REVIEW ARTICLE

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Safety of the Nonselective NSAID Nabumetone

Focus on Gastrointestinal Tolerability

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Abstract

Although effective in the treatment of pain associated with rheumatic conditions such as osteoarthritis and rheumatoid arthritis, long-term use of NSAIDs is primarily limited by their association with upper gastrointestinal (GI) toxicity. Adverse effects range from dyspepsia and abdominal pain to ulceration and bleeding. GI damage elicited by NSAIDs arises as the result of biochemically induced topical irritant effects and by topical and systemic pharmacological suppression of gastroprotective prostaglandins. Variation in the physicochemical properties and pharmacological profiles among the individual NSAIDs translate into inter-agent differences regarding propensity to cause adverse GI effects. Nabumetone is a nonselective NSAID that offers distinct advantages over other agents in this class with regard to GI tolerability. Its non-acidic nature and prodrug formulation, together with the lack of biliary secretion of its active metabolite, 6-methoxy-2-naphthylacetic acid, are thought to contribute to the improved

GI tolerability of this drug. In head-to-head trials with other NSAIDs, nabumetone has demonstrated significant benefits regarding the incidence of GI events and more serious perforations, ulcers and bleeds (PUBs). Pooled data from eight postmarketing, randomized, controlled trials demonstrated a lower cumulative frequency of PUBs with nabumetone (0.03%; 95% CI 0.0, 0.08) versus comparator NSAIDs (1.4%; 95% CI 0.5, 2.4). Large-scale database studies also indicate that risk of serious GI complications is lower with nabumetone than comparator NSAIDs. Limited comparative data suggest that nabumetone offers a GI tolerability profile similar to that of cyclo-oxygenase-2 selective NSAIDs (coxibs). Although adverse cardiovascular outcomes appear to be a class effect of the coxibs, conventional NSAIDs may also have the potential for causing atherothrombotic complications. However, based on available data, nabumetone does not appear to be associated with increased cardiovascular risk. Finally, there is no particular concern about the nephrotoxic and hepatotoxic potential of nabumetone. Nonetheless, the potential for adverse drug reactions remains, and hence nabumetone, as with any NSAID, should be used at the lowest dose, which is effective for each patient, and for the shortest time necessary to control symptoms.

NSAIDs are used widely in the treatment of painful conditions such as osteoarthritis (OA) and rheumatoid arthritis (RA). The analgesic activity of the NSAIDs arises through their inhibition of prostaglandin G/H synthase, the enzyme responsible for converting arachidonic acid into various prostaglandins and thromboxanes.[1] It is now accepted that there are at least two distinct forms of this enzyme, referred to as cyclo-oxygenase-1 (COX-1) and COX-2, each of which carries out different functions in the body. Of particular relevance to this discussion, COX-2 has been implicated in inflammatory processes while COX-1 activity exerts protective effects in the gastric mucosa,[2] and the balance of these distinct actions has implications for the effectiveness and tolerability of NSAID treatment. Conventional NSAIDs inhibit both forms of the COX enzyme, with substantial variation across individual agents with regard to the relative balance of COX-1 versus COX-2 inhibition.[1]

Despite providing effective analgesic relief, the long-term use of NSAIDs is primarily limited by their upper gastrointestinal (GI) adverse effects including dyspepsia and abdominal pain and, more rarely, gastric or duodenal ulcers, perforation or bleeding.[3] Lower GI adverse effects may also be problematic.[4,5] The risk of GI toxicity is dose- and time-dependent.[3,5-7] Other risk factors include older age, previous history of upper GI events, use of multiple NSAIDs and concomitant use of low-dose aspirin (acetylsalicylic acid), anticoagulants or corticosteroids.[3,6,8]

Different drug formulations, such as enteric coating or encapsulation, and alternative routes of administration have been developed in attempts to improve GI tolerability of NSAIDs. However, these efforts have not been particularly successful in reducing long-term GI ulcer complications.[6]

Nabumetone is a non-acidic NSAID prodrug specifically designed to improve the GI tolerability of conventional NSAIDS. Nabumetone has demonstrated at least similar efficacy to other conventional NSAIDs in treating the symptoms of OA and RA.[9] This article examines the processes underlying NSAID-induced GI injury, discusses the unique pharmacological properties of nabumetone and reviews the clinical data for this drug, focusing primarily on its GI tolerability in comparison with other conventional NSAIDs and selective COX-2 inhibitors. Cardiovascular, renal and hepatic effects of nabumetone are also briefly discussed, although a comprehensive examination of these topics lies beyond the scope of the present article.

1. Sources of NSAID-Induced Gastrointestinal (GI) Toxicity

The GI toxicity of NSAIDs arises in multiple ways including direct and indirect topical effects of these drugs on the gastric mucosa, as well as the local and systemic suppression of prostaglandin levels that results in impairment of the protective mucus-bicarbonate layer in the stomach.[10] These processes have been reviewed in depth elsewhere[11] and are outlined briefly in the following sections.

1.1 Direct and Indirect Topical Biochemical Effects

In approaching the GI toxicity of the NSAIDs, much emphasis historically has been placed on the effects of prostaglandin deficiency induced by mucosal COX-1 inhibition. However, evidence from a variety of sources argues against systemic inhibition of mucosal COX-1 activity as the sole factor involved in eliciting mucosal injury, and direct topical injury of the mucosa by these drugs is supported.[11]

The weakly acidic nature of most NSAIDs[12] facilitates their accumulation inside gastric epithelial cells during GI transit and during the absorption phase. Once in the higher pH of the intracellular environment, these NSAID molecules rapidly dissociate into their ionized form, which cannot readily re-cross the phospholipid membrane; this process has been referred to as 'ion trapping'.[13] The gastric and upper duodenal epithelial layer maintains strictly regulated permeability to protect against acid entry. Acidic NSAIDs have been shown experimentally to inhibit or uncouple mitochondrial oxidative phosphorylation, with consequent decreases in intracellular adenosine triphosphate. This, in turn, causes loss of cytoskeletal control over tight junctions and, as a result, an increase in mucosal permeability.[14-17] Cells on the surface of the stomach lining also secrete mucus and bicarbonate ions to protect against acid insult.[18] Another mechanism by which NSAIDs inflict topical injury appears to involve weakening of this protective mucus-bicarbonate layer as NSAIDs are able to disrupt the hydrophobic barrier of the GI mucosa through interactions with surface phospholipids.[19-21]

As a result of this increased cell permeability and impairment of the mucus-bicarbonate protective lining, back diffusion (towards mucosal cells) of the hydrogen ions from dissociated hydrochloric acid can occur,[10] and proteolytic enzymes from the gastric lumen are easily able to access gastric epithelial cells, together resulting in erosive mucosal damage or ulceration arising from disruption of cell continuity. Eventually, damage may reach the underlying blood vessels resulting in bleeding and, ultimately, perforations.

Many NSAIDs or their active metabolites, having been absorbed and processed in the liver, may then be then secreted back into the small intestine with bile, subsequently undergoing several cycles of enterohepatic recirculation. This means that the duodenal mucosa and proximal regions of the small intestine may be repeatedly exposed to the irritative effects of topical exposure to these drugs.[22] Gastric cells may also be further exposed to damage through this route as a result of duodenogastric reflux of bile-excreted NSAIDs.

