ORIGINAL ARTICLE

Impact of Drugs as a Cause of Acute Pancreatitis: A Single Institutional Case-Matched Study

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ABSTRACT

Context and Objectives Many prescription drugs have acute pancreatitis as a reported side effect. In a clinical situation, however, it is difficult to identify a specific drug as a causative factor for acute pancreatitis. **Design** The study employed a case–control approach to investigate the role of prescription drugs with acute pancreatitis as a documented side effect (PDPS) as a cause of acute pancreatitis or pancreatic necrosis. **Patients** The use of PDPS in 1107 consecutive patients admitted with acute pancreatitis were compared with the use of PDPS in a control group consisting of 1107 sex- and age-matched patients admitted with acute abdominal emergencies other than acute pancreatitis. **Results** In total, 87 different PDPS were recorded: 76 in patients with acute pancreatitis, and 57 in patients with acute abdominal emergencies other than pancretitis. A significantly higher number of patients admitted with acute pancreatitis (419/37.9%) used PDPS compared to patients with other acute abdominal emergencies (373/33.7%) (p=0.041). Of the 214 patients who used more than one PDPS, there were more with acute pancreatitis (125/11.3%) than in patients with other abdominal emergencies (89/8.0%), but the difference was not significant (p=0.774). There was no association between the use of PDPS and development of pancreatic necrosis in patients with acute pancreatitis. **Conclusion** There was a higher frequency of use of PDPS in patients admitted with acute pancreatitis than in patients admitted with other acute abdominal conditions. Drugs may thus contribute to the development of acute pancreatitis, but identification of a specific drug as the definitive cause is still challenging. There was no association between the use of PDPS and the development of pancreatic necrosis.

INTRODUCTION

The role of drugs as a cause of acute pancreatitis (AP) is a topic of continued debate. Worldwide, 525 different drugs have been reported as a possible cause of AP in patient series and case reports [1, 2, 3, 4, 5, 6, 7]. Most reported drug-induced cases are mild and self-limiting, but necrotizing pancreatitis and fatal cases have been described [8, 9, 10]. The incidence of drug-induced AP is considered low, at 0.5–2% of all cases [4, 8]. Some even question whether drug-induced pancreatitis exists [11], although others suggest it is under-reported [12].

Many patients admitted to hospital with acute pancreatitis use prescription drugs with acute pancreatitis as a documented side effect (PDPS). A reasonable timespan between the start of drug administration and attack of acute pancreatitis is suggested [13]. Most patients have used these drugs on a regular basis for years, and several patients use more than one PDPS. It is therefore very difficult to conclude with certainty that a specific drug is the main cause of or a significant contributor to AP. There exists no diagnostic test to confirm or discard this conclusion during a patient's hospital stay.

In the present study, a risk analysis was performed. Drugs differ in their probability of inducing AP, reported on a spectrum from 'frequent' (1/10 patients) to 'rare' (<1/10.000) and 'case reports', which might help when considering the probability of a drug as causative factor [14, 15]. In a clinical situation, examinations to rule out other more frequent and recognized causes of pancreatitis should be performed before a diagnosis of drug-related cause is decided [16, 17].

To investigate the potential pancreatitis-inducing effect of drugs in a clinical situation, we conducted a study comparing drugs used by a group of patients admitted with AP with drugs used by a sex- and age-matched control group of patients admitted with AA. The hypothesis was that the patients admitted with AP used more PDPS than the control group with AA.

METHODS

In total, 1107 consecutive patients admitted to a tertiary university centre with AP from January 2010 to December 2018 were included in the study. The control

Received September 29th, 2021 - Accepted October 20th, 2021
Keywords Pancreas; Pancreatic drugs; Acute pancreatitis; Drug-induced pancreatitis; Aetiology; Pancreatic necrosis; Polypharmacy
Nonstandard abbreviations AA Acute Abdominal Emergencies Other Than Acute Pancreatitis; AP Acute Pancreatitis; PDPS Prescription Drugs with Acute Pancreatitis as a Documented Side Effect
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group consisted of 1107 consecutive patients admitted to the hospital with AA from January 2018. Recruitment continued until sex- and age-matched groups were achieved. There were 583 (52.7%) males and 524 (473%) females in both groups, with a mean age of 55.6 years (±18.8 years): aged 1–9 years (4/0.4%), 10–19 years (25/2.2%), 20–29 years (75/6.8%), 30–39 years (137/12.3%), 40–49 years (175/15.8%), 50–59 years (209/18.9%), 60–69 years (197/17.8%), 70–79 years (155/14.0%), 80–89 years (106/9.6%), and >90 years (24/2.2%). The control group consisted of patients with acute abdominal pain not further specified (540/48.9%), acute appendicitis (112/10.2%), acute cholecystitis/cholangitis (109/9.8%), readmitted after surgery (103/9.3%), acute bowel obstruction (97/8.8%), acute perineal abscess (39/3.5%), acute diverticulitis (29/2.6%), rectal bleeding (29/2.6%), incarcerated hernia (20/1.8%), acute obstipation (12/1.1%), bezoar in oesophagus/stomach (9/0.8%), hematemesis (6/0.5%).

