gastroenterology insights

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Does the Use of Potential Pancreatotoxic Drugs Increase the Risk of Post-Endoscopic Cholangiopancreatography Pancreatitis?

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Abstract: Background and Aim: Endoscopic retrograde cholangiopancreatography (ERCP) is a valuable procedure for pancreatobiliary disorders but carries significant risks, including post-ERCP pancreatitis (PEP). The exact cause of PEP is unclear, but mechanical and thermal injuries during the procedure and patient-related factors have been implicated. This study aims to investigate the possible contribution of potential pancreatotoxic drug (PPD) exposure to PEP risk. Methods: This was a retrospective, single-centre, cohort study conducted at Canberra Hospital, a tertiary university hospital. Consecutive ERCP performed with native papillae within a 4-year period from January 2019 to January 2023 were evaluated. Details of ERCP procedures, patient characteristics, and all medications were contemporaneously collected. All patients had follow-up phone calls or review within 24 h post procedure. The diagnosis of PEP was based on the Cotton consensus definition. Results: A total of 32 out of 444 patients (7.2%) developed PEP. There was no significant difference in the incidence of PEP between patients taking PPD compared to patients who were not (7.1% vs. 7.6%, $p = 0.845$). Three factors were independently associated with PEP in the multivariate analysis: the presence of a periampullary diverticulum (OR = 5.4, 95% CI 1.7–15.3, $p = 0.002$), the performance of pre-cut sphincterotomy (OR = 2.8, 95% CI 1.2–6.4, $p = 0.017$), and pancreatic duct cannulation (OR = 3, CI 1.3–7, $p = 0.01$). Conclusions: The overall incidence of pancreatitis in our selected group of ERCP patients with native papillae was 7.2%. Our study did not find the use of PPD to be a statistically significant risk factor for PEP.

Keywords: ERCP; post-ERCP pancreatitis; potential pancreatotoxic drugs

Citation: Siu, W.; Ahmadzai, H.; Hasnol, M.H.; Fauzi, M.N.; Khoo, A.L.; Zhao, M.; Thomson, A. Does the Use of Potential Pancreatotoxic Drugs Increase the Risk of Post-Endoscopic Cholangiopancreatography Pancreatitis? *Gastroenterol. Insights* **2024**, *15*, 744–753. https://doi.org/10.3390/gastroent15030053

Academic Editor: Yasushi Sasaki

Received: 19 May 2024
Revised: 18 August 2024
Accepted: 22 August 2024
Published: 26 August 2024

1. Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is a valuable diagnostic and therapeutic procedure for managing pancreatobiliary disorders; however, it is not without significant risks. One of the most frequently encountered adverse events associated with ERCP is post-ERCP pancreatitis (PEP), a complication that can have severe consequences, including pancreatic necrosis and multiorgan failure. The precise pathogenesis of PEP remains inadequately elucidated. Several potential mechanisms contribute to the risk of PEP, encompassing mechanical or thermal injury inflicted upon the pancreatic orifice and the pancreatic duct (PD) during instrumentation, as well as hydrostatic injury stemming from the injection of contrast agents [1]. Additionally, certain patient-related risk factors have been identified, including younger age, female gender, a history of previous pancreatitis, and suspected sphincter of Oddi dysfunction [2]. Recent investigations have shed light on strategies to mitigate the risk of PEP. Notably, rectally administered non-steroidal anti-inflammatory drugs (NSAIDs) such as diclofenac have been demonstrated to reduce the incidence of pancreatitis when compared to placebo [3]. In cases in which diclofenac is contraindicated, sublingual nitrates have been proposed as an alternative [4]. Furthermore,

a meta-analysis has shown that aggressive intravenous fluid resuscitation is associated with a decreased risk of PEP in comparison to standard volume hydration [5]. Despite extensive research related to the role of pharmacologic prophylaxis, limited attention has been given to the potential role of pancreatotoxic drugs (PPD) in the development of PEP. The World Health Organization database lists over 500 drugs with the potential to induce acute pancreatitis. Recently, Simon-Linares et al. [6] updated and categorized these potential culprit drugs into four distinct classes based on the strength of evidence for each agent's contribution to pancreatitis development and the pattern of presentation. Although drugs have frequently been used to try to prevent PEP, their possible contribution to its development has not been studied extensively. Drug administration at the time of ERCP may heighten the PEP risk either by direct toxicity to the pancreas itself or by more indirect mechanisms such as inducing local ischemia [7,8]. The primary objective of our study was to investigate whether patients exposed to PPD are at an elevated risk of developing PEP. By exploring this association, we aimed to contribute insights into the complex interplay between pharmacologic agents and the occurrence of PEP, thereby enhancing our understanding of this clinically significant issue.