1.2 Local and Systemic Cyclo-Oxygenase (COX) Inhibition

Exposure to the pharmacological action of NSAIDs, namely COX inhibition, also contributes to GI damage. Such a pharmacological effect is produced locally (during GI transit and absorption) and systemically (when NSAIDs reach GI cells through the circulatory system). Evidence from early animal studies implicated decreased prostaglandin synthesis, a consequence of COX-1 inhibition, in the aetiology of NSAID-induced gastric mucosal injury.[23,24] This hypothesis is further supported by the protective effects of synthetic prostaglandin administration against gastric ulcer formation and other serious GI damage in patients treated with NSAIDs.[25,26]

In summary, damage initiated by topical effects of NSAIDs and further aggravated by prostaglandin-depletion underlies the GI toxicity associated with these drugs. Interestingly, the combination of both topical toxicity and prostaglandin deficiency might be needed to cause progress to actual ulceration.[27]

2. Chemical and Pharmacological Properties of Nabumetone

2.1 Non-Acidity

The physicochemical properties of an individual NSAID affect its propensity to cause GI toxicity.[12] Nabumetone is a non-acidic molecule. This feature limits its ability to enter and accumulate in gastric cells, thereby minimizing the opportunity to exert the damaging topical effects on gastric mucosa described above for acidic NSAIDs. Indeed, a study in isolated rat liver mitochondria showed that nabumetone, in contrast to acidic NSAIDs, did not induce topical damage involving uncoupling of mitochondrial oxidative phosphorylation.[16]

2.2 Prodrug

Furthermore, nabumetone is formulated as a pharmacologically inactive prodrug that only becomes active after absorption, predominantly in the small intestine, and through hepatic conversion to the active metabolite, 6-methoxy-2-naphthylacetic acid (6-MNA). Thus, during its transit along the GI tract and absorption, a deleterious pharmacological effect on gastric prostaglandin synthesis is avoided.[12,28,29]

2.3 Lack of Biliary Secretion

Enterohepatic circulation appears to be a major driver of NSAID-induced lower GI toxicity.[30] Nabumetone undergoes extensive first-pass metabolism and the active metabolite, 6-MNA, is eliminated by the kidneys as a conjugate or as a demethylated metabolite.[11,28] Importantly, 6-MNA does not undergo biliary secretion and therefore enterohepatic recirculation.[31] This means that exposure of the duodenal mucosa and proximal regions of the small intestine to 6-MNA is virtually avoided, as is additional exposure of gastric cells via duodenogastric reflux. This is likely to explain why nabumetone, unlike other NSAIDs that do undergo biliary excretion, does not affect intestinal permeability and therefore does not appear to cause inflammation in the small intestine.[32,33]

2.4 Reduced Systemic Effects

The fact that, as a prodrug, nabumetone causes minimal COX inhibition (and thereby does not reduce prostaglandin synthesis) until it has been absorbed in the small intestine and converted in the liver into pharmacologically active 6-MNA, together with the lack of biliary excretion of pharmacologically active 6-MNA, suggests that systemic exposure is the only means by which nabumetone is available to elicit GI toxicity. Interestingly, the systemic effect nabumetone exerts on the gastric mucosa appears to be lower than that associated with other NSAIDs, especially indomethacin. For example, a study examining the effects of 3 days of systemic dosing of 6-MNA, via intravenous administration, across a wide-dose range (approximately 2.5–45 times the dose estimated to achieve an anti-inflammatory effect) in rats did not find any evidence of gastric or intestinal mucosal damage, whereas similar experiments using indomethacin resulted in dose-related damage to the stomach and intestine.[34]

6-MNA is extensively bound to plasma albumin,[28] and it has been suggested that this tight binding of 6-MNA to circulating proteins can restrict the amount that is systemically available to be accumulated in mucosal cells.[12]

2.5 COX-1/COX-2 Equiselectivity

Another factor that may explain the relative lack of a systemic effect by nabumetone with regard to GI toxicity is that this agent is equiselective for COX-1 and COX-2. Some early studies refer to nabumetone and its active metabolite 6-MNA as having a certain preferential affinity for COX-2, based on oxygenase assays using microsomal membrane extracts from cos-1 cells transfected with murine prostaglandin endoperoxide synthase (PGHS)-1 and -2.[35] However, this and other early studies using various assays based on cell preparations or purified enzymes from animal sources, purified recombinant human enzymes and isolated human cells to investigate the selectivity of NSAIDs were found to be unreliable in their ability to predict effects on human COX-1 and -2 activity *in vivo*.[36] More reliable whole blood cell assays have been developed in which thromboxane A_2 or prostaglandin E_2 levels

are measured as markers of the COX-1 activity (elicited by calcium ionophore or spontaneous clotting) and the COX-2 activity stimulated by lipopolysaccharide.[36,37] Studies using such whole blood cells assays demonstrate that 6-MNA shows equiselectivity for COX-1 and COX-2 (figure 1).[1,37] Furthermore, studies in healthy volunteers administered oral nabumetone have demonstrated nonselective inhibition of COX-1 and COX-2.[37,38] Conversely, some other NSAIDs (e.g. naproxen, ibuprofen and indomethacin) have stronger affinity for COX-1 (figure 1), which may have implications regarding the relative effects of these agents on the production of gastroprotective prostaglandins.

3. GI Tolerability of Nabumetone

Nabumetone has shown comparable clinical efficacy to other conventional NSAIDs in the treatment of pain related to OA and RA and is generally well tolerated (reviewed in detail by Hedner et al.[11]). A safety experience analysis published in the early 1990s comprising the initial clinical trials and postmarketing studies performed with nabumetone showed that this agent is associated with a low incidence of serious GI adverse events.[39] In this analysis, the cumulative incidence of perforations, ulcers or bleeds (PUBs) ranged from 0.02 to 0.95%. The adverse events profile for nabumetone in children and adolescents appears to be similar to that reported for adults, based on data from 89 juvenile RA patients enrolled in an open-label trial.[40] In contrast to other NSAIDs, dose increase from the minimum to maximum recommended dose for nabumetone (i.e. from 1000 to 2000 mg/day) was not found to be associated with a worsening in tolerability, including in elderly patients.[41-43]

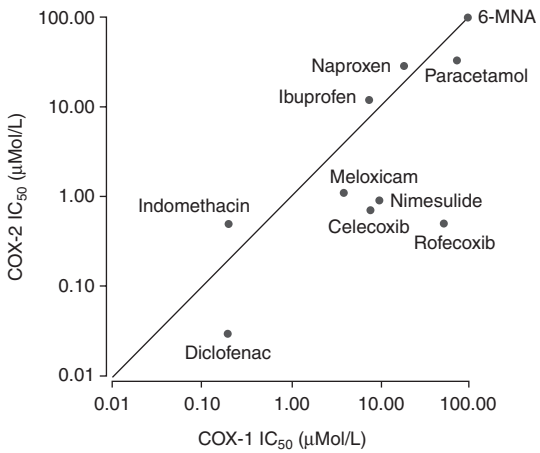

Fig. 1. Concentrations of NSAIDs required for inhibition of cyclooxygenase (COX)-1 and COX-2 activity by 50% (IC_{50}) in whole blood assays. The diagonal line indicates equiselectivity for COX-1 and COX-2. **6-MNA** = 6-methoxy-2-naphthylacetic acid, the active metabolite of nabumetone (reproduced from Fitzgerald and Patrono,[1] with permission. Copyright© 2001, Massachussetts Medical Society. All rights reserved.)

