

# Drug-induced peptic ulcer disease

Valerie Vella B Pharm(Hons), PgDip Clin Pharm (Aberdeen)

Clinical Pharmacist, St Luke's Hospital, Guardamangia, Malta

Email: valerie.vella@gov.mt

Key words: Peptic ulcer, medicines, prostaglandins, gastrointestinal protection, gastrointestinal toxicity

**For more than a century, peptic ulcer disease has been a major cause of morbidity and mortality.<sup>1</sup> Peptic ulcer disease is a heterogeneous group of disorders involving the gastrointestinal tract and results from an imbalance between the aggressive forces of gastric acid and pepsin and the defensive mechanisms of the gastric mucosa.<sup>1,2,3</sup>**

## Introduction

Following the discovery of the association of peptic ulcer disease with *Helicobacter pylori* infection there has been a decline in the prevalence of uncomplicated peptic ulcer disease. In contrast, a striking rise in admissions for ulcer haemorrhage and perforation among elderly people is now being observed. This rise has been attributed to the increased use of non-steroidal anti-inflammatory drugs (NSAIDs) and low-dose aspirin.<sup>1</sup> Drug-induced peptic ulcers are not exclusive to anti-inflammatory drugs, other medicines such as bisphosphonates, potassium

supplements, corticosteroids, anticoagulants and chemotherapy play a role.

## Non-steroidal anti-inflammatory drugs (NSAIDs)

Commonly prescribed for a variety of musculoskeletal complaints such as rheumatoid arthritis and short-term management of pain in osteoarthritis,<sup>4,5</sup> NSAIDs are associated with both upper and lower gastrointestinal tract complications. Prevalence rates vary significantly<sup>6</sup> as estimates do not make a distinction between causal and non-causal associations or because estimates are observed in high-

risk populations only.<sup>7</sup> The prevalence of endoscopically confirmed gastrointestinal ulcers in NSAID users is quoted to be between 15% and 30%. Between 12% to 30% of NSAID-induced ulcers are gastric ulcers, whereas 2% to 19% are duodenal ulcers. NSAID-induced ulcers are symptomatic only in 1% of patients after three to six months and in 2 to 4% of patients after one year. Inappropriately they do not correlate well with pain because the analgesic action of NSAIDs may mask the ulcer pain.<sup>2</sup>

Understanding the method by which NSAIDs cause gastric damage has helped in the development of prophylactic agents that reduce their toxicity.<sup>1</sup> The mechanism by which NSAIDs are thought to damage the gastrointestinal tract is four-fold.

### a) Topical injury

Originally it was thought that NSAIDs damaged the gastric epithelium by intracellular accumulation of these drugs in an ionised state.<sup>1</sup> However the fact that enteric-coated formulations, pro-drugs, rectal and parenteral administration of NSAIDs still resulted in gastrointestinal damage despite the apparent absence of direct mucosal contact implies a minor role for topical injury.<sup>1,2</sup>

### b) Inhibition of prostaglandin synthesis

In 1971 Vane discovered that NSAIDs act by the inhibition of cyclooxygenase the enzyme that converts arachidonic acid to prostaglandins. As prostaglandins play a major role in the maintenance of gastroduodenal defence mechanisms; their depletion due to NSAIDs and aspirin impairs cytoprotection resulting in mucosal injury, erosions and ulceration.<sup>1,8</sup>

### c) Nitric Oxide

Recent attention has focused on the role of nitric oxide (NO) in maintenance of gastric-mucosal blood flow.<sup>1</sup> Like prostaglandins nitric oxide has been shown to increase mucosal blood flow, stimulate mucus secretion and inhibit neutrophil

adherence.<sup>1</sup> In animals NO-releasing NSAIDs produce less gastric damage than their parent drugs and they even promote ulcer-healing.<sup>1,9</sup>

#### **d) Neutrophil-mediated injury**

Neutrophil adherence to the endothelium of gastric microcirculation damages the mucosa by liberating oxygen-free radicals, releasing proteases and obstructing capillary blood flow. NSAIDs are thought to stimulate neutrophil adherence by up-regulation of adhesion molecules.<sup>1</sup>