AP was diagnosed if two of the three following criteria were fulfilled: acute upper abdominal pain, serum amylase level above three times the upper normal level, or CT scans indicating AP [18]. The aetiology of AP was thoroughly investigated via clinical history, blood samples, ultrasonography and CT scans; moreover, on clinical suspicion of bile stones or anatomical variations, MRI and endoscopic ultrasonography (EUS) were performed. Genetic evaluation was not performed. The presence of pancreatic necrosis was diagnosed by CT scans during the patient's hospital stay. The use of PDPS was recorded in all patients by generic names, number of drugs per patient and the risk of acute pancreatitis according to the Norwegian Pharmaceutical Product Compendium [14] and case reports.

The risk of acute pancreatitis for a specific drug was based on information about side effects provided by the manufacturer, and was sorted into six different categories:

a) very common (>1/10 patients),

b) common (>1/100–<1/10 patients),

c) less common: (>1/1000–<1/100 patients),

d) rare: (>1/10.000–<1/1000 patients),

e) very rare: (<1/10.000 patients), and

f) acute pancreatitis has been described in case reports/ frequency not known.

STATISTICS

In this comparative observation study, no advanced statistical methods were used. The aim was to investigate a possible difference between the study group and a control group with regards to the use of drugs that might induce acute pancreatitis. Pearson's Chi-Square was used to test significance between these groups. Age is given as mean (SD).

RESULTS

A significantly higher number of patients admitted with AP (419/37.9%) used PDPS than patients with AA (373/33.7%; p=0.041; see **Table 1**. A list of drugs used in the AP and AA groups, stratified according to the risk of acute pancreatitis, is shown in **Tables 2 and 3**, respectively. The number of patients using these drugs is shown as parentheses in these tables, and integrated into **Table 4**. Eighty-seven different PDPS were recorded in the 2214 patients: 76 in patients with AP, and 57 in patients with AA. Forty-six of these drugs were used in both groups, and were used by the highest number of patients.

There were no significant differences between the groups with regards to the drugs' risk of inducing acute pancreatitis (p=0.087). Drugs with the risk-categories 'very common', 'common' and 'less common' were mainly antineoplastic, immunosuppressant, anti-inflammatory, antihypertensive and lipid-lowering drugs. Drugs with a frequency of 'rare' and 'less rare' were lipid-lowering, anti-inflammatory, antidiabetic, antidepressant/psychotics, antiepileptic, drugs for oral anticonception and others.

A total of 214 patients-125 (11.3%) with AP and 89 (8%) with AA used more than one PDPS (**Table 5**). The number of patients with polypharmacy was higher in the group with AP, but the difference was not significant (p=0.774).

The aetiology of pancreatitis is presented in **Table 6** with the corresponding use of PDPS. Apart from the group where drugs were diagnosed as the cause of pancreatitis, PDPS were used by 27–47% of the patients in the other groups, with no significant difference between them (p=0.476). Patients where drugs were diagnosed as the cause of pancreatitis were excluded from this statistical analysis, as all of them used drugs and this would mask the importance of PDPS in the other groups. Drug-induced pancreatitis was diagnosed by the physician in charge in 38 patients who used *azathioprine* (n=10), *atorvastatin* (n=3), *simvastatin* (n=2), *methotrexate* (n=2), *asparaginase* (n=1), *diclofenac* (n=1), *mycophenolate tacrolimus* + *prednisolone* (n=1), *mesalazine* (n=1), *simvastatin* + *hydrochlorotiazide* (n=1), *pregabalin* (n=1), *pravastatin* (n=1), *dasatinib* + *linotinib* (n=1), *clozapine* (n=1), *losartan hydrochloride* + *enalapril* (n=1), *infliximab* + *sulfasalazine* (n=1), *ibuprofen* (n=1), *methylprednisolone* (n=1), *ezetimibe*

Table 1. Number of patients using prescription drugs with acute pancreatitis as documented side effect (PDPS) with acute pancreatitis and acute abdominal pain.