3.1 Comparison with Other Conventional NSAIDs

GI toxicity related to NSAIDs ranges from more common 'nuisance' symptoms such as dyspepsia, nausea, heartburn and abdominal pain, through mucosal lesions such as ulcers that may be symptomatic or asymptomatic, to serious complications such as perforated ulcers and serious bleeding.[44]

Results from head-to-head, randomized, controlled trials suggest that nabumetone, administered in its therapeutic dose range of 1–2 g/day,[11] offers improved GI tolerability compared with other conventional NSAIDs (table I).

In short-term studies of 4–12 weeks duration in patients with OA or RA, while overall rates of adverse events were generally similar, nabumetone 1–2 g/day was associated with significantly lower incidences of overall GI adverse events,[45] severe upper GI adverse events,[46] abdominal pain[42,48] and treatment withdrawal related to GI toxicity[42,46] compared with slow-release diclofenac and naproxen (table I). Conversely, a 3-month, randomized, double-blind trial conducted in 346 RA patients showed no statistically significant difference in the occurrence of GI symptoms between nabumetone 2 g/day and naproxen 1g/day.[49] Of note, no serious GI adverse event was recorded in this study.[49] A lower incidence of GI adverse events with nabumetone (26%) compared with indomethacin (38%) was noted in a 6-week study, although this difference did not reach statistical significance possibly because of the low number of patients included (<100 per group).[41] Nevertheless, significantly fewer nabumetone-treated patients experienced severe adverse events (30% vs 11%). The comparative safety of nabumetone versus diclofenac, naproxen, piroxicam and ibuprofen was evaluated in a 12-week, study

Table I. Incidence of gastrointestinal (GI) adverse events (AEs) with nabumetone vs conventional NSAIDs in randomized, controlled trials

Study (y)	Study design (duration)	Diagnosis (no. of pts)	Comparators/dosage (mg/day)	Incidence of GI AEs (% pts) [p-value]			
				overall	PUBs	pain (as specified)	other GI AEs (as specified)
Laws et al.[45] (1990)	R, DB (6 wk)	OA (243)	Nabumetone (1000)	17	NR	3.3 (abdominal pain)	6.6 (withdrawal for GI AE)
			Diclofenac SR (100)	29 [p = 0.03]	NR	11.6 (abdominal pain)	9.9 (withdrawal for GI AE)
Emery et al.[46] (1992)	R, DB (3 mo)	RA (298)	Nabumetone (2000)	21[a]	0	5 (abdominal/epigastric pain[a])	3 (severe upper GI AE)
			Naproxen (1000)	28[a]	1	10 (abdominal/epigastric pain[a])	11 (severe upper GI AE) [p ≤ 0.01]
Carle et al.[41] (1992)	R, DB (6 wk)	OA (197)	Nabumetone (1000–2000)	26[a]	0	2 (abdominal pain[a])	7 (withdrawal for upper GI AE)
			Indomethacin (75–150)	38[a]	0	12 (abdominal pain[a])	13 (withdrawal for upper GI AE)
Eversmeyer et al.[42] (1993)	R, OL (12 wk)	OA, RA (4411)	Nabumetone (1000)	NR	0.03	4.3 (abdominal pain[b])	0.4 (gastritis[b])
			Diclofenac (100–200)	NR	0.3	8.8 (abdominal pain[b]) [p < 0.002]	1.7 (gastritis[b]) [p ≤ 0.02]
			Naproxen (500–1500)	NR	0.7 [p ≤ 0.002]	5.7 (abdominal pain[b])	0 (gastritis[b])
			Piroxicam (10–20)	NR	0.3	4.5 (abdominal pain[b])	0.4 (gastritis[b])
			Ibuprofen (1200–3200)	NR	0.9 [p ≤ 0.02]	6.8 (abdominal pain[b])	1.3 (gastritis[b])
Bellamy et al.[47] (1995)	R, DB (6 mo)	OA (380)	Nabumetone (1000–1500)	26	0	4.7 (abdominal pain[a])	15 (upper GI AE[a])
			Diclofenac SR 100–150	38 [p ≤ 0.02]	2	11.6 (abdominal pain[a])	25 (upper GI AE[a]) [p ≤ 0.01]
Fleischmann et al.[48] (1997)	R, DB, PC (4 wk)	OA (279)	Nabumetone (1500)	17.2[c]	NR	2.2 (abdominal pain[c])	
			Naproxen (1000)	19.6[c]		9.8 (abdominal pain[c]) [p ≤ 0.05]	
Krug et al.[49] (2000)	R, DB (3 mo)	RA (346)	Nabumetone (2000)	27[a]	0	4.6 (abdominal pain[a]) 1 (upper abdominal pain[a])	
			Naproxen (1000)	19[a]	0	6.4 (abdominal pain[a]) 5 (upper abdominal pain[a])	

a Considered related or possibly related to study treatment.

b Considered related or probably related to study treatment.

c Considered to be related to treatment.

DB = double blind; **EB** = endoscopy-blinded; **NR** = not reported; **NS** = not statistically significant; **OA** = osteoarthritis; **OL** = open label; **PC** = placebo-controlled; **PUBs** = perforations, ulcers and bleeds; **R** = randomized; **RA** = rheumatoid arthritis; **SR** = slow release.

Table II. Incidence of gastrointestinal (GI) adverse events (AEs) with nabumetone vs conventional NSAIDs in randomized, controlled endoscopy trials

Study (y)	Study design (duration)	Diagnosis (no. of pts)	Comparators/dosage (mg/day)	Overall incidence of GI AEs (% of pts)	Number of ulcers/lesions (specified) [p-value]
Roth et al.[52] (1993)	R, EB (12 wk)	OA (171)	Nabumetone (1000)	NR	1 (number of ulcers >5 mm)
			Ibuprofen/misoprostol (2400/0.8)	NR	0 (number of ulcers >5 mm)
			Ibuprofen (2400)	NR	8 (number of ulcers >5 mm) [$p \leq 0.01$ vs nabumetone and ibuprofen/misoprostol]
Bianchi Porro et al.[51] (1995)	R, DB (4 wk)	RA (52)	Nabumetone (1000)	NR	9 (gastric and/or duodenal mucosal lesions)
			Naproxen (1000)		40 (gastric and/or duodenal mucosal lesions) [$p \leq 0.01$]
Becvar et al.[50] (1999)	R, OL, EB (12 wk)	OA (395)	Nabumetone (1500)	11	Significantly less worsening in oesophageal endoscopy grade [$p = 0.007$] and stomach mucosal grade [$p < 0.001$] following nabumetone vs diclofenac treatment
			Diclofenac SR (100)	16.5	

DB = double blind; **EB** = endoscopy-blinded; **NR** = not reported; **NS** = not statistically significant; **OA** = osteoarthritis; **OL** = open label; **PC** = placebo controlled; **R** = randomized; **RA** = rheumatoid arthritis; **SR** = slow release.

enrolling >4000 patients that was designed to mimic routine clinical practice.[42] The incidence of drug-induced adverse events was similar in all groups. However, a significantly lower incidence of abdominal pain and clinically diagnosed gastritis was observed with nabumetone compared with diclofenac (table I) and a lower incidence of dyspepsia compared with naproxen (6.6% vs 12.2%, respectively), whereas there was a higher incidence of diarrhoea in patients treated with nabumetone (7%) versus comparator NSAIDs (between 0.9% and 5.4%).[42]

A 6-month study comparing nabumetone with slow-release diclofenac (diclofenac SR) demonstrated significantly less upper GI toxicity with nabumetone over long-term treatment (table I), mostly due to lower rates of upper abdominal pain and dyspepsia.[47] In addition, significantly fewer patients withdrew from the nabumetone arm because of upper GI adverse events (5%) than in the diclofenac SR group (14%; $p < 0.002$).[47]

Randomized, controlled trials assessing endoscopic outcomes have also indicated significantly better GI tolerability with nabumetone versus comparator conventional NSAIDs (table II).[50-52] The significantly lower risk of endoscopically detectable ulcers in nabumetone-treated patients compared with those administered naproxen is maintained over long-term (5 years') treatment.[53]

With regard to the incidence of PUBs in these comparative studies, a significantly lower risk was found with nabumetone versus conventional NSAIDs (0.03% vs 0.5%; $p = 0.001$) in a large-scale, randomized trial.[42] This difference arose from significantly higher incidences of PUBs in patients treated with diclofenac or ibuprofen compared with patients in the nabumetone arm (table I).