2. Materials and Methods

A consecutive series of ERCP procedures conducted at Canberra Hospital (an Australian tertiary referral centre) from 1 January 2019 to 3 January 2023 were included in this study. These procedures were performed by a single experienced operator (AT) or an advanced trainee/endoscopy fellow under his supervision. Only ERCPs involving 'native' papillae (no previous sphincterotomy) were evaluated. Data collected were initially recorded in an Excel spreadsheet and subsequently transferred to the R programme for comprehensive statistical analysis. Patient-related variables encompassed gender, age at the time of ERCP, the American Society of Anaesthesiologists (ASA) physical status classification, prior history of pancreatitis, and an exhaustive listing of the patients' medications. Total propofol dosage administered and the use of intravenous fluid and rectal NSAID were also recorded.

Procedure-related variables were recorded contemporaneously in a manner previously described [6]. Included were the duration of the procedure, whether it was conducted on an inpatient or outpatient basis, its classification as an emergency or an elective procedure, the primary indication for ERCP, presence or absence of trainee involvement. Furthermore, procedure characteristics that might signify challenging bile duct cannulation were recorded. These factors encompassed the presence of a periampullary diverticulum, the use of a pre-cut sphincterotomy technique, and instances where more than one guide-wire insertion into the PD occurred in achieving successful biliary cannulation. All ERCP patients received follow-up via phone calls or ward reviews to assess abdominal pain, nausea, vomiting, and oral intake both on the evening of the procedure and the next day (day 1). Any post-procedure complications, including but not limited to perforation, bleeding, and pancreatitis, were documented contemporaneously for subsequent analysis. The day 1 phone calls were made over 24 h after the procedure, which in our experience has been shown to be more effective at capturing ERCP-related events than has previously been reported [9,10].

2.1. Definitions

Patients' medications prescribed within one month prior to their ERCP procedures were meticulously evaluated to discern any potential associations with pancreatitis, employing the classification framework established by Simons-Linares et al. [6], as outlined in Table 1. This classification system categorizes drugs into five classes, each characterized by its respective likelihood of inducing acute pancreatitis. For a comprehensive listing of all 183 drugs encompassed by this classification, please refer to Appendix A.

Table 1. Classification of PPD by Simons-Linares et al. [6].

Class Ia	• At least 1 case report with positive rechallenge • Excluding all other causes, such as alcohol, hypertriglyceridemia, gallstones, and other drugs
Class 1b	• At least 1 case report with positive rechallenge • Case report failed to document exclusion of other causes or • Other possible etiologies were available
Class II	• At least 4 cases in the literature with consistent latency
Class III	• At least 2 cases in the literature with no consistent latency among cases and no rechallenge
Class IV	• Drugs not fitting into the earlier described classes • Single case report published in medical literature, without rechallenge

The determination of indications for ERCP adhered to the novel classification system advocated by Yuen et al., as delineated in Table 2 [11]. These indications were categorized into primary and secondary, with primary indications prioritized in a specific order. Each patient was assigned a single primary indication, with the highest-priority indication being the operative one. Secondary indications were invoked exclusively for patients whose clinical presentation did not align with any of the primary indications.

Table 2. Classification of ERCP indication.

