CASE REPORT

Lower gastrointestinal adverse effects of NSAIDs: an extreme example of a common problem

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SUMMARY

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed throughout the world. Their adverse effects on the upper gastrointestinal (GI) tract are well documented and well known among clinicians and often mitigated against by coprescribing proton pump inhibitors. This case exemplifies the lesser-known lower GI adverse effects of NSAIDs. A 55-year-old patient took a large mixed overdose including more than 11 g of diclofenac. He went onto require subtotal colectomy following widespread perforations of an ulcerated large bowel as a direct result of exposure to a high-dose of NSAIDs. However, the upper GI tract remained relatively unaffected in comparison. This case highlights important lessons from recent literature identifying an increasing incidence of lower GI complications of NSAIDs, the limited protective effect of PPIs on the lower GI tract and the need for clinicians to now consider the integrity of the whole GI tract when prescribing NSAIDs.

BACKGROUND

This particular case describes the severe side-effects of diclofenac overdose. More importantly, however, it highlights a key learning point that is often overlooked in day-to-day clinical practice. The potential adverse effects of non-steroidal anti-inflammatory drugs (NSAIDs) are far reaching and include gastrointestinal (GI) complications, increased risk of cardiovascular disease, renal impairment and platelet dysfunction.¹ In particular, effects of NSAIDs on the upper GI tract such as erosions, ulcers, dyspepsia as well as serious complications such as overt upper GI bleeds are both well documented within literature and well known among clinicians. Likewise, the advent of proton pump inhibitors and their increasingly widespread use in both the treatment and prevention of NSAID-induced ulcers has resulted in a dramatic decrease in upper GI tract-related complications of NSAIDs.^{2–3} However, NSAID-related damage of the GI tract is not limited to the upper GI tract and the potential lower GI complications are rarely considered by physicians and furthermore, poorly researched in comparison. Despite these trends, lower GI complications of NSAIDs have until recently, remained poorly studied. Though effects of upper GI have been investigated with numerous randomised controlled trials as well as meta analyses, prior to 2010, studies into the lower GI complications of NSAIDs had been limited to case-control studies and prospective endoscopic studies with limited patient numbers.^{4–8}

This case example demonstrates that even in excessive NSAID doses the upper GI tract complications may be relatively minimal while the lower GI tract complications may be catastrophic. This leads us to consider recent clinical trial data highlighting the true extent of lower GI tract complications of NSAIDs and provides a valuable lesson to clinicians that the potential adverse GI effects of NSAIDs go far beyond the reaches of the gastroscop.

CASE PRESENTATION

A 55-year-old lorry driver was admitted to the emergency department following the deliberate ingestion of 238 tablets of diclofenac 50 mg, 48 tablets of paracetamol 500 mg, 80 tablets of dihydrocodeine 60 mg and 12 shots of Bacardi rum within a period of half an hour. This was precipitated by an argument with his wife, whom he called within half an hour of ingesting the above. She immediately arranged for an ambulance, who administered naloxone to the patient during transfer to hospital as his respiratory rate had already begun to decline. Besides a history of chronic obstructive pulmonary diseases (COPD) and long-term smoking, the patient had no other significant medical or psychiatric history.

Upon admission, he continued to receive naloxone to reverse respiratory depression in addition to N-acetylcysteine in response to the paracetamol overdose. Within 2 days of admission, he was transferred to higher dependency care and intubated owing to a decline in Glasgow Coma Scale (7/15). Soon after this, the patient developed abdominal pain. A surgical opinion was that he did not have an acute abdomen. Though this pain settled, a gradual decline in haemoglobin was noted over the subsequent week (12.7–6.8 g/dl) until the patient developed overt melaena. Several units of blood were transfused over this time and gastroscopy performed as an upper GI bleed was suspected, which identified small linear duodenal erosions and oesophagitis thought to be NSAID-induced (stomach otherwise normal). At this stage, it was felt that the combination of upper GI erosions and inflammation in addition to impaired platelet function secondary to NSAID overdose were responsible for the steady haemoglobin decline. The patient was therefore managed conservatively with intravenous omeprazole but continued to experience melaena and declining haemoglobin necessitating further transfusions over the next 5 days. A second gastroscopy was performed, this time identifying ongoing oesophagitis, but normal appearances of the stomach and duodenum.

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Figure 1 Portable anteroposterior chest radiograph taken shortly after the patient became peritonitic demonstrating pneumoperitoneum.

The following day, the patient developed severe generalised abdominal pain with generalised tenderness and guarding upon examination. An emergency chest radiograph revealed the presence of free air under the diaphragm (see figure 1) and the patient underwent an emergency laparotomy for a suspected perforated viscus. Upon opening the abdomen, free intraperitoneal fluid and gas were noted. The ascending colon was dilated with perforations apparent in both the caecum and splenic flexure and evidence of impending perforation in the transverse colon. The stomach and small bowel appeared normal.

TREATMENT

A subtotal colectomy was performed with the colon transected below the pelvic brim and an end ileostomy formed in the right iliac fossa. Histological examination confirmed extensive foci of ulceration and associated inflammation throughout the colon with perforations evident in the sigmoid colon and caecum (maximum perforation diameter 15 mm).

The patient steadily improved following a surgery with a functioning ileostomy and tolerating enteral nutrition, though intermittently developed spiking temperatures thought likely to be because of pelvic collections noted on CT imaging. These could not be aspirated radiologically and further surgery was avoided as the spiking temperatures resolved with intravenous antibiotics.