3.1.1 Pooled Data and Meta-Analyses

The GI tolerability of nabumetone has been examined in pooled analyses and meta-analyses (table III).

The first analysis of pooled data from eight post-marketing, randomized, controlled trials of up to 6 months' duration, including 4471 patients randomly allocated to nabumetone treatment and 2261 patients treated with comparator conventional NSAIDs, demonstrated that the cumulative frequency of PUBs was substantially lower with nabumetone than diclofenac, ibuprofen, naproxen, piroxicam and indomethacin (figure 2).[54] The Kaplan-Meier life test showed a cumulative frequency of clinically detected ulcers and bleeding of 0.03% (95% CI 0.0, 0.08) with nabumetone and 0.8–1.8% (point estimate 1.4%; 95% CI 0.5, 2.4) with compa-

Table III. Adverse gastrointestinal events in rheumatoid arthritis and osteoarthritis patients treated with nabumetone or conventional NSAIDs: data from pooled and meta-analyses

Studies (y)	Sources of data	No. patients	Nabumetone	Comparator conventional NSAIDs
			Cumulative frequency of clinically detected PUBs (95% CI)[a]	
Lipani et al.[54] (1995)	Seven post-NDA studies	n = 2368 (1184 nabumetone; 1184 comparators[b])	0%	0.4–1.8%
Eversmeyer et al.[50] (1993)		n = 4364 (3287 nabumetone, 1077 comparators[c])	0.03%	0.4–1.3%
	Combined	n = 6732 (4471 nabumetone, 2261 comparators)	0.03% (0.0, 0.08)	0.8–1.8%; point estimate 1.4% (0.5, 2.4)
			Ulcer formation event rate per 100 patient-years (95% CI)	
Freston[55] (1999)	NDA studies	n = 1677	0.42 (0.3, 0.6) 0.1 [complicated ulcers]	NR
	Seven post-NDA studies	n = 2368 (1184 nabumetone; 1184 comparators[b])	0 (0, 0.98)	3.69 (1.5, 6.0)
Eversmeyer et al.[50] (1993)		n = 4364 (3287 nabumetone, 1077 comparators[c])	0.15 (0, 0.4)	2.72 (0.9, 5.0)
			PUBs event rate per 100 patient-years (95% CI)	
Huang et al.[56] (1999)	Six non-endoscopic studies	n = 5972 (4098 nabumetone, 1874 comparators[d])	0.087	2.882
			OR 35.5 (5.3, 757.5)	
	Four endoscopic studies	n = 236 (117 nabumetone, 119 comparators[e])	2.5	20.9
			OR 10.11 (2.8, 43.5)	

a Kaplan-Meier Life Test.

b Diclofenac, diclofenac SR, indomethacin, piroxicam and naproxen.

c Ibuprofen, piroxicam, diclofenac and naproxen.

d Naproxen, diclofenac, diclofenac SR, piroxicam, aspirin (acetylsalicylic acid) and indomethacin.

e Diclofenac, naproxen and ibuprofen.

NDA = new drug application; **PUBs** = perforations, ulcers or bleeds; **SR** = slow release.

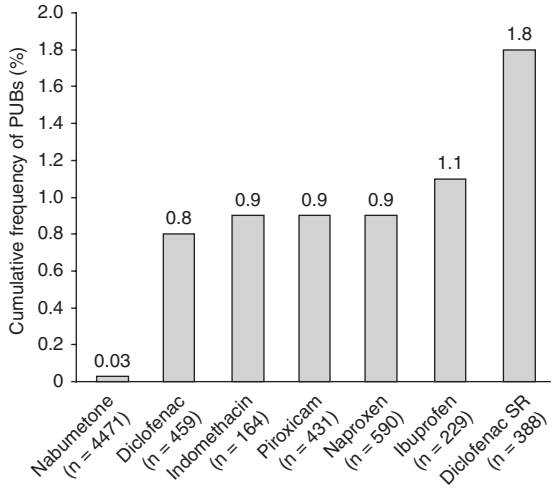

Fig. 2. Cumulative frequency of clinically detected perforations, ulcers and bleedings (PUBs) in postmarketing clinical trials of NSAID therapy in patients with osteoarthritis or rheumatoid arthritis, based on Kaplan-Meier Life Test. **SR** = slow release (Reproduced from Lipani and Poland,[54] with kind permission from Springer Science and Business Media.)

rator NSAIDs (table II).[54] The lack of overlap between 95% CIs for nabumetone and the comparator NSAIDs suggests this difference was statistically significant.

This conclusion was supported by a further analysis conducted on a complete database of nabumetone studies provided by the manufacturer of nabumetone in the US in 1999.[55] Pooled data from clinical trials contained in the nabumetone New Drug Application (NDA) encompassing information on 1677 RA or OA patients and 4033 patient-years of nabumetone exposure showed that 17 nabumetone-treated patients developed ulcers (25% of which were complicated).[55] The Kaplan-Meier cumulative incidence rate at 6 years was 2.35% (95% CI 1.1, 3.6). The cumulative life-table of ulcer formation with nabumetone was essentially linear, allowing the event rate to be expressed in terms of events per 100 patient-years of exposure. As such, the incidence rate of ulcers in nabumetone treated patients was 0.42% (95% CI 0.3, 0.6) per 100 patient-years.[55] Data derived from post-NDA trials found markedly lower rates of ulcer formation with nabumetone compared with conventional NSAIDs (table III).[55]

Furthermore, a meta-analysis of comparative studies reporting PUB outcomes supported the consistently superior GI tolerability profile of nabumetone over other conventional NSAIDs.[56] In eight non-endoscopic comparative trials (n = 7468 patients) included in the meta-analysis, overall rates of GI adverse events and PUBs were significantly lower with nabumetone than with comparator NSAIDS (25.3% vs 28.2%; $p = 0.007$, and 0.062% vs 0.916%; $p < 0.0001$, respectively). Stratification by treatment duration showed that the significant difference between nabumetone and comparator NSAIDs regarding overall GI adverse events was apparent only in patients treated for 6 months, while the significant difference in the rate of PUBs was consistent over treatment durations of 3–6 months. Analysis of event rate per 100 patient-exposure years (data derived from six studies) showed that the risk of PUBs was 35.5-fold lower with nabumetone than comparator NSAIDs, although the wide 95% CI should be noted when interpreting these results (table III).[56] As expected, PUBs were reported in higher proportions of patients in the four endoscopic comparative trials than in the non-endoscopic studies, occurring in 2.6% of patients treated with nabumetone and 21% of patients treated with comparator conventional NSAIDs. Data on the event rate per 100 patient-exposure years showed that the risk of endoscopically detected PUBs was 10-fold lower with nabumetone, however, the 95% CI was wide (table III). Finally, treatment-related hospitalizations were nearly 4-fold lower with nabumetone than with conventional NSAIDs (odds ratio [OR] 3.7; 95% CI 1.3, 10.7).[56]