The overall result is that NSAIDs cause damage as they impair the ability of the gastrointestinal mucosa to respond to injury.<sup>9</sup> Not all NSAIDs have the same potential to cause peptic ulcer disease, in fact ibuprofen in low doses (up to 1200mg daily) is said to have the same Odds Ratio<sup>2</sup> as paracetamol in causing upper gastrointestinal bleeding.<sup>7</sup> Diclofenac also has a low odds ratio although higher than that for ibuprofen. Indomethacin, naproxen and piroxicam have an intermediate odds ratio<sup>†</sup> whereas azapropazone and ketoprofen, has a very high odds ratio, and should thus be avoided in high-risk patients<sup>7, 8,10,11,12,13</sup>

### **Cyclo-oxygenase (COX 2) selective inhibitors**

There are at least two isoforms of cyclo-oxygenase: COX 1 and COX 2. The former is found in high concentrations in platelets, vascular endothelial cells, the stomach and in kidney collecting tubules and is responsible for the prostaglandins which are essential for maintenance of normal endocrine function, renal function, gastric mucosal integrity and haemostasis.<sup>4</sup> COX 2 is significantly increased by inflammatory and mitogenic stimuli. By selectively blocking COX 2, COX 2 selective inhibitors have a theoretical advantage over the traditional NSAIDs with respect to reduction in GI side-effects.<sup>4,14</sup> Published clinical trials assessing the gastroerosive

potential of coxibs demonstrate conflicting data.<sup>9, 15, 16,17</sup>

### **Cyclo-oxygenase inhibiting nitric oxide donators**

COX-inhibiting nitric oxide donators, CINODs, are a new class of analgesic drugs designed to provide analgesic efficacy through COX-inhibition and gastrointestinal safety through the protective effects of controlled nitric oxide donation<sup>9,18</sup>. AZD3582 was the first CINOD to enter clinical development.<sup>19</sup> Although initial reports were promising, a recent study has indicated that the much expected superior gastrointestinal tolerability of AZD3582 is no better than that provided by naproxen.<sup>20</sup>

### **Aspirin**

Aside from its use as an anti-inflammatory, aspirin in low dose is frequently indicated for the secondary prevention of thrombotic cerebrovascular or cardiovascular disease.<sup>4,5,21</sup> Incidence of peptic ulcers has been reported to be as high as 35%.<sup>7</sup> Advising patients to take enteric coated tablets or to take the preparation after food may minimise gastrointestinal symptoms as dyspepsia, but as for NSAIDs ulceration is mainly attributable to its systemic effect on prostaglandin synthesis.<sup>5</sup> Co-prescription of aspirin with standard NSAIDs augments the risk of such complications and risk reduction of upper gastrointestinal events associated with COX 2 selective inhibitors may not be evident when they are combined with aspirin.<sup>4</sup>

### **Clopidogrel**

Clopidogrel is an antiplatelet drug indicated for the prevention of atherothrombotic events in patients suffering from myocardial infarction, ischaemic stroke or established peripheral arterial disease.<sup>21,22</sup> It is also given in combination with aspirin in patients suffering from non-ST segment elevation

acute coronary syndrome.<sup>22</sup> The risk of gastric and duodenal ulcers with clopidogrel is between 0.1 – 1.0%.<sup>22</sup> Unfortunately clopidogrel is not a solution to patients who are unable to take aspirin because of gastrointestinal complications. A number of small studies have in fact revealed that in patients with a history of bleeding and peptic ulcer the combination of aspirin and a proton pump inhibitor is safer than clopidogrel in terms of bleeding side effects.<sup>23</sup>

### **Bisphosphonates**

Bisphosphonates such as alendronate, etidronate and risedronate, are now used extensively in the treatment of patients with osteoporosis and Paget's disease and prophylaxis of osteoporosis.<sup>24,25</sup> All bisphosphonates cause gastrointestinal side-effects<sup>14,26</sup> however post-marketing surveillance indicated that alendronate and risedronate are associated with severe oesophageal reactions and gastric and duodenal ulceration.<sup>14,25,27,28,29</sup> It is unclear whether variation in ulcerogenic potential reflects differences in dosing, formulation or chemical structure.<sup>29</sup>

