The effect of non-steroidal anti-inflammatory drugs on severity of acute pancreatitis and pancreatic necrosis

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ABSTRACT

INTRODUCTION Acute pancreatitis (AP) is a common emergency presentation and can be disabling. There is significant morbidity and mortality associated with AP, and it places a considerable burden on the healthcare system. Non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to have a protective effect in some elective contexts. This retrospective study aimed to evaluate the effect of NSAIDs on the course of AP and the severity of the disease.

METHODS A retrospective analysis was carried out of 324 patients admitted as an emergency with a diagnosis of AP to two UK hospitals. Patients were divided into two groups: those already taking NSAIDs for other co-morbidities and those not taking NSAIDs. Variables compared included: admission to a high dependency or intensive care unit; pancreatic necrosis; pseudocyst development; need for surgery; serum inflammatory markers; modified early warning scores on days 1, 3 and 5; length of stay; and mortality.

RESULTS Patients not taking NSAIDs were more likely to have a C-reactive protein level of $\geq 150\text{mg/l}$ ($p=0.007$). Patients in the NSAID group experienced less pancreatic necrosis ($p=0.019$) and lower rates of pseudocyst formation ($p=0.010$). Other variables showed no difference between the two groups, specifically length of stay and mortality.

CONCLUSIONS Routine NSAID use may exert a protective effect on the development of AP, its severity, and complications. Therapeutic use of NSAIDs in acute presentations with pancreatitis should be further evaluated.

KEYWORDS

Acute pancreatitis – Non-steroidal anti-inflammatory drugs

Accepted 27 August 2017

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Acute pancreatitis (AP) is a common disease, with an incidence ranging from 150 to 420 cases per million population in Western countries and overall trends suggesting that presentations of AP are on the rise.¹ Up to 10% of patients with AP develop necrosis of pancreatic and peripancreatic tissues.² Necrosis results from the impairment of pancreatic perfusion and evolves over a period of several days.³ Pancreatic necrosis may become infected irrespective of the area of necrosis or the duration of symptoms, and sepsis secondary to infected pancreatic necrosis is the leading cause of multi-system organ failure.⁴ The mortality rate in AP can exceed 50% in patients who have organ failure persisting for more than 48 hours.⁵

The cellular response to AP is known to involve both local and systemic inflammatory and immune responses. It is thought that the severity is related to proinflammatory cytokines and mediators causing local tissue damage that cannot be sufficiently counteracted by the systemic anti-inflammatory immune response.⁶ Mediators involved in this interplay

include proinflammatory cytokines (TNF α , IL-1 β , IL-6, IL-8 and PAF) as well as transcription factors (NF- κ B and AP-1).^{6–8}

Considering the systemic inflammatory response cascade and its role in the natural progression of pancreatitis (especially severe pancreatitis), it has been suggested that inhibition or attenuation of proinflammatory mediators may reduce not only inflammation in AP but also disease severity. Many research efforts during the past several decades have attempted to ease pancreatitis severity by inhibiting the deranged intracellular processes that occur during the course of AP. Non-steroidal anti-inflammatory drugs (NSAIDs) are potent inhibitors of phospholipase A2, cyclooxygenase and neutrophil endothelial interactions, all believed to play role in AP.⁹ In addition to the aforementioned actions, acetylsalicylic acid has been shown to reduce inflammation via several other mechanisms. Kopp and Ghosh found that important proinflammatory cytokines (including IL-1 and IL-6) and adhesion molecules are reliant on transcription factor NF- κ B.¹⁰ The activation of NF- κ B is inhibited by

acetylsalicylic acid and so these proinflammatory cytokines are reduced.

Cosen-Binker *et al* showed that pancreatitis severity was significantly ameliorated by nitric oxide releasing NSAIDs in an animal model of pancreatitis.¹¹ The optimal timing for drug administration was one hour before and four hours after induction of pancreatitis. The authors believed that the reduction in severity of pancreatitis in the rats in their study was in part due to improved microcirculatory function brought about by nitric oxide.

