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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

**Kerstin B. Blomgren · Anders Sundström
Gunnar Steineck · Sven Genell · Svante Sjöstedt
Bengt-Erik Wiholm**

A Swedish case-control network for studies of drug-induced morbidity – acute pancreatitis

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Abstract *Objective*: To evaluate risk factors – notably drugs – for developing acute pancreatitis.
Methods: A population-based, case-control study, encompassing 1.4 million inhabitants aged 20–85 years from four regions in Sweden between 1 January 1995 and 31 May 1998. A total of 462 cases were hospitalised in surgical departments with their first episode of acute pancreatitis without previously known biliary stone disease. From a population register, 1781 controls were randomly selected. Information was obtained from medical records and through telephone interviews.
Results: Fifty-seven percent of the cases were males. An expert group found evidence for biliary stones in 50% of the cases, alcohol intake in 23%, but in 29% neither of these factors were present. In all, ''other'' factors, e.g. drugs, could have contributed to the development of acute pancreatitis in 52% of the cases. In a multivariate analysis, the adjusted odds ratios (ORs) for H_2 antagonists were 2.4 (95% CI 1.2–4.8) for proton pump inhibitors (PPIs), 2.1 (1.2–3.4) for non-steroidal anti-inflammatory drugs (NSAIDs), 2.3 (1.3–4.0) for those derived from acetic acid and 1.9 (1.1–3.2) for antibacterials for systemic use. Significant ORs were found for a history of gastrointestinal tract disorders [1.5 (1.1–1.9)] and inflammatory bowel disease (IBD) [3.4 (1.5–7.9)]. Smoking was significantly associated with acute pancreatitis [1.7 (1.2–2.1)] and, for those smoking more than 20 cigarettes per day, the OR was 4.0 (2.2–7.5). Alcohol in moderate amounts did not increase the risk, but for those drinking more than 420 g alcohol per week the OR was 4.1 (2.2–7.5).
Conclusion: In addition to cholelithiasis, smoking and heavy alcohol use, drugs may be an important risk factor for acute pancreatitis.

Keywords Acute pancreatitis · Case-control study · Risk factors

K.B. Blomgren (✉)
The Pharmacoepidemiological Unit,
Department of Clinical Pharmacology, Karolinska Institutet,
Huddinge University Hospital 141 86 Stockholm, Sweden
E-mail: Kerstin.Blomgren@mpa.se
Tel.: +46-8-58581182
Fax: +46-8-58581185

A. Sundström · B.-E. Wiholm
Medical Product Agency, Uppsala Sweden

G. Steineck
Clinical Cancer Epidemiology, Stockholm City Council
and Department of Oncology and Pathology,
Karolinska Institutet, Sweden

S. Genell
Department of Surgery, Malmö University Hospital, Sweden

S. Sjöstedt
Department of Medical and Surgical Gastroenterology
Huddinge University Hospital, Sweden

Introduction

Premature activation of the proenzymes within the pancreas has been suggested as the cause of acute pancreatitis for many years. The importance of trypsinogen activation and trypsin activity in acute pancreatitis is today generally accepted, even if relationships to other inflammatory reactions are debated [1].

Only a limited number of epidemiological studies on large populations concerning acute pancreatitis have been performed. Data concerning frequency, age and sex distribution and aetiological causes vary considerably by study, country and time period. The best-documented causes are cholelithiasis and excessive intake of alcohol, possibly accounting for about 80% of the cases [2]. Pancreatic trauma, infections, tumours, inflammatory bowel disease (IBD), hyperlipidemia, and hyperparathyroidism have been suggested as additional risk factors. Drugs have rarely been considered as possible causes for acute pancreatitis. There is, however, unequivocal evidence from clinical trials of a causal association with didanosine [3] and azathioprine [4]. A case-control study in the 1970s found a significant association with diuretic treatment [5], but the

bulk of information comes from spontaneous reports of pancreatitis in association with intake of various drugs [6].

Within a nationwide case-control surveillance network of drug-induced disease, we have investigated risk factors for acute pancreatitis, notably drugs. Here, we describe the case-control network and the quality assurance process, and present the distribution of aetiologies of acute pancreatitis in Sweden. We also present the extent to which drugs, diseases, smoking and alcohol are risk factors for acute pancreatitis. From the investigation, we have previously reported obesity and the drug glibenclamide to be risk factors for acute pancreatitis [7].

Materials and methods

Organisation of the Swedish case – control network

The Medical Product Agency is responsible for pharmacovigilance in Sweden. Between 1992 and 2000, operations were gradually decentralised, with one surveillance centre in each of the six healthcare regions. These centres are located in the departments of clinical pharmacology at the regional university hospitals. There are two nurses in each centre who are educated and trained in clinical pharmacology, pharmacovigilance and epidemiology. The nurses have clinical pharmacologists as consultants. The nurses also run a case control study network, used in the present study – which was managed by the MPA. In addition to the study co-ordinator (KB) there were seven monitors who participated in the study during the whole study period and four others who were involved during a limited time. The central and the regional research ethics committees approved this study.

