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Current approaches to prevent NSAID-induced gastropathy – COX selectivity and beyond

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Gastrointestinal (GI) toxicity associated with nonsteroidal anti-inflammatory drugs (NSAIDs) is still an important medical and socio-economic problem – despite recent pharmaceutical advances. To prevent NSAID-induced gastropathy, three strategies are followed in clinical routine: (i) coprescription of a gastroprotective drug, (ii) use of selective COX-2 inhibitors, and (iii) eradication of *Helicobacter pylori*. Proton pump inhibitors are the comedication of choice as they effectively reduce gastrointestinal adverse events of NSAIDs and are safe even in long-term use. Co-medication with vitamin C has only been little studied in the prevention of NSAID-induced gastropathy. Apart from scavenging free radicals it is able to induce haeme-oxgenase 1 in gastric cells, a protective enzyme with antioxidant and vasodilative properties. Final results of the celecoxib outcome study (CLASS study) attenuated the initial enthusiasm about the GI safety of selective COX-2 inhibitors, especially in patients concomitantly taking aspirin for cardiovascular prophylaxis. *Helicobacter pylori* increases the risk for ulcers particularly in NSAID-naive patients and therefore eradication is recommended prior to long-term NSAID therapy at least in patients at high risk. New classes of COX-inhibitors are currently evaluated in clinical studies with very promising results: NSAIDs combined with a nitric oxide releasing moiety (NO-NSAID) and dual inhibitors of COX and 5-LOX. These drugs offer extended anti-inflammatory potency while sparing gastric mucosa.

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly prescribed drugs worldwide. It is a well-known phenomenon that NSAIDs cause gastric mucosal damage resulting in outcomes ranging from nonspecific dyspepsia to ulceration, upper gastrointestinal (GI) bleeding and death – summarized by the term 'NSAID gastropathy'. The mechanisms of NSAID-induced GI injury are not fully understood. Topical damage occurs in acidic NSAIDs such as acetylic-salicylic acid (ASA) and includes the accumulation of ionized NSAID in the gastric epithelial cell called 'ion trapping' effect [1], the reduction of the hydrophobicity of the gastric mucosal surface [2] and uncoupling of oxidative phosphorylation [3]. Disruption of the epithelial barrier allows back-diffusion of acid into the mucosa.

By inhibiting cyclo-oxygenases (COX) NSAIDs block the formation not only of proinflammatory but also of gastroprotective prostaglandins [4]. This is a key element in NSAID gastropathy as prostaglandins maintain gastric mucosal blood flow and increase protective mucus as well as bicarbonate production. The discovery of two different cyclo-oxygenases led to the development of drugs preferentially inhibiting the COX-2 isoform, on the proposition that prostaglandins produced by the constitutively expressed COX-1 protect gastric

mucosa, whereas the inducible isoform COX-2 is responsible for inflammation and pain. Inhibition of cyclo-oxygenases by NSAIDs is furthermore associated with an altered inflammatory mediator production. As a consequence of COX-inhibition enhanced synthesis of leukotrienes may occur by shunting the arachidonic acid metabolism towards the 5-lipoxygenase pathway [5–7]. Leukotrienes are supposed to contribute to gastric mucosal injury by promoting tissue ischaemia and inflammation [7, 8]. Increased expression of adhesion molecules such as intercellular adhesion molecule-1 [9, 10] by proinflammatory mediators such as tumour necrosis factor-α [11] leads to an increased neutrophil–endothelial adherence and activation [9]. Wallace [12] postulated that NSAID-induced neutrophil adherence might contribute to the pathogenesis of gastric mucosal damage by two principal mechanisms: (i) occlusion of gastric microvessels by microthrombi leading to reduced gastric blood flow and ischaemic cell damage; (ii) increased liberation of oxygen-derived free radicals (Figure 1). Free oxygen radicals react with poly unsaturated fatty acids of the mucosa leading to lipid peroxidation and tissue damage. NSAIDs not only damage the stomach, but may affect the entire GI tract [13] and may cause a variety of severe extraintestinal complications like renal impairment [14, 15] up to acute renal failure in predisposed patients, sodium and fluid retention [14] and arterial hypertension [16] and, subsequently, heart failure.

Clinically and socio-economically, upper GI NSAID-induced injury is predominant: a recent meta-analysis showed that approximately one-third of patients taking NSAIDs long-term had gastric or duodenal ulcers detected by endoscopy [17]. However, the probability of clinically important serious GI complications is much lower (odds ratio between 5.36 in