Randomised trials have suggested that a single dose of NSAIDs including rectal indometacin or ibuprofen can reduce the risk and severity of pancreatitis following endoscopic retrograde cholangiopancreatography (ERCP).^{12–14} During these trials, there was no increase in the adverse events related to administration of NSAIDs. Specifically, there was no increase in the incidence of gastrointestinal bleeding or renal failure. Despite these data, however, it is not known whether NSAIDs could have a similar effect on ameliorating pancreatitis relating to other aetiologies. A meta-analysis from 2014 confirmed that NSAIDs could help prevent pancreatitis following ERCP.¹⁵ Curiously, this effect was conferred only by rectal administration of NSAIDs and was not seen with oral or intravenous administration. The authors were unable to account for this but did also concede the relatively poor quality of the majority of currently available trial literature on the topic. Clearly, further investigation is required.

Our retrospective study was designed to assess the effect of routine NSAID use on the risk of development of non-ERCP related AP. The effect on the severity of the disease was also examined.

Methods

Data were retrieved retrospectively for patients presenting with AP to two large English teaching hospitals, University Hospital Southampton NHS Foundation Trust and University Hospitals Coventry and Warwickshire NHS Trust, over a one-year period (2013–2014). Patients were identified based on diagnostic codes from the tenth revision of the International Statistical Classification of Diseases, and data were retrieved and analysed in an anonymised manner.

Patient demographics were recorded. All presentations of AP, regardless of underlying or associated pathology (eg gallstones, alcohol abuse), were included. Patients with acute bouts of chronic pancreatitis were excluded since the disease course in these cases tends to be milder than for sporadic AP and this in itself would act as a confounder, potentially influencing results. Patient outcomes and disease severity were assessed using the modified early warning score (MEWS) on days 1, 3 and 5, and C-reactive protein (CRP) on day 1 as well as white cell count, renal function, whether admission to a high dependency or intensive care unit occurred, need for surgery (ie pancreatic necrosectomy), length of stay and mortality. Presence or absence of pancreatic necrosis was also recorded, as seen on computed

tomography performed on day 4–5 after admission. A pseudocyst was diagnosed on follow-up imaging if patients were symptomatic.

Drug charts and patient records were reviewed to establish whether patients were taking NSAIDs prior to admission. For the purposes of this study, no discrimination was made between types of NSAIDs (eg acetylsalicylic acid, ibuprofen, diclofenac) other than to determine whether patients were taking these on a routine and daily basis at the time of presentation to hospital. Patients included in the study were divided into two groups (NSAID vs non-NSAID) accordingly.

Statistical analysis

The characteristics of the two groups were compared using the chi-squared test and Student's t-test depending on whether data values were categorical or continuous. Analysis was undertaken using SPSS® version 23 (IBM, New York, US). A *p*-value of <0.05 was considered statistically significant.

Results

A total of 324 patients were included in the study: 83 in the NSAID group and 241 in the non-NSAID group. The mean age of patients taking NSAIDs was 71 years compared with 52 years for the non-NSAID group (*p*=0.001). The findings for the two groups are summarised in Table 1.

Patients in the NSAID group were more likely to suffer from prior co-morbidities. There was a greater proportion of patients classified as ASA (American Society of Anesthesiologists) grade 2 or 3 in this group (*p*=0.001).

Comparison of clinical outcomes revealed that the NSAID group experienced significantly fewer necrotic pancreatic events (2% vs 11%, odds ratio [OR]: 0.20, 95% confidence interval [CI]: 0.047–0.879; *p*=0.019). The incidence of pseudocysts on follow-up imaging was lower in the NSAID group (1% vs 10%, OR: 0.11, 95% CI: 0.014–0.828; *p*=0.010).

Patients in the non-NSAID group were more likely to have a serum CRP of ≥150mg/l as measured on day 2 (30% vs 14%, OR: 2.4, 95% CI: 1.23–5.30; *p*=0.007). There was no significant difference in white cell count.

