Therapeutics and Clinical Risk Management

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Mesalazine-Induced Acute Pancreatitis in Inflammatory Bowel Disease Patients: A Systematic Review

Juan Pan[1,*], Zuyi Li[1,*], Chao Ye[2], Xiaojuan Zhang[1], Qiongliang Yang[1], Xu Zhang[1], Ya Zhou[3], Jianjun Zhang[2]

[1]Department of Pharmacy, Liuyang Hospital of Traditional Chinese Medicine, Changsha, Hunan, 410300, People's Republic of China; [2]Department of Pharmacy, Guangdong Provincial second Hospital of Traditional Chinese Medicine (Guangdong Provincial Engineering Technology Research Institute of Traditional Chinese Medicine), Guangzhou, Guangdong, 510095, People's Republic of China; [3]Department of Pharmacy, People's Hospital of Ningxiang City Affiliated to Hunan University of Chinese Medicine, Changsha, Hunan, 410600, People's Republic of China

*These authors contributed equally to this work

Correspondence: Chao Ye, Department of Pharmacy, Guangdong Provincial second Hospital of Traditional Chinese Medicine (Guangdong Provincial Engineering Technology Research Institute of Traditional Chinese Medicine), No. 60, Hengfu Road, Guangzhou, Guangdong, 510095, People's Republic of China, Email yechao1234256@163.com

Objective: Mesalazine is a widely used medication for treating mild to moderate inflammatory bowel disease (IBD). First identified as a potential cause of acute pancreatitis (AP) in 1989, the link between mesalazine and AP has primarily been established through case reports and a limited number of retrospective studies. This study aims to explore the characteristics of mesalazine-induced AP.

Methods: The databases of CNKI, Wanfang Data, VIP, PubMed and Web of Science were searched (up to March, 2024), and the case reports of mesalazine-related AP in IBD patients were collected and descriptively analyzed.

Results: Thirty-four reports were included, describing 42 patients (22 males, 16 females, 4 unspecified) with mesalazine-related AP. The onset of pancreatitis occurred a median of 14 days (range 1–730 days) after starting mesalazine. Common symptoms included abdominal pain (100%), vomiting (38.1%), fever (21.4%), and nausea (21.4%). Most patients had elevated serum amylase and lipase levels, with some showing raised C-reactive protein and erythrocyte sedimentation rate. Imaging tests, such as computed tomography and B-scan ultrasonography, revealed edematous infiltration and inflammation. Discontinuation of mesalazine led to symptom resolution in all patients, with 93.3% improving within a week. Alternative treatments or switching to other forms of 5-aminosalicylic acid may be considered for ongoing management. Rechallenge with mesalazine led to recurrence of AP in 21 cases, with a shorter median time to symptom onset.

Conclusion: Mesalazine-induced AP is a rare but significant adverse reaction, not related to drug dosage, and can occur at any point during treatment, typically within two weeks. The reaction can recur upon rechallenge. Discontinuation of mesalazine and symptomatic treatment typically resolves the condition.

Keywords: mesalazine, acute pancreatitis, adverse drug reactions, clinical characteristics, systematic review

Introduction

Inflammatory bowel disease (IBD) encompasses chronic, relapsing inflammatory disorders of the gastrointestinal tract, including ulcerative colitis (UC), Crohn's disease (CD), and unclassified IBD (IBD-U). These conditions require long-term management due to their recurrent nature. Mesalazine (also known as 5-aminosalicylic acid or 5-ASA) is a first-line treatment for inducing and maintaining remission in patients with mild to moderate UC.[1–3] Despite limited evidence supporting the clinical benefits of oral 5-ASA compounds in CD, these medications are commonly used in practice, especially for colonic CD.[4,5] Ensuring adequate delivery of mesalazine to the large intestine and maintaining high concentrations in the intestinal mucosa are crucial for effective mucosal healing.

Received: 9 October 2024
Accepted: 13 January 2025
Published: 27 January 2025

Initially approved by the US Food and Drug Administration (FDA) in 1992 for the treatment of mild to moderate IBD, mesalazine is available in various forms, including oral tablets, suppositories, and enemas.[6] Oral formulations include delayed-release, controlled-release, multimatrix, and extended-release preparations. The recommended daily oral dose ranges from 2 to 4.8 grams, while the rectal dosage is typically 1 gram per day. For pediatric patients, the oral dose ranges from 60 to 80 mg/kg/day up to a maximum of 4.8 grams daily, with a rectal dose of 25 mg/kg up to 1 gram daily.[7]

Mesalazine is generally well tolerated, but it can cause a range of adverse effects, including fever, hyperamylasemia, headache, diarrhea, skin rashes, liver function abnormalities, abdominal pain, and gastrointestinal symptoms such as nausea and vomiting.[8] Previous investigations suggested that acute pancreatitis (AP) was listed as rare in occurrence with a significant lower prevalence (0.3–1.8%).[9] However, Lee AA et al conducted a study on IBD medications and their association with AP, reporting that 791 out of 4223 cases (18.73%) of drug-induced acute pancreatitis (DIAP) were linked to mesalazine. The study found a reporting odds ratio (ROR) of 17.44 (95% CI 16.24–18.72) and an empirical Bayesian estimate (EBE) of 15.81, indicating a significant association between mesalazine and DIAP.[10] Despite these findings, the exact relationship between mesalazine use and AP remains unclear, as most data comes from case reports. The purpose of this study is to explore the clinical characteristics, diagnosis, and management of mesalazine-induced AP and provide insights to guide its safer clinical use.