Studies with alendronate indicate that the oesophageal damage is consistent with a topical irritant effect.<sup>28</sup> Failure of alendronate tablets to pass through the oesophagus may result in prolonged local mucosal exposure to the drug, leading to erosive or ulcerative mucosal damage with inflammation and thickening of the oesophageal wall.<sup>30</sup> For most part such reactions can be avoided by appropriate administration of the alendronate tablets. These include swallowing the tablet whole with plenty of water (not less than 200ml) on an empty stomach at least thirty minutes before food while sitting or standing. Patients should also be reminded to stand or sit upright for at least one hour after taking the tablet.<sup>31</sup> On the other hand gastroduodenal injury appears to be an acute phenomenon not associated with significant complications, except in high-

† Odds ratio (OR) is defined as the odds of an event happening in the experimental group expressed as a proportion of the odds of an event happening in the control group. If OR is greater than one, then the effects of the treatment are more than those of the control treatment.

risk situations such as the presence of motility disorders or concurrent use of NSAIDs or anticoagulants.<sup>25</sup> In a small study carried out on 26 healthy volunteers the risk of gastric ulcers in patients taking alendronate and naproxen increased to 38% compared to 8% in those receiving alendronate alone.<sup>32</sup>

### Potassium supplements

Potassium chloride in some of its solid forms may be retained in a fixed location within the oesophagus resulting in oesophageal haemorrhage. It is thought that oesophageal injury is caused by the wax-matrix of slow release tablets. These tablets should be avoided in patients with significant cardiomegaly particularly those who have undergone cardiac surgery as these conditions seem to favour tablet retention in the oesophagus. They should also be prescribed with caution in patients with a history of peptic ulcers.<sup>30</sup>

Patients should always be advised to swallow potassium chloride tablets whole with fluid during meals while sitting or standing.<sup>21</sup>

### Corticosteroids

Although controversial over the years, current evidence suggests that corticosteroids alone do not impart detectable risk for peptic ulceration.<sup>33</sup> Nevertheless the product characteristics of commonly used corticosteroids still indicate that they should be used with caution in patients with a history of peptic ulceration.<sup>34,35</sup> Additionally they state that corticosteroids may be responsible for peptic ulcers with possible perforation and haemorrhage.<sup>34,35</sup>

Corticosteroids may exacerbate NSAID-induced ulceration.<sup>33,34,35</sup> Combination use in a case control study of 1415 patients increased the risk for peptic ulcer disease compared to corticosteroid alone by four times.<sup>33</sup> Some studies have in fact theorised that corticosteroids act only as an NSAID specific risk magnifier.<sup>7</sup>

### Practice Points

- Patients should always receive correct administration instructions. This is especially important when dispensing medicines known to cause topical gastrointestinal damage.
- Gastroprotective agents as proton pump inhibitors and misoprostol should be co-prescribed with NSAIDs to protect against gastrointestinal side-effects.
- Patients complaining of dyspepsia or frequently consuming antacids should be questioned about gastrointestinal symptoms and referred if deemed necessary.
- Patients with active peptic ulcers should be advised to avoid smoking, excessive alcohol intake and over-the-counter preparations containing aspirin and NSAIDs.
- Bleeding peptic ulcers have a mortality rate of about 6%, therefore patients should thus be made familiar with the symptoms of peptic ulcers such as lack of appetite an early sense of fullness with eating, nausea, vomiting, bloating, blood in the stools or black, tarry stools.

### Anticoagulants

Acute gastrointestinal haemorrhage is a severe complication of peptic ulcers in patients receiving long-term oral anticoagulant therapy.<sup>36</sup> Correspondingly the risk of peptic ulcer in patients receiving intravenous or subcutaneous unfractionated heparin can be as high as 10%.<sup>37,38</sup> Although the risk of peptic ulcer with low molecular weight heparins has not yet been quantified, their use in patients with either a history or an active peptic ulcer is contraindicated,<sup>39,40</sup> the same holds for the use of unfractionated heparin.