OUTCOME AND FOLLOW-UP

The patient was discharged home 64 days after admission with ongoing psychiatric follow-up. He has returned to work and to this day is managing well.

DISCUSSION

Colonic perforation is a recognised, yet rare, complication of NSAID use with a handful of documented case reports in the literature. These cases all involve regular ingestion of diclofenac within recommended doses typically associated with chronic use over years.^{9–11} Interestingly, one case even identifies isolated colonic perforation after short-term regular use of 5 days in a previously well 16-year-old following tooth extraction, though coingestion of clindamycin may have contributed to a more susceptible bowel mucosa.¹² To our knowledge, this is the first case

report identifying isolated colonic perforation after a single episode of excessive NSAID ingestion, demonstrating similar histological findings and outcome to the documented cases involving more chronic use at recommended doses. It is worth mentioning that the median lethal dose of oral diclofenac has been shown to be 170 mg/kg (extrapolated from mouse studies) and in this case, fell just short of this figure at 159 mg/kg.¹³ Catastrophic lower GI events may therefore occur in isolation with regular ingestion of NSAIDs at recommended doses as well as one-off mucosal exposure to excessive doses—presenting as the chief complication at near lethal doses as exemplified in this case.

Colonic perforation may be a rare outcome. However, these case examples of catastrophic lower GI complications and relatively preserved upper GI tract in the presence of prolonged use or excessive doses highlight the potential susceptibility of the lower GI tract to NSAIDs. Moreover, they demonstrate the importance of considering the integrity of the complete GI tract when prescribing NSAIDs. As mentioned previously, the true extent of lower GI adverse effects of NSAIDs has, until recent years, remained poorly studied and poorly appreciated by most clinicians.

Notably, though clinical trials have reported on lower GI complications of NSAIDs, prior to 2010, the primary endpoints of any such trials were related to either upper GI or cardiovascular events. One such trial was the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) study, which concluded higher rates of incidence for lower GI complications of NSAIDs compared with higher GI complications (0.56% and 0.47% of patients with lower and upper GI complications, respectively).¹⁴ It should be noted, however, that the primary endpoint for this study was confirmed thrombotic cardiovascular events. Despite large patient numbers, the drawback of trials such as the MEDAL study with unrelated primary endpoints is that reports on lower GI complications have been restricted to ‘overt’ lower GI complications such as identified sources of bleeding, ulceration or perforation. As such, these studies have failed to capture GI complications where a responsible lesion is unidentified. Given technical difficulties of exploring the small and large bowels, not to mention incidences where there is a lack of facilities for exploration and delays in performing appropriate tests, it is reasonable to assume that such studies considering only ‘overt’ lower GI complications fail to capture the true extent of complications, such as cases of new onset of anaemia of presumed occult GI blood loss.

The first study attempting to identify the incidence of both overt and occult lower GI complications of NSAIDs began in 2010, the Celecoxib versus Omeprazole and Diclofenac for at-risk OA and RA patients (CONDOR) study.¹⁵ This study adopted a novel composite endpoint developed by Chan *et al* in 2009 designed to assess both upper and lower GI events *with or without* endoscopic lesions and thereby assess damage to the GI tract as a whole, entitled ‘clinically significant upper or lower GI events (CSULGES)’.¹⁶ As such, by also considering cases of acute GI haemorrhage of unknown origin as well as clinically significant anaemia of presumed occult GI origin, this was the first study endpoint designed to assess the incidence of *all* overt and occult GI complications of NSAIDs for the very first time. In total, 4484 osteoarthritis or rheumatoid arthritis sufferers testing negative for *Helicobacter pylori* were randomly allocated to receiving either celecoxib 200 mg twice a day or slow release diclofenac 75 mg twice a day+omeprazole 20 mg once a day for 6 months.

Critically, only 0.9% of patients (20) receiving celecoxib met the CSULGES endpoint and were considered to have a

significant event. In contrast, 3.8% (81) receiving diclofenac+omeprazole experienced a significant event. Furthermore, only 26% (21) patients with significant events receiving diclofenac+omeprazole had identifiable upper GI complications noted on oesophagogastroduodenoscopy, while 65% (53) of patients with significant events in this group were owing to 'clinically significant anaemia of presumed occult GI origin'. These findings highlight three important learning points. First, that the protection offered by proton pump inhibitors against the non-selective NSAIDs they are typically coprescribed with is far from absolute and in comparison to COX2 selective NSAIDs, highly limited. Second, and as is exemplified by the case described, GI-related complications of NSAIDs are far from limited to upper GI damage as is the common perception among many physicians, with incidence of lower GI complications now comparable to upper GI complications. Finally, as is exemplified by the CONDOR study, GI complications of NSAIDs identifiable on endoscopic examination significantly underestimate the true extent of GI damage secondary to NSAID use.

Learning points

- ▶ Incidence of upper and lower gastrointestinal (GI) complications of non-steroidal anti-inflammatory drugs (NSAIDs) are now comparable.
- ▶ The notion of NSAIDs damaging only the upper GI tract is out of date and inaccurate. As clinicians, we need to consider the integrity of the complete GI tract when prescribing NSAIDs.
- ▶ Proton pump inhibitors have limited protective effect on the lower GI tract when coprescribed with NSAIDs.
- ▶ A significant proportion of patients with GI-related complications of NSAIDs will have normal endoscopic studies.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned, externally peer reviewed.

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