A pooled analysis of two long-term, randomized studies comparing 6 months' nabumetone 1500–2000 mg/day with slow-release diclofenac or piroxicam found that the risk of serious GI adverse events, i.e. ulceration or bleeding, was significantly reduced in patients treated with nabumetone (1.1% vs 4.3%; $p < 0.001$).[57]

3.1.2 Observational Studies

Additional information regarding rates of GI adverse events with nabumetone and other NSAIDs comes from epidemiological studies, including the Tayside Medicine Monitoring Unit Study[58] and the

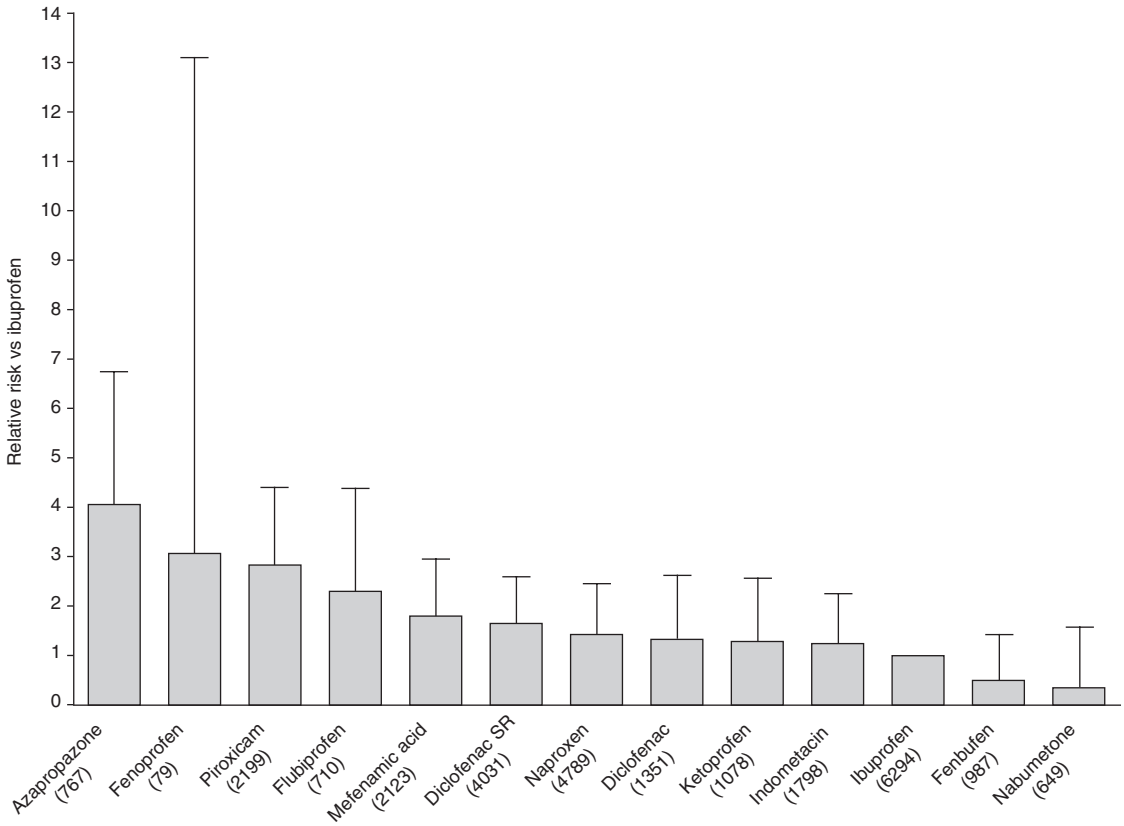

Fig. 3. Relative risk (with the upper limit of the 95% CIs indicated by the T bars), compared with ibuprofen, of upper gastrointestinal toxicity with individual NSAIDs.[58] The numbers in parentheses represent the patient-years of exposure for each NSAID. **SR** = slow release.

Arthritis, Rheumatism and Aging Medical Information System (ARAMIS) database.[59]

The population-based Tayside Medicine Monitoring Unit study compared rates of upper GI adverse events in 52 293 patients aged >50 years who had received treatment with one or more NSAID during the period January 1989 to December 1991 (mean 5.7 prescriptions per patient) with 73 792 control subjects who did not receive NSAID treatment during this period. The risk of upper GI events rose nearly 4-fold in NSAID-treated patients compared with controls (relative risk [RR] 3.94; 95% CI 3.21, 4.83).[58] Point estimates for the relative risk of upper GI toxicity, relative to ibuprofen, varied across the different individual NSAIDs; the lowest risk level was seen with nabumetone (figure 3).[58]

The prospective, observational ARAMIS study has been used to examine the rates of hospitalizations and deaths due to GI events in RA and OA patients treated with NSAIDs.[59] Data derived from 3883 RA patients revealed an annual incidence for GI complications resulting in hospitalization of 1.31% in patients taking NSAIDs and 0.19% in patients not taking NSAIDs (RR while taking NSAIDs: 6.77).[59] Among 1283 OA patients, serious GI adverse events requiring hospitalization occurred at an annual rate of 0.73% in those patients receiving NSAID treatment and 0.29% in patients not taking NSAIDs (RR: 2.51).[59] Consistent with findings from the Tayside Medicine Monitoring Unit study, point estimates for the adjusted rate of serious GI adverse events across individual NSAIDs showed lowest risk with nabumetone (figure 4).[60]

Furthermore, a population-based historical cohort study reported that nabumetone was associated with a lower risk of admission to hospital with a primary diagnosis of peptic ulcer disease than other widely prescribed nonselective NSAIDs.[61] Data were obtained from four linked health service databases in Saskatchewan, Canada, regarding all patients (n = 18 424) who filled a prescription for one of four NSAID treatments (naproxen, diclofenac plus a gastroprotective agent dispensed separately, diclofenac/misoprostol combination tablet or nabumetone) during 1995. The crude rates of hospitalization for nabumetone and the combination tablet were significantly lower (0.4% and 0.2%, respectively) than for naproxen and diclofenac plus a gastroprotective agent (1.0% for both). Compared with nabumetone, hospitalizations for peptic ulcer increased by 3.1-fold for naproxen (adjusted OR 3.1; 95% CI 1.3, 7.1) and 2.7-fold for diclofenac plus a cytoprotective agent (adjusted OR 2.7; 95% 1.2, 6.0). Although compared with the combination tablet there were more hospitalizations for peptic ulcer with nabumetone, the difference was not statistically significant (adjusted OR 2.6; 95% CI 1.0, 6.6).[61]

3.1.3 High-Risk Patients

NSAID use is particularly common in older patients, who are a patient group at increased risk of developing adverse reactions to treatment.[8] Data from elderly patients enrolled in randomized trials suggest nabumetone offers better GI tolerability than other conventional NSAIDs in this high-risk patient group.[43,62] In the subgroup of elderly patients enrolled in a 12-week study, nabumetone-treated subjects were significantly less likely to experience abdominal pain than those treated with