Primary indications	(1) Cholangitis (CH) (2) Biliary leak (BL) (3) Acute pancreatitis (AP) (4) Positive intraoperative cholangiogram (IOC)
Secondary Indications	(1) Abdominal pain with abnormal imaging and liver function test (PIL) (2) Abdominal pain with abnormal imaging (PI) (3) Abdominal pain with abnormal liver function test (PL)

Post-ERCP pancreatitis (PEP) was defined as the occurrence of new-onset epigastric pain concomitant with a serum lipase level exceeding five times the upper limit of normal, necessitating hospital admission after the ERCP procedure. The duration of the ERCP procedure, which was recorded contemporaneously by the supervising endoscopist, was defined as the interval spanning the moment the duodenoscope traversed the cricopharyngeus to its eventual withdrawal from the patient. "Emergency ERCP" was designated for procedures conducted outside of regular working hours and thus deviating from the standard scheduled lists.

2.2. Statistical Analysis

Univariate analysis was conducted to compare patients who experienced PEP with those who did not. In the analysis of continuous variables, a two-sample *t*-test was employed to assess the impact of these variables, while for categorical variables, both the Chi-squared test and the Fisher's exact test for independence were utilized. In all statistical tests, we deemed the effect of a covariate to be statistically significant if the associated *p*-value was less than the predetermined significance level, which was set at 0.05. In the subsequent multivariate analysis, we sought to explore the influence of covariates on the incidence rates of PEP. To accomplish this, we employed logistic regression to model the data, employing a backward selection technique for model selection. This technique utilized the likelihood ratio test statistic as the decision rule for covariate inclusion or exclusion in the final model to assess the impact of covariates on PEP incidence rates.

3. Results

A total of 883 patients underwent ERCP procedures between 1 January 2019 and 3 January 2023. Among them, 444 patients had 'native' papillae. Patient demographics and procedural characteristics are summarized in Table 3.

Table 3. Demographics and procedural characteristics of study patients.

Variables	All Patients	Patients Not Taking PPD (*n* = 132)	Patients Taking PPD (*n* = 312)	*p* Value
Age, median (IQR)	70 (55.4–79.6)	55 (38.2–71.3)	73.2 (63–80.6)	0
Gender, male, *n* (%)	180 (40.5)	42 (31.8)	138 (44.2)	0.015
Previous history of pancreatitis, yes, *n* (%)	21 (4.7)	5 (3.8)	16 (5.1)	0.539
ASA, *n* (%)				0
1	27 (6.1)	20 (15.2)	7 (2.2)	0
2	207 (46.6)	71 (53.8)	136 (43.6)	0.061
3	173 (39)	33 (25)	140 (44.9)	0
4	36 (8.1)	8 (6.1)	28 (9)	0.347
5	1 (0.2)	0 (0)	1 (0.3)	1
Year of procedure, *n* (%)				0.491
2019	123 (27.7)	30 (22.7)	93 (29.8)	0.133
2020	118 (26.6)	34 (25.8)	84 (26.9)	0.906
2021	109 (24.5)	37 (28)	72 (23.1)	0.279
2022	92 (20.7)	30 (22.7)	62 (19.9)	0.523
2023	2 (0.5)	1 (0.8)	1 (0.3)	0.507
In- or outpatient, outpatient, *n* (%)	158 (35.6)	57 (43.2)	101 (32.4)	0.03
Emergency procedure, yes, *n* (%)	31 (7)	6 (4.5)	25 (8)	0.19
Trainee involvement, yes, *n* (%)	304 (68.5)	85 (64.4)	219 (70.2)	0.229
Indication, *n* (%)				0.016
AP	43 (9.7)	13 (9.8)	30 (9.6)	1
BL	8 (1.8)	2 (1.5)	6 (1.9)	1
CH	72 (16.2)	7 (5.3)	65 (20.8)	0
IL	93 (20.9)	29 (22)	64 (20.5)	0.799
IOC	55 (12.4)	22 (16.7)	33 (10.6)	0.084
PI	22 (5)	8 (6.1)	14 (4.5)	0.48
PIL	124 (27.9)	43 (32.6)	81 (26)	0.166
PL	8 (1.8)	2 (1.5)	6 (1.9)	1
Other	19 (4.3)	6 (4.5)	13 (4.2)	0.803
Procedure time, median (IQR)	20 (13–30)	20 (13–30.2)	20 (13–30)	0.459
Propofol dosage median (IQR)	240 (150–385)	250 (160–400)	230 (140–380)	0.317
Intravenous fluid given, yes, *n* (%)	372 (83.8)	114 (86.4)	258 (82.7)	0.372
Rectal NSAID, yes, *n* (%)	314 (70.7)	98 (74.2)	216 (69.2)	0.31
Periampullary diverticulum, yes, *n* (%)	26 (5.9)	4 (3)	22 (7.1)	0.097
Pre-cut sphincterotomy, yes, *n* (%)	119 (26.8)	37 (28)	82 (26.3)	0.704
PD cannulation, yes, *n* (%)	129 (29.1)	47 (35.6)	82 (26.3)	0.048
Successful biliary access, yes *n* (%)	406 (91.4)	120 (90.9)	286 (91.7)	0.794
Extraction balloon for stone, yes, *n* (%)	136 (30.6)	42 (31.8)	94 (30.1)	0.678
Biliary stent insertion, yes, *n* (%)	226 (50.9)	60 (45.5)	166 (53.2)	0.137
PD stent insertion, yes *n* (%)	74 (16.7)	25 (18.9)	49 (15.7)	0.4
Post ERCP pancreatitis, yes *n* (%)	32 (7.2)	10 (7.6)	22 (7.1)	0.845