Other parameters did not show significant differences between the two groups. The median length of stay was 6 days for both groups (*p*=0.463), and the mortality rates were 3% for the NSAID group and 4% for the non-NSAID group (*p*=0.898).

Discussion

This retrospective study suggests that NSAID use may benefit patients presenting with AP, regardless of the underlying aetiology. A significant negative association was found between NSAIDs and serum inflammatory markers (CRP) as well as clinical complications (necrosis and pseudocyst formation).

CRP is used as a predictor of severity by the APACHE II (Acute Physiology and Chronic Health Evaluation II) scoring

Table 1 Summary of findings for the two groups of patients

		NSAIDs (n=83)	No NSAIDs (n=241)	p-value
Sex	Female	54 (65%)	107 (44%)	0.002
	Male	29 (35%)	134 (56%)	
ASA grade	1	17 (20%)	144 (60%)	0.001
	2	53 (64%)	88 (37%)	
	3	13 (16%)	9 (4%)	
HDU	Yes	6 (7%)	21 (9%)	0.673
	No	77 (93%)	220 (91%)	
Necrosis	Yes	2 (2%)	26 (11%)	0.019
	No	82 (98%)	215 (89%)	
Pseudocyst	Yes	1 (1%)	24 (10%)	0.010
	No	82 (99%)	217 (90%)	
Surgery	Yes	1 (1%)	4 (2%)	0.772
	No	82 (99%)	237 (98%)	
CRP day 5	<150mg/l	71 (86%)	170 (70%)	0.007
	≥150mg/l	12 (14%)	71 (30%)	
WCC	<15 × 10 ⁹ /l	58 (70%)	183 (77%)	0.226
	≥15 × 10 ⁹ /l	25 (30%)	56 (23%)	
MEWS day 1	<5	81 (98%)	236 (98%)	0.856
	≥5	2 (2%)	5 (2%)	
MEWS day 2	<5	81 (98%)	233 (97%)	0.679
	≥5	2 (2%)	8 (3%)	
MEWS day 5	<5	79 (95%)	232 (97%)	0.414
	≥5	4 (5%)	7 (3%)	
Median LOS		6 days	6 days	0.463
Death	Yes	3 (4%)	8 (3%)	0.898
	No	79 (96%)	233 (97%)	

ASA = American Society of Anesthesiologists; CRP = C-reactive protein; HDU = high dependency unit; LOS = length of stay; MEWS = modified early warning score; NSAIDs = non-steroidal anti-inflammatory drugs; WCC = white cell count

system for AP, which is well recognised and recommended by both the American Gastroenterological Association¹⁶ and the British Society of Gastroenterology.¹⁷ Although the APACHE II score was not developed specifically for AP, it is an early and reliable assessment tool for the disease.¹⁸ Furthermore, the use of CRP >150mg/l as an independent predictor for complications in pancreatitis has been advocated¹⁶ as it has been demonstrated that CRP is the most useful prognostic inflammatory marker. A CRP level of >150mg/l in the first 72 hours after onset of symptoms suggests that pancreatitis is likely to follow a complicated course (sensitivity 85%).¹⁸ Consequently, if taking NSAIDs can reduce CRP, one can postulate that it may reduce complications of pancreatitis and therefore overall disease severity.

The effects of NSAIDs on prevention and amelioration of pancreatitis have mostly been studied in the setting of post-ERCP pancreatitis. However, evidence for the protective or beneficial use of NSAIDs in other contexts exists in animal studies. Akyazi *et al* assessed the effects of various doses of aspirin as pretreatment in ceruletide induced pancreatitis in rats.¹⁹ The study measured tissue and plasma cytokines, levels of oedema and pancreatic tissue necrosis. Pretreatment with low and medium dose aspirin reduced white blood cell count to a level significantly lower than that of the AP control group and near that of the group with no AP. High and medium dose aspirin resulted in a significant reduction of IL-6, and medium dose aspirin showed significant reduction in oedema, necrosis and total histopathological score. In this study, all cases of pancreatitis were caused by ceruletide, eliminating differences in aetiology as a confounding variable.