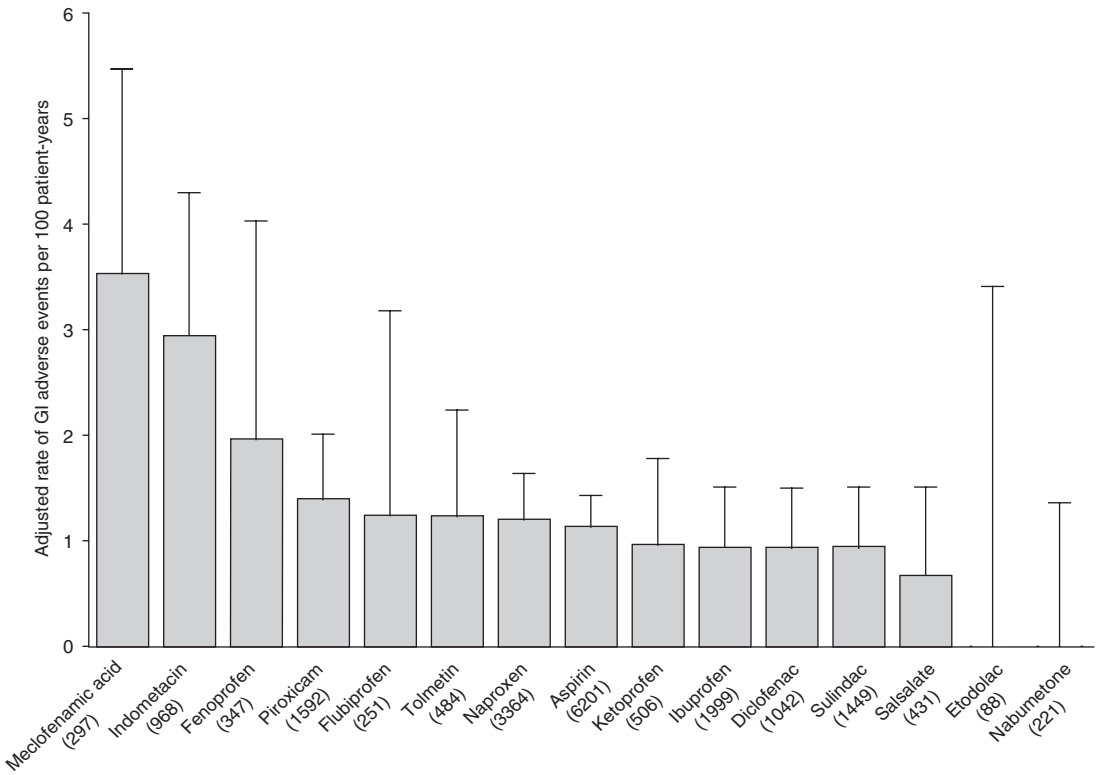

Fig. 4. Adjusted rate (with the upper limit of the 95% CIs indicated by the T bars) of serious gastrointestinal (GI) adverse events (AEs) per 100 patient-years exposure to individual NSAIDs in the ARAMIS database. Serious events were defined as gastrointestinal bleeds and other clinically significant events requiring hospitalization.[60] The numbers in parentheses represent the patient-years of exposure for each NSAID.

ibuprofen or diclofenac (4.1% vs 8.5% and 13.1%, respectively; $p < 0.05$ for both comparisons); however, as seen in the overall study population, diarrhoea was significantly more common in the nabumetone group.[43] In another 12-week study in 335 elderly OA patients (mean age 72 years), GI bleeding occurred in two diclofenac-treated patients and in none of the patients treated with nabumetone.[62]

Co-administering a gastroprotective agent, such as misoprostol, with an NSAID is one strategy used to ameliorate the GI toxicity of treatment in patients at risk for ulcer disease.[3] Therefore, it is interesting to compare the GI tolerability of this strategy with that of nabumetone treatment. There is some evidence that older patients treated with nabumetone show at least comparable GI tolerability to those in whom NSAID therapy has been supplemented with a gastroprotective agent. A 12-week endoscopic study involving 171 patients with OA aged ≥60 years showed that nabumetone was significantly less ulcerogenic than ibuprofen alone and equivalent in ulcerogenicity to co-therapy of ibuprofen with misoprostol.[52] Further to this, a decision-analysis model comparing treatment with nabumetone or ibuprofen administered with or without misoprostol in older patients indicated that the use of nabumetone would reduce overall medical resource utilization,[63] and a pharmacoeconomic analysis of direct medical costs of NSAID treatment in elderly OA patients found that the lower costs associated with nabumetone compared with ibuprofen and ibuprofen/misoprostol were due in part to the lower cost of treating drug-related adverse events.[64]

Somewhat conflicting results were seen in a 6-week, placebo-controlled endoscopic study that compared the upper GI safety of a fixed-dose combination tablet of diclofenac 75 mg with misoprostol 200 μg administered twice daily with that of nabumetone 1500 mg/day in 1203 patients with a documented history of endoscopically confirmed gastroduodenal ulcers or >10 gastroduodenal erosions.[65] The combined incidence of gastric and duodenal endoscopically detected ulcers was significantly lower in the twice daily combination tablet arm (4%) and in the placebo arm (5%) than in the nabumetone arm (11%). However, examination of serious symptomatic GI events (bleeding, perforation and/or gastric outlet obstruction) showed a low incidence with both drugs (one patient [0.2%] with nabumetone and two patients [0.5%] with diclofenac plus misoprostol).[65] A small, 24-week, randomized clinical trial comparing nabumetone 1000–1500 mg/day (n = 45) versus co-therapy of naproxen 500–1000 mg/day and misoprostol 400 μg/day (n = 45) in patients with a recent history of gastroduodenal ulcer bleeding found the two treatment strategies did not differ significantly regarding the incidence of upper GI bleeding (6.7% and 22.2% respectively, $p = 0.069$).[66] Even though the lack of significance is likely a result of the small sample size, the noteworthy proportion of bleeding recurrences indicates that neither treatment was adequate for patients with a history of ulcer bleeding and suggests that nabumetone, as with other NSAIDs, should be avoided in patients at very high GI risk.

3.1.4 Mortality

Data from the ARAMIS study showed that, in the US, the incidence of deaths related to GI toxicity in RA patients was 0.22% per person-year while exposed to NSAIDs, compared with 0.05% while not taking NSAIDs, which translated in to a relative risk for death while taking NSAIDs of 4.21.[59] Against this background, an epidemiological study using data from four linked health service databases in Saskatchewan, Canada, has shown that nabumetone and the diclofenac/misoprostol combination tablet are associated with lower all-cause mortality than other conventional NSAIDs.[67] In a multivariate model, the adjusted risk for all cause mortality was similar in patients treated with the combination tablet relative to nabumetone-treated patients (OR 1.39; 95% CI 0.90, 2.14), but was nearly 2-fold higher (OR 1.96; 95% CI 1.25, 3.07) in those treated with diclofenac and a separate gastroprotective agent and nearly 3-fold higher in those treated with naproxen (OR 2.95; 95% CI 1.88, 4.62). This finding suggests that the favourable GI tolerability profile of nabumetone may contribute to a lower mortality rate, although a definitive conclusion cannot be drawn in the absence of cause-specific mortality data.