Patients who were taking PPD exhibited statistically significant distinct characteristics, including advanced age and increased frailty. Additionally, there was a higher proportion of male patients, inpatient procedures and cases with cholangitis as the indication for ERCP within this group. Among the study participants, 32 patients developed PEP, resulting in an incidence rate of 7.2%. Of these cases, 4 were classified as severe, 14 as moderate and 14 as mild pancreatitis according to the consensus definition by Cotton et al. [1]. One patient succumbed to multiorgan failure and died within 30 days of the procedure. This was an 86-year-old gentleman with multiple comorbidities, including ischemic heart disease, who

had been hospitalized due to severe sepsis secondary to cholangitis. Out of the 444 patients included in the study, 312 (70%) were taking at least one PPD before undergoing ERCP. Many of the patients were taking more than one PPD, and the total number of medicines taken was 562. These PPDs were categorized into different classes, including Class 1a, Class 1b, Class II, Class III, and Class IV drugs, with 172, 49, 41, 178, and 122 patients falling into these respective categories. The comprehensive list of PPDs taken by patients and the corresponding incidence of PEP is presented in Table 4. It is of note that propofol (Class 1b drug) was administered to all patients and was therefore not included in the analysis.

Table 4. List of PPDs and number of PEP incidences.

	Total No. of Patients	**No. of Patients with Pancreatitis *n* (%)**
Overall, *n* (%)	444	32 (7.2)
Class Ia drug, *n* (%)	172	13 (7.6)
Acetaminophen	56	6 (10.7)
Acetaminophen-codeine	4	0 (0)
Furosemide	25	2 (8)
Metronidazole	32	3 (9.4)
Rosuvastatin	26	4 (15.4)
Amiodarone	3	0 (0)
Oestrogen and related products	6	0 (0)
Ranitidine	4	0 (0)
Perindopril	30	1 (3.3)
Simvastatin	16	1 (6.2)
Pravastatin	3	0 (0)
Trimethoprim/sulfamethoxazole	3	0 (0)
Class Ib drug, *n* (%)	49	3 (6.1)
Carbamazepine	2	0 (0)
Omeprazole	14	1 (7.1)
Clonidine	1	0 (0)
Dexamethasone	11	1 (9.1)
Mirtazapine	3	0 (0)
Fenofibrate	6	0 (0)
Propofol	1	0 (0)
Hydrocortisone	1	0 (0)
Prednisone	3	0 (0)
Quetiapine	1	0 (0)
Valproic acid	1	0 (0)
Valsartan	9	1 (11.1)
Class II drug, *n* (%)	41	2 (4.9)
Hydrochlorothiazide	17	2 (11.8)
Olanzapine	3	0 (0)
Prednisolone	11	0 (0)
Sitagliptin	10	0 (0)
Class III drug, *n* (%)	178	10 (5.6)
Aspirin	63	3 (4.8)
Atorvastatin	50	5 (10)
Ceftriaxone	35	4 (11.4)
Everolimus	1	0 (0)
Irbesartan	42	2 (4.8)
Metformin	47	3 (6.4)
Celecoxib	9	0 (0)
Doxycycline	1	0 (0)
Cyclosporine	1	0 (0)
Naproxen	1	0 (0)
Tacrolimus	4	0 (0)