Methods

Search Strategy

We searched the databases of China National Knowledge Infrastructure (CNKI), Wanfang Data, Chinese VIP, Web of Knowledge, PubMed/Medline, Embase, OVID, Elsevier, Springer Link and Cochrane Library databases, with no language restrictions. The search terms were “mesalamine” OR “mesalazine” OR “mesalizine” OR “5-aminosalicylic acid” OR “5-aminosalicylate” OR “5-ASA” OR “5ASA” AND “pancreatitis” OR “lipase” OR “amylase” OR “abdominal pain”. A case report and case analysis of medications-related AP were included as a preliminary study. The retrieval time limit is from the establishment of the database to March, 2024.

Inclusion and Exclusion Criteria

Studies considered for this review had to fulfill the following inclusion criteria: (1) a case report and case analysis of mesalazine-induced AP were included as a preliminary study; (2) the diagnosis of AP meets the diagnostic criteria in Atlanta diagnostic criteria[11] and (3) the clinical data of primary disease, mesalazine application, clinical manifestations and prognosis of AP were relatively complete. The studies were excluded if they described: (1) literatures with repeated publication or repeated cases and (2) cases with incomplete important information and unclear rare adverse reaction (ADR). According to the Atlanta classification system for AP severity, it was divided into mild acute pancreatitis (MAP), moderately severe acute pancreatitis (MSAP), and severe acute pancreatitis (SAP).[11]

Data Extraction

Two investigators independently conducted a preliminary review of the literature according to the inclusion and exclusion criteria, followed by a panel discussion. The following information were collected for each included case using a self-designed data extraction table: region, sex, age, primary disease, accompanying diseases, concomitant medication, mesalazine application, pancreatitis occurrence, clinical manifestations, laboratory examination, imaging examination, treatment, and prognosis.

Statistical Analysis

Descriptive analyses were performed on patient characteristics and the features and patterns of ADR, and narrative synthesis was performed on the main outcomes of the included studies. Statistical analysis was performed using SPSS 26.0 (IBM Corporation, Armonk, NY). The count data are expressed as n (%), and the measurement data are expressed as the median value (minimum, maximum).

Correlation Evaluation

The Naranjo Adverse Drug Reaction Probability Scale was used to assess the association between mesalazine and AP.[12] Probability was assigned via a score termed definite (≥9), probable (5–8), possible (1–4), or doubtful (≤0).

Results

Basic Information

After retrieval and screening, forty-two patients from 34 studies were included in this analysis, involving 30 case reports[13–42] and 4 case series.[43–46] The literature search process is outlined in Figure 1. There are 22 males (52.4%) and