Study design and quality assurance

This study on acute pancreatitis was the first population-based, case-control study performed in the network setting. All monitors were initially trained in interview technique based on the standardised interview form. A study protocol and a study manual were composed in detail for all procedures. Co-ordinating activities during the study period included visits to all study centres and all participating departments. Monitors and co-ordinator meetings were held every 6 months, complemented with regular telephone conferences and e-mail communication. Quality assurance and validity activities during the study period were performed through fictitious interviews and coding tests. A fictitious interview was conducted by two co-ordinators from the present study and an international pancreatitis study where one illustrated the case or control and the other acted as an observer and registered the interview dialog between monitor and the fictitious subject. Feedback to the monitor concerning interview technique was given afterwards. Quality assurance, organisation and preparation of the potential case material for the expert evaluation were made by the co-ordinator. Validation of all interview data in the database was performed by the co-ordinator after the study was closed. The monitors submitted all quality-screened interviews on diskettes together with a log-list and all screened ascertainment sheets every month to the co-ordinating centre. The ascertainment sheet included information concerning identity, demographics, telephone number and dates for symptom debut, admission and discharge, together with all discharge diagnoses. For all potential cases with primary exclusions, an ascertainment sheet was obtained with the same information as for the included subjects excluding the date of discharge and the discharge diagnoses but including the reason for exclusion.

The procedure for first contact between the monitor and case was recorded. Laboratory values for amylase/lipase and liver enzymes were also recorded in the ascertainment forms. Furthermore, information on all diagnostic examinations performed, with dates, was obtained together with information regarding length of hospitalisation and possible ICU treatment. A short narrative history based on information from the medical record was recorded. Screening concerning exclusion criteria was made and recorded. All copies of medical records were kept in the regional monitoring centre until the date of the expert meetings. Two surgeons experienced in upper gastrointestinal surgery, including the management of acute pancreatitis, evaluated the records. They had no access to information concerning current medication before admission. In addition, the hospital identities were hidden. The experts evaluated every case according to the case definition criteria in the protocol as a possible, probable or certain case of acute pancreatitis. For each case, an index day was defined as the date on which abdominal pain leading to admission was first experienced. The cases were further classified in three aetiological classes, gallstone, alcoholic and other. Furthermore, they classified the probability of the different aetiologies into certain, probable and possible. Every case could be assigned to more than one aetiological group with different degrees of probability. The experts met on six occasions during the study for evaluation of the cases.

Study population

Four areas around the cities of Umeå, Uppsala, Stockholm and Malmö with eight participating hospitals encompassing 2.2 million inhabitants were included. The population from which the cases and controls were drawn was restricted to persons between 20 years and 85 years of age who had been resident in the study area for at least 6 months, had a telephone with a publicly listed number, and spoke Swedish. This population was estimated to be 1.4 million people. Collection of data took place between 1 January 1995 and 31 May 1998. The study base comprised 4.7 million person years.

Cases

Cases were patients hospitalised in surgical departments in the participating hospitals for their first episode of acute pancreatitis and without previously known gallstone disease. The cases were identified through daily scanning of laboratory printouts of serum-amylase. Patients were included irrespective of other predisposing factors such as excess alcohol consumption, hyperlipidaemia or IBD. All patients were screened by the study monitors concerning inclusion and exclusion criteria. These patients were followed up, and a copy of the medical case summary including relevant clinical investigations was collected.

Case definition

A possible case of acute pancreatitis was diagnosed if the patient had clinical symptoms compatible with acute pancreatitis and serum amylase was increased to at least twice the upper limit of the normal reference value within 72 h of admission to hospital. A probable case was diagnosed if, in addition, there was a typical picture on the ultrasound screening. A certain case was diagnosed if, in addition, there was a typical picture on computed tomography (CT) scan or a surgical procedure or post-mortem diagnosis of acute pancreatitis was made irrespective of laboratory values. All cases with at least a possible acute pancreatitis were included in the analysis.

Data collection

The screening procedure of all potential cases started with identification of all increased serum-amylase values received by the monitors from the laboratory in the participating hospitals. Twice

a week, the monitors visited the surgery departments to screen the medical records concerning clinical symptoms such as abdominal pain related to the increased value of serum-amylase in the potential cases.

The monitors recorded the judgement of the admitting physician, including relevant investigations. They also recorded the initial values of serum amylase, serum-lipase and a liver screen performed at the participating hospitals. Patients without obvious exclusion criteria were contacted personally in the hospital or by a letter containing information about the study, a request for participating in the study and a permission statement for obtaining a copy of the medical record. Further contacts were taken by telephone 1 week after discharge for agreement on an interview. The interviews were conducted by telephone within 30 days of hospital admission.

The interviews were performed according to a standardised form. Information was collected about demographic details, previous hospitalisations, previous and present diseases, and drug consumption during the last 6 months. The questions about diseases were used as prompts for treatments and drug intake. Twelve disease groups were included (cardiovascular, rheumatological, pulmonary, gastrointestinal, renal/urinary, endocrine, allergic, psychiatric, gynaecological, neurological, blood and tumour) diseases. Information on infections, unspecified diseases and drugs such as pain relievers, vitamins, vaccinations and herbal drugs was also obtained. There were questions regarding previous adverse drug reactions; whether they knew that medicines could cause acute pancreatitis and whether they had been told that their present disease could have been caused by one of their medicines.

For each disease group including one or more specific diseases, the standardised question was ''do you have/have you had?'' followed by the specific disease, e.g. hypertension or diabetes. If positive, the follow-up question was: ''have you taken any drugs to treat this condition during the last 6 months? If ''yes'': ''which drug/drugs have you used?''. Information about strength, dosage and time of treatment was also obtained.

Only diseases diagnosed by a physician classified the interviewee as ''exposed'' to the condition. All conditions were coded according to ICD-9 CM. Self-reported body height and weight were also recorded in order to allow a calculation of the body mass index (BMI). An extensive mapping of alcohol and tobacco use during the past 6 months was also performed.