Table IV. Incidence of gastrointestinal (GI) adverse events (AEs) with nabumetone vs cyclo-oxygenase-2 inhibitors in randomized, controlled trials

Study (y)	Study design (duration)	Diagnosis (no. of pts, age)	Comparators (mg/day)	Incidence of GI AEs (% pts)		
				overall	PUBs	other (specified)
Truitt et al.[71] (2001)	R, PC (6 wk)	OA (340, ≥80 years)	Nabumetone (1500)	NR	0	4.3 (nausea)
			Rofecoxib (12.5)	NR	0	3.4 (nausea)
			Rofecoxib (25)	NR	0	5.4 (nausea)
			Placebo	NR	0	1.9 (nausea)
Kivitz et al.[70] (2004)	R, DB, PC (6 wk)	OA (1042)	Nabumetone (1000)	NR	2[a]	5.1 (GI nuisance AE)[b]
			Rofecoxib (12.5)	NR	0	6.8 (GI nuisance AE)[b]
			Placebo	NR	0	6.7 (GI nuisance AE)[b]
Weaver et al.[72] (2006)	R, DB, PC (6 wk)	OA (978)	Nabumetone (1000)	14.5	NR	5.1 (GI nuisance AE)[b]
			Rofecoxib (12.5)	16.2	NR	6.7 (GI nuisance AE)[b]
			Placebo	7.7	NR	4.1 (GI nuisance AE)[b]

a GI bleeding not considered to be related to the study drug.

b Acid reflux, dyspepsia, epigastric pain, heartburn, nausea or vomiting.

DB = double blind; **NR** = not reported; **OA** = osteoarthritis; **PC** = placebo controlled; **PUBs** = perforations, ulcers and bleeds; **R** = randomized.

3.2 Comparison with COX-2 Selective Inhibitors

The COX enzyme exists in at least two distinct isoforms, COX-1 and COX-2. The COX-2 isoform was initially thought to be strictly induced by inflammatory stimuli and involved in prostanoid synthesis at sites of inflammation, while COX-1 was thought to be constitutively expressed and associated with production of prostaglandins involved in gastroprotection. These ideas, though having since been found to be overly simplistic, led to the development of COX-2 selective agents (coxibs) aimed at providing effective analgesia and anti-inflammatory effects without incurring GI toxicity.[2,55]

Selective COX-2 inhibitors offer generally similar efficacy but a lower incidence of serious GI adverse events compared with conventional NSAIDs.[68,69] Only limited data are available specifically comparing GI tolerability outcomes for nabumetone and COX-2 selective inhibitors. In three randomized, 6-week trials in OA patients, nabumetone was found to have a generally similar or improved adverse events profile compared with rofecoxib and a similar GI tolerability (table IV).[70-72] In a study enrolling 1042 OA patients, nuisance GI adverse event rates did not differ significantly between nabumetone, rofecoxib and placebo treatment groups and there were no cases of GI perforation or ulceration.[70] In a second study in over 900 OA patients, adverse events were significantly more frequent in the rofecoxib arm (56.4% vs 49.2% of nabumetone-treated patients; $p = 0.045$), as were serious adverse events and treatment discontinuations arising from adverse events, and more patients experienced a thrombotic cardiovascular serious adverse event with selective COX-2 inhibitor therapy (five rofecoxib-treated patients and one nabumetone-treated patient).[72] Overall, digestive system adverse events occurred in similar proportions of patients in the rofecoxib and nabumetone groups, as did GI nuisance events (table IV). In both studies, rofecoxib showed greater efficacy than nabumetone 1000 mg/day. By contrast, the third trial enrolling 340 elderly patients (≥80 years) with symptomatic OA demonstrated similar treatment responses for nabumetone 1500 mg/day, rofecoxib 12.5 mg/day and rofecoxib 25 mg/day. Regarding

the overall safety profile, no significant differences were observed between active treatment groups.[71] It is worthy of note that in the two studies in which nabumetone dose was 1000 mg/day, rofecoxib showed greater efficacy. By contrast, in the trial in which nabumetone dose was 1500 mg/day, nabumetone demonstrated similar treatment responses to rofecoxib 12.5 mg/day and rofecoxib 25 mg/day. This is in line with other studies indicating that appropriate symptom control with nabumetone requires an individual dose adjustment within the therapeutic dose range (1–2 g/day) and that more than half of patients with OA or RA require daily doses above 1000 mg/day.[9,43] While the available data, although limited, did not demonstrate a GI safety advantage of rofecoxib over nabumetone, establishing whether the risk of PUBs with nabumetone is similar to that of COX-2 selective inhibitors would require an appropriate long-term trial.

4. Other Safety Concerns

4.1 Cardiovascular Safety

Although NSAIDs pose primarily a GI hazard, their influence on cardiovascular health has been much debated and cannot be omitted from any discussion on the safety of these agents. Whilst the COX-2 selective inhibitors were developed to improve GI tolerability, cardiovascular safety data have emerged leading to the voluntary worldwide withdrawal of rofecoxib in 2004.[73] Valdecoxib too was taken off the US and European market in 2005 because of similar cardiovascular concerns, in addition to an increased risk of serious skin reactions.[73] More recently, etoricoxib marketing authorization has been denied in the US because of the significant cardiovascular risk associated to its use. Consequently, adverse cardiovascular outcomes, particularly arterial thrombotic events, in patients receiving COX-2 selective agents have been examined in numerous retrospective analyses.

There is evidence that the cardiovascular hazard of coxibs is a class effect. This has been recognized by regulatory authorities, including the European Agency for the Evaluation of Medicinal Products and the US FDA.[74] Moreover, nonselective NSAIDs may also have the potential for causing atherothrombotic complications, possibly through inducing an increase in systolic blood pressure.[73] It is worthy of note that unlike the European Medicines Agency, the FDA requires that all NSAIDs carry a black-box warning on the package insert advising patients of the potential increased cardiovascular risk.[74] Interestingly, a meta-analysis of published and unpublished tabular data from randomized, controlled trials indicated that high-dose regimens of diclofenac and ibuprofen, but not high-dose naproxen, led to an excess risk of atherothrombosis similar to that of coxibs.[75] However, another meta-analysis of randomized placebo-controlled trials found no significant effect of nonselective NSAIDs on the risk for cardiovascular events or death, although a small adverse effect could not be excluded.[76] Furthermore, no difference was seen for naproxen compared with other non-naproxen NSAIDs, suggesting that naproxen does not have any significant cardioprotective effect.[76]

Epidemiological studies comparing conventional NSAID-treated patients with non-users of NSAIDs or patients with remote use of NSAIDs that report specific outcomes for nabumetone have consistently failed to show an increase in cardiovascular risk with this agent.[77-81] A retrospective case-control analysis encompassing 8688 patients with first-time myocardial infarction (MI) and 33 923 controls (matched by age, gender, index date and general practice attended) identified from the UK General Practice Research Database found that current use of a conventional NSAID was not significantly associated with first-time MI (OR 1.07; 95% CI 0.96, 1.19).[78] The point estimate for risk of first-time MI was lowest with nabumetone (0.62; 95% CI 0.25, 1.53) and highest with fenbufen (3.08; 95% CI 1.18, 8.06). A nationwide case control study exploring the potential relationship between NSAID use and first MI was conducted in Finland during 2000–2003.[79] A total of 33 309 first-time MI cases were identified from the national Hospital Discharge Register and matched by age, gender, hospital catchment area and index-date to 138 949 controls. Overall, current use of NSAIDs conferred a clear but moderate increase in risk (adjusted OR 1.40; 95% CI 1.33, 1.48). Current use of the COX-2 selective agent's etoricoxib or rofecoxib, but not celecoxib, was found to significantly elevate the risk of a first-time MI.