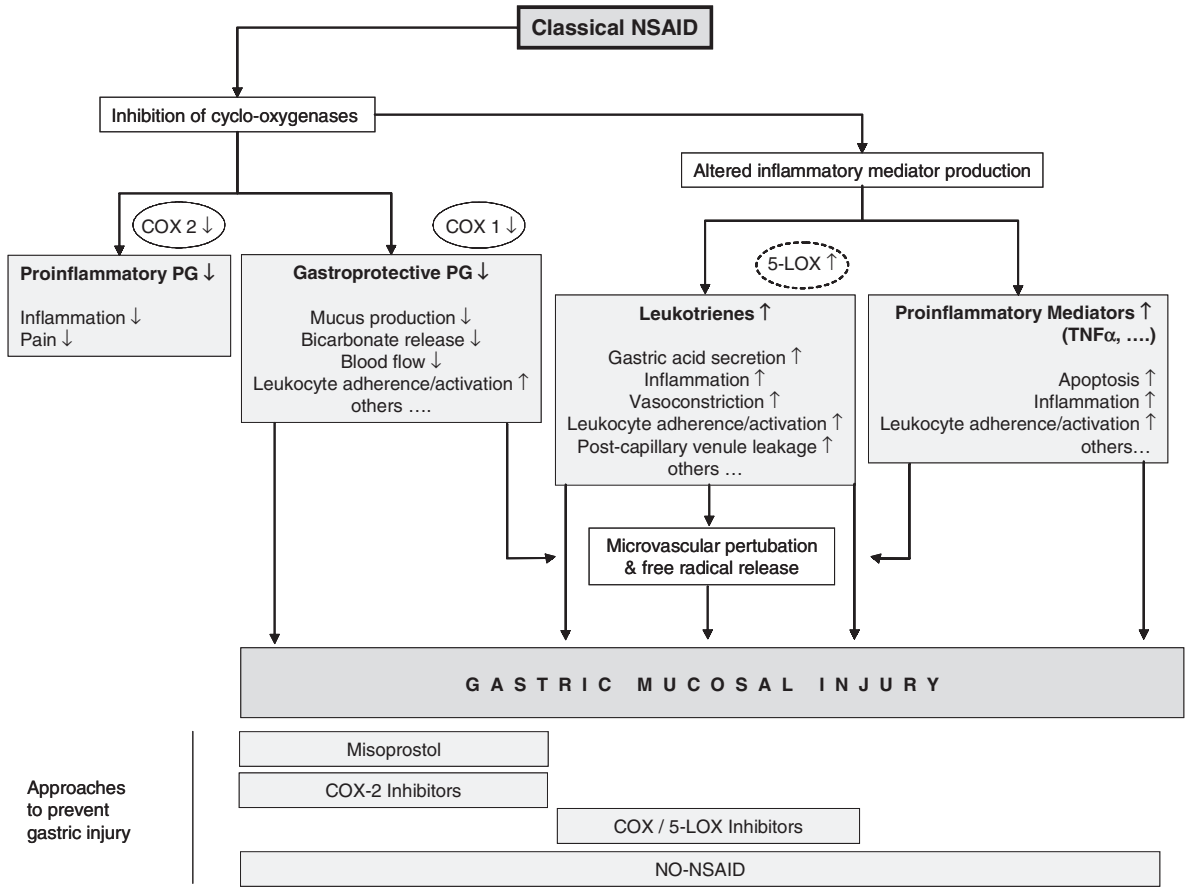

Figure 1

Illustration of NSAID-induced gastric damage: NSAID use alters the production of deleterious as well as gastroprotective prostaglandins, whereas other proinflammatory mediators such as tumour necrosis factor-α and leukotrienes – by a shift towards the 5-LOX pathway – are increased. Damage of gastric mucosa occurs by multiple mechanisms such as microvascular perturbations and neutrophil-mediated free radical release. The lower part of the illustration shows pharmaceutical approaches to prevent gastropathy with specific targets. For mechanisms of action, see Table 3 (modified according to [12])

Table 1
Risk factors for the development of NSAID gastropathy – modified according to [21]

Older age (over 60–65 years)
History of peptic ulcer disease
Helicobacter pylori infection prior to NSAID therapy
First few months of NSAID use
High doses of NSAID
Other debilitating disease (especially cardiovascular)
Concomitant use of anticoagulants and corticosteroids

randomized controlled trials and 2.7 in cohort studies according to a meta-analysis by Ofman *et al.* [18]). Based upon an analysis of patients in the Arthritis, Rheumatism, and Aging Medical Information System (ARAMIS), it is estimated that approximately 107 000 patients are hospitalized per year for NSAID-related GI complications and at least 16 500 NSAID-related deaths occur annually among arthritis patients alone in the USA [19]. The estimated annual costs of direct and indirect NSAID-related adverse effects exceed 7 billion dollars in the USA, which corresponds to $272 per NSAID user [20].

These data emphasize the need to develop strategies to improve gastric tolerability of NSAIDs – especially for patients at high risk for severe GI complications. Principle risk factors for these complications are listed in Table 1 (for review see [21]). In a clinical setting either comedication such as a proton pump inhibitor (PPI) will be prescribed or medication will be switched to a COX-2 preferential drug. This regimen will solve the issue for most patients, but results in higher costs for medication. In this review, currently applied pharmacological strategies to prevent NSAID gastropathy as well as experimental/preclinical approaches will be discussed.

Clinical routine

Three strategies are currently followed in clinical routine to prevent NSAID-induced gastric damage: (i) coprescription of gastroprotective agents, (ii) use of selective COX-2 inhibitors, and (iii) eradication of *H. pylori*.