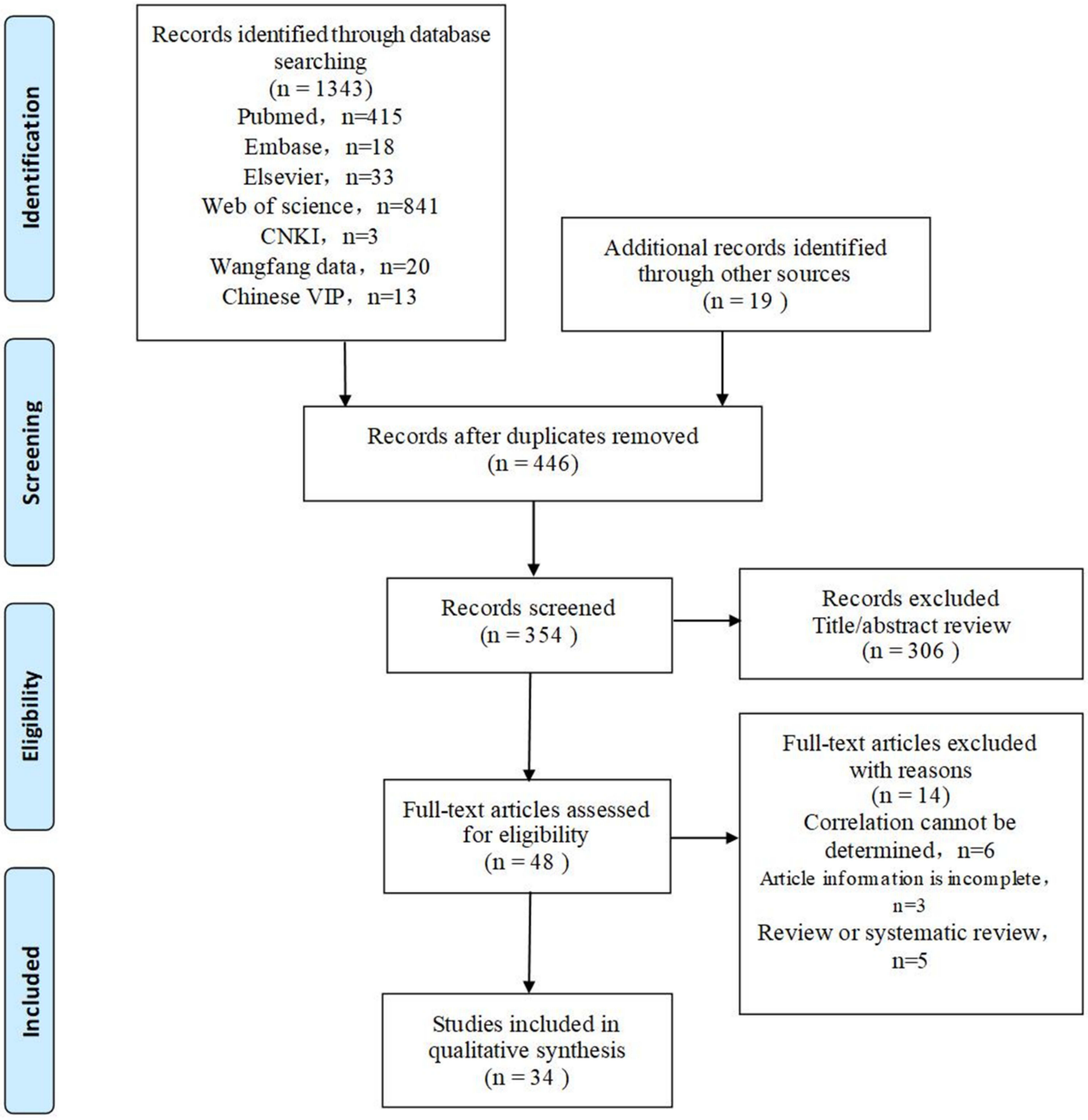

Figure 1 Flowchart of literature screening.

https://doi.org/10.2147/TCRM.S493371

16 females (38.1%). The sex of 4 patient was not reported (Table 1). The median age of these patients was 25 years (range 7–63). Among these patients, 19 patients were from Europe (Germany, N = 5; France, N = 4; Italy, N = 3; Belgium, N = 2; Spain, N = 1; Denmark, N = 1; Greece, N = 1; Portugal, N = 1; Hungary, N = 1), 13 patients were from Asia (Japan, N = 4; People's Republic of China, N = 4; South Korea, N = 4; Korea, N = 1), 9 patients were from North

Table 1 Characteristics of the 42 Included Patients

Parameter		Value
Sex (42)[a]	Male	22 (52.4%)
	Female	16 (38.1%)
	No data	4(9.5%)
Age (42)[a]	Years	25 (7,63)[b]
Region (42)[a]	The United States	7 (16.7%)
	Germany	5(11.9%)
	Japan	4(9.5%)
	China	4(9.5%)
	France	4 (9.5%)
	South Korea	4 (9.5%)
	Italy	3 (7.1%)
	Belgium	2 (4.8%)
	Canada	2 (4.8%)
	Denmark	1(2.4%)
	Portugal	1(2.4%)
	Spain	1 (2.4%)
	Greece	1 (2.4%)
	Hungary	1 (2.4%)
	Korea	1 (2.4%)
	Australia	1 (2.4%)
Indication (42)[a]	UC	30(71.4%)
	CD	12(28.6%)
BMI (6)[a]	kg/m2	28.61(18.70–37.50)[b]
Usage (42)[a]	Oral	34(81.0%)
	Topical	5(11.9%)
	Combination	3(7.1%)
Daily dose (36)[a]	<2 g	16(44.4%)
	2–4 g	18(50.0%)
	>4 g	2(5.6%)
Time of symptom onset (37)[a]	Days	14(1–730)[b]
	≤14 days	21(56.8%)
Preexisting pancreatic disease	Yes	0
	No	42(100.0%)
Risk factors for acute pancreatitis (42)[a]	Total	3(7.1%)
	Alcohol use	2(4.8%)
	Smoking	1(2.4%)
Underlying diseases (42)[a]	Mild asthma, perianal abscess, history of subtotal thyroidectomy, oligozoospermia, hypothyroidism, seasonal allergies, eczema, tonic/clonic seizure disorder, multiple sclerosis, psoriasis, atrial fibrillation, mitral valve prolapse	10(23.8%)
Concomitant medications (17)[a]	Corticosteroids: prednisone, methylprednisolone	11(64.7%)

(*Continued*)

Table 1 (Continued).

Parameter		Value
	Thyroid hormones	2(11.8%)
	Antibacterials: metronidazole	1(5.9%)
	Antiepileptic drugs: carbamazepine	1(5.9%)
	Interferon beta 1b	1(5.9%)
	Hydrogen pump inhibitors: pantoprazole	1(5.9%)
	Beta blockers: metoprolol	1(5.9%)
	Other drugs for IBD: azathioprine, cyclosporin	1(5.9%)

Notes: [a] Represents the number of patients out of 42 in whom information regarding this particular parameter was provided. [b] Median (minimum-maximum).
Abbreviations: UC, ulcerative colitis; CD, Crohn's disease; IBD, inflammatory bowel disease.

America (United States of America, N = 7, Canada N = 2), and 1 patient was from Oceania (Australia, N = 1). Thirty cases (71.4%) were indicated for UC, 12 cases (28.6%) for CD. The route of administration was mainly oral (34 cases, 81.0%) and topical (5 cases, 11.9%), and 3 cases (7.1%) were treated with oral combined with topical administration. The dose range of mesalazine was 0.8–5 g, of which 16 cases (44.4%) received <2 g/d, 2 cases (5.6%) received >4 g/d, and the remaining 18 cases (50.0%) received 2–4 g/d. The median time to onset of symptoms of AP was 14 days (range 1–730). Five patients had a history of allergies (3 patients had AP with sulfasalazine, 1 patient had liver injury with sulfasalazine, and 1 patient had allergies to trimethoprim and lactose). Ten patients (23.8%) of these 42 patients had other underlying diseases at the same time, and 17 patients (40.5%) took other drugs in combination, including corticosteroids therapy in 11 patients (64.7%).