	Acute pancreatitis (AP) n (%)	Acute abdominal pain (AA) n (%)	p
PDPS	419 (37.9)	373 (33.7)	0.041
No PDPS	688 (62.1)	734 (66.3)	
All	1107 (100)	1107 (100)	

Table 2. Drugs used by patients admitted with acute pancreatitis (AP) stratified according to the risk of acute pancreatitis.

Very common n=1	Common	Less common n=146	Rare n=228	Very rare n=75	Case reports n=118
>1/10	>1/100 <1/10	>1/1000 <1/100	>1/10.000 <1/1000	<1/10.000	Unknown
asparaginase(1)		atorvastatin(71)	simvastatin(103)	diclofenac(21)	oestradiol(18)
		azathioprine (19)	prednisolone(42)	amlodipine(13)	furosemide(18)
		ramipril(19)	candesartan hydroclotiazid(17)	klopidogrel(8)	losartan(17)
		enalapril(11)	lansoprazole(13)	lisinopril(7)	gabapentin(9)
		etorikoksib(6)	pregabalin(12)	pravastatin(6)	ezitimib(6)
		methotrexat(5)	mesalazin(7)	ciprofloxacin(5)	irbesartan hydroklortiazid(6)
		tacrolimus(4)	kvetiapin(6)	metylprednisolon(4)	kodeinfosfat(6)
		infliximab(3)	venlafaksin(5)	ciklosporin(3)	oestrogen(5)
		topiramat(2)	mirtazipin(4)	okskarbazepin(3)	losartan hydroclorid(4)
		adalimumab(1)	cannabis(3)	karbamazepin(2)	kokain(3)
		dasatinib(1)	valpronat(3)	oktreotid(2)	levonogestrel(3)
		linotinib(1)	olanzapine(2)	ibuprofen(1)	drospirenon(3)
		sorafenib(1)	rosovastatin(2)		heroin(2)
		sunitinib(1)	sertraline hydrochloride(2)		mycofenolat(2)
		tamoxifen(1)	azithromycin(1)		sitagliptin(2)
			clozapine(2)		sulfasalazine(2)
			hydroclortiazid(1)		aripiprazol(1)
			levetiracetan(1)		buprenorfin(1)
			linagliptin(1)		etanercept(1)
			olmesartan hydroclorid(1)		gbh(1)
			trimetoprim sulfametoxazol(1)		karbimazol(1)
			vinorelbin(1)		klaritromycin(1)
					memantin hydroclorid(1)
					olasalazin(1)
					rivastigmin(1)
					terbinafin(1)

Numbers in parenthess are number of patients who used the specified drug

Table 3. Drugs used by patients admitted with acute abdominal pain (AA) stratified according to risk of acute pancreatitis (AP).

Very common	Common n=2	Less common n=149	Rare n=169	Very rare n=53	Case reports n=116
>1/10	>1/100 <1/10	>1/1000 <1/100	>1/10.000 <1/1000	<1/10.000	Unknown
		atorvastatin(97)	simvastatin(75)	amlodipine(25)	gabapentin(22)
		enalapril(14)	prednisolone(32)	diclofenac(6)	furosemide(18)
				pravastatin(6)	losartan(15)
	sirolimus(2)	azatioprin(13)	pregabalin(11)	klopidogrel(5)	losartan hydroclorid(11)
		ramipril(10)	candesartan hydroclotiazid(8)	bisoprolol hydroclortiazid(2)	ezitimib(10)
		methotrexat(4)	kvetiapin(10)	leflunomid(2)	estradiol(8)
		tacrolimus(4)	mirtazipin(4)	liraglutid(2)	irbesartan hydroklortiazid(8)
		sunitinib(2)	rosovastatin(5)	ciklosporin(1)	kodeinfosfat(5)
		adalimumab(1)	valpronat(4)	karbamazepin(1)	levonogestrel(5)
		eluksadolin(1)	levetiracetan(3)	lisinopril(1)	mycofenolat(5)
		linezolid(1)	linagliptin(3)	metylprednisolon(1)	lanreotid(3)
			mesalazin(5)	okskarbazepin(1)	estrogen(2)
			risperidone(3)		aripiprazol(1)
			kortison(2)		drospirenon(1)
			olanzapine(2)		enolapril(1)
			hydroclortiazid(1)		rivastigmin(1)
			piroxicam(1)		
			sertraline hydrochloride(1)		
			venlafaksin(1)		

Numbers in parentheses are number of patients who used the specified drug

Table 4. Number of prescription drugs with acute pancreatitis as a documented side effect (PDPS) in patients admitted with acute pancreatitis and acute abdominal pain stratified according to the risk for drug-induced pancreatitis.