Gastroprotective drugs

Misoprostol Misoprostol is a prostaglandin analogue used to locally replace prostaglandins the formation of which is inhibited by NSAIDs. According to a meta-analysis performed by Koch [22], misoprostol prevents NSAID-induced GI damage: gastric ulceration was found to be significantly reduced in both acute and chronic NSAID treatment, whereas duodenal ulceration was significantly reduced only in chronic treatment. In the MUCOSA study co-application of 200 μg misoprostol four times a day was shown to reduce the overall rate of NSAID-induced complications by about 40% [23]. Unfortunately, its use is limited by a high rate of GI adverse events [23, 24]. Furthermore, misoprostol use was not associated with a reduction of dyspeptic symptoms [25].

Sucralfate/antacids Apart from diminishing acid exposure to the damaged epithelium by forming a protective gel (sucralfate) or by neutralization of gastric acid (antacids), both regimens have been shown to induce various gastroprotective mechanisms [26–29].

There are only limited data on the use of the aluminium salt of sucrose octasulphate (sucralfate) in the long-term prevention of NSAID-induced gastric damage. Despite promising results with sucralfate in smaller studies [30] or for short-term prophylaxis [26, 31], a randomized, controlled trial conduced by Agrawal and coworkers failed to show a significant benefit of sucralfate in the prevention of gastric ulcers in contrast to misoprostol [32].

Data concerning antacids in the prevention of NSAID-related gastric mucosal injury are scarce, and also disappointing. Especially for long-term prophylaxis no clinical effect was observed with low-dose antacids [26]. In one endoscopic study subjects that were treated with an antacid to prevent naproxen-induced gastric injury developed even greater numbers of gastric erosions compared with placebo [33].

Inhibitors of acid secretion Acid enhances NSAID-induced mucosal damage, and might activate proteolytic pepsin and increase gastric absorption of acidic NSAID [34]. Interestingly, H_2-receptor antagonists and PPIs seem to protect gastric mucosa not only by inhibiting acid secretion and thus elevating gastric pH but also by scavenging free radicals [35, 36]. Biswas *et al.* [36] recently demonstrated that omeprazole plays an important role in gastroprotection by acting as a potent antioxidant and antiapoptotic molecule – independent of its role in acid secretion.

H2-receptor antagonists H_2-receptor antagonists presented the standard of ulcer treatment up to the development of PPIs. They were the first drugs effectively to heal reflux oesophagitis as well as peptic ulcers. However, in the prevention of NSAID-induced gastric ulcer-

ation [37, 38], H_2-receptor antagonists at standard doses are not only ineffective but might also increase the risk of ulcer bleeding [39], perhaps because of masking warning symptoms [39, 40]. Doubling the standard dose (famotidine 40 mg twice daily) significantly decreased the 6-month incidence of gastric ulcers [41]. Formation of duodenal ulcers on the other hand can be prevented [37, 38] and upper GI symptoms improved by H_2-receptor antagonists [41–43]. Taken together, nowadays H_2-receptor antagonists can no longer be recommended to prevent NSAID gastropathy.

Proton-pump inhibitors Acid suppression by PPI is more effective compared with H_2-receptor antagonists and is now standard therapy for the treatment of both peptic ulcers and gastro-oesophageal reflux-disease (GERD). Omeprazole (20 mg once a day) has been demonstrated to be significantly more effective in the prevention of gastroduodenal ulcers than ranitidine (150 mg twice daily) [44] or misoprostol (200 µg bid) [45]. In both studies the PPI provided greater symptomatic relief of dyspepsia associated with NSAID; omeprazole was tolerated better than misoprostol [45]. Graham and coworkers [24] showed in a double-blind, randomized, multicentre study that lansoprazole is superior to placebo in the prevention of NSAID-induced gastric ulcers in *H. pylori*-negative subjects but not superior to full-dose misoprostol (200 µg four times daily). By week 12 of the study, percentages of ulcer-free patients were: 51% for placebo, 93% for misoprostol and 82% for lansoprazole. Taking into account the poor compliance associated with misoprostol (due to adverse effects and the requirement of four doses), lansoprazole and full-dose misoprostol are clinically equivalent [24]. Esomeprazole, the S-isomer of omeprazole, possesses a higher systemic bioavailability and provides significantly more effective and more sustained gastric acid control compared with other PPIs [46]. Most recently, 20 and 40 mg of esomeprazole have been shown to relieve upper GI symptoms significantly in patients continuing to take NSAID or selective COX-2 inhibitors [47, 48]. Due to the selectivity of their target enzyme the rate of adverse events associated with PPIs is low. Long-term use of PPIs is safe [49, 50]. However, in *H. pylori*-positive subjects accelerated progression of corpus gastritis may occur [50–52]. Prior to long-term use of PPIs, *H. pylori* should be eradicated [52]. A disadvantage of PPIs may be that they are unlikely to protect against mucosal injury in more distal parts of the intestine (e.g. in NSAID colonopathy). However, in summary, PPIs present the comedication of choice to prevent NSAID-induced gastropathy.

