AIDS and tuberculosis, respectively; pancreatitis did not seem to have contributed materially to their death. In conclusion, drugs rarely cause acute pancreatitis, and drug induced acute pancreatitis usually runs a benign course.

Keywords: acute pancreatitis, aetiology, drugs.

Ever since the first reports on cortisone and thiazides inducing acute pancreatitis, a large number of single case reports were published on – often fatal – drug induced acute pancreatitis. Subsequent review articles criticised the time interval between drug application and the onset of acute pancreatitis, dose, and rechallenge trials. Published reports have identified about 50 drugs that definitely or possibly may be held responsible for inducing acute pancreatitis. 1-6

Our report deals for the first time with the question of how frequently drug induced acute pancreatitis actually occurs and whether it takes as severe a course as indicated in many case reports.

Results
During the 12 month period of 1993, 1613 patients with acute pancreatitis had been treated by the 45 participating centres of gastroenterology. Alcoholism was the most prevalent aetiology, followed by biliary tract disease. Smaller groups had other (post-endoscopic retrograde cholangiopancreatography and post-traumatic, postoperative, viral or unknown aetiologies) or unknown aetiologies. In 22 patients (12 female, 10 male, mean age 45, range 19-80 years), drug induced acute pancreatitis was diagnosed, the incidence being 1.4% (Table I). Drugs considered responsible were azathioprine (n=6), mesalazine/sulfasalazine (n=5), 2',3'-dideoxyinosine (ddI) (n=4), oestrogens (n=3), frusemide (n=2), and hydrochlorothiazide and rifampicin (n=1) each (Table II). For ethical reasons, a rechallenge was refused by most participating hospitals and performed with positive results in only three cases (azathioprine, n=2; mesalazine, n=1) (Table II). Mean hospital stay was 25-5 days, but varied considerably from patient to patient (range 2-78 days). Less than one third necroses were found on ultrasonography or computed tomography.

Patients and methods
To determine the incidence of drug induced pancreatitis, we asked 45 German centres of gastroenterology how many patients they had treated in 1993 for acute pancreatitis and how often the aetiology was drug related. To obtain an impression of disease severity, we further asked for the length of the hospital stay, the occurrence of acute respiratory and renal failure, the development of pancreatic pseudocysts and necroses, and resulting death rate.

All data on drug induced pancreatitis were evaluated by us. We included only those patients for whom the centres had already excluded all other aetiologies, except drugs, which have been shown either in published reports or in the specifically reported patient to reinduce acute pancreatitis on rechallenge, or which are among those – according to previous reports – strongly suspected of inducing acute pancreatitis. 1-6 When fatal outcome was reported, we tried to establish whether this resulted from pancreatitis or the underlying disease.
Table II  Severity of the disease in 22 patients with drug induced acute pancreatitis

<table>
<thead>
<tr>
<th>Parameters of severity</th>
<th>No of patients (%)</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Necroses on ultrasound/computed tomography</td>
<td>19 (86)</td>
<td>ddi (2×) Azathioprine</td>
</tr>
<tr>
<td>Absent</td>
<td>3 (14)</td>
<td></td>
</tr>
<tr>
<td>&lt;33%</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>33–50%</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>&gt;50%</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pseudocysts</td>
<td>22 (100)</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Acute respiratory failure</td>
<td>17 (77)</td>
<td>ddi Frusemide</td>
</tr>
<tr>
<td>PO2 &gt;70 mm Hg</td>
<td>4 (18)*</td>
<td>Oestrogens Hydrochlorothiazide</td>
</tr>
<tr>
<td>PO2 ≤60 mm Hg</td>
<td>1 (5)</td>
<td>Frusemide</td>
</tr>
<tr>
<td>Artificial ventilation</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>1 (5)*</td>
<td>Frusemide</td>
</tr>
<tr>
<td>Serum creatinine &lt;1-2 mg/dl</td>
<td>2 (9)</td>
<td>ddi Frampicin</td>
</tr>
<tr>
<td>Dialysis</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Fatal outcome</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*One patient with chronic renal failure was excluded.

Discussion

Our data show that drug induced acute pancreatitis occurs rarely in clinical practice and usually takes a benign course.

It may be argued, however, that the retrospective design of our study is a drawback and that in a prospective trial the frequency would have been higher. A prospective trial would mean that all patients receiving drugs definitely or probably associated with acute pancreatitis would have been screened for possible development of acute pancreatitis. Such a study is not easy for several reasons. The number of drugs possibly inducing acute pancreatitis is large, time intervals between first application of any one drug and development of acute pancreatitis differ; and screening procedures for drug induced pancreatitis such as enzyme measurement and ultrasound examination may be ineffective.

The incidence of drug induced acute pancreatitis in our study possibly reflects the normal clinical situation. A higher incidence rate has been found among patients with diseases especially associated with acute pancreatitis, such as inflammatory bowel disease and AIDS.

Table III  Review of published reports on cases and fatal outcome of acute pancreatitis induced by drugs held responsible for the induction of the disease in the reported 22 patients

<table>
<thead>
<tr>
<th>Drug</th>
<th>Reported cases</th>
<th>Fatal outcome (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine</td>
<td>21</td>
<td>5 (23-8)</td>
</tr>
<tr>
<td>Mesalazine/sulfasalazine</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>2',3'-dideoxyinosine (ddI)</td>
<td>35</td>
<td>5 (14-3)</td>
</tr>
<tr>
<td>Oestrogens</td>
<td>31</td>
<td>0</td>
</tr>
<tr>
<td>Frusenide</td>
<td>21</td>
<td>3 (14-9)</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>10</td>
<td>5 (50-0)</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>15</td>
<td>0</td>
</tr>
</tbody>
</table>

Severe drug induced acute pancreatitis was low in our study. This differs from published reports, which show a high incidence of fatal outcome at least from azathioprine, and ddi, frusenide, and hydrochlorothiazide. However, a high incidence probably does not reflect clinical routine.

In accordance with our findings, there are no fatal cases of acute pancreatitis in published reports following mesalazine/sulfasalazine, oestrogens or rifampicin.

Despite the low incidence and the moderate severity of drug induced acute pancreatitis, all patients with acute pancreatitis of unknown etiology should be carefully questioned on drugs possibly responsible for the induction of the disease. In positive cases, the drug held responsible should be omitted to reduce the possibility of further episodes of acute pancreatitis.

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