Exclusions

A total of 2453 patients was screened as potential cases of acute pancreatitis. Patients who did not have a telephone subscription and those who could not speak Swedish were excluded as a restriction in the study base (Table 1). Patients with malignancies in the gastrointestinal tract (including the pancreas) and those with endoscopic retrograde cholangiopancreatography-induced pancreatitis were excluded. We also excluded patients with a previous attack of acute pancreatitis and cholelithiasis since the choice and ascertainments of proper controls for such cases would have been extremely difficult. Among the potential cases there were many who had inter-current reasons for an increased serum-amylase, e.g. perforations and bleedings within the gastrointestinal tract, ileus, abdominal trauma, aneurysm of the abdominal aorta, treatment with cytostatic drugs, and symptomatic human immunodeficiency virus infections. Patients hospitalised for more than 30 days after admission were also excluded because the interview had to be conducted within 30 days. We have no information about this category apart from the inclusion data from the screening form. There were 779 eligible cases of the total 2453 screened.

Controls

Controls were selected quarterly as a random sample of persons between 20 years and 85 years of age from a population register. They were residents within the geographic areas specified in the study base. We received information concerning name, sex, age, and address from the population register. The secretary in the coordinating centre identified the telephone number before distribution to the local monitoring centres. Controls were selected and interviewed continuously and no matching to the cases was done. The recommendation was that every monitor should interview five controls per week.

Table 1. Potential cases and controls

Reasons for exclusion	2453 Cases		2245 Controls	
	No.	%	No.	%
Malignancy, gastrointestinal/pancreas	180	7.3	1	0
Prevalent gallstone disease	390	16	60	2.6
Previous pancreatitis + chronic	509	20.8	10	0.4
Endoscopic retrograde cholangiopancreatography-pancreatitis	168	6.8	0	–
Pancreatitis after admission	33	1.3	0	–
Intercurrent disease*	194	7.9	0	–
Hospitalised more than 30 days after admission/index	42	1.7	1**	–
Hospitalised within 30 days before admission/index	32	1.3	6	0.3
No telephone	37	1.5	15	0.6
Language problems	89	3.6	23	1.0
Eligible cases and controls	779	32	2129	95
Reasons for non-participation	No	%	No	%
Transferred to other clinic	21	2.7	0	–
Too ill for interview, because of concomitant disease	15	1.9	21	0.9
Unreliable interview	3	0.4	1	0.04
No permission from physician	2	0.3	0	–
Dementia	64	8.2	7	0.3
Refusal	55	7.1	187	8.8
Missing medical records	22	2.8	0	–
Failure to establish contact	74	9.4	129	6.0
No available monitor	17	2.2	1	0.04
Erroneous exclusions	33	4.2	0	–
Deceased; no interview	11	1.4	2	0.09
Cases and controls providing information	462	59	1781	84

*See methods
**Nursing home

A total of 2245 controls were screened. The reasons for exclusions are depicted in Table 1. Initially, we tried to contact controls with unlisted telephone numbers, but due to a minimal response rate, we decided to exclude such persons. Of 5,065,000 telephone subscriptions in Sweden, there are between 8% and 10% with secret numbers. There were 2128 eligible controls of the total 2245 screened.

Analyses

Any drug intake during the 30 days prior to hospital admission classified a subject as exposed to the drug in question. Relative risks (estimating the incidence ratio in the study base) were depicted by crude odds ratios (ORs). ORs were also calculated using unconditional logistic regression models allowing for adjustment by covariates and giving 95% confidence intervals [8]. Goodness of fit was investigated using Hosmer-Lemeshaw's test [9].

Results

All 50 cases and 219 controls interviewed by one monitor were excluded since the validation process identified a significantly lower number of previous diseases and exposures obtained by this monitor relative to the other's. Of the 779 eligible cases, 462 were interviewed (Table 1). Characteristics of cases and controls are depicted in Table 2. On clinical judgement, 29% of the cases did not have an obvious aetiology for acute pancreatitis such as cholelithiasis or alcohol (Fig. 1).

Every case could be assigned to more than one aetiological group. Only two cases (1%) were classified as a certain "other" aetiology, whilst 120 (65%) were classified as probable and 64 (34%) as possible. For cholelithiasis-related cases, figures were 53 (22%) certain, 120 (51%) probable and 64 (27%) possible associations. Among alcohol-related cases, there were 25 (23%) certain, 32 (30%) probable, and 51 (47%) possible associations.

There were 19 different groups of drugs that showed significant increases in the crude ORs for any use during the last month before admission (Table 3). In a multivariate logistic regression model, we controlled for factors that showed a significant crude OR and could be potential confounders; sex, age, BMI, alcohol use, tobacco use, diabetes, previous and present psychiatric, cardiac, gastrointestinal, kidney and prostate disorders, back problems and sleep disorders. Present use of oral antidiabetics, calcium, vitamin B, antipsychotics, cardiac medications, gastrointestinal medications, antibiotics, sedatives, hypnotics, antidepressants, non-steroidal anti-inflammatory drugs (NSAIDs) and analgesics were also introduced in the model. After adjustment in the multivariate analysis, significant ORs remained for H_2 antagonists with an OR of 2.4 (1.2–4.8), proton pump inhibitors (PPIs) with an OR of 2.1 (1.2–3.4), acetic acid based NSAIDs with an OR of 2.3 (1.3–4.0) and antibacterials for systemic use 1.9 (1.1–3.2).