Table 4. *Cont.*

	Total No. of Patients	No. of Patients with Pancreatitis *n* (%)
Class IV drug, *n* (%)	122	10 (8.2)
Allopurinol	25	3 (12)
Ampicillin	13	3 (23.1)
Atenolol	8	1 (12.5)
Famciclovir	1	1 (100)
Ibuprofen	3	0 (0)
Telmisartan	20	1 (5)
Amitriptyline	16	1 (6.2)
Amoxicillin/clavulanate	6	0 (0)
Ramipril	19	1 (5.3)
Sertraline	8	0 (0)
Calcium carbonate	5	0 (0)
Diclofenac	1	0 (0)
Etecavir	1	0 (0)
Ezetimibe	10	1 (10)
Mycophenolate mofetil	4	0 (0)
Lacosamide	1	0 (0)
Levetiracetam	1	0 (0)
Venlafaxine	7	1 (14.3)

The influence of PPD on the incidence rate of PEP was not found to be statistically significant, irrespective of the specific drug classes, as shown in Table 5. Additionally, our analysis explored the impact of various combinations of drug classes on the PEP incidence rate, and none of these combinations exhibited a statistically significant effect on the PEP rate.

Table 5. The relationship between taking PDD and PEP.

	PEP with PPD	PEP without PPD	*p* Value
Class Ia drug *n* (%)	13/172 (7.6)	19/272 (7)	0.82
Class Ib drug *n* (%)	3/49 (6.1)	29/395 (7.3)	0.756
Class II drug *n* (%)	2/41 (4.9)	30/403 (7.4)	0.545
Class III drug *n* (%)	10/178 (5.6)	22/266 (8.3)	0.289
Class IV drug *n* (%)	10/122 (8.2)	22/322 (6.8)	0.62

Univariate analysis of potential risk factors for PEP is presented in Table 6. Patient-related variables that exhibited statistical significance with respect to PEP included female gender, the year in which the procedure was performed, the presence of periampullary diverticulum, and biliary leak as an indication for ERCP. In terms of procedure-related risk factors, both the duration of the procedure and PD cannulation were found to be significant. It is worth noting that among the 129 patients who underwent PD cannulation during their ERCP, 75 of them (58%) received a PD stent as prophylaxis against pancreatitis. The comparison between those who received a pancreatic stent and those who did not revealed that the difference in PEP was not statistically significant, as indicated by a *p* value of 0.195.

Table 6. Univariate analysis of potential risk factors for PEP.

Variables	All Patients (*n* = 444)	Patients without PEP (*n* = 412)	Patients with PEP (*n* = 32)	*p* Value
Age, median (IQR)	70 (55.4–79.6)	70.3 (55.4–79.8)	66 (55.9–75.9)	0.667
Gender, male, *n* (%)	180/444 (40.5)	166/412 (40.3)	14/32 (43.8)	0.015
Previous history of pancreatitis, yes, *n* (%)	21 (4.7)	5 (3.8)	16 (5.1)	0.712

