

ORIGINAL ARTICLE

Drug-Induced Acute Pancreatitis in a Cohort of 328 Patients. A Single-Centre Experience from Australia

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ABSTRACT

Context Acute pancreatitis is associated with risk of morbidity and even mortality. Routine prescription drugs have been linked to the causation of acute pancreatitis. **Objective** To determine the incidence, presentation, course and outcome of drug-induced acute pancreatitis amongst patients admitted to a public hospital. **Design/setting** A retrospective analysis of patients presenting with acute pancreatitis to the Modbury Hospital, South Australia from January 2006 to April 2011. **Main outcome measure** Each admission was reviewed within the electronic database for patient details as well as to determine the aetiological factor. In patients with drug-induced acute pancreatitis, the WHO Probability Scale was used to evaluate causality relationship. **Results** Three-hundreds and 28 patients were treated for acute pancreatitis during the study period. Biliary and alcohol-induced acute pancreatitis accounted for 80.8% of cases. Eleven patients (2 male and 9 female patients; median age: 59 years) were diagnosed with drug-induced acute pancreatitis. These included 5 cases of codeine-, 2 cases of azathioprine-, and 1 case each of chlorothiazide-, valproic acid-, oestradiol- and rosuvastatin-induced acute pancreatitis. Nine patients had a mild disease while 2 patients had severe acute pancreatitis with a median hospital stay of 4 days. Withdrawal of the drug resulted in cessation of the attacks in all patients over a median follow-up of 24 months. **Conclusions** Routine prescription drugs, as an aetiological factor, accounted for 3.4% of cases of acute pancreatitis. The disease appeared to be more common in middle-aged women. It is likely that the overall incidence of this entity is under-reported owing to the stringent criteria needed to conclusively determine a causal relationship.

INTRODUCTION

Acute pancreatitis is associated with morbidity and even the risk of mortality [1, 2]. In the absence of a specific therapeutic agent [3], removal of the offending agent, fluids resuscitation [4], and antibiotic therapy (when indicated) constitute the best chance of cure. Alcohol and gallstones are the most important causes of acute pancreatitis around the world [5, 6, 7], as well as in Australia [8].

Routine prescription drugs have been linked to the causation of acute pancreatitis [9, 10]. However, the precise nature of this association (incidence and pathogenesis) is unclear owing to the fact that much of our current knowledge of drug-induced acute pancreatitis has been obtained from case reports [11]. A few large studies from Europe [12, 13, 14] have estimated the percentage of drugs as a cause for acute pancreatitis to be between 0.3 to 5.3%.

To date, there is no study elucidating the incidence of drug-induced acute pancreatitis in adult Australians. The aim of this study was to determine the incidence, presentation, course and outcome of drug-induced acute pancreatitis amongst patients admitted to a public hospital in Australia.

METHODS

A retrospective search of a prospectively maintained electronic database of the Modbury Hospital, South Australia was undertaken. International Classification of Diseases (ICD) codes for acute pancreatitis for a 64-month period, from January 2006 to April 2011 were analysed with the aim of identifying all patients admitted to the hospital with acute pancreatitis. 'Acute pancreatitis', 'biliary acute pancreatitis', 'idiopathic acute pancreatitis', 'alcohol-induced acute pancreatitis', 'drug-induced acute pancreatitis', 'acute pancreatitis unspecified' codes were included in the search amongst others. This resulted in a total of 7 ICD codes being used with 429 admissions being identified. Each admission was reviewed within the electronic database for patient admission details. The case records of patients identified to have acute pancreatitis were manually reviewed.

Acute pancreatitis was diagnosed by the concurrence of at least two of the following findings [15]: 1) acute-onset epigastric abdominal pain; 2) elevated serum amylase and/or lipase levels more than 3 times the

Received July 14th, 2011 - Accepted September 6th, 2011

Keywords Australia; Pancreatitis, Acute Necrotizing /etiology; Prescriptions

Abbreviations DM: diabetes mellitus; PCOS: polycystic ovarian syndrome

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upper level of normal range; and 3) imaging evidence of pancreatic inflammation. Disease severity was classified on the basis of the Atlanta Classification [16].