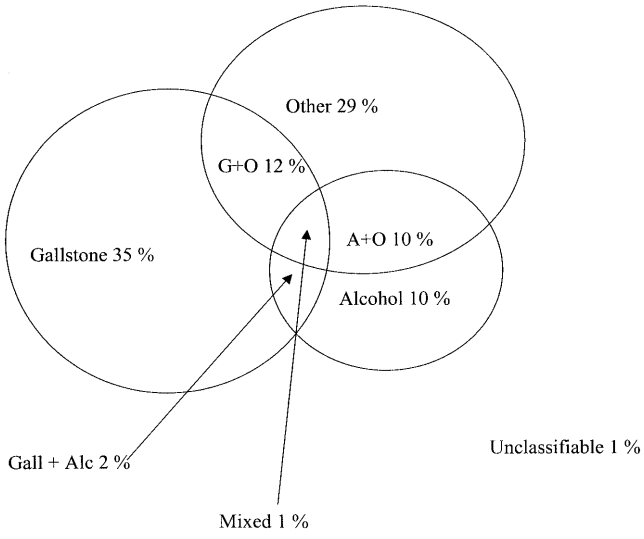

Fig. 1. Distribution of aetiologies for acute pancreatitis and their interrelations according to the judgement of an expert group

In the analysis concerning previous diseases, we found 14 disease groups with a significant crude OR (Table 4). However, after the multivariate logistic regression analysis, significant associations only remained for gastrointestinal disorders (mostly peptic ulcer and non-ulcer dyspepsia) giving an OR of 1.5 (1.1–1.9) and for the group of regional enteritis and ulcerative colitis, giving an OR of 3.4 (1.5–7.9).

In this material, we found that 152 (33%) of the cases and 407 (23%) of the controls were current smokers, giving an overall OR of 1.7 (1.2–2.1). There was a significant dose–risk association, and, for subjects smoking more than 20 cigarettes per day, the OR was 4.0 (2.2–7.5) (Table 6). Within the group smoking more than 20 cigarettes per day, males were over represented – 73% among cases and 81% among the controls.

The proportion of alcohol users was similar among cases and controls – 85.0% and 87.3% – respectively, giving an overall crude OR of 0.8 (0.6–1.1) for any use of alcohol. In moderate amounts, alcohol did not increase the risk of acute pancreatitis; but for those drinking more than 420 g alcohol per week, a significant risk was seen [OR 4.1 (2.2–7.5)].

Table 2. Characteristics of cases and controls

Characteristics	472 Cases		1781 Controls	
Age (years)	No.	%	No.	%
20–29	35	7.4	228	12.8
30–39	47	10.1	247	13.8
40–49	73	15.5	263	14.8
50–59	105	22.2	422	23.7
60–69	84	17.8	309	17.3
70–79	102	21.6	237	13.3
80–85	26	5.5	76	4.3
Mean (SD)	56.3	(16.4)	51.9	(16.9)
Median (range)	56	(20–84)	53	(20–85)
Sex				
Male	269	57.0	865	48.6
Female	204	43.0	916	51.4
Died due to pancreatitis	11	1.4		

Table 3. Significant risks among substances used during the last month before admission

Substance groups	ATC codes	462 Cases	(%)	1781 Controls	(%)	Odds ratio	95% CI
Gastrointestinal drugs	A02						
Antacids	A02AA, A02EA, A02BX	9	1.9	10	0.6	3.5	1.4–7.7
H_2 Antagonists	A02BA	22	4.8	23	1.3	3.8	2.1–6.9
Proton pump inhibitors	A02BC	37	8.0	44	2.5	2.4	2.2–5.4
Anti-diabetic drugs							
Oral antidiabetics	A10BA, A10BB	16	3.5	30	1.7	2.1	1.1–3.9
Vitamins & minerals							
Vitamin B (comb)	A11EA, A11EB	12	2.6	19	1.1	2.5	1.2–5.1
Calcium	A12A	12	2.6	21	1.2	2.2	1.1–4.6
Cardiovascular drugs	C01						
Nitrates	C01DA	26	5.6	62	3.5	1.6	1.0–2.7
Diuretics	C03	49	10.6	126	7.1	1.6	1.1–2.2
β-Blockers	C07AA, C07AB	65	14.1	145	8.1	1.8	1.4–2.5
Calcium antagonists	C08	38	8.2	80	4.5	1.9	1.3–2.8
Lipid-lowering drug	C10, B04A	29	6.3	63	3.5	1.8	1.2–2.9
Antibacterials for systemic use	J01	29	6.3	55	3.1	2.1	1.3–3.3
Penicillins	J01C	12	2.6	21	1.2	2.2	1.1–4.6
NSAIDS and analgetics							
Acetic-acid derivatives	M01AB	27	5.8	39	2.2	2.8	1.7–4.6
Dextropropoxyphene and combination	N02AC	27	5.8	64	3.6	1.7	1.1–2.6
Antipsychotics, sedatives and hypnotics	N05						
Phenothiazines	N05A, N05BB, N05CM	17	3.8	18	1.0	3.7	1.9–7.3
Benzodiazepines	N05BA, N05CD	29	6.3	47	2.6	2.5	1.5–4.0
Zopiclone, Zolpidem	N05CF, N05CG	13	2.8	26	1.5	1.95	1.0–3.8
Antidepressants							
SSRI, tricyclic	N06A	18	3.9	34	1.9	2.1	1.2–3.72

Table 4. Crude and adjusted odds ratios (ORs) for diseases with significant association to acute pancreatitis. Variables included in the model were: sex, age, BMI, alcohol use, tobacco use, diabetes, psychiatric, cardiac, gastrointestinal, kidney, and prostate disorders, back problems, sleep disorders, antidiabetics, calcium, vitamin B, antipsychotics, cardiac medications, gastrointestinal medications, antibiotics, sedatives, hypnotics, antidepressants, NSAIDS and analgetics