Selective COX-2 inhibitors/Coxibs

The benefit of selective COX-2 inhibitors for the protection of the GI tract is generally accepted. Overall incidences of GI symptoms are lower in patients on rofecoxib [53] or celecoxib [54] compared with unselective COX-inhibitors. Rates of developing GI ulceration were not significantly different from those of placebo [55, 56] in endoscopic studies. In contrast, large prospective outcome studies were less impressive: the VIGOR study [53] comparing rofecoxib 50 mg with naproxen 1 g daily demonstrated a reduction of all upper GI events in 54% – with similar efficacy against rheumatoid arthritis. Six months' data of the CLASS study [54] even failed to show significant differences in rates of serious upper GI complications between celecoxib compared with ibuprofen and diclofenac. An important difference between the VIGOR and CLASS studies was that low-dose aspirin was permitted for cardiovascular prophylaxis in the latter. Subgroup analysis showed that GI complications were only reduced in patients not taking aspirin, but the benefit was abolished in this subgroup (21% of the patients) taking aspirin [54]. Much less attention has been paid to the data of the entire CLASS study (12 and 15 months), which questions the benefit of celecoxib: according to a prespecified protocol analysis the rates of serious upper GI complications were similar in the celecoxib group compared with diclofenac or ibuprofen [57–60]; most of the ulcer complications that occurred after 6 months were in users of celecoxib [57–60]. However, bias by confounding factors in the NSAID group can not be completely ruled out [57, 61].

We now know that the differentiation between 'protective COX-1' and 'evil COX-2' was simplistic and had to be abandoned in favour of a more detailed evaluation of both isoforms [62]: although entitled an inducible isoform, COX-2 is constitutively expressed in several organs maintaining tissue homeostasis [7, 63, 64], e.g. in kidney [65], brain, and reproductive system [7, 64]. COX-2 plays an important role in gastric mucosal defence and ulcer healing [63]. On the other hand, it has been shown that prostaglandins derived from COX-1 significantly contribute to inflammation [66]. The main functions of both isoforms are summarized in Table 2. However, the 'COX-story' turns out to be even more complex: in 2002 Chandrasekharan and colleagues [67] identified another cyclo-oxygenase isoform with highest expression in the brain: COX-3. Inhibition of this enzyme by analgesic/antipyretic drugs including acetaminophen and some NSAIDs might be a primary central mechanism by which these drugs decrease pain and possibly fever [68]. As this isoform is a spliced COX-1

Table 2
Physiological and pathophysiological functions of COX isoforms 1 and 2 – modified according to [7]

	COX-1	COX-2
Physiological functions		
GI mucosal protection	X	
Kidney function	X	X
Kidney development		X
Reproduction		X
Regulation of blood flow	X	X
CNS function	X	X
Bone metabolism	X	X
Lung function	X	?
Platelet aggregation	X	
Pathophysiological functions		
Inflammatory signs	X	X
Inflammation resolution		X
GI mucosal protection under inflammatory conditions	X	X
Gastric ulceration	X*	X*
Tissue repair/ulcer healing		X
(gastrointestinal) Cancer	X	X

**Inhibition of both isoforms necessary.*

variant it is possible that some effects originally attributed to COX 1 were indeed mediated by COX-3 [68]. The discovery that multiple COX isoenzymes can derive from just one gene will provide new insights into the mode of action of the different COX-inhibitors.

Because of the notion that COX-2 is essentially involved in several physiological processes, attention must be drawn to side-effects of coxibs. Ulcer healing has been shown to be impaired by selective COX-2 inhibitors [69, 70], and with regard to renal adverse events, they do not offer an advantage [15] compared with conventional NSAIDs. Results of the VIGOR study made cardiovascular safety a further critical issue: the rate of myocardial infarction was four-fold, the rate of cardiovascular thrombotic events two-fold higher in the rofecoxib group compared with naproxen [53]. On the other hand, the lack of antiplatelet effects might be advantageous in patients with coagulation disorders or patients on anticoagulants. Coxibs of the second generation such as valdecoxib, etoricoxib, lumaricoxib, and the water-soluble parecoxib (given i.v.), possess a several-fold higher selectivity for COX-2. According to the present data these drugs have proven efficacy in the treatment of inflammation and pain, but a further reduction of NSAID-related adverse events is doubtful [71].

Taken together, compared with classical NSAIDs the use of selective COX-2 inhibitors seems to be associated with reduced GI toxicity in patients not taking aspirin concomitantly even in supratherapeutic doses, but further studies have to clarify the risk–benefit profile of these drugs definitively.

Eradication of H. pylori

The interaction between NSAIDs and *H. pylori* has been a matter of debate, but a recently published meta-analysis showed that both *H. pylori* and NSAIDs independently increase the risk for – and have synergistic effects in – the development of peptic ulcers as well as ulcer bleeding [17]. Uncomplicated peptic ulcer disease in *H. pylori*-positive NSAID takers occurred significantly more frequently (41.7%) than in patients not infected with *H. pylori* (25.9%) [17].