Concomitant administration of anticoagulation with NSAIDs magnifies the risk and is preferably avoided.<sup>33,36</sup>

### Chemotherapy

A number of cytotoxics used in the management of cancer may induce acute mucosal injury to the stomach and duodenum.<sup>40</sup> In two separate studies carried out on a total of 410 patients receiving either a combination of cyclophosphamide, methotrexate and 5-fluorouracil, or 5-fluorouracil alone revealed that if gastroprotection with omeprazole was not provided the risk of chemotherapy-induced gastroduodenal mucosal injury was significantly higher.<sup>41,42</sup>

Another study indicates that duodenal, gastric or pyloric ulcerations and erosions associated with hepatic artery infusion of 5-fluorouracil have responded to discontinuation of chemotherapy.<sup>33</sup>

### Illicit drugs

Crack was introduced as an illicit street drug in 1986 and since then in America the number of patients treated for gastroduodenal perforations due to crack has increased significantly.<sup>43</sup> In a retrospective study of all patients undergoing surgical management for peptic ulcer disease in a teaching hospital in California it was revealed that patients with recent use of crack cocaine and/or alcohol are more likely to present with duodenal perforations.<sup>44</sup> Occurrence rate is believed to be of 16%.<sup>43</sup>

### Conclusion

In theory any drug, which is administered via the oral route, can cause gastrointestinal injury. Highly caustic coatings and direct medication injury can lead to acute inflammation, which can for the most part be avoided by appropriate administration instructions.<sup>30</sup> Drugs causing gastrointestinal toxicity as a consequence of a systemic effect should be co-prescribed with suitable prophylactic agents such as proton pump inhibitors and misoprostol. The importance of gastroprotection is vital in preventing patient morbidity and mortality especially in patients with a number of risk factors which include patients over the age of sixty, smokers, patients with a history of peptic ulcer disease, and patients on high doses of NSAIDs, or concomitant use of anticoagulants, aspirin, bisphosphonates or corticosteroids.<sup>3,6,8</sup>