Probability of acute pancreatitis	Acute pancreatitis (AP) n (%)	Acute abdominal pain (AA) n (%)	p
Very common: >1/10	1 (0.2)	0 (0)	0.087
Common: >1/100, <1/10	0 (0)	2 (0.4)	
Less common: >1/1000, <1/100	146 (25.7)	147 (30.1)	
Rare: >1/10.000, <1/1000	230 (40.5)	171 (35.0)	
Very rare: <10.000	75 (13.2)	53 (10.8)	
Case reports	116 (20.4)	116 (23.7)	
All	568 (100)	489 (100)	

Table 5. Number of prescription drugs with acute pancreatitis as a documented side effect (PDPS) in patients admitted with acut pancreatitis and acute abdominal pain stratified according to the risk for drug-induced pancreatitis.

Number of PDPS	Acute pancreatitis (AP) n (%)	Acute abdominal pain (AA) n (%)	p polypharmacy	p all
1	294 (70.2)	284 (76.2)		0.325
2	98 (23.4)	68 (18.2)	0.774	
3	20 (4.8)	15 (4.0)		
4	6 (1.4)	6 (1.6)		
5	1 (0.2)	0 (0)		
All	419 (100)	373 (100)		

Table 6. Cause of acute pancreatitis and corresponding use of prescription drugs with acute pancreatitis as a documented side effect (PDPS).

	Cause of pancreatitis n (%)	Patients using PDPS n (%)	p
Gall stone	496 (44.8)	165 (33.3)	0.476
Alcohol	143 (12.9)	48 (33.6)	
ERCP	75(6.8)	25 (33.3)	
Drugs	38 (3.4)	38 (100)*	
Tumor pancreas	11 (1.0)	3 (27.3)	
Hyper-triglyceridemia	10 (0.9)	4 (40)	
Others	21 (1.9)	10 (47.6)	
Unknown	313 (28.3)	126 (40.3)	
All	1107 (100)	419 (37.9)	

*patients were not included in the statistical analyses

Table 7. Patients with or without necrosis categorized according to use of prescription drugs with acute pancreatitis as a documented side effect (PDPS).

	No PDPS n (%)	PDPS n (%)	p
Interstitial	593 (86.2)	363 (86.6)	0.835
Necrotic	95 (13.8)	56 (13.4)	
All	688 (100)	419 (100)	

(n=1), *infliximab* + *azathioprine* + *prednisolone* (n=1), *simvastatin* + *furosemide* + *prednisolone* + *lansoprazole* (n=1), *adalimumab* (n=1), *methotrexate* + *trimethoprim* + *sulfamethoxazole* (n=1), *olanzapine* (n=1), *tacrolimus* (n=1) and *simvastatin* + *atorvastatin* (n=1). The aetiology in the 21 patients named 'others' were pancreas divisum (n=5), postoperative pancreatitis (n=4), stone in the pancreatic duct (n=4), hyperparathyroidism (n=2), viral aetiology (n=2), pancreatitis after percutaneous transhepatic drainage (n=2), trauma (n=1) and acupuncture (n=1). Of these patients, 47.6% used potential pancreatitis-inducing drugs, as did 40.3% of the patients with unknown aetiology. In 313 patients (28.3%), the cause of acute pancreatitis could not be determined, despite extensive investigation. However, 40.3% used PDPS, which did not differ from the other groups.

The possible effect of drugs on the development of necrotizing pancreatitis was investigated, and is shown in **Table 7**. There was no association between the use of PDPS and development of necrosis in this study (p=0.835).

DISCUSSION

The main finding in the present study is that the group of patients admitted to hospital with AP used more PDPS than patients in a control group with AA. This supports the findings in many reports and patient series that drugs are a contributing factor in acute pancreatitis.

Previous studies have described an additive effect of polypharmacy [19]. In a case report, Bracamonte et al. described an increased risk of pancreatitis in a patient using two potential pancreatitis-inducing drugs: *lisinopril* and *olanzapine* [20]. In a population study, polypharmacy increased the incidence of AP, and the increase was proportional to the number of drugs [21]. The drugs in this report were not classified according to their probability to induce AP, and the interpretation of polypharmacy data

was not helpful to identify a specific drug as the causative factor [22]. The previous findings of an additive effect of polypharmacy on the risk of AP were not supported by the present study.