Cases of drug-induced acute pancreatitis were defined after a careful analysis using an algorithm previously published [17]. In all patients, a history of an alcohol binge or prior admission for alcohol-related acute pancreatitis was obtained. Additionally, all patients underwent an ultrasound to confirm/rule out gallstones as a cause. A history for new onset diabetes mellitus was sought. Trauma as a cause was ruled out based on history. All patients had complete biochemical investigations including serum calcium and triglyceride levels. Based on these investigations, if a cause for acute pancreatitis could not be found, a computed tomography (CT) scan of the abdomen was performed to rule out malignancies. In case of suspected malignancies, serum CA 19-9 levels were performed. Despite this, if no cause could be found, a magnetic resonance cholangiopancreatography was performed to rule out congenital malformations/autoimmune pancreatitis. If all the above were unremarkable, the patients drug history was sought and the relationship between the commencement of the drug and the attack of acute pancreatitis was noted. If all this failed to reveal the aetiology, the patient was labelled as having idiopathic acute pancreatitis. Viruses were considered as a cause for acute pancreatitis when the patients developed a severe viral illness necessitating admission and who went on to develop abdominal pain and CT findings consistent with acute pancreatitis. In some of our patients with drug-induced acute pancreatitis, the causality of the drug was directly considered as the patients presented with acute pancreatitis with the only positive history being consumption of the offending drug prior the attack and no confounding history of alcohol and lack of gallstones on ultrasound. In the only patient with suspected autoimmune pancreatitis based on imaging, the entire screen for markers including immunoglobulin 4 (IgG4) and autoantibodies as well as an endoscopic ultrasonography and fine needle aspiration were performed which were inconclusive for autoimmune pancreatitis. The drugs were classified based on the review of drug-induced acute pancreatitis by Badalov *et al.* [18].

If drug reaction was suspected to be an aetiological factor and all other causative factors were excluded by appropriate diagnostic methods, the WHO Probability Scale for the evaluation of causality relationship

between acute pancreatitis and the suspected drug therapy was used case-by-case [14]. Drug aetiology was definitively assessed only if the case met the criteria of certain, probable, or possible causality of adverse drug reaction [19].

ETHICS

No approval of the institutional review committee was needed because the data of the present study were collected in the course of common clinical practice and, accordingly, the signed informed consent was obtained from each patient for any surgical and clinical procedure. The study protocol conforms to the ethical guidelines of the “World Medical Association Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects” adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, as revised in Tokyo 2004.

STATISTICS

All statistical analyses were performed using the Statistical Product and Service Solutions, SPSS 14.0 for Windows. Nominal data is provided as absolute and relative frequencies and continuous data as median (range).

RESULTS

A total of 429 admissions over the 64-month period were identified for further analysis. Three-hundreds and 28 patients, confirmed to have acute pancreatitis, accounted for these 429 admissions (indicating that more than one patient had multiple admissions) and were included in the final analysis.

Overall Cohort of Acute Pancreatitis

Biliary disease (52.4%) and alcohol (28.4%) were the most common aetiological factors for acute pancreatitis in the overall cohort. The other causes for acute pancreatitis have been listed in Table 1. Acute pancreatitis was found to be more common in women (177; 54.0%) as compared to men (151; 46.0%). The median age for the disease was 54 years (range: 16-98 years) with a median hospital duration stay of 4 days (range: 1-27 days).

Drug-Induced Acute Pancreatitis

Eleven out of 328 patients (3.4%) were diagnosed with drug-induced acute pancreatitis. These included 9 female and 2 male patients with a median age of 59 years (range: 17-70 years). These included 5 cases of codeine-, 2 cases of azathioprine- (in patients with Crohn’s disease), and 1 case each of chlorothiazide-, valproic acid-, oestradiol- and rosuvastatin-induced acute pancreatitis (Table 2).