Chan and coworkers [72] studied the effect of *H. pylori* eradication prior to therapy with diclofenac in infected, NSAID-naive patients with dyspepsia or history of peptic ulcer. Eradication of *H. pylori* significantly reduced the incidence of ulcers (12.1% *vs.* 34.4%) and ulcer complications (4.3% *vs.* 27.1%). Konturek *et al.* were able to show that *H. pylori* interferes with the gastric adaptation to ASA [73]. On the other hand, *H. pylori* eradication alone did not affect the risk for ulcers or dyspepsia in patients on long-term NSAID therapy [74]. Eradication therapy alone has been shown to be less effective in the prevention of recurrent upper GI bleeding (18.8%) in *H. pylori*-positive patients taking naproxen compared with omeprazole comedication (4%) [75]. Obviously, there seems to be a difference in the role of *H. pylori* in NSAID-naive patients and long-term NSAID takers [72]. According to the Maastricht 2–2000 consensus report [52], it is advisable to test for and eradicate *H. pylori* in patients in whom NSAID therapy is planned and who are at increased risk of peptic ulcers [72, 76]. There are no general recommendations if these patients require additional long-term prophylaxis by, for example, PPI. The high incidence of peptic ulcers even after *H. pylori* eradication (12.1%) in the study performed by Chan [72] pleads for a prophylactic therapy in patients at high risk [76]. According to Hawkey and Langman [77], eradication is also required in appropriate patients using selective COX-2 inhibitors, as *H. pylori* doubles the risk of ulcers in patients taking rofecoxib. For long-term NSAID takers *H. pylori* eradication alone is not sufficient to prevent recurrent ulceration/bleeding; in these patients secondary prophylaxis with PPI or switch to selective COX-2 inhibitors is necessary. Which of the two strategies is superior can not be decided from the present data [76]. In a recently

published study, celecoxib and diclofenac plus omeprazole were equivalent with regard to the incidence of recurrent ulcer bleeding (4.9% *vs.* 6.4%), but neither regimen offered complete protection [78].

Recommendations differ in *H. pylori*-positive patients on low-dose aspirin. Screening for *H. pylori* infection prior to treatment with low-dose aspirin is not generally recommended and would enormously increase costs due to the high number of patients treated with low-dose aspirin for cardiovascular prophylaxis [76], but it is advisable in those patients with a history of peptic ulcer disease [52]. After successful *H. pylori* eradication, patients on low-dose aspirin do not necessarily need further prophylactic comedication [76].

Agents/regimens commercially available, but not in general use

Besides the above generally accepted approaches to reduce the GI adverse effects of NSAIDs, gastroprotective formulations, especially for aspirin, have been developed: enteric coated/sustained release aspirin and aspirin combined with vitamin C. Although used in clinical routine for decades, the effects of a fixed combination of aspirin and vitamin C have rarely been investigated with regard to its GI side-effects.

Enteric coating

Enteric coating is especially used as a formulation of aspirin. The removal of topically damaging effects associated with NSAIDs due to intestinal release of the drug is the basis of the protection. Because of its use for cardiovascular prophylaxis, a large patient population is exposed to aspirin in daily dosages ranging between 75 and 300 mg. Even low-dose aspirin can be associated with severe GI complications [79–82], although the risk is relatively low. It has recently been demonstrated that the enteric coated formulation does not adversely affect the antithrombotic properties of aspirin [83]. The results of endoscopic studies showed a trend towards a reduction of gastroduodenal lesions of enteric coated compared with plain aspirin both in low and higher dosages [84–87]. Therefore, coating seems to be a promising approach to reduce gastric injury of low-dose aspirin. However, there are conflicting data about the benefit of the enteric coated formulation to prevent ulcer bleeding, in that two studies failed to show a difference compared with plain aspirin [80–82]. Furthermore, care has to be taken concerning mucosal injury in more distal parts of the intestine: sustained release and enteric coating formulations of NSAIDs can be associated with small and large intestinal injury and severe complications [88]. Additionally, when taken together with a PPI, early disruption of enteric coating and intragastric release of the drug might occur due to an increased gastric pH [89] – thus abolishing the desired effect of coating.

Addition of antioxidants/vitamin C

The role of antioxidants, especially vitamins C and E, in the prevention of NSAID-induced gastric injury is relatively little studied, and large outcome studies are missing. We [90] and others [36, 91] demonstrated that ASA generates reactive oxygen metabolites which significantly contribute to gastric mucosal damage in humans – probably by initiating lipid peroxidation. On the other hand, mRNA expression and activity of protective antioxidizing enzymes like superoxide dismutase and glutathione peroxidase in the stomach as well as intragastric vitamin C levels were impaired by ASA. Comedication with vitamin C abolished these effects, was able to scavenge free radicals, and significantly attenuated gastric damage [90]. In animal studies vitamin E protected against ASA-induced gastric injury by inhibition of lipid peroxidation and accumulation of activated neutrophils [92, 93]. Both vitamins C and E seem to play a role in the preservation of gastric mucosal integrity; vitamin C is actively secreted into the gastric lumen of healthy subjects, and its concentrations are decreased in patients with gastroduodenal diseases such as peptic ulcer disease, gastric malignancy [94, 95], or *H. pylori*-associated gastritis [96]. The underlying molecular mechanisms, however, are not fully understood.