Clinical Presentation

The clinical manifestations of the 42 patients are shown in Table 2. The most common symptoms were abdominal pain (42 cases,100.0%), vomiting (16 cases,38.1%), fever (9 cases,21.4%) and nausea (9 cases, 21.4%). An analysis of 42 patients with AP caused by mesalazine revealed that 40 patients (95.2%) developed MAP, and 2 patients (4.8%) developed MSAP.

Laboratory Tests

The laboratory test results of the 42 patients are summarized in Table 2. Pancreatic enzyme increased in all patients, and amylase or lipase in 37 patients (88.1%) exceeded 3 times the upper limit of normal value. The median levels of serum amylase and serum lipase were 350 (range 54–1596) IU/L and 1117 (range 158–5651) IU/L, respectively. Among the 23 reported patients, elevated total leukocyte counts were observed in 15 patients (65.2%), with a median value of 15,850 (range 9360–41,700) mm^3 Among the 12 reported patients, 8 (66.6%) had elevated C-reactive protein (CRP) levels, with a median value of 34.2 (1.3–189) mg/L. Erythrocyte sedimentation rate (ESR) was measured in 10 patients, of which 7 cases (70.0%) were elevated and 3 cases (30.0%) were normal. The median ESR was 41 mm/h (range 22–85).

Imaging Examination

The computed tomography (CT) scan and abdominal ultrasound examination results are summarized in Table 2. Four patients did not undergo abdominal ultrasound or CT examination. The CT scan in 20 patients showed edema or enlargement of the pancreas (14 patients, 70.0%), normal (3 patients, 15.0%), AP (2 patients, 10.0%), and inflammation (1 patient, 5.0%). Abdominal ultrasound examination in 23 patients revealed normal (11 patients,47.8%), edema or enlargement of the pancreas (11 patients, 47.8%) and AP (1 patients, 4.4%).

Treatment and Prognosis

The treatment and prognosis of these 42 patients are summarized in Table 3. All patients immediately discontinued mesalazine when AP occurred. No patients developed necrotizing pancreatitis or organ failure, and only one patient[19]

Table 2 Clinical Information on the 42 Included Patients

Parameter	Clinical Features	Value, n (%)
Presenting symptoms (42)[a]	Abdominal pain	42(100.0%)
	Vomiting	16(38.1%)
	Fever	9(21.4%)
	Nausea	9(21.4%)
	Diarrhea	2(4.8%)
	Abdominal distension	1(2.4%)
	Poor appetite	1(2.4%)
	Tachycardia	1(2.4%)
Severity of acute pancreatitis (42)[a]	Mild	40(95.2%)
	Moderate	2(4.8%)
Serum amylase levels (33)[a]	IU/L	350(54–1596)[b]
Serum lipase levels (29)[a]	IU/L	1117(158–5651)[b]
Total leukocyte count (23)[a]	Normal	8(34.8%)
	Elevated	15(65.2%)
	mm^3	15,850(9360–41,700)[b]
CRP levels (12)[a]	Normal	4(33.3%)
	Elevated	8(66.6%)
	mg/L	34.2(1.3–189)[b]
ESR levels (10)[a]	Normal	3(30.0%)
	Elevated	7(70.0%)
	mm/h	41(22–85)[b]
CT (20)[a]	Edema or enlargement of the pancreas	14(70.0%)
	Normal	3(15.0%)
	Acute pancreatitis	2(10.0%)
	Inflammation	1(5.0%)
Ultrasonogram of the abdomen (23)[a]	Normal	11(47.8%)
	Edema or enlargement of the pancreas	11(47.8%)
	Acute pancreatitis	1(4.4%)

Notes: [a] Represents the number of patients among a total of 42 on whom information regarding this particular parameter was provided. [b] Median (minimum-maximum).
Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; CT, computed tomography.

was admitted to ICU for treatment. After discontinuation of mesalazine, 16 patients (38.1%) received corticosteroids, 3 (7.1%) received 4-ASA, 2 (4.8%) received azathioprine, 1(2.4%) received infliximab and balsalazide, respectively. All 42 patients recovered after relevant treatment with a median hospital stay of 7 days (range 2–30). The time of symptom disappearance was recorded in 30 patients. The clinical symptoms disappeared immediately after treatment in 5 patients (16.7%), disappeared within 1 week after treatment in 23 patients (76.7%), and disappeared more than 1 week after treatment in 2 patients (6.6%). The median time for amylase and lipase to recovered to normal range was 5 days (range 1–45) and 7 days (range 2–45), respectively. AP occurred in 21 cases (50.0%) after rechallenging with mesalazine, and the onset time was recorded in 19 patients. The median time to AP occurrence of rechallenge patients was 1 day (range 0.33–14), which was shorter than that of the first occurrence.

Relevance Evaluation

Of all 42 cases, 24 patients (57.1%) were assessed as probable mesalazine-induced AP, of which 7.1% (n=3) received a score of 8, 31.0% (n=13) were rated as 7, 2.4% (n=1) scored 6, and 16.7% (n=7) received a score of 5 using the Naranjo algorithm for estimating the probability of ADRs. Seventeen patients (40.5%) were classified as definite with a score of 9, and 1 patient (2.4%) with a score of 3 could be considered to have possible pancreatitis.