Despite being an animal-based study and therefore not directly comparable with humans, it also demonstrates the protective effects of NSAIDs on pancreatitis not induced by ERCP but originating from a different cause.¹⁹ This supports the notion that other causes of pancreatitis in humans may be treated with NSAIDs early in the course of the disease.

Beyond NSAIDs, other pharmacological therapies (eg prophylactic antibiotics and somatostatin analogues) in pancreatitis have been extensively studied, unfortunately with little success in ameliorating disease severity. As a result, the treatment of AP remains largely supportive.^{20–25}

Although the findings of our study are preliminary, it is noteworthy that patients in the NSAID group had much better outcomes despite having a larger proportion of patients classified as ASA grade 2 or 3. These included biochemical markers (lower CRP concentration), radiological diagnoses (lower incidence of pancreatic necrosis) and clinical complications (lower incidence of pseudocyst formation). With NSAIDs already given routinely to prevent post-ERCP pancreatitis, this study suggests that they may confer a more generally protective effect on pancreatitis regardless of cause. Further study is required to assess other confounders and variables including aetiology.

Study limitations

Our findings must be considered in the context of this study's limitations. As a retrospective study, variables such as detailed co-morbidities, complications and follow-up were not available. Owing to the retrospective, non-randomised nature of the study, there were various confounders including age, sex and other risk factors such as smoking history, which could influence disease severity and prognosis.

The sample size was relatively small. There was heterogeneity between the two patient groups, which could not be controlled for using the available data. The NSAID patients were older and generally in poorer health with higher rates of co-morbidities (for which they were taking the NSAIDs). Furthermore, although most patients included in the study were taking low dose aspirin for previous myocardial ischaemic events, this was not exclusively the case. The type of NSAIDs varied, as did the timing of administration in terms of disease onset, dose and compliance with treatment.

Despite the limitations mentioned above, this study provides additional evidence for the protective effect of NSAIDs on the development and progression of all-cause AP, and it strengthens the call for further investigation in this area. If this association can be established, low or medium dose NSAIDs taken early in the course of AP should possibly be considered in future (in conjunction with a rigorous risk/benefit assessment).

Future study

While the question of whether treatment with NSAIDs reduces the incidence of pancreatitis of all causes is an important one, designing a randomised trial reliant on the identification of those patients most likely to present with AP is unrealistic. As a result, we suggest focusing on a different question, which can be assessed using a double blind, prospective, randomised controlled trial: Does administration of NSAIDs early in the disease process (once a diagnosis has been made) reduce severity and improve outcomes such as length of stay, need for interventions, morbidity and mortality?

Using randomisation, this study could control for confounding variables inherently associated with retrospective studies, thereby eliminating potential bias and producing more robust data. In such a study, a standardised protocol for imaging could be used so that it is carried out on the same day in the course of the disease in individual subjects. A prospective, randomised, double blind study would also allow for completion of data, particularly APACHE II scores. If an association between early pharmacological intervention with NSAIDs and reduction in severity is proven, this could inform future treatment of AP.