We were recently able to show that the gastroprotective effects of vitamin C as observed in humans might – at least in part – be mediated by haeme-oxygenase-1 (HO-1) [97]. HO-1 is a ubiquitous and crucial tissue-protective enzyme with vasodilative, anti-inflammatory and antioxidant properties. Its pathway and functions are illustrated in Figure 2. In the stomach HO-1 might counteract the two major mechanisms of NSAID-induced gastric injury: disturbance of gastric microcirculation and free radical release (Figure 1). The mechanisms of HO-1 induction seem to be cell-type specific; a nonstressful induction was recently postulated as a therapeutic target [98]. We identified vitamin C as a potential nonstressful inducer of HO-1 in the stomach. However, to date there are only very limited data about this enzyme in the stomach. Guo *et al.* [99] showed that healing of gastric ulcers in rats is paralleled by an upregulation of HO-1. Further studies are needed to examine the role of HO-1 in the stomach *in vivo*. Our recent findings, however, are in favour of the supplementation of vitamin C in order to prevent NSAID gastropathy

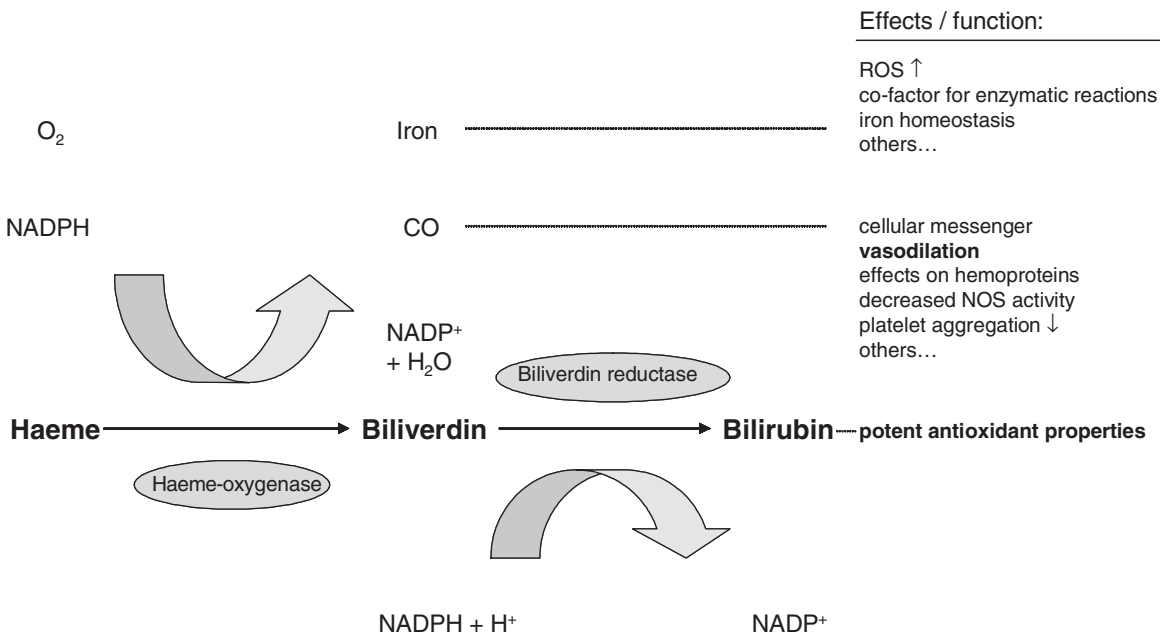

Figure 2

Pathway of haeme-oxygenase-1 (HO-1) – modified according to [98]. Various stressful and nonstressful stimuli induce HO-1; it catalyses the degradation of haeme into equimolar amounts of carbon monoxide (CO), iron and biliverdin, which is subsequently reduced to bilirubin. These products exert vasodilative, anti-inflammatory and antioxidant effects

– showing an impact beyond its sole antioxidant properties.

Experimental/preclinical approaches

Two very promising alternatives to clinically applied comedication are currently studied in clinical trials: NO-NSAID and dual inhibitors of COX and 5-LOX. Both seem to have extended anti-inflammatory activity while sparing gastric mucosa.