The classification of PDPS according to the risk of inducing acute pancreatitis showed that only one drug is *L-asparaginase*, used in the treatment of leukaemia—was a 'very common' (>1/10 patients) inducer of AP; it was consequently defined as the cause of acute pancreatitis in that patient with a high degree of certainty. A number of drugs classified as having a less-common risk of AP (>1/1000, <1/100 patients)—e.g., *azatioprin*, *methotrexate* and *tacrolimus*, some of them in combination with other drugs—were defined as the cause of AP with a lesser degree of certainty. There was also no significant difference between AP and AA with regards to drugs when the risk of pancreatitis was considered. Thus, apart from cases in which drugs with a high risk of pancreatitis were used, a diagnosis of drug-induced pancreatitis based on risk analysis is not helpful.

The timespan between drug administration and attack of pancreatitis is considered important, but is also under discussion. Reported timespans from drug administration to AP differ greatly in prior reports. In one report, the authors suggest that AP was induced by dapsone, administered five years prior to the acute pancreatitis and used regularly since then, this was termed a delayed drug-induced pancreatitis [23]. In another study, 40% of the cases of acute drug-induced pancreatitis occurred within 4 weeks of administration [13]. In the present study, almost all patients had used the suspected drug for a long time. This renders arguments about cause and effect speculative, as the timespan from drug administration to acute pancreatitis was not recorded.

Several other drug-classification systems have been published [17, 24, 25]. Karch et al. propose a classification system of drugs according to the scientific proof of drug-inducing effect, including duration of use, de-challenge and re-challenge: definitive effect-reasonable timespan from drug administration to attack of pancreatitis, symptoms eventually subside upon stopping medication (de-challenge), and symptoms reoccur upon new administration of drug (re-challenge); probable effect-reasonable timespan, symptoms eventually subside upon stopping medication (de-challenge), and acute pancreatitis cannot be explained by other causes after extensive investigation; and possible effect-reasonable timespan, follows a known response pattern, but may be explained by other factors [17, 24]. A summary of drugs with definitive and probable cause of drug-induced pancreatitis, including a summary of 149 drugs that have been re-challanged has been published by Bellocchi et al. [17]. The World Health Organization also states that definitive proof of causality is indicated if AP reoccurs upon re-challenge [1, 26]. In the present study, no re-challenge tests were performed.

We did not find any association between the use of PDPS and development of pancreatic necrosis, nor between the use of PDPS and patients with causes of acute pancreatitis other than drugs.

The pathological mechanisms for drug-induced pancreatitis remain unclear. Hung et al. divide the physiological mechanisms for drug-induced acute pancreatitis into structural, metabolic, vascular, toxin- or immune-mediated mechanisms [27]. The mechanism for the drug-induced pancreatitis in the present study is not known. It is possible that drugs in some patients may sensitize the body to pancreatitis. Further clinical studies in this field are therefore needed, as the prescription of drugs to prevent and treat many diseases is increasing alongside the incidence of acute pancreatitis.

Strengths and weaknesses of the study

The strength of the study is the detailed, accurate reports concerning medication obtained from the hospital records of one university hospital. The high number of patients (>1000 patients in each group) also strengthen study findings.

The fact that no ideal control group exists represents a weakness of this study. We selected patients with acute abdominal emergencies clinically resembling acute pancreatitis, which should be a relevant control group. A high number of study patients used drugs with acute pancreatitis as a reported side effect, but with unknown or low frequency. The probable causative effect of these drugs is thus debatable. However, there were no differences in the distribution of these drugs in the two groups, so this does not change our main conclusions.

CONCLUSIONS

The use of PDPS is significantly higher in the group of patients admitted with AP compared to the use of PDPS in patients with comparable acute abdominal conditions other than pancreatitis. This indicates that these drugs may contribute to the development of acute pancreatitis. Identification of a specific drug as a causative agent remains challenging, however. There was no additional effect of polypharmacy or risk-profile of the PDPS, and no association with other causes of pancreatitis or development of pancreatic necrosis.

ACKNOWLEDGEMENTS

The study was approved by the hospital's patient protection board and the Norwegian Ethical Committee.

FUNDING

Support from surgical research funds, Department of Medicine, Ahus Campus, University of Oslo, Norway.

COMPETING AND CONFLICTING INTERESTS

The authors report no conflict of interest. The authors are responsible for the content of the paper. The corresponding author may communicate with the editor on behalf of the other authors.

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