Disease group	9 ICD	462 Cases (%)	1781 Controls (%)	OR	95% CI	Adjusted OR	95% CI
Diabetes mellitus	250	5.8	3.1	2.0	1.2–3.1	1.3	0.6–3.0
Psychiatric disorder	291–311	15.4	9.9	1.7	1.2–2.2	1.26	0.9–1.8
Hypertension	401–405	25.3	16.7	1.7	1.3–2.2	1.2	0.8–1.6
Acute myocardial infarction	410	5.2	2.0	2.7	1.6–4.5	1.8	1.0–3.4
Heart failure	428	2.2	1.0	2.3	1.0–5.1	1.3	0.5–3.3
Disorder of gastrointestinal tract	522–553	31.8	17.8	2.2	1.7–2.7	1.5	1.1–1.9
Regional enteritis and ulcerative colitis	555–556	2.6	0.8	3.1	1.5–6.8	3.4	1.5–7.9
Other disorder of gastrointestinal	558–569	7.6	3.9	2.0	1.3–3.1	1.5	1.1–1.9
Renal and ureter stones	592–594	8.2	5.4	1.6	1.1–2.3	1.2	0.8–1.9
Hyperplasia of prostate	600	9.6	5.5	2.1	1.3–3.4	1.4	0.8–2.4
Unspecific disorder of back	724	5.6	3.3	1.7	1.1–2.8	1.31	0.77–2.23
Sleep disorders	780F	12.8	6.6	2.1	1.5–2.9	1.21	0.8–1.9
Skin disorders	680–708	10.0	17.5	0.5	0.4–0.7	n.a.	
Tendon and ligament disorder	726–728	1.1	3.0	0.4	0.1–0.9	n.a.	

Discussion

According to the clinical judgement, the classic aetiologies of acute pancreatitis, cholelithiasis and alcohol were involved in 50% and 23%, respectively, in this study population. In 29%, no obvious cause could be found and, in another 23%, other risk factors were combined with gallstone, alcohol or both (Fig. 1). We excluded patients with previous known gallstone disease – 390 (16%) for validity and efficiency reasons. Thus, the real proportion of gallstone-related pancreatitis was higher.

We found intake of H_2 antagonists [OR 2.4 (1.2–4.8)] and PPI [OR 2.1 (1.2–3.4)], as well as exposure to acetic acid-based NSAIDs, e.g. diclofenac [OR 2.3 (1.3–4.0)] and antibacterials [OR 1.9 (1.1–3.2)] to have significant associations. Gastrointestinal disorders including gastrointestinal ulcers [OR 1.5 (1.1–1.9)] and IBD [OR 3.4 (1.5–7.9)] were also associated with an increased risk of acute pancreatitis. We also found heavy smoking to be a strong risk factor, and not only in cases with alcohol pancreatitis.

Case reports concerning H_2 antagonists and acute pancreatitis exist [10, 11, 12]. One report concerns an old

woman who developed three bouts of acute pancreatitis after (re) starting ranitidine [10]. In addition, there exist five case reports in the Swedish Adverse Drug Reactions Register, and one of these cases developed a new attack of acute pancreatitis after re-exposure to ranitidine. Evans et al. [13] performed a case-control study based on an automated database complemented with information from hospital and GP medical records to investigate the association between H_2 antagonists and acute pancreatitis. Eland et al. [14] performed a retrospective cohort study with a nested case-control design (within the GPRD database in UK) to evaluate the risk of acute pancreatitis associated with use of acid-suppressing drugs including PPIs. Confounding by indication was suggested to be an explanation in both of these studies; H_2 antagonists and PPIs are widely used for a variety of gastrointestinal symptoms. In contrast to these studies, we have collected information from both medical records and a telephone interview with the subjects including information concerning a life-time medical history, use of alcohol and tobacco, and a detailed history of medicines taken during the last 6 months prior to admission. The adjusted risks remains (Table 5) after controlling for potential confounders.

In a separate publication, we will analyse dose, time and duration effects to investigate a potentially remaining effect of "confounding by indication" (by many investigators called protopathic bias, that is, the drug was given for early symptoms of the disease it is accused of causing). Fifteen cases and six controls had started taking acid-suppressing drugs within 5 days of hospital admission and interview, respectively. The median and mean duration of abdominal pain leading to hospitalisation were 0 days and 1.1 days, respectively. Therefore, for the majority of these cases, therapy with acid-suppressing drugs preceded the start of symptoms of acute pancreatitis (Table 6).

Table 5. Adjusted significant odds ratios (ORs) among substances associated with acute pancreatitis. Variables included in the model were: sex, age, BMI, alcohol use, tobacco use, diabetes, psychiatric, cardiac, gastrointestinal, kidney, and prostate disorders, back problems, sleep disorders, antidiabetics, calcium, vitamin B, antipsychotics, cardiac medications, gastrointestinal medications, antibiotics, sedatives, hypnotics, antidepressants, NSAIDS and analgetics

Substances	Adjusted OR	95% Confidence interval
H_2 antagonists	2.4	1.2–4.8
Proton pump inhibitors	2.1	1.2–3.4
Acetic acid derivates	2.3	1.3–4.0
Antibacterials for systemic use	1.9	1.1–3.2

NSAIDs, especially sulindac but also diclofenac, have been reported to be associated with acute pancreatitis [15, 16, 17, 18, 19, 20, 21, 22]. In our study there were only 1 case and 3 controls exposed to indomethacin but 25 cases and 36 controls had been exposed to diclofenac.