NO-NSAIDs

Under physiological conditions, small amounts of nitric oxide (NO) synthesized by the constitutive isoform enzymes [endothelial (eNOS) and neuronal (bNOS) nitric oxide synthase] contribute to gastric mucosal defence by influencing key elements of gastroprotection. Like prostaglandins, NO increases mucus and bicarbonate secretion as well as microcirculation and decreases neutrophil–endothelial adherence [100] – a key pathogenic element in NSAID gastropathy. We were able to show that in humans the adaptation to chronic aspirin intake is accompanied by an increased expression of mucosal eNOS, which may be responsible for the observed enhancement of mucosal blood flow despite reduced prostaglandin synthesis [101]. The underlying mechanisms involved in the gastroprotection by NO are complex. As the pathways of NO and HO are closely related to each other [102] it seems possible that some of the gastroprotective effects of NO – like those of vitamin C – might be mediated by HO.

The recognition of NO as an important mediator of gastric mucosal defence led to the development of a new class of drugs: nitric oxide releasing NSAIDs (NO-NSAIDs). These drugs consist of a conventional NSAID esterified to a NO-releasing moiety. Multiple studies in animals impressively demonstrated the ability of NO-NSAID to spare GI mucosa in acute [103–105] and chronic administration [106] (for review see [107]). For example, NO-aspirin did not produce detectable mucosal injury, in contrast to aspirin administration, in rats when given in equimolar dosages [103]. Similar results have been obtained with other parent NSAIDs such as NO-naproxen [104] and NO-indomethacin [105]. In experimental models, NO-NSAIDs even protected gastric mucosa against damage induced by other deleterious stimuli and maintained gastric mucosal blood flow [107–109]. Ukawa *et al.* [110] showed that healing of gastric ulcers was not impaired by NO-aspirin whereas the parent substance as well as a selective COX-2 inhibitor in equimolar dosages delayed the healing process. Apart from diminishing GI toxicity, NO-NSAIDs improve anti-inflammatory and antinociceptive

efficacy [111]. Additionally, NO-aspirin has an increased antithrombotic potency compared with conventional aspirin [107, 112]. The broad biological effects of slowly released NO combined with COX inhibition are likely to extend the indication of NO-NSAIDs from the therapy of inflammation and pain to the treatment/prevention of various other diseases such as cancer or cardiovascular disorders as discussed by Keeble and Moore [107]. A recently published study involving a total of 31 volunteers supported the data obtained in animal studies showing significantly reduced but not completely abolished GI toxicity associated with NO-naproxen compared with conventional naproxen in humans [113].

In summary, NO-NSAIDs represent a promising therapeutic alternative to conventional and COX-2 selective NSAIDs with not only reduced profile of GI side-effects but also ameliorated power of desired effects. Large, randomized studies are needed to evaluate definitively the clinical benefit of NO-NSAIDs in humans.

Dual inhibitors of COX and 5-LOX

Beside prostaglandins, leukotrienes are metabolized in the arachidonic acid pathway by the lipoxygenase (5-LOX) enzyme. Leukotrienes are important mediators of inflammation complementary to prostaglandins [7]. Experimental studies demonstrated that particularly cysteinyl leukotrienes contribute to gastric mucosal damage by inducing microvascular injury and promoting a breakdown of the mucosal barrier [7, 8]. Inhibition of COX is often associated with an enhanced synthesis of leukotrienes due to shunting the arachidonic acid metabolism towards the leukotriene pathway [5–7]. Dual inhibitors of COX/5-LOX have been developed in order to achieve enhanced anti-inflammatory activity while sparing gastric mucosa. Licofelone (or ML3000) was demonstrated to exhibit these properties in animal trials [7, 114, 115]. Phase II trials have indicated that this COX/5-LOX inhibitor spares human gastric mucosa. Endoscopically normal findings were reported after 4 weeks of treatment with 200 mg licofelone bid in 93%, with 400 mg licofelone in 89% compared with only 37% in individuals treated with naproxen 500 mg bid [116, 117]. Similar results were obtained in a 12-week, Phase III, randomized, double-blind trial in 148 patients with osteoarthritis. The incidence of gastroduodenal ulcers turned out to be 1.5% with licofelone 200 mg bid compared with 15.3% with naproxen 500 mg bid while analgesic activity was equivalent [118]. In the control of pain licofelone 200 mg bid was as effective as celecoxib 200 mg once daily with identical GI safety in a 12-week randomized trial [119]. In contrast to selective COX-2 inhibitors [54], licofelone has been shown to retain its GI safety profile when taken together with low-dose aspirin in a study involving 75 patients [120]. Fiorucci *et al.* [121] recently described an underlying mechanism for this difference between selective/nonselective COX inhibitors and licofelone: the balance in the production of the deleterious leukotriene LTB_4 *vs.* the protective lipoxin ATL (aspirin triggered lipoxin, generated by acetylated COX-2) is involved in controlling acute and chronic responses to aspirin. While administration of either selective or non-selective COX inhibitors to aspirin-pretreated rats exacerbated gastric injury due to inhibition of ATL and increase in LTB_4 formation, licofelone did not – because it additionally inhibited LTB_4 generation. Another advantage of licofelone compared with selective COX-2 inhibitors might be its antithrombotic and platelet aggregation inhibiting function [122]. Most data regarding COX/5-LOX inhibitors have been published as an abstract only, and therefore represent only preliminary findings. Previous dual COX/5-LOX inhibitors such as benoxaprofen were withdrawn because of hepatic and other toxicity [123]. This problem may be molecule-specific. Although licofelone has so far not been associated with hepatotoxicity [7], careful monitoring of liver function is advisable during treatment. Again, large outcome studies have to show if these promising findings can be translated into clinical benefit and if the long-term use of this drug is safe.