References

- Toh SK, Phillips S, Johnson CD. A prospective audit against national standards of the presentation and management of acute pancreatitis in the South of England. *Gut* 2000; **46**: 239–243.
- Bollen TL. Imaging of acute pancreatitis: update of the revised Atlanta classification. *Radiol Clin North Am* 2012; **50**: 429–445.
- Isenmann R, Büchler M, Uhl W *et al*. Pancreatic necrosis: an early finding in severe acute pancreatitis. *Pancreas* 1993; **8**: 358–361.
- Besselink MG, van Santvoort HC, Boermeester MA *et al*. Timing and impact of infections in acute pancreatitis. *Br J Surg* 2009; **96**: 267–273.
- Johnson CD, Abu-Hilal M. Persistent organ failure during the first week as a marker of fatal outcome in acute pancreatitis. *Gut* 2004; **53**: 1,340–1,344.
- Granger J, Remick D. Acute pancreatitis: models, markers, and mediators. *Shock* 2005; **24**(Suppl 1): 45–51.
- Bhatia M, Wong FL, Cao Y *et al*. Pathophysiology of acute pancreatitis. *Pancreatology* 2005; **5**: 132–144.
- Makhija R, Kingsnorth AN. Cytokine storm in acute pancreatitis. *J Hepatobiliary Pancreat Surg* 2002; **9**: 401–410.
- Vane JR, Botting RM. Mechanism of action of aspirin-like drugs. *Semin Arthritis Rheum* 1997; **26**(6 Suppl 1): 2–10.
- Kopp E, Ghosh S. Inhibition of NF-kappa B by sodium salicylate and aspirin. *Science* 1994; **265**: 956–959.
- Cosen-Binker LI, Binker MG, Cosen R *et al*. Influence of nitric oxide-donating nonsteroidal anti-inflammatory drugs on the evolution of acute pancreatitis. *Shock* 2006; **25**: 190–203.
- Sethi S, Sethi N, Wadhwa V *et al*. A meta-analysis on the role of rectal diclofenac and indomethacin in the prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis. *Pancreas* 2014; **43**: 190–197.
- Elmunzer BJ, Scheiman JM, Lehman GA *et al*. A randomized trial of rectal indomethacin to prevent post-ERCP pancreatitis. *N Engl J Med* 2012; **366**: 1,414–1,422.
- Sotoudehmanesh R, Khatibian M, Kolahdoozan S *et al*. Indomethacin may reduce the incidence and severity of acute pancreatitis after ERCP. *Am J Gastroenterol* 2007; **102**: 978–983.
- Li X, Tao LP, Wang CH. Effectiveness of nonsteroidal anti-inflammatory drugs in prevention of post-ERCP pancreatitis: a meta-analysis. *World J Gastroenterol* 2014; **20**: 12,322–12,329.
- Banks PA, Freeman ML. Practice guidelines in acute pancreatitis. *Am J Gastroenterol* 2006; **101**: 2,379–2,400.
- UK Working Party on Acute Pancreatitis. UK guidelines for the management of acute pancreatitis. *Gut* 2005; **54**(Suppl 3): iii1–iii9.
- Khanna AK, Meher S, Prakash S *et al*. Comparison of Ranson, Glasgow, MOSS, SIRS, BISAP, APACHE-II, CTSI scores, IL-6, CRP, and procalcitonin in predicting severity, organ failure, pancreatic necrosis, and mortality in acute pancreatitis. *HPB Surg* 2013; 367581.
- Akyazi I, Eraslan E, Gülçubuk A *et al*. Long-term aspirin pretreatment in the prevention of cerulein-induced acute pancreatitis in rats. *World J Gastroenterol* 2013; **19**: 2,894–2,903.
- Jiang K, Huang W, Yang XN, Xia Q. Present and future of prophylactic antibiotics for severe acute pancreatitis. *World J Gastroenterol* 2012; **18**: 279–284.
- Yao L, Huang X, Li Y *et al*. Prophylactic antibiotics reduce pancreatic necrosis in acute necrotizing pancreatitis: a meta-analysis of randomized trials. *Dig Surg* 2010; **27**: 442–449.
- Johnson CD, Kingsnorth AN, Imrie CW *et al*. Double blind, randomised, placebo controlled study of a platelet activating factor antagonist, lexipafant, in the treatment and prevention of organ failure in predicted severe acute pancreatitis. *Gut* 2001; **48**: 62–69.
- Cavallini G, Frulloni L. Somatostatin and octreotide in acute pancreatitis: the never-ending story. *Dig Liver Dis* 2001; **33**: 192–201.
- Paran H, Mayo A, Paran D *et al*. Octreotide treatment in patients with severe acute pancreatitis. *Dig Dis Sci* 2000; **45**: 2,247–2,251.
- Uhl W, Büchler MW, Malfertheiner P *et al*. A randomised, double blind, multicentre trial of octreotide in moderate to severe acute pancreatitis. *Gut* 1999; **45**: 97–104.