

# 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 pseudocysts did not occur. A decrease of arterial  $PO_2$  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.

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Keywords: acute pancreatitis, aetiology, drugs.

Ever since the first reports on cortisone<sup>1</sup> and thiazides<sup>2</sup> 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.<sup>3-6</sup>

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.

## 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.<sup>3-6</sup> When fatal outcome was reported, we tried to establish whether this resulted from pancreatitis or the underlying disease.

Each centre was responsible for the exclusion of the main aetiologies of acute pancreatitis, namely alcohol and biliary disease, which was done by means of case history given by the patient or his relatives/friends (alcohol) or ultrasound (biliary disease).

Furthermore, all centres were responsible for the diagnosis of acute pancreatitis, which was usually based on typical signs and symptoms, an increase in enzyme activity, and the signs of the disease upon imaging procedures, such as ultrasound and computed tomography, which were asked for.

## 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 (ERCP), post-traumatic, postoperative, viral genesis) or unknown aetiologies. In 22 patients (12 female, 10 male, mean age 42, 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

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TABLE I Aetiology of acute pancreatitis in 1613 patients

Aetiology	No of patients (%)
Alcohol	729 (45.2)
Biliary	635 (39.4)
Other	92 (5.7)
Unknown	135 (8.4)
Drugs	22 (1.4)

TABLE II Severity of the disease in 22 patients with drug induced acute pancreatitis

Parameters of severity	No of patients (%)	Drug
Necroses on ultrasound/computed tomography		
Absent	19 (86)	
<33%	3 (14)	ddI (2×) Azathioprine
33–50%	0	
>50%	0	
Pseudocysts		
Absent	22 (100)	
Present	0	
Acute respiratory failure		
PO <sub>2</sub> >70 mm Hg	20 (91)	
PO <sub>2</sub> 60–70 mm Hg	1 (5)	Rifampicin
PO <sub>2</sub> <60 mm Hg	1 (5)	ddI
Artificial ventilation	0	
Acute renal failure		
Serum creatinine <1.2 mg/dl	17 (77)	
Serum creatinine >1.2 mg/dl	4 (18)*	ddI Frusemide Oestrogens Hydrochlorothiazide
Dialysis	1 (5)*	Frusemide
Fatal outcome	2 (9)	ddI Rifampicin

\*One patient with chronic renal failure was excluded.

tomography in three (14%) patients. None of the patients developed pancreatic pseudocysts. Arterial PO<sub>2</sub> was below normal in two (9%) patients, but neither required artificial ventilation. Serum creatinine was above normal in five (23%), two (9%) of them requiring dialysis, of whom one had chronic renal failure. Two (9%) patients died, but death was caused by AIDS and tuberculosis, respectively. The first patient had had ddI, the second rifampicin induced acute pancreatitis.

### 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<sup>3,6</sup>; 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<sup>7</sup> and ultrasound examination<sup>8</sup> may be ineffective.

The low 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

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

Drug	Reported cases	Fatal outcome (%)
Azathioprine	21	5 (23.8)
Mesalazine/sulfasalazine	19	0
2',3'-dideoxyinosine (ddI)	35	5 (14.3)
Oestrogens	31	0
Frusemide	21	3 (14.9)
Hydrochlorothiazide	10	5 (50.0)
Rifampicin	15	0

pancreatitis, such as inflammatory bowel disease<sup>9,10</sup> and AIDS.<sup>11–16</sup> In inflammatory bowel disease, Haber *et al*<sup>10</sup> saw acute pancreatitis in 13 (3.3%) of 400 patients treated with 6-mercaptopurine, and Sturdevant *et al*<sup>17</sup> in six (5.3%) of 113 patients treated with azathioprine. In patients with AIDS treated with 2',3'-ddI, the incidence rate varied from 7.4% (seven of 95 patients),<sup>14</sup> 15.9% (seven of 44 patients)<sup>15</sup> to 23.5% (12 of 51 patients).<sup>18</sup> It should be noted that in this study drug induced acute pancreatitis was only reported in adults and that in paediatric patients the incidence of asparaginase, corticosteroid, or valproic acid induced acute pancreatitis, or all three, may be more frequent.<sup>3–6</sup>

Severity of 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,<sup>17,19–26</sup> ddI,<sup>11–16,18,27</sup> frusemide,<sup>28–34</sup> and hydrochlorothiazide.<sup>2,35,36</sup> However, such a high incidence probably does not reflect clinical routine (Table III). Most studies on drug induced acute pancreatitis are case reports that are meant to serve as a warning or signpost for other clinicians. This explains why there are more reports on severe than mild cases.

Furthermore, all fatal cases after an intake of azathioprine occurred after renal transplantation, and all ddI induced cases coincided with AIDS, both underlying diseases being not infrequently associated with acute pancreatitis. Of the three patients with fatal frusemide pancreatitis, one had a myocardial infarction and the other a cardiac problem, in addition,<sup>30</sup> and the third patient was an alcoholic with pancreatic calcifications, a sign of chronic pancreatitis, who died of renal failure in a diabetic coma.<sup>31</sup> Three of the five fatal hydrochlorothiazide<sup>2,35</sup> cases were treated at a time when modern intensive treatment of acute pancreatitis was unknown.

In accordance with our findings, there are no fatal cases of acute pancreatitis in published reports following mesalazine/sulfasalazine,<sup>37–52</sup> oestrogens,<sup>53,54</sup> and rifampicin.<sup>55</sup>

Despite the low incidence and the moderate severity of drug induced acute pancreatitis, all patients with acute pancreatitis of unknown aetiology 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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