Several reports concerning acute pancreatitis associated with different antibiotics exist [6, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32]. In an experimental study, tetracycline was shown to cause pancreatitis by impairing pancreatic protein synthesis and secretion [25]. Steinberg [26] suggests that a toxic metabolite of tetracycline may be responsible for the development of pancreatitis. Other antibiotics, e.g. erythromycin and sulphonamides [27, 28, 29, 30, 31, 32], have been identified as possibly causing acute pancreatitis. Erythromycin stimulates contractions of the gastrointestinal tract and gallbladder [28] and may increase the pressure of the sphincter of Oddi [27]. An immune-mediated mechanism has been

Table 6. Smoking and alcohol history among cases and controls

Smoking status	462 Cases			1781 Controls			Odds ratio	95%CI
	Female	Male	Total	Female	Male	Total		
Not current smokers	137	173	310	685	694	1379		
Current smokers	65	87	152	231	171	407	1.7	1.2–2.1
No. of cigarettes per day								
1–10	22	23	45	129	67	196	1.1	0.8–1.5
11–20	38	50	88	98	86	184	2.6	1.9–3.5
>20	5	14	19	4	18	22	4.0	2.2–7.5
Unknown (-1)			0	3	4	7	n.a.	
Only pipe/or cigar	0	2	2	0	5	5	n.a.	
Alcohol habits								
Current user	160	233	393	762	793	1555	0.8	0.6–1.1
Current non-user	42	27	69	154	72	226		
Gram alcohol per week								
Average (95% CI)	140.8 (120.8 –160.8)			96.8 (92.0–101.6)				
>0, <20 g ref	48	28	76	168	66	234	1.0	
≥20 g, <120 g	91	98	189	486	399	885	0.7	0.5–0.9
≥120 g, <220 g	11	42	53	81	215	296	0.6	0.4–0.8
≥220 gG <320 g	5	29	34	19	68	87	1.2	0.8–1.9
≥320 g, <420 g	3	9	12	7	24	31	1.2	0.6–2.4
≥420* g	2	27	29	1	21	22	4.1	2.2–7.5

* = 52.5 cl pure alcohol = 21 cans strong beer

suggested for sulphonamides since acute pancreatitis develops rapidly after re-exposure. In some cases, a positive lymphocyte transformation test accompanied by rash or fever has been seen [31]. In our study there was a statistically significant OR for antibacterials as a group [OR 1.9 (1.1–3.2)]. There were only two cases and two controls exposed to macrolides. However, there were 7 cases and 11 controls exposed to tetracyclines, 9 cases and 20 controls to betalactams and 7 cases and 5 controls to norfloxacin. IBD has previously been reported to be associated with acute pancreatitis. However, most published data consists of case reports and epidemiological data are sparse and it has been discussed whether the conditions by themselves or their treatment are responsible [33].

Rasmussen et al. [34] found a fourfold increase in risk of acute pancreatitis for patients with Crohn's disease and a twofold increase in risk for patients with ulcerative colitis compared with the general population. However, in their register study, potential confounding factors such as alcohol, smoking and drug treatment could not be accounted for. Most of the literature cases in which acute pancreatitis is associated with IBD are considered to be elicited by drug treatments such as 5-aminosalicylic acids, azathioprine, and 6-mercaptupurine [35, 36, 37]. Aminosalicylate-associated acute pancreatitis has been suggested to be immune mediated [36]. Acute pancreatitis in IBD has also been discussed as an extra-intestinal manifestation of systemic inflammation [33].

Smoking has previously been reported as a risk factor for chronic and alcoholic pancreatitis [38, 39, 40, 41, 42, 43, 44]. There is some experimental evidence that smoking might be a risk factor for pancreatitis. Smoking has been shown to inhibit pancreatic secretion in vivo [45]. Four studies have found smoking to be an independent risk factor for acute alcoholic pancreatitis and chronic pancreatitis [38, 41, 42, 43] in various settings. In one retrospective study, a dose–effect relationship between smoking and alcoholic pancreatitis was demonstrated [40]. However, one study in alcoholics [44] failed to find an association between smoking and pancreatitis, probably because of the very high prevalence of smoking among alcoholics (86.5% and 87.2%). The present study showed a significant dose–risk association where the OR increased to 4.0 (2.2–7.5) in those who smoked more than 20 cigarettes per day (Table 6). Heavy smoking (>20 cigarettes per day) was a risk factor both among cases attributed to gallstones [OR 2.9 (1.2–7.3)] and alcohol [OR 23.1 (8.8–60.5)]. Among cases classified as "other causes", smoking 10–20 cigarettes per day had an OR 2.0 (1.4–3.0).

The first report concerning an association between heavy alcohol consumption and acute pancreatitis was by Friedreich [46] in 1878. Several authors have suggested that alcohol-induced pancreatitis has become more common with time [47, 48, 49, 50]. However, information concerning at what levels of alcohol consumption the risk increases is sparse. In this study, the detailed alcohol history allowed a dose–risk calculation. We found no increase in risk until 420 g/week for which OR was 4.1 (2.2–7.5). Our findings of just 23% of the cases being related to alcohol is somewhat less than the 31% found in another recent Swedish study [51]. However, their study was based on a retrospective analysis. The number of current alcohol users in our control population was 87.3%, which is similar to data from "Statistics Sweden" (Ingrid Sjöberg, personal communication) during the present period.

The validity of the present study needs to be scrutinised. As a result of the quality assurance activities, we detected that the results from one of the monitors deviated significantly from these of the others. All cases and controls interviewed by this monitor were excluded. To the best of our knowledge there are no other reports published where such a situation has been described. Measuring errors of outcome was minimised by the case validation process by our experts. The quality assurance process identified 33 erroneous exclusions. There are, however, no indications that this misclassification was selective. We tried to minimise misclassification of exposure by applying a very detailed and standardised interview using diseases and symptoms as prompts for drug exposure. We studied 20- to 85-year-old patients from defined geographic areas who developed a first episode of acute pancreatitis and did not have a previously diagnosed gallstone disease. This procedure decreases the risk of selective exposures and the problem of finding relevant controls for patients with previous pancreatitis or gallstone disease. We decided not to match controls to cases by age or gender, thereby allowing evaluation of these variables as risk factors [OR 1.1 (1.0–1.2) per 10 years, OR 1.3 (1.0–1.7) for male gender]. If drug exposures differed among patients transferred to other clinics, or among those hospitalised for more than 30 days or among those who had a fatal outcome, our results cannot be generalised to the risk of acquiring acute pancreatitis with these characteristics. Age and gender distribution of these patients was similar to that of those included. To identify potentially confounding variables, we first performed a crude screening analysis of demographic variables, life-style factors as well as diseases and drug exposures. Variables that had significant ORs were then introduced in the multivariate model used to define those with a significantly increased adjusted OR.