Conclusions

The best way to prevent NSAID gastropathy is to avoid these drugs. This is, of course, not possible in most cases. When using nonselective NSAIDs, it is important to reduce the doses to a minimum, as most of the adverse events occur dose-dependently. Drugs with a low GI toxicity profile such as ibuprofen [124] should be preferred. It is crucial to identify patients at high risk for NSAID-induced GI complications (Table 1). At least these patients require a gastroprotective comedication or should be switched to a selective COX-2 inhibitor. The different approaches to reduce NSAID gastropathy are listed in Table 3. Comedication with vitamin C in the prevention of NSAID gastropathy has been only little studied, but apart from scavenging free radicals it is able to induce haeme-oxygenase-1 in gastric cells, a protective enzyme with antioxidant and vasodilative properties. PPIs are the comedication of choice, especially because adverse events even in long-term use are minimal. COX-2 inhibitors have been aggressively marketed; although overall GI toxicity seems to be reduced with these coxibs, final data of the CLASS study failed

Table 3
Advantages and disadvantages of different pharmacological approaches to reduce gastrointestinal toxicity of NSAIDs as well as principal mechanisms of action differentiated in (a) established regimens, (b) less investigated, but clinically used strategies, and (c) experimental/preclinical approaches

Regimen	Principal mechanism of protective action	Advantages	Disadvantages
A)			
Classical NSAID + misoprostol	Prostaglandin substitution	Effective in reducing occurrence of gastroduodenal ulceration and associated complications*	GI adverse events Ineffective in preventing dyspepsia Dosing at least three times daily
Classical NSAID + PPI	Elevation of intragastric pH (Antioxidant and antiapoptotic properties)	Effective in reducing dyspepsia and occurrence of gastroduodenal ulcers and associated complications* Minimal adverse events attributable to PPI	Possibly acceleration of corpus gastritis in *H. pylori*-infected patients
Selective COX-2 inhibitors	Sparing gastroprotective prostaglandins generated by COX-1 isoform	Effective in reducing dyspepsia and occurrence of gastroduodenal ulcers and associated complications*	Lack of gastroprotection with concomitant use of aspirin Lack of antiplatelet effect/possibly prothrombotic effects
B)			
Enteric coating formulations	Abrogation of topical damaging effects	Cheap	Benefit not proven Possibly shift of mucosal damage to more distal parts of the intestine
Classical NSAID + vitamin C	Antioxidant properties (Activation of gastric mucosal defence mechanisms Induction of HO-1)	Physiological concept No adverse effects attibutable to vitamin C Cheap	No data of large outcome studies available
C)			
NO-NSAID	Slow release of gastroprotective NO, thereby maintenance of microvascular integrity (Antiapoptotic effects)	Reduction of gastrointestinal toxicity* Increased anti-inflammatory and anti-nociceptive efficacy Antithrombotic effects Physiological concept	Lack of clinical data
COX/5-LOX inhibitors	Inhibition of deleterious leukotriene formation	Reduction of gastrointestinal toxicity* Maintenance of gastroprotection despite concomitant use of aspirin Antithrombotic effects	Lack of clinical data

**Compared with classical NSAID without comedication.*

to show an advantage in the reduction of serious upper GI complications compared with unselective NSAIDs.

Large outcome studies comparing coxibs with PPI comedication in the prevention of NSAID gastropathy are lacking. According to the present data, in elderly patients without further risk factors both strategies seem to be appropriate. Comedication with PPIs should be preferentially used in patients with cardiovascular disease, patients concomitantly taking low-dose aspirin for cardiovascular prophylaxis and in patients with a history of peptic ulcer disease. Although both regimens have been shown to be equivalent in the prevention of recurrent ulcer bleeding [78], PPIs seems to be more appropriate as, in contrast to coxibs, these drugs promote ulcer healing. A switch to selective COX-2 inhibitors might be advantageous in patients on anticoagulants or with coagulation disorders as well as in patients requiring high doses of NSAIDs [77]. There is no evidence justifying a simultaneous prescription of coxibs together with PPIs in order to reduce GI adverse events further

[125] according to National Institute for Clinical Excellence (NICE) guidance on the use of COX-2 selective inhibitors. However, this guidance will be reviewed soon. In case ulcers occur under therapy with coxibs and COX-2 inhibition is still required, the addition of a PPI seems reasonable.

New treatment modalities such as dual COX/5-LOX inhibitors and NO-NSAIDs may be superior to coxibs in many pathophysiological aspects. According to preclinical studies, indications for NO-NSAIDs might extend from simply reducing inflammation and pain to the therapy of various other diseases. However, large outcome studies of both NO-NSAIDs and COX/5-LOX inhibitors are still awaited.

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