## References

- Chan FKL, Leung WK. Peptic-Ulcer disease. *Lancet* 2002; 360:933-941.
- Kradjan WA. Gastrointestinal Disorders. In: Koda-Kimble MA, Young LY, editors. *Applied Therapeutics – The Clinical Use of Drugs*. 7<sup>th</sup> ed. Maryland: Lippincott Williams & Wilkins; 2000.
- Laurence DR, Bennett PN, Brown MJ. Stomach and oesophagus. In: Laurence DR, Bennett PN, Brown MJ, editors. *Clinical Pharmacology*, 8<sup>th</sup> ed. London: Churchill Livingstone; 1997.
- NICE Clinical Guideline. Guidance on the use of cyclo-oxygenase (Cox) II selective inhibitors, celecoxib, rofecoxib, meloxicam and etodolac for osteoarthritis and rheumatoid arthritis. London: *National Institute for Clinical Excellence*, 2001.
- Martindale – The Extra Pharmacopoeia. Reynolds JEF, editor. 13<sup>th</sup> ed. London: The Pharmaceutical Press; 1993.
- Lanas A. Prevention and treatment of non-steroidal anti-inflammatory drug gastroenteropathy. *Rev Gastroenterol Mex*. 2004; 69(6):251-260.
- Hawkey CJ, Longman MJS. Non-steroidal anti-inflammatory drugs: overall risks and management. Complementary roles for COX-2 inhibitors and proton pump inhibitors. *Gut* 2003; 52:600-608.
- Palmer KR, Penman ID, Paterson-Brown S. Alimentary tract and pancreatic disease. In: Haslett C, Chilvers ER, Boon NA, Colledge NR, editors. *Davidson's Principles and Practice of Medicine*, 19<sup>th</sup> ed. Edinburgh: Churchill Livingstone; 2002.
- Perini R, Fiorucci S, Wallace JL. Mechanisms of Nonsteroidal anti-inflammatory drug-induced gastrointestinal injury and repair: a window of opportunity for cyclooxygenase-inhibiting nitric oxide donors. *Can J Gastroenterol* 2004; 18(4):229-236.
- Rodriguez G, Jick H. Risk of upper gastrointestinal bleeding and perforation associated with individual non-steroidal anti-inflammatory drugs. *Lancet* 1994; 343(8900):769-772.
- Langman MJ, Weil J, Wainwright P, et al. Risks of bleeding peptic ulcer associated with individual non-steroidal anti-inflammatory drugs. *Lancet* 1994; 343(8905):1075-1078.
- Russell RI. Defining patients at risk of non-steroidal anti-inflammatory drug gastropathy. *Ital J Gastroenterol Hepatol* 1999; 31(S1):14-18.
- Lewis SC, Langman MJ, Laporte JR, et al. Dose-response relationships between individual nonaspirin Nonsteroidal anti-inflammatory drugs and serious upper gastrointestinal bleeding: a meta-analysis based on individual patient data. *Br J Clin Pharmacol* 2002; 54(3):320-326.
- Kinnear M, Ghosh S. Peptic Ulcer Disease. In Walker R, Edwards C editors. *Clinical Pharmacy and Therapeutics*, 2<sup>nd</sup> ed. Edinburgh: Churchill Livingstone; 1999.
- Hooper L, Brown TJ, Elliott R et al. The effectiveness of five strategies for the prevention of gastrointestinal toxicity induced by non-steroidal anti-inflammatory drugs: systematic review. *BMJ* 2004; 329:948-958.
- Gomez Cerezo J, Lubomirov Hristov R, Carcas Sansuan AJ et al. Outcome trials of COX-2 selective inhibitors: global safety evaluation does not promise benefits. *Eur J Clin Pharmacol* 2003; 59(2):169-175.
- Kwong MR. Have Cox2 inhibitors lived up to expectations? *Best Pract Res Clin Gastroenterol*; 2004; 18(S):13
- Lanas A, Bajador E, Serrano P et al. Nitrovasodilators, low-dose aspirin, other Nonsteroidal anti-inflammatory drugs and the risk of upper gastrointestinal bleeding. *N Engl J Med* 2000; 343(12):834-839
- Hoogstrate J, Anderson LI, Berge OG, Jonzon B, Ojteg G. COX-inhibiting nitric oxide donors (CINODs) – a new paradigm in the treatment of pain and inflammation. *Inflammopharmacology* 2003;11(4):423-428.
- Lohmander LS, McKeith D, Svensson O. A randomised, placebo controlled, comparative trial of the gastrointestinal safety and efficacy of AZD3582 versus naproxen in osteoarthritis. *Ann Rheum Dis* 2005; 64:449-456.
- British Medical Association and Royal Pharmaceutical Society of Great Britain. *British National Formulary*. Edition 48 UK:Pharmaceutical Press; 2004
- Electronic Medicines Compendium for the Professional. Specific Product Characteristics. Plavix. 2005. <http://www.emc.medicines.org.uk> (Last accessed on 27<sup>th</sup> April 2005).
- Chan FK, Ching JY, Hung LC, et al. Clopidogrel versus aspirin and esomeprazole to prevent recurrent ulcer bleeding. *N Engl J Med* 2005; 352(3):238-244