Table 3 Treatment and Prognosis of the 42 Included Patients

Parameter	Clinical Features	Value, n (%)
Therapy (42)[a]	Discontinued	42(100.0%)
	Antibiotics	5(11.6%)
	Surgery	1(2.3%)
	Switched to another drug	21(50.0%)
	Corticosteroids	16(38.1%)
	4-ASA	3(7.1%)
	Azathioprine	2(4.8%)
	Infliximab	1(2.3%)
	Balsalazide	1(2.3%)
Symptom disappearance time (30)[a]	Immediately	5(16.7%)
	0–7d	23(76.7%)
	>7d	2(6.6%)
Time to recovery of amylase (26) [a]	Days	5(1–45)[b]
	0–7d	19(73.1%)
	>7d	7(26.9%)
Time to recovery of amylase (23) [a]	Days	7(2–45)[b]
	0–7d	15(65.2%)
	>7d	8(34.8%)
Hospitalization day (26)[a]	Days	7(2–30)[b]
Time of acute pancreatitis after mesalazine rechallenge (19)[a]	Days	1(0.33–14)[b]
	0–7d	15(78.9%)
	>7d	4(21.1%)
Prognosis (42)[a]	Recover	42(100.0%)

Notes: [a] Represents the number of patients among a total of 42 on whom information regarding this particular parameter was provided. [b] Median (minimum-maximum).

Discussion

AP is a common inflammatory condition of the pancreas that can cause severe abdominal pain and multi-organ dysfunction, potentially leading to pancreatic necrosis and persistent organ failure, with a mortality rate of 1–5%.[47] Gallstones, alcohol use, and elevated triglyceride levels are well-established risk factors for AP.[48] DIAP is estimated to account for up to 5% of AP cases.[49] Among patients with IBD, approximately 25% experience some form of pancreatitis, including both acute and chronic pancreatitis.[50] Medications, including azathioprine and mesalazine, are common causes of medication-induced pancreatitis. Mesalazine, the most widely prescribed medication for IBD, was used by 65% of UC patients and 41% of CD patients in a large UK cohort study from 2012–2015.[51] Similarly, a cross-sectional study in Greece found mesalazine to be the most commonly used drug (64.2%) among UC patients.[52] A study by Meczker Á et al showed that mesalazine-induced DIAP occurred predominantly in UC patients (71%), with 25% of cases seen in CD patients.[53] Our findings align with these, suggesting that the higher incidence of pancreatitis in UC patients may be related to the more widespread use of mesalazine in this group.

Previous research has indicated that mesalazine-related DIAP is not clearly dose-dependent, with cases occurring across a range of dosages (800 to 5000 mg daily).[50] Sehgal P et al found that higher doses of mesalazine (>2.4g/day) did not appear to increase the risk of adverse events compared to lower doses.[54] In our study, most patients (94.6%) who developed AP were on the standard recommended dose, with only two patients[18,19] receiving higher doses, further suggesting that the occurrence of AP is not linked to mesalazine dosage.

The time to onset of mesalazine-induced AP varied significantly in our study, with more than half of the cases occurring within two weeks of starting treatment. Most patients (56.8%) developed symptoms within this period, highlighting the importance of monitoring for symptoms like abdominal pain, vomiting, and nausea early in treatment. However, in some patients, AP developed months or even years after initiating mesalazine. Interestingly, increasing the

dose did not seem to shorten the onset time, which further suggests that the timing of AP is unrelated to the dosage.[21,36,37]

Clinically, mesalazine-related AP primarily presents with abdominal pain, often preceded by prodromal symptoms such as nausea and vomiting. A smaller proportion of patients also experience fever and diarrhea. Laboratory tests typically show elevated amylase and/or lipase levels, and imaging may reveal pancreatic or peripancreatic inflammation, effusion, or edema, mimicking pancreatitis caused by other medications.[55,56]

The management of mesalazine-induced AP is largely based on identifying and eliminating the causative medication. Discontinuation of mesalazine typically leads to rapid symptom resolution, with 93.3% of patients improving within one week. Alternative treatments, including switching to other 5-aminosalicylic acid (5-ASA) formulations, may be considered for ongoing therapy.[57] European, American, and Chinese guidelines suggest corticosteroids or biologics as potential alternatives for patients intolerant to mesalazine, although corticosteroids should not be used for UC maintenance.[1,2,58] Switching to other 5-ASA drugs, such as balsalazide, or using 4-ASA enemas can also be effective strategies for patients who cannot tolerate mesalazine.[34,46]

The exact mechanism of AP induced by mesalazine is unclear. Hypersensitivity[21,22,24,26,30,37,43] and idiosyncrasy[21,37] are usually thought to be involved in the pathogenic mechanism of mesalazine induced AP. Mesalazine allergy is a type IV allergic reaction in which inflammation is caused by a reaction between antigens and T cells that recognize antigens (especially T helper 1 cells).[59] Type IV allergic reaction occurs in the sensitization stage and the excitation stage. Upon initial antigen invasion, they are internalized by antigen-presenting cells, thereby activating T cells in regional lymph nodes. In this process, memory T cells and effector T cells are produced together and respond quickly to the second and subsequent invasion. When the second or subsequent invasion occurs, antigen-presenting cells activate memory T cells, causing an inflammatory response and reaching a peak at 48 h.[59] That is a reasonable explanation why the median time of AP in patients with recurrence is shorter than that of the first occurrence. Based on previous literature reports and the results of this study, mesalazine-related AP seems to be dose-independent, unpredictable, and an idiosyncratic reaction, but the specific mechanism needs further study.