Nine of these 11 patients (81.8%) had a mild disease while 2 patients had severe acute pancreatitis with a median hospital stay of 4 days (range: 1-11 days). Three patients (Patient #1, #2 and #5; Table 2) had undergone a cholecystectomy prior to their presentation with the attack of acute pancreatitis.

Table 1. Aetiology of acute pancreatitis in 328 patients.

Aetiology	No. of patients
Biliary	172 (52.4%)
Alcohol	93 (28.4%)
Idiopathic	33 (10.1%)
Drugs	11 (3.4%)
Malignancy	6 (1.8%)
Viral	4 (1.2%)
Others	9 (2.7%)

Withdrawal of the drug resulted in cessation of the attacks in all patients with no further episodes of follow-up. The median follow-up in this series was 24 months (range: 6-62 months).

Drug Re-Challenge

Owing to the retrospective nature of the study, as well as for ethical reasons, a re-challenge could not be undertaken in all patients. However, failure to recognise the drug as a cause for the attack of acute pancreatitis resulted in an inadvertent re-challenge in 3 patients with a replication of the symptoms.

Patient #3 (Table 2) was admitted with mild acute pancreatitis following recent increase in the number of tablets consumed of a combination of codeine and ibuprofen for treating her migraines. At that time, the association was not considered significant. Six months later, when she restarted herself on codeine again for migraines, she developed another attack of acute pancreatitis necessitating admission. It was at this admission that the drug was recognised as the cause for acute pancreatitis.

Patient #10 (Table 2) was on valproic acid for treatment of her psychiatric problems for 4 years and was started on metformin for management of her polycystic ovarian syndrome disease. One year into the combination treatment, she presented with an attack of acute pancreatitis (confirmed on computed tomography scan) and metabolic acidosis. Recognising the potential of valproic acid to cause acute pancreatitis, the drug was ceased temporarily. However, in order to manage her psychiatric complaints, the drug was restarted resulting in the patient representing with acute pancreatitis one month later. At this time, the drug was permanently replaced by lithium.

Similarly, Patient #11 (Table 2) was admitted with mild acute pancreatitis following treatment with a combination medication of codeine and ibuprofen. At that time, the association was not considered

significant. One year later, when prescribed the combination again for pain, she developed another attack of acute pancreatitis necessitating admission. It was at this admission that the drug was recognised as the cause for acute pancreatitis.

DISCUSSION

The incidence of acute pancreatitis is increasing around the world [20]. While alcohol and gallstones account for the most important aetiological factors [6, 7], the impact of other agents, such as prescribed drugs, is being increasingly appreciated owing to the accumulating evidence in published literature [9, 10, 17, 18]. Our study demonstrates an important role for prescription drugs in the causation of acute pancreatitis in Australian adults similar to a previous report in children [21]. The patients tended to be older females. Codeine was the drug most commonly associated with the causation of acute pancreatitis. Our study also indicates that biliary diseases and alcohol are the predominant causes of acute pancreatitis in Australia.

Current understanding of drug-induced acute pancreatitis is largely based on case reports and critical reviews [11]. The importance of population-based studies in understanding this disease entity has been emphasized [11].

The incidence of drug-induced acute pancreatitis in our study of 3.4% compares with other large studies of drug-induced acute pancreatitis [12, 13, 14]. On comparing our results with these reports from Europe, drug-induced acute pancreatitis in our patients was more common in older patients (median age of 59 years) as compared to a mean age of 39-42 years noted in those studies [13, 14]. The female preponderance noted in our study appears to be similar to other studies.

Codeine, a class Ia drug associated with acute pancreatitis [18], caused an attack of acute pancreatitis in 5 patients in our series. The putative mechanisms by

Table 2. Variables of the cohort of patients admitted with drug-induced acute pancreatitis.