Table 6. *Cont.*

Variables	All Patients (*n* = 444)	Patients without PEP (*n* = 412)	Patients with PEP (*n* = 32)	*p* Value
ASA, *n* (%)				0.459
1	27/444 (6.1)	26/412 (6.3)	1/32 (3.1)	0.71
2	207/444 (46.6)	187/412 (45.4)	20/32 (62.5)	0.068
3	173/444 (39)	164/412 (39.8)	9/32 (28.1)	0.259
4	36/444 (8.1)	34/412 (8.3)	2/32 (6.2)	1
5	1/444 (0.2)	1/412 (0.2)	0/32 (0)	1
Year of procedure, *n* (%)				0.041
2019	123/444 (27.7)	116/412 (28.2)	7/32 (21.9)	0.541
2020	118/444 (26.6)	102/412 (24.8)	16/32 (50)	0.003
2021	109/444 (24.5)	104/412 (25.2)	5/32 (15.6)	0.288
2022	92/444 (20.7)	88/412 (21.4)	4/32 (12.5)	0.363
2023	2/444 (0.5)	2/412 (0.5)	0/32 (0)	1
In- or outpatient, outpatient, *n* (%)	158/444 (35.6)	148/412 (35.9)	10/32 (31.2)	0.703
Emergency procedure, yes, *n* (%)	31/444 (7)	29/412 (7)	2/32 (6.2)	1
Trainee involvement, yes, *n* (%)	304/444 (68.5)	281/412 (68.2)	23/32 (71.9)	0.844
Indication, *n* (%)				0.012
AP	43/444 (9.7)	41/412 (10)	2/32 (6.2)	0.757
BL	8/444 (1.8)	5/412 (1.2)	3/32 (9.4)	0.015
CH	72/444 (16.2)	69/412 (16.7)	3/32 (9.4)	0.453
IL	93/444 (20.9)	87/412 (21.1)	6/32 (18.8)	1
IOC	55/444 (12.4)	48/412 (11.7)	7/32 (21.9)	0.097
IP	22/444 (5)	22/412 (5.3)	0/32 (0)	0.39
PIL	124/444 (27.9)	116/412 (28.2)	8/32 (25)	0.839
PL	8/444 (1.8)	8/412 (1.9)	0/32 (0)	1
Other	19/444 (4.3)	16/412 (3.9)	3/32 (9.4)	0.15
Procedure time, median (IQR)	20 (13–30)	20 (12–29.8)	28 (19.8–35.8)	0.028
Propofol dosage median (IQR)	240 (150–385)	240 (150–380)	310 (190–470)	0.157
Intravenous fluid given, yes, *n* (%)	372/443 (84)	114 (86.4)	258 (82.7)	0.372
Rectal NSAID, yes, *n* (%)	314 (70.7)	345/412 (83.7)	27/31 (87.1)	0.801
Periampullary diverticulum, yes, *n* (%)	26/436 (6)	20/404 (5)	2/14 (14.3)	0.01
Pre-cut sphincterotomy, yes, *n* (%)	119/444 (26.8)	101/412 (24.5)	6/14 (42.9)	0
PD cannulation, yes, *n* (%)	129/444 (29.1)	109/412 (26.5)	4/14 (28.6)	0
Successful biliary access, yes *n* (%)	406/444 (91.4)	377/412 (91.5)	29/32 (90.6)	0.747
Extraction balloon for stone, yes, *n* (%)	136/406 (33.5)	128/377 (34)	8/29 (27.6)	0.546
Biliary stent insertion, yes, *n* (%)	226/406 (55.7)	206/377 (54.6)	20/29 (69)	0.174
PD stent insertion, yes *n* (%)	74 (16.7)	25 (18.9)	49 (15.7)	0.4
Taking PPD, yes *n* (%)	312/444 (70.3)	290/412 (70.4)	22/32 (68.8)	0.842

4. Discussion

To our knowledge, only three studies have investigated the role PPD in PEP. The first study from France was retrospective [12]. It utilized the classification of PPD established by Biour et al. [13]. This study revealed an increased incidence of PEP in patients taking one of six "highly pancreatotoxic drugs", namely oestrogen, azathioprine, valproic acid, mesalazine, morphine derivatives, and prednisolone. Among the patients in our study, three of these drugs were taken by at least one subject: oestrogen, valproic acid, and prednisolone. It is worth noting that this study was conducted during an era when the routine administration of rectal nonsteroidal anti-inflammatory drugs (NSAIDs) and the insertion of pancreatic stents for pancreatitis prophylaxis was not commonplace. This may account for the higher post-ERCP pancreatitis rate observed, which stood at 18%.