This study provides a secondary analysis and summary of existing reports on mesalazine-associated AP, which carries certain limitations. First, not all case reports fully document information on mesalazine-related AP, and the quality of the available literature varies. This inconsistency may introduce bias in the conclusions drawn. To strengthen the findings, more high-quality prospective cohort studies are needed. Additionally, some studies only describe factors linked to the occurrence of AP without assessing the relationship with adverse reactions. As this analysis relies on descriptive data for a retrospective evaluation, the results may also be subject to bias.

Conclusions

Mesalazine-induced AP is a relatively rare but serious adverse drug reaction. Clinicians should be alert to the possibility of AP in patients presenting with abdominal pain, vomiting, and related symptoms, particularly within two weeks of starting treatment. Diagnostic workup should include measuring pancreatic enzymes and performing imaging, such as CT or abdominal ultrasound. If rechallenge with mesalazine is considered after an episode of AP, extreme caution is advised, as the onset of AP tends to occur more quickly upon re-exposure. Prompt diagnosis and discontinuation of mesalazine generally lead to rapid symptom resolution.

Data Sharing Statement

Data sharing is not applicable to this article as no datasets were generated or analysed.

Ethics Approval and Informed Consent

The data and information used in this study is publicly available, and the researchers recorded the information in a way that does not directly identify the subjects. According to the item 1 and 2 of Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects dated February 18, 2023, China, this study was exempt from ethical review by Ethics Committee of Liuyang Hospital of Traditional Chinese Medicine.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosure

The authors declare that they have no competing interests in this work.

References

1. Raine T, Bonovas S, Burisch J, et al. ECCO guidelines on therapeutics in ulcerative colitis: medical treatment. *J Crohns Colitis*. 2022;16(1):2–17. doi:10.1093/ecco-jcc/jjab178
2. Feuerstein JD, Isaacs KL, Schneider Y, et al. AGA clinical practice guidelines on the management of moderate to severe ulcerative colitis. *Gastroenterology*. 2020;158(5):1450–1461. doi:10.1053/j.gastro.2020.01.006
3. Lamb CA, Kennedy NA, Raine T, et al. British society of gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut*. 2019;68(Suppl 3):s1–s106. doi:10.1136/gutjnl-2019-318484
4. Hart A, Ng SC, Watkins J, et al. The use of 5-aminosalicylates in crohn's disease: a retrospective study using the UK clinical practice research datalink. *Ann Gastroenterol*. 2020;33(5):500–507. doi:10.20524/aog.2020.0521
5. Burisch J, Bergemalm D, Halfvarson J, et al. The use of 5-aminosalicylate for patients with crohn's disease in a prospective European inception cohort with 5 years follow-up - an Epi-IBD study. *United Eur Gastroenterol J*. 2020;8(8):949–960. doi:10.1177/2050640620945949
6. Lahiff C, Kane S, Moss AC. Drug development in inflammatory bowel disease: the role of the FDA. *Inflamm Bowel Dis*. 2011;17(12):2585–2593. doi:10.1002/ibd.21712
7. Turner D, Ruemmele FM, Orlanski-Meyer E, et al. Management of paediatric ulcerative colitis, part 1: ambulatory care-an evidence-based guideline from European Crohn's and Colitis Organization and European Society of Paediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr*. 2018;67(2):257–291. doi:10.1097/MPG.0000000000002035
8. Tsujii Y, Nishida T, Osugi N, et al. Classification and clinical features of adverse drug reactions in patients with ulcerative colitis treated with 5-aminosalicylate acid: a single-center, observational study. *Scand J Gastroenterol*. 2022;57(2):190–196. doi:10.1080/00365521.2021.1998601
9. Le Berre C, Roda G, Nedeljkovic Protic M, et al. Modern use of 5-aminosalicylic acid compounds for ulcerative colitis. *Expert Opin Biol Ther*. 2020;20(4):363–378. doi:10.1080/14712598.2019.1666101
10. Lee AA, Gupta S, Labban M, et al. Drug-induced acute pancreatitis due to medications used for inflammatory bowel disease: a VigiBase pharmacovigilance database study. *Pancreatology*. 2023;23(6):569–573. doi:10.1016/j.pan.2023.06.003
11. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. *Gut*. 2013;62(1):102–111. doi:10.1136/gutjnl-2012-302779
12. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30(2):239–245. doi:10.1038/clpt.1981.154
13. Sachedina B, Saibil F, Cohen LB, et al. Acute pancreatitis due to 5-aminosalicylate. *Ann Intern Med*. 1989;110(6):490–492. doi:10.7326/0003-4819-110-6-490
14. Deprez P, Descamps C, Fiasse R. Pancreatitis induced by 5-aminosalicylic acid. *Lancet*. 1989;2(8660):445–446. doi:10.1016/s0140-6736(89)90620-x
15. Isaacs KL, Murphy D. Pancreatitis after rectal administration of 5-aminosalicylic acid. *J Clin Gastroenterol*. 1990;12(2):198–199. doi:10.1097/00004836-199004000-00019
16. Tran K, Froguel E, Jian R, et al. Acute pancreatitis induced by mesalazine. *J Clin Gastroenterol*. 1991;13(6):715–716. doi:10.1097/00004836-199112000-00021
17. Tromm A, Hüppe D, Micklefield GH, et al. Acute pancreatitis complicating Crohn's disease: mere coincidence or causality? *Gut*. 1992;33(9):1289–1291. doi:10.1136/gut.33.9.1289
18. Abdullah AM, Scott RB, Martin SR. Acute pancreatitis secondary to 5-aminosalicylic acid in a child with ulcerative colitis. *J Pediatr Gastroenterol Nutr*. 1993;17(4):441–444. doi:10.1097/00005176-199311000-00019
19. Radke M, Bartolomaeus G, Muller M, et al. Acute pancreatitis in crohn's disease due to 5-ASA therapy. *J Pediatr Gastroenterol Nutr*. 1993;16(3):337–339. doi:10.1097/00005176-199304000-00022
20. Debongnie JC, Dekoninck X. Sulfasalazine, 5-ASA and acute pancreatitis in Crohn's disease. *J Clin Gastroenterol*. 1994;19(4):348–349. doi:10.1097/00004836-199412000-00024
21. Paerregaard A, Krasilnikoff PA. Pancreatitis in a child after rectal administration of 5-aminosalicylic acid. *Inflamm Bowel Dis*. 1997;3(1):20–21. doi:10.1097/00054725-199703000-00004
22. Adachi E, Okazaki K, Matsushima Y, et al. Acute pancreatitis secondary to 5-aminosalicylic acid therapy in a patient with ulcerative colitis. *Int J Pancreatol*. 1999;25(3):217–221. doi:10.1007/BF02925970
23. Lhee HY, Kim BI, Yoo TW, et al. Acute pancreatitis induced by 5-aminosalicylic acid in a patient with ulcerative colitis. *Korean J Gastroenterol*. 2002;40(4):282–285.
24. Toubanakis C, Batziou E, Sipsas N, et al. Acute pancreatitis after long-term therapy with mesalazine, and hyperamylasaemia associated with azathioprine in a patient with ulcerative colitis. *Eur J Gastroenterol Hepatol*. 2003;15(8):933–934. doi:10.1097/00042737-200308000-00019
25. Inoue H, Shiraki K, Okano H, et al. Acute pancreatitis in patients with ulcerative colitis. *Dig Dis Sci*. 2005;50(6):1064–1067. doi:10.1007/s10620-005-2705-7
26. Song SI, Torre M. Pancreatitis induced by topical 5-aminosalicylic acid. *Am J Gastroenterol*. 2006;101:S273–S274. doi:10.14309/00000434-200609001-00663
27. Kim KH, Kim TN, Jang BI. A case of acute pancreatitis caused by 5-aminosalicylic acid suppositories in a patient with ulcerative colitis. *Korean J Gastroenterol*. 2007;50(6):379–383.