Patient	Age (years)	Drug (class) [18]	Class of risk [17]	Disease severity [16]	Duration of medication	Pre-existing disease	Causality [19]	Duration of Peak lipase stay (days)	Peak level (U/L)	Duration of follow up since cessation (months)
#1	68	Codeine (Ia)	I	Mild	3 days	Type 2 DM	Probable	2	2,860	54
#2	45	Azathioprine (Ib)	I	Mild	2 months	Crohn's disease, bowel cancer	Probable	7	1,864	42
#3	21	Codeine (Ia) Ibuprofen	I	Mild	3 months ^a	Iron deficiency anaemia	Certain	7	2,040	62
#4	65	Chlorothiazides (II)	II	Severe	2 years	Type 2 DM	Possible	8	6,788	42
#5	70	Azathioprine (Ib)	I	Mild	6 months	Crohn's disease	Probable	4	1,376	43
#6	17	Codeine (Ia)	I	Mild	3 days	-	Probable	1	923	24
#7	64	Oestradiol (II)	I	Severe	5 months	Menopause	Possible	11	773	6
#8	38	Codeine (Ia)	I	Mild	1 day	-	Probable	2	1,119	19
#9	59	Rosuvastatin (IV)	Implicated	Mild	2 months	Type 2 DM	Probable	3	7,000	19
#10	35	Valproic acid (Ia) Metformin (III)	I	Mild	4 years 1 year	PCOS	Certain	6	2,000	19
#11	59	Codeine (Ia) Ibuprofen	I	Mild	1 day	-	Certain	3	2,584	19

^a with overdose just prior to presentation
DM: diabetes mellitus; PCOS: polycystic ovarian syndrome

which codeine causes acute pancreatitis have been opined to be due to a spasm of the sphincter of Oddi [22]. Only one of these patients had had a prior cholecystectomy.

Two patients in our series were suffering from Crohn's disease and following treatment with azathioprine (a class Ib drug), developed acute pancreatitis, necessitating a change of the drug. An immune-mediated mechanism or a hypersensitivity to the drug is postulated in the pathogenesis of azathioprine-induced acute pancreatitis [23].

Although the effect of oestrogens on plasma triglycerides has been postulated as a potential mechanism for its causation of acute pancreatitis, our patient with acute pancreatitis secondary to oestradiol had normal triglyceride levels. The exact cause at this time is not clear but appears similar to a previous report [24] that suggested a different mechanism responsible for oestrogen-induced acute pancreatitis.

In the case of chlorothiazide-induced acute pancreatitis, the potential mechanisms involved in the causation of acute pancreatitis include thiazide-induced hyperparathyroidism, hyperlipidaemia and hypercalcaemia or hypotension-inducing pancreatic ischaemia [25]. In the case of the patient reported in our series, neither hyperlipidaemia nor hypercalcaemia were noted. The duration of therapy to the occurrence of the acute pancreatitis has been variable and reported to be even up to 1 year [25].

Acute pancreatitis as a complication of valproic-acid therapy has been well documented in children [26]. The exact mechanism is unclear although idiosyncratic reactions have been postulated to be a cause [26]. Cases of acute pancreatitis developing even after 10 years of therapy have been reported [27].

The role of statins in the causation of acute pancreatitis has been well documented. There has been one prior case report of acute pancreatitis following treatment with rosuvastatin [28]. The exact mechanism responsible for the causation of acute pancreatitis by statins remains unclear.

CONCLUSIONS

Routine prescription drugs, as an aetiological factor, accounted for 3.4% of cases of acute pancreatitis. The disease appeared to be more common in middle-aged women. It is likely that the overall incidence of this entity is under-reported owing to the stringent criteria needed to conclusively determine a causal relationship.

Acknowledgements The authors wish to acknowledge Martin Moyses, Heather Hills and Emma Venning for their assistance in the data collection

Sources of support None

Grant support Nil

Conflicts of interest None declared

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