The second study, which was also retrospective, came from New York and was conducted by Li et al. [14]. It explored the impact of 13 medications, including propofol, finding that patients on angiotensin receptor blockers (ARB) were four times more likely to develop PEP compared to those who were not taking ARBs. The study concluded that propofol is a safe sedative drug for patients undergoing ERCP and was not associated with an increased

risk of pancreatitis. In our study, 4 out of 71 (5.6%) patients taking angiotensin receptor blockers (ARBs) (valsartan, irbesartan, and telmisartan) developed pancreatitis, but the increase in PEP compared to the overall rate in the cohort was not statistically different. It is hard to account for the difference between the results of the present study and those of the New York study. Most of the patients in our study underwent ERCP in the afternoon and patients are routinely advised not to take their regular medications, including ARBs on the morning of the procedure. The blood levels of these medications may have been lower than those in the New York study patients, although data concerning exact timing of medication use were not given in that study. In addition, the use of preprocedural intravenous fluids in our study (which would not have occurred in the New York study), may have mitigated against ARB induced pancreatitis due to transient ischemia of the pancreas related to ARB associated hypotension.

The most recent study in this area, which was published in 2013, came from Greece [15]. It was an unselected prospective cohort study. The use of PPD before ERCP was found to be associated with an increased risk of PEP. In this study, the Badalov classification was employed [16]. The study included only Class 1a (23 medications), Class 1b (18 medications), and Class II (10 medications), as these were deemed more clinically relevant with the most compelling evidence linking them to acute pancreatitis. The study found that patients prescribed Class I or II medications were four times more likely to develop PEP. Again, these results were not confirmed in our study.

The Badalov classification system was updated by Simon-Linares et al. [6] in light of new medications and evidence. The number of reported PPDs increased from 120 drugs in 2007 (Badalov classification) to 183 in 2019. This update revealed a decrease in the proportion of PPD classified as Class Ia—drugs with the strongest evidence linking them to PEP—and an increase in the number of Class IV drugs, which have the weakest evidence in this respect. Our study is thus the most comprehensive to date, encompassing all five classes of PPD, totaling 183 medications. Additionally, we accounted for multiple patient and procedure-related variables.

Drug-induced pancreatitis remains a relatively infrequent clinical occurrence. The body of evidence pertaining to drug-induced pancreatitis is characterized by low-quality data, predominantly drawn from case reports. However, there is noteworthy high-quality evidence from randomized clinical trials identifying three drugs associated with pancreatitis: 6-mercaptopurine (6-MP), azathioprine, and didanosine [17]. The pathophysiological underpinnings of drug-induced pancreatitis remain incompletely elucidated and are believed to involve a multifaceted interplay of mechanisms. Similarly, the pathophysiology of PEP is not fully understood with several proposed mechanisms, including mechanical trauma, dysfunction of the papillary sphincter, ischemia, chemical irritation from the injection of contrast dye, pancreatic ductal obstruction, and the potential introduction of infection during the procedure [18]. Numerous well-established patient and procedure-related risk factors are recognized in the context of PEP, some of which have demonstrated significance in our own investigation including PD cannulation, the presence of periampullary diverticulum, and pre-cut sphincterotomy [19]. In contrast, there is a paucity of research focusing on the role of PPD in relation to PEP. Our study represents the first study that showed the use of PPD does not confer an elevated risk of PEP. There may have been a type II error due to the study size and the relatively low rate of PEP. Nonetheless, our data suggest that there is no compelling justification for the discontinuation of PPD prior to ERCP procedures.

It is acknowledged that our study has several limitations. It was a single-centre, single-operator study, which may limit the generalizability of the results. The matching of the baseline characteristics of both study groups was also not possible. In this regard, patients taking PPD were significantly older and more frequently male, both of which could act as protective factors against PEP [2]. Moreover, medication history relied on self-reported data from patients prior to their ERCP, introducing the potential for recall bias. Nevertheless, our study represents the largest investigation to date into the role of PPD in PEP.

5. Conclusions

In conclusion, the overall incidence of pancreatitis in our selected group of ERCP patients with native papilla was 7.2%. This incidence rate aligns with acceptable norms when compared to a recent meta-analysis where the overall PEP incidence rate was 9.7% [20]. Our study did not find being on a PPD to be a statistically significant risk factor for PEP.

Author Contributions: Conceptualization, W.S. and A.T.; methodology, W.S. and A.T.; resources, A.T.; data collection, M.H.H., M.N.F., and A.L.K. writing—original draft preparation, W.S.; writing—review and editing, A.T., H.A., and W.S.; statistical analysis, M.Z.; supervision, A.T. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the low risk Ethics Committee of Research Ethics and Governance Office at ACT health (ACT Reference 2022.LRE.00198 and REGIS Reference 2022/ETH02145).