28. Son CN, Lee HL, Joo YW, et al. A case of acute pancreatitis induced by multiple drugs in a patient with ulcerative colitis. *Korean J Gastroenterol*. 2008;52(3):192–195.
29. Shin DH, Lee KH, Kim CH, et al. A case of inferior vena cava thrombosis and acute pancreatitis in a patient with ulcerative colitis. *Korean J Gastroenterol*. 2010;56(4):255–259. doi:10.4166/kjg.2010.56.4.255
30. Arai Y, Arihiro S, Ide D, et al. Acute pancreatitis due to pH-dependent mesalazine that occurred in the course of ulcerative colitis. *Case Rep Gastroenterol*. 2011;5(3):610–616. doi:10.1159/000333605
31. Yi FM, Xiao J, Huang MF, et al. A case report of acute pancreatitis induced by mesalazine sustained-release agent in ulcerative colitis patient. *Chin J Dig*. 2012;32(5):347–348. doi:10.3760/cma.j.issn.0254-1432.2012.05.020
32. Kutsenko A, Herzog K, Cohen M, et al. A case of lialda®-induced pancreatitis: 995. *Am J Gastroenterol*. 2014;109:S295. doi:10.14309/00000434-201410002-00995
33. Zhou LG, Guo LX, Xiao SX. A case report of drug-induced acute pancreatitis caused by mesalazine. *Chinese J Clin Ration Drug Use*. 2015;(13):27–27,61. doi:10.15887/j.cnki.13-1389/r.2015.13.019
34. Chung MJ, Lee JH, Moon KR. Mesalizine-induced acute pancreatitis and interstitial pneumonitis in a patient with ulcerative colitis. *Pediatr Gastroenterol Hepatol Nutr*. 2015;18(4):286–291. doi:10.5223/pghn.2015.18.4.286
35. Eto H, Kawabe K, Miyahara Y, et al. Drug-induced pancreatitis diagnosed by mesalazine challenge test: case report. *J Gastroenterol Hepatol*. 2016;31(Suppl. 3):255.
36. Uribarri-Gonzalez L, Barreiro-de Acosta M, Dominguez-Muñoz JE. Acute pancreatitis secondary to topical and oral treatment with mesalamine in a patient with ulcerative colitis. *Int J Hepatobiliary Pancreat Dis*. 2016;66:64–67. doi:10.5348/ijhpd-2016-56-CR-12
37. Meczker Á, Mikó A, Hegyi P. 5-ASA induces mild acute pancreatitis. Case report and review of the literature. *J Gastrointestin Liver Dis*. 2018;27(2):189–194. doi:10.15403/jgld.2014.1121.272.asa
38. Zhang YF, Hu XF, Zhao JH, et al. A case of pancreatic diabetes mellitus caused by mesalazine and reviewed in the literature. *J pract diabetol*. 2018;15(1):72.
39. Correia JP, Ponte AI, Silva JC, et al. Mesalazine-induced acute pancreatitis: a rare adverse reaction but with important therapeutic implications in ulcerative colitis. *Eur J Gastroenterol Hepatol*. 2021;33(4):595. doi:10.1097/MEG.0000000000001901
40. Zhao Y, Pu T, Guo CQ, et al. A case report of acute pancreatitis induced by mesalazine in ulcerative colitis patient. *Chin J Inflamm Brnvel Dis*. 2021;05(4):367–368. doi:10.3760/cma.j.cn101480-20210414-00028
41. Beattie W, Ting A, Heerasing N. A rare case of 5-aminosalicylic acid suppository-induced pancreatitis. *J Gastroenterol Hepatol*. 2021;36(Suppl. 3):115.
42. Piazza I, Burti C, Assolari A, et al. Acute myocarditis as first presentation of severe ulcerative colitis in a young man. Multidisciplinary management and long-term follow-up. *J Cardiol Cases*. 2022;26(1):46–50. doi:10.1016/j.jccase.2022.02.008
43. Fiorentini MT, Fracchia M, Galatola G, et al. Acute pancreatitis during oral 5-aminosalicylic acid therapy. *Dig Dis Sci*. 1990;35(9):1180–1182. doi:10.1007/BF01537594