- Graham DY. What the gastroenterologist should know about the gastrointestinal safety profiles of bisphosphonates. *Dig Dis Sci* 2002; 47(8):1665-16678.
- Lanza FL. Gastrointestinal adverse effects of bisphosphonates: etiology, incidence and prevention. *Treat Endocrinol* 2002; 1(4):210.
- Taggart H, Bolognese MA, Lindsay R et al. Upper gastrointestinal tract safety of risedronate: a pooled analysis of 9 clinical trials. *Mayo Clin Proc*. 2002; 77(3):262-270.
- Marshall JK, Rainsford KD, James C, et al. A randomised controlled trial to assess alendronate-associated injury of the upper gastrointestinal tract. *Aliment Pharmacol Ther*. 2000; 14(11):1451-1457.
- Graham DY, Malaty HM. Alendronate gastric ulcers. *Aliment Pharmacol Ther*. 1999; 13(4):515-519.
- Marshall JK. The gastrointestinal tolerability and safety of oral bisphosphonates. *Expert Opin Drug Saf* 2002; 1(1):71-78.
- Jaspersen D. Drug-Induced Oesophageal Disorders, Pathogenesis, Incidence, Prevention and Management. *Drug Safety* 2000; 22(3):237-249
- Electronic Medicines Compendium for the Professional. Specific Product Characteristics. Fosamax Once Weekly 70mg Tablets. 2005. <http://www.emc.medicines.org.uk> (Last accessed on 27<sup>th</sup> April 2005).
- Graham DY, Malaty HM. Alendronate and naproxen are synergistic for development of gastric ulcers. *Arch Intern Med* 2001; 161(1):107-110.
- Unusual causes of and diseases associated with peptic ulcer disease. [http://www.uptodate.com/physicians/gasthepa\\_toclist.asp#Gastrointestinal\\_disease](http://www.uptodate.com/physicians/gasthepa_toclist.asp#Gastrointestinal_disease) (Last accessed on 23<sup>rd</sup> April 2005).
- Electronic Medicines Compendium for the Professional. Specific Product Characteristics. Decadron. 2004. <http://www.emc.medicines.org.uk> (Last accessed on 25<sup>th</sup> May 2005).
- Electronic Medicines Compendium for the Professional. Specific Product Characteristics. Deltacortril. 2004. <http://www.emc.medicines.org.uk> (Last accessed on 25<sup>th</sup> May 2005).
- Thomopoulos KC, Mimidis KP, Theocharis GJ et al. Acute upper gastrointestinal bleeding in patients on long-term oral anticoagulation therapy: endoscopic findings, clinical management and outcome. *World J Gastroenterol* 2005; 11(9):165-1368.
- Electronic Medicines Compendium for the Professional. Specific Product Characteristics. Heparin Sodium Solution for Infusion. 2002. <http://www.emc.medicines.org.uk> (Last accessed on 25<sup>th</sup> May 2005).
- Electronic Medicines Compendium for the Professional. Specific Product Characteristics. Calciparine. 2004. <http://www.emc.medicines.org.uk> (Last accessed on 25<sup>th</sup> May 2005).
- Electronic Medicines Compendium for the Professional. Specific Product Characteristics. Enoxaparin. 2004. <http://www.emc.medicines.org.uk> (Last accessed on 20<sup>th</sup> May 2005).
- Electronic Medicines Compendium for the Professional. Specific Product Characteristics. Dalteparin. 2004. <http://www.emc.medicines.org.uk> (Last accessed on 20<sup>th</sup> May 2005).
- Sartori S, Trevisani L, Nielson I, et al. Misoprostol and omeprazole in the prevention of chemotherapy-induced acute gastroduodenal mucosal injury. A randomised, placebo-controlled pilot study. *Cancer* 1996; 78(7): 1477-1482.
- Sartori S, Trevisani L, Nielson I, et al. Randomized trial of omeprazole or ranitidine versus placebo in the prevention of chemotherapy-induced gastroduodenal injury. *J Clin Oncol*. 2000; 18(3): 463-467.
- Lee HS, LaMaute HR, Pizzi WF, et al. Acute gastroduodenal perforations associated with use of crack. *Ann Surg* 1990; 211(1):15-17.
- Sharma R, Organ CH Jr, Hirvela ER et al. Clinical Observation of the temporal association between crack cocaine and duodenal ulcer perforation. *Am J Surg* 1997; 174(6):629-632.
- Kimmy MB. Cardioprotective effects and gastrointestinal risks of aspirin: maintaining the delicate balance. *Am J Med* 2004; 117(S5A):72S-78S.
- Rostom A, Dube C, Wells G, Tugwell P, Welch V, Jolicoeur E, McGowan J. Prevention of NSAID-induced gastroduodenal ulcers (Cochrane Review). In: *The Cochrane Library*, Issue 2, Chichester, UK: John Wiley & Sons, Ltd, 2004.