It can be suspected that the group of "failure to establish contact" would contain a higher than average proportion of severe alcoholics. This would lead to an underestimation of the risk of very high consumption of alcohol. A general underestimate of alcohol intake is hard to avoid in an interview setting. Failure to account properly for alcohol as a confounder leads to an overestimate of the risks of alcohol and for alcohol-related diseases such as dyspepsia and peptic ulcers and their treatments. However, an extrapolation of the alcohol intake obtained from the interviews of controls corresponds to an average yearly consumption of 5.5 l

pure alcohol per inhabitant. The Swedish state-controlled company for the sales of wines and spirits declares a figure of 5.92 l per year from 15 years of age. Thus, this problem cannot be large in our study. Cholelithiasis was the most common cause of acute pancreatitis. Alcohol was, by clinical judgement, judged to be responsible for acute pancreatitis in 23% of the cases but according to the interviews alcohol intake did not confer an increased risk until more than 420 g per week was ingested. Such a high consumption was only reported by 29 of the cases (6.2%) and 22 of the controls (1.2%). In addition to under reporting of alcohol intake, this difference can also be due to an overclassification by the experts.

In conclusion, we found several drugs to be associated with acute pancreatitis in addition to glibenclamide which has previously been presented [7]. IBD and other gastrointestinal disorders also had an increased risk in the adjusted analyses. Whilst the associations to cholelithiasis are well documented, the dose–risk relationship for alcohol and smoking are additions to our knowledge. The associations to acid supressants, antibacterials and NSAIDs need further detailed analyses to exclude possible residual confounding and to describe time, duration and dose effects. These will be presented in forthcoming publications.

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References

1. Ohsson K, Balldin G, Bohe M, Borgström A, Genell S, Lasson Å (1988) Pancreatic proteases and antiproteases in pancreatic disease; biochemical, pathofysiological and clinical aspects. Int J Pancreatol 3:67–78
2. Steinberg W, Tenner S (1994) Acute pancreatitis. N Engl J Med 17:1198–1210
3. Faulds D & Brodgen RN. Didanosine (1992) A review of its antiviral activity, pharmacokinetic properties and therapeutic potential in human immunodeficiency virus infection. Drugs 44:94–116
4. Sturdevant RA, Singleton JW, Deren JL, Law DH, McCleery JL (1979) Azathioprine-related pancreatitis in patients with Crohn's disease. Gastroenterology 77:883–886
5. Bourke JB, McIllmurray MB, Mead GM, Langman MJS (1978) Drug-associated primary acute pancreatitis. Lancet 1:706–708
6. Mallory A, Kern F Jr (1980) Drug-induced pancreatitis a critical review. Gastroenterology 78:813–820
7. Blomgren K, Sundström A, Steineck G, Wiholm BE (2002) Obesity and treatment of diabetes with glyburide may both be risk factors for acute pancreatitis. Diabetes Care 25:298–302
8. Rothman KJ, Grenland S (1998) Modern epidemiology,2nd edn. Lippincott-Raven, Philadelphia
9. Hosmer D, Lemeshow S (1989) Applied logistic regression. John Wiley and Sons, New York
10. Herrman R, Shaw RG, Fone DJ (1990) Ranitidine-associated recurrent acute pancreatitis. Aus N Z J Med 20:243–244
11. Nott DM, Sousa BA (1989) Suspected cimetidine-induced acute pancreatitis. Br J Clin Pract 43:264–265
12. Hainaut P, Scharpira M, Mugabo P, Cerulus G, Coche E (1987) Acute pancreatitis induced by cimetidine. Rev Med Interne 8:516–518
13. Evans JMM, McMahon AD, Steinke DT et al (1998) Do H2-receptor antagonists cause acute pancreatitis? Pharmacoepidemiology and drug safety 7:383–388
14. Eland IA, Huerta Alvarez C, Stricker BHC, Garcia Rodriguez LA (2000) The risk of acute pancreatitis associated with acid-suppressing drugs. Br J Clin Pharmacol 49:473–478
15. Goldstein J, Laskin DA, Ginsberg GH (1980) Sulindac associated with pancreatitis Ann Intern Med 93:151
16. Siefkin AD (1980) Sulindac and pancreatitis. Ann Intern Med 93:932–933
17. Memon AN (1982) Pancreatitis and Sulindac. Ann Intern Med 97:139
18. Sugerman H (1989) Sulindac-induced acute pancreatitis mimicking gallstone pancreatitis. Am Surg 55:536–538
19. Izhar H, Edward N, Edward K (1993) Pancreatitis associated with diclofenac. Postgrad Med J 69:486–487
20. Ibanez L, Laporte JR, Carne X (1991) Adverse drug reactions leading to hospital admission. Drug Saf 6:450–499
21. Jick H, Derby LE, Garcia Rodriguez LA, Jick SS, Dean AD (1993) Nonsteroidal antiinflammatory drugs and certain rare, serious adverse events: a cohort study. Pharmacotherapy 13:212–217
22. Sammet D, Greben C, Sayeed-Shah U (1998) Acute pancreatitis caused by penicillin. Dig Dis Sci 43:1778–1783
23. Nicolau DP, Mengedoth DE, Kline JJ (1991)Tetracycline-induced pancreatitis. Am J Gastroenterol 86:1669–1671
24. Sura M, Heinrich K, Suseno M (2000) Metronidazole-associated pancreatitis. Ann Pharmcother 34:1152–1155
25. Tucker PC, Weloster PD (1972) Effects of tetracyclines on pancreatic protein synthesis and secretion. Clin Res 20:76
26. Steinberg WM (1985) Acute drug and toxin induced pancreatitis. Hosp Pract 20:95–102
27. Fang CC, Wang HP, Lin JT (1996) Erythromycin-induced acute pancreatitis. J Toxicol Clin Toxicol 34:93–95
28. Fiorucci S, Bosso R, Mrelli A (1992) Erythromycin stimulates gallbladder emptying and motilin release by atropine-sensitive pathways. Dig Dis Sci 37:1678–1684
29. Alberti-Flor JJ, Hernadez ME, Ferrer JP, Howell S, Jeffers L (1989) Fulminant liver failure and pancreatitis associated with the use of sulfamethoxazole-trimethoprim. Am J Gastroenterol 84:1577–1579
30. Bartles RH, van der Spek JA, Ooster HR (1992) Acute pancreatitis due to sulfamethoxazole-trimethoprim. South Med J 85:1006–1007
31. Brazer SR, Mcdoff JR (1988) Sulfonamide-induced pancreatitis Pancreas 3:583–586
32. Brett AS, Shaw SV (1999) Simultaneous pancreatitis and hepatitis associated with trimethoprim-sulfamethoxazole. Am J Gastroenterol 94:267–268
33. Matsumoto T, Matsui T, Iida M, Nunoi K, Fujishima M (1989) Acute pancreatitis as a complication of Crohn's disease. Am J Gastroenterol 84:804–807
34. Rasmussen H, Fonager K, Sorensen H, Pedersen L, Dahlerup J, Steffensen F (1999) Risk of acute pancreatitis in patients with chronic inflammatory bowel disease. Scand J Gastroenterol 2:199–201
35. Nogueira JR, Feedman MA (1972) Acute pancreatitis as a complication of Imuran therapy in regional enteritis. Gastroenterology 62:1040–1041
36. Adachi E, Okazaki K, Matsushima Y, Seno H, Uchida K, Nakasi H, et al (1999) Acute pancreatitis secondary to 5-aminosalicylic acid therapy in a patient with ulcerative colitis. J Pancreatol 5:217–221
37. Haber CJ, Meltzer SJ, Present DH, et al (1986) Nature and course of pancreatitis caused by 6-mercaptupurine in the treatment of inflammatory bowel disease. Gastroenterology 91:982–986