44. Eckardt VF, Kanzler G, Rieder H, et al. Pancreatitis associated with 5-aminosalicylic acid. *Dtsch Med Wochenschr*. 1991;116(14):540–542. doi:10.1055/s-2008-1063645
45. Sugerman KS, Keljo DJ. 5-aminosalicylic acid related pancreatitis in pediatric IBD a chart review. *J Pediatr Gastroenterol Nutr*. 1995;21(3):340. doi:10.1002/j.1536-4801.1995.tb11858.x
46. Daniel F, Seksik P, Cacheux W, et al. Tolerance of 4-aminosalicylic acid enemas in patients with inflammatory bowel disease and 5-aminosalicylic-induced acute pancreatitis. *Inflamm Bowel Dis*. 2004;10(3):258–260. doi:10.1097/00054725-200405000-00013
47. Petrov MS, Yadav D. Global epidemiology and holistic prevention of pancreatitis. *Nat Rev Gastroenterol Hepatol*. 2019;16(3):175–184. doi:10.1038/s41575-018-0087-5
48. Mederos MA, Reber HA, Girgis MD. Acute pancreatitis: a review. *JAMA*. 2021;325(4):382–390. doi:10.1001/jama.2020.20317
49. Vinklerová I, Procházka M, Procházka V, et al. Incidence, severity, and etiology of drug-induced acute pancreatitis. *Dig Dis Sci*. 2010;55(10):2977–2981. doi:10.1007/s10620-010-1277-3
50. Pitchumoni CS, Rubin A, Das K. Pancreatitis in inflammatory bowel diseases. *J Clin Gastroenterol*. 2010;44(4):246–253. doi:10.1097/MCG.0b013e3181cadbe1
51. Jairath V, Hokkanen SRK, Guizzetti L, et al. No increased risk of nephrotoxicity associated with 5-aminosalicylic acid in IBD: a population-based cohort and nested case-control study. *Aliment Pharmacol Ther*. 2019;50(4):416–424. doi:10.1111/apt.15408
52. Kyriakos N, Papaefthymiou A, Giakoumis M, et al. Prevalence of inflammatory bowel disease in young Greek army male recruits from 2006 to 2018: a 13-year retrospective study from a tertiary center. *Eur J Gastroenterol Hepatol*. 2022;34:153–160. doi:10.1097/MEG.0000000000002071
53. Meczker Á, Mikó A, Gede N, et al. Retrospective matched-cohort analysis of acute pancreatitis induced by 5-aminosalicylic acid-derived drugs. *Pancreas*. 2019;48(4):488–495. doi:10.1097/MPA.0000000000001297
54. Sehgal P, Colombel JF, Aboubakr A, et al. Systematic review: safety of mesalazine in ulcerative colitis. *Aliment Pharmacol Ther*. 2018;47(12):1597–1609. doi:10.1111/apt.14688
55. Fang W, Yi D, Sun L, Wang C. Analysis of clinical characteristics of tigecycline-induced acute pancreatitis. *J Clin Pharm Ther*. 2020;45(6):1320–1324. doi:10.1111/jcpt.13212
56. Cheng J, Zhang GJ, Han YX. Analysis of clinical features of metronidazole induced acute pancreatitis based on literature cases. *Adverse Drug React J*. 2020;22(10):568–572. doi:10.3760/cma.j.cn114015-20191230-01099
57. Mikami Y, Tsunoda J, Suzuki S, et al. Significance of 5-aminosalicylic acid intolerance in the clinical management of ulcerative colitis. *Digestion*. 2023;104(1):58–65. doi:10.1159/000527452
58. Inflammatory Bowel Disease Group, Chinese Society of Gastroenterology, Chinese Medical Association; Inflammatory Bowel Disease Quality Control Center of China. 2023 Chinese national clinical practice guideline on diagnosis and management of ulcerative colitis. *Chin Med J*. 2024;137(14):1642–1646. doi:10.1097/CM9.0000000000003221
59. Matsumoto S, Mashima H. Mesalazine allergy and an attempt at desensitization therapy in patients with inflammatory bowel disease. *Sci Rep*. 2020;10(1):22176. doi:10.1038/s41598-020-79207-z