Informed Consent Statement: Not applicable.

Data Availability Statement: Data are unavailable due to privacy restrictions.

Conflicts of Interest: The authors declare no conflicts of interest.

Appendix A

Table A1. Classification of implicated medications by Simon-Linares et al. [6].

Class Ia	Class Ib	Class II	Class III		Class IV
Acetaminophen	Azathioprine	All-trans retinoic acid	Aspirin	L-Arginine	Interferon β1a
Acetaminophencodeine	Bortezomib	L-Asparaginase/peg asparaginase	Atorvastatin	Adefovir	Interleukin 2
5-Aminosalicylate	Carbamazepine	Canagliflozin	Capecitabine	Ado-traztuzumab emtansine	Ketoprofen
Amiodarone	Clonidine	Chlorothiazide	Captopril	Albiglutide	Lacosamide
Androgenic Anabolic steroids	Clozapine	Codeine	Ceftriaxone	Allopurinol	Lamivudine
Arsenic trioxide	Cytosine arabinoside Dapsone	Dideoxy inosine	Celecoxib	Amitriptyline	Lamotrigine
Cannabis	Dexamethasone Fenofibrate	Gold therapy	Chlorthalidone	Amoxicillin/clavulanate	Lanreotide autogel
Carbimazole Cimetidine	Hydrocortisone	Hydrochlorothiazide	Ciprofloxacin	Ampicillin	Levetiracetam
Clomiphene	6-Mercaptopurine Methimazole	Interferon α2b/ribavirin	Clarithromycin	Anagrelide hydrochloride	Mefenamic acid
Enalapril	Mirtazapine	Lisinopril	Cocaine	Artesunate	Micafungin sodium
Estrogen and related products	Nelfinavir	Liraglutide	Cyclosporine	Atenolol	Miltefosine
Furosemide	Nitrofurantoin	Meglumine antimonate	Doxycycline	Axitinib	Montelukast
In vitro fertilization	Omeprazole	Nilotinib	Erythromycin	Benazepril	Motesanib
Isoniazid	Paclitaxel	Olanzapine	Everolimus Exenatide	Bendroflumethiazide	Mycophenolate mofetil
Losartan	Pentamidine	Prednisolone	Indomethacin	Bezafibrate	Naltrexone
Methyldopa	Prednisone Propofol	Riluzole	Interferon α2b	Boceprevir	Nifuroxazide
Metronidazole	Quetiapine	Sitagliptin	Irbesartan	Brentuximab vendontin	Nivolumab
Nadolol	Sodium stibogluconate		Ketorolac	Calcium carbonate kondoi	Octreotide
Pravastatin	Sorafenib		Metformin	Danazol	Oxacalcitriol
Perindopril	Tigecycline		Metolazone	Diclofenac	Oxyphenbutazone
Procainamide	Valproic acid		Minocycline	Dideoxycytidine	Paromomycin
Pyritinol	Valsartan		Naproxen	Dimethyl fumarate	Phenolphthalein
Ranitidine			Orlistat	Entecavir	Ramipril
Rosuvastatin			Pazopanib	Ergotamine tartrate	Risperidone
Saxagliptin			Phenformin	Estramustine phosphate	Roxithromycin
Simvastatin			Ritonavir	Ethacrynic acid	Secnidazole
Sulindac			Saw palmetto	Ezetimibe	Sertraline
Tamoxifen			Tacrolimus	Famciclovir	Stavudine
Telaprevir			Vildagliptin	Fluconazole	Sunitinib
Tetracycline					Tacalcitol
Trimethoprim/ sulfamethoxazole					Telmisartan
				Fluvastatin	Theophylline Tinidazole
				Gadobenate dimeglumine (Multihance)	Tocilizumab
				Glimepiride	Vedolizumab
				Horsetail infusions (E. arvense)	Vemurafenib
				Ibuprofen	Venlafaxine
				Icodextrin	Vinblastine
				Ifosfamide Imatinib	Ziprasidone
				Interferon α2a	

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