38. Yen S, Hsieh C, MacMahon B (1982) Consumption of alcohol and tobacco and other risk factors for pancreatitis. Am J Epidemiol 6:407–414
39. Bourliere M,Barthet M, Berthenze P, Durbec JP, Sarles H (1991) Is tobacco a risk factor for chronic pancreatitis and alcoholic cirrhosis? Gut 32:1392–1395
40. Lowenfels AB, Zwemer FL, Jhangiani S, Pitchumoni CS (1987) Pancreatitis in a native American Indian population. Pancreas 6:694–697
41. Talami G, Bassi C, Falconi M, Sartori N, Salvia R, Rigo L, Castagini A, di Francesco V, Frulloni L, Bovo P, Vaona B, Angelini G, Vantini I, Cavallini G (1996) Cigarette smoking: an independent risk factor in alcoholic pancreatitis. Pancreas 12:131–137
42. Talami G, Bassi C, Falconi M,Sartori N, Salvia R, Rigo L, Castagini A, di Francesco V, Frulloni L, Bovo P, Vaona B, Angelini G, Vantini I, Cavallini G, Pederzoli P (1999) Alcohol and smoking as risk factors in chronic pancreatitis and pancreatic cancer. Dig Dis Sci 44:1303–1311
43. Lin Y, Tamakoshi A, Hayakawa T, Ogawa M, Ohno Y, and the research committee on intractable pancreatic diseases (2000) 21:109–114
44. Haber PS, Wilson JS, Pirola RC (1993) Smoking and alcoholic pancreatitis. Pancreas 8:568–572
45. Bynum T, Solomon T, Johnson L, Jacobsen E (1972) Inhibition of pancreatic secretion in man by cigarette smoking. Gut 13:361–365
46. Friedreich N (1878) Chronic pancreatitis. In: Von Ziessen H (ed) Cyclopaedia of the practice of medicine. William Wood, New York, pp 599–608
47. Corfield AP, Cooper MJ, Williamsson RCN (1985) Acute pancreatitis: a lethal disease if increasing incidence. Gut 26:724–729
48. Lankisch PG, Schirren CA, Schmidt H, Scholfelder G, Creutzfeldt W (1989) Etiology and incidence of acute pancreatitis: a 20-year study in a single institution. Digestion 44:20–25
49. Svensson JO, Nordback B, Bokey EL, Edlund Y (1979) Changing pattern in aetiology of pancreatitis in an urban Swedish area. Br J Surg 66:159–161
50. Mero M (1982) Changing aetiology of acute pancreatitis. Ann Chir Gynaecol 71:126–129
51. Appelros S, Borgström A (1999) Incidence, aetiology and mortality rate of acute pancreatitis over 10 years in a defined urban population in Sweden. Br J Surg 86:465–470
52. The Swedish state-controlled company for the sale of wines and spirits