Among the conventional agents, MI risk was significantly increased with current use of nimesulide, indomethacin, ibuprofen, diclofenac, and to a lesser extent with naproxen, but not with piroxicam, etodolac, ketoprofen or nabumetone.

A nested case control study using data from patients with arthritis from the California Medicaid programme who were treated with an NSAID between 1 January 1999 and 30 June 2004 examined the potential association between NSAID use and MI.[81] For each case of MI, four age-, gender- and index date-matched controls were included. There were a total of 15 343 cases of MI during 2 356 885 person-years of follow-up. By multivariate analysis, adjusted for confounding risk factors including concomitant aspirin treatment, the risk of MI with current nabumetone versus remote NSAID use was not significant (OR 0.83; 95% CI 0.60, 1.14; p = 0.26), but risk was significantly increased with the COX-2 selective agents (celecoxib and rofecoxib) and some conventional NSAIDs (indomethacin, sulindac, ibuprofen and meloxicam). A separate nested case control study examining the risk of MI or sudden cardiac death associated with NSAID treatment failed to find evidence of increased risk with nabumetone.[80] The cohort included 1 394 764 patients who received at least one NSAID prescription between 1 January 1999 and 31 December 2001. From this cohort, 8143 cases of MI or sudden cardiac death were identified; each case was matched with four controls based on age, gender and health plan region (n = 31 496). Compared with remote NSAID use, current use of nabumetone was not associated with increased cardiac risk (adjusted OR 1.09 (95% CI 0.81, 1.47), with similar findings for diclofenac, etodolac, ibuprofen, piroxicam and sulindac. In contrast, current use of indomethacin or naproxen significantly increased the risk of MI or sudden cardiac death.

4.2 Renal Effects

Renal prostaglandins, particularly COX-2 derived prostaglandins, have a major role when pathological states compromise physiological processes in the kidney.[82] These prostanoids help to maintain renal blood flow and glomerular filtration rate in patients with chronic renal insufficiency or low effective plasma volume by antagonising arteriolar vasoconstriction. In such patients, both conventional and COX-2 selective NSAIDs may precipitate acute renal failure. Furthermore, renal prostaglandins modulate sodium and water homeostasis. As a result, all NSAIDs may cause sodium retention, possibly leading to oedema, increased blood pressure or cardiac decompensation in patients with pre-existing heart failure.[54,83-85]

Clinical studies specifically investigating the renal effects of nabumetone have generally been conducted in patients at low risk for adverse renal events and show that such patients experience no problematic effects on renal function when taking nabumetone.[11] In clinical trials in patients with arthritis, the incidence of oedema in those treated with nabumetone has been found to be low (0–1.7%) and not significantly different from that with placebo[70,71] or comparator conventional NSAIDs.[42,46]

Nabumetone treatment was associated with modest increases in daytime and night-time blood pressure (+2.9/+3.2 and +5/+4.9 mmHg, respectively, in systolic/diastolic blood pressure) in a study in patients with OA who had stable arterial hypertension.[86] However, nabumetone was found to have an incidence of clinically significant elevations in systolic blood pressure similar to that of placebo in a hypertensive patients stabilized on ACE inhibitor therapy in another study.[87] An examination of spontaneous adverse events reports submitted to the FDA regarding nabumetone during its first 3 years of marketing (February 1992 to January 1995) found, among 16 million prescriptions, no cases of serious hypertension requiring hospitalization attributed to this drug; corresponding rates of hypertension leading to hospitalization per 10 million prescriptions for celecoxib and rofecoxib were 1.3 and 5.0, respectively.[88] Nevertheless, as with other NSAIDs, blood pressure as well as renal function should be monitored regularly in patients receiving long-term therapy with nabumetone.

4.3 Hepatic Effects

The use of NSAIDs and coxibs has been associated with liver toxicity, the underlying causes of which are not fully understood. Diclofenac, nimesulide and sulindac appear to be associated with the highest level of risk among individual NSAIDs.[89] For example, diclofenac, but not other conventional

NSAIDs and COX-2 selective agents (naproxen, ibuprofen, celecoxib, valdecoxib or meloxicam), was associated with a significant increase in risk of elevated aminotransferase levels (>3 times upper limit of normal) and liver-related treatment discontinuation in a systematic review of randomized trials.[90] Notably, no agent was associated with a significantly increased risk of liver-related hospitalizations or deaths in this study, a finding supported by a systematic review of population-based epidemiological studies reporting clinically significant liver toxicity events, i.e. those resulting in hospitalization or death.[91] Recently the European Agency for the Evaluation of Medicinal Products has recommended the withdrawal of the COX-2 inhibitor lumiracoxib, as well as restricted use of the NSAID nimesulide, because of liver toxicity.[92,93] Previously lumiracoxib had been withdrawn in Canada, and the marketing authorization had been rejected in the US.

Focusing on nabumetone, the incidence of marked elevations in liver transaminase levels in clinical trials of this agent has been low (≤1%), including in elderly patients[11,42,43,47,49,62,65,94,95] and significantly lower than observed with diclofenac.[42,43,47,62] During its first 7 years on the market, the cumulative rates of spontaneous reports to the FDA of any hepatic adverse event and hepatic events with serious sequelae (fatal, life-threatening or requiring hospitalization) were 3.4 and 1.3 per million nabumetone prescriptions, respectively.[96] These rates were markedly lower than for diclofenac (13.6 and 4.3 for any and for serious adverse events, respectively) and generally similar to those for naproxen and piroxicam (1.8–2.9 and 0.2–1.2).

5. Conclusions

NSAID-induced GI toxicity reflects a complex interplay of events including topical irritant effects of the drug on GI cells as well as prostaglandin depletion arising form both local and systemic COX-1 inhibition. As a result, there is an altered permeability of the GI epithelium and a compromised mucus-bicarbonate layer, leading to increased vulnerability of the GI wall to chemical damage exerted by luminal aggressive agents, such as the hydrogen ions from hydrochloric acid, digestive enzymes, bile acids, pancreatic juices or bacterial-derived toxins. Nabumetone is a non-acidic prodrug whose pharmacologically active metabolite, 6-MNA, does not undergo biliary secretion and therefore enterohepatic recirculation. Data arising from human whole blood assays indicate that 6-MNA is equiselective for COX-1 and COX-2. As a result of these unique combination of pharmacological and chemical properties, nabumetone appears to be associated with fewer serious GI adverse effects whilst retaining analgesic and anti-inflammatory efficacy equivalent to that of other conventional NSAIDs and offers a GI tolerability profile that might be similar to that of the COX-2 selective inhibitors.

Adverse cardiovascular outcomes appear to be a class effect of the coxibs, and conventional NSAIDs may also have the potential for causing atherothrombotic complications. However, based on available data, there is no major concern regarding the cardiovascular safety of nabumetone. Similarly, there is no particular concern about the nephrotoxic and hepatotoxic potential of nabumetone. Nonetheless, the potential for adverse drug reactions remains, and hence nabumetone, as with any NSAID, should be used at the lowest dose, which is effective for each patient, and for the shortest time necessary to control symptoms.

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