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Nabumetone

Therapeutic Use and Safety Profile in the Management of Osteoarthritis and Rheumatoid Arthritis

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Contents

Abstract

Nabumetone is a nonsteroidal anti-inflammatory prodrug, which exerts its pharmacological effects via the metabolite 6-methoxy-2-naphthylacetic acid (6-MNA). Nabumetone itself is non-acidic and, following absorption, it undergoes extensive first-pass metabolism to form the main circulating active metabolite (6-MNA) which is a much more potent inhibitor of preferentially cyclo-oxygenase (COX)-2. The three major metabolic pathways of nabumetone are *O*-demethylation, reduction of the ketone to an alcohol, and an oxidative cleavage of the side-chain occurs to yield acetic acid derivatives. Essentially no unchanged nabumetone and <1% of the major 6-MNA metabolite are excreted unchanged in the urine from which 80% of the dose can be recovered and another 10% in faeces.

Nabumetone is clinically used mainly for the management of patients with osteoarthritis (OA) or rheumatoid arthritis (RA) to reduce pain and inflammation. The clinical efficacy of nabumetone has also been evaluated in patients with ankylosing spondylitis, soft tissue injuries and juvenile RA.

The optimum oral dosage of nabumetone for OA patients is 1g once daily, which is well tolerated. The therapeutic response is superior to placebo and similar to nonselective COX inhibitors. In RA patients, nabumetone 1g at bedtime is optimal, but an additional 0.5–1g can be administered in the morning for patients with persistent symptoms. In RA, nabumetone has shown a comparable clinical efficacy to aspirin (acetylsalicylic acid), diclofenac, piroxicam, ibuprofen and naproxen.

Clinical trials and a decade of worldwide safety data and long-term postmarketing surveillance studies show that nabumetone is generally well tolerated. The most frequent adverse effects are those commonly seen with COX inhibitors, which include diarrhoea, dyspepsia, headache, abdominal pain and nausea.

In common with other COX inhibitors, nabumetone may increase the risk of GI perforations, ulcerations and bleedings (PUBs). However, several studies show a low incidence of PUBs, and on a par with the numbers reported from studies with COX-2 selective inhibitors and considerably lower than for nonselective COX inhibitors. This has been attributed mainly to the non-acidic chemical properties of nabumetone but also to its COX-1/COX-2 inhibitor profile. Through its metabolite 6-MNA, nabumetone has a dose-related effect on platelet aggregation, but no effect on bleeding time in clinical studies. Furthermore, several short-term studies have shown little to no effect on renal function.

Compared with COX-2 selective inhibitors, nabumetone exhibits similar anti-inflammatory and analgesic properties in patients with arthritis and there is no evidence of excess GI or other forms of complications to date.

Nabumetone is one of the most commonly used NSAIDs in the world today. The popularity of this drug lies in both its unique pharmacokinetic profile and special safety features in pharmacodynamic terms. The recent introduction of selective cyclo-oxygenase (COX)-2 inhibitors and their increasing clinical use has led to a need for a comparative overview of nabumetone versus the current array of

NSAIDs. Hence, this article reviews the pharmacology, pharmacokinetic disposition, dosage recommendations, adverse effects, drug interactions and efficacy of nabumetone in patients with selected rheumatic disorders especially in comparison with other NSAIDs.

Medical literature dealing with nabumetone published in any language since 1983 was identified by database searches in Medline and EMBASE. The reference lists of published articles were used to identify additional references. The company developing the drug supplemented bibliographical information, including contributory unpublished data on request.[1] Nabumetone and osteoarthritis (OA) or rheumatoid arthritis (RA) were used as search terms and searches were last updated January 2004. The selection of studies included in this review was based mainly on whether the methods section of the trials described the inclusion of patients with OA and RA. Large, well controlled trials with appropriate statistical methodology were preferred when available. Studies with relevant pharmacodynamic and pharmacokinetic data were also included.

1. Clinical Pharmacology of Nabumetone

1.1 Cyclo-oxygenase (COX) Isoenzymes

COX has the structural features of a 'housekeeping' enzyme and its expression may also be regulated.[2-4] From the early suggestions that there appeared to be more than one form of COX,[5-7] genomic studies resulted in identification of a novel gene that was highly homologous to the gene for the original COX or COX-1.[8-10] This novel isoform was termed COX-2. Further research demonstrated that COX-2 could be up-regulated by cytokines, growth factors and tumour promoters.[8-12]

The expression of both COX-1 and COX-2 is increased in inflammatory processes and in atherosclerotic plaques.[13,14] The catalytic activities and tertiary structures of COX-1 and COX-2 are largely similar,[15-17] but COX-2 has a broader affinity for substrates because the hydrophobic channel leading to the active site of this enzyme is larger. In early research COX-1 was generally considered as a constitutive enzyme and COX-2 as an inducible enzyme for prostanoid formation during different pathological conditions. However, later research has demonstrated that this is an oversimplification since COX-2 may also act as a constitutive enzyme.

COX-1 and COX-2 are thus differentially expressed in different tissues during physiological and various pathophysiological conditions, which are of major relevance to the clinical effects of drugs inhibiting the different COX isoforms.

1.2 COX Inhibitory Properties of Nabumetone

Nabumetone itself is a prodrug but, while the parent compound is a weak COX inhibitor, the main active metabolite, 6-methoxy-2-naphthylacetic acid (6-MNA), strongly inhibits COX.[18-21] Therefore, it is important to note that the data regarding its COX-2 preferential actions relates to 6-MNA. Several studies have investigated the COX-1/COX-2 selectivity of 6-MNA. Such studies over a wide concentration range indicate that 6-MNA is a COX-2 preferential inhibitor.[22,23] Moreover, comparative studies with other COX inhibitors using the human enzyme have also reported preferential COX-2 inhibition by 6-MNA, though less pronounced. Using purified human enzyme, Barnett et al.[22] found 6-MNA to be approximately three to five times more active on COX-2 than COX-1 (COX-2/COX-1 ratio 0.28), despite describing this as 'equiselectivity'. Similarly, in another study, Patrignani et al.[24] have also reported 6-MNA to be equipotent despite a COX-2/COX-1 ratio of 0.67. In addition to these studies, Laneuville et al.[23] did not report any preferential selectivity of 6-MNA for COX-2, describing it to be a largely equipotent inhibitor of both COX-1 and COX-2. However, also in this study, 6-MNA showed preferential activity against COX-2 over the major part of the concentration range tested.[23]

However, it is now evident that estimates of COX-2/COX-1 ratios *in vitro* of different COX inhibitors or NSAIDs cannot easily be translated into comparative gastric, cardiovascular or renal tolerability in clinical practice. Rather, collective evidence indicates that there are multiple pharmacological mechanisms involved in the events leading to COX inhibitor-related gastropathy as well as cardiovascular or renal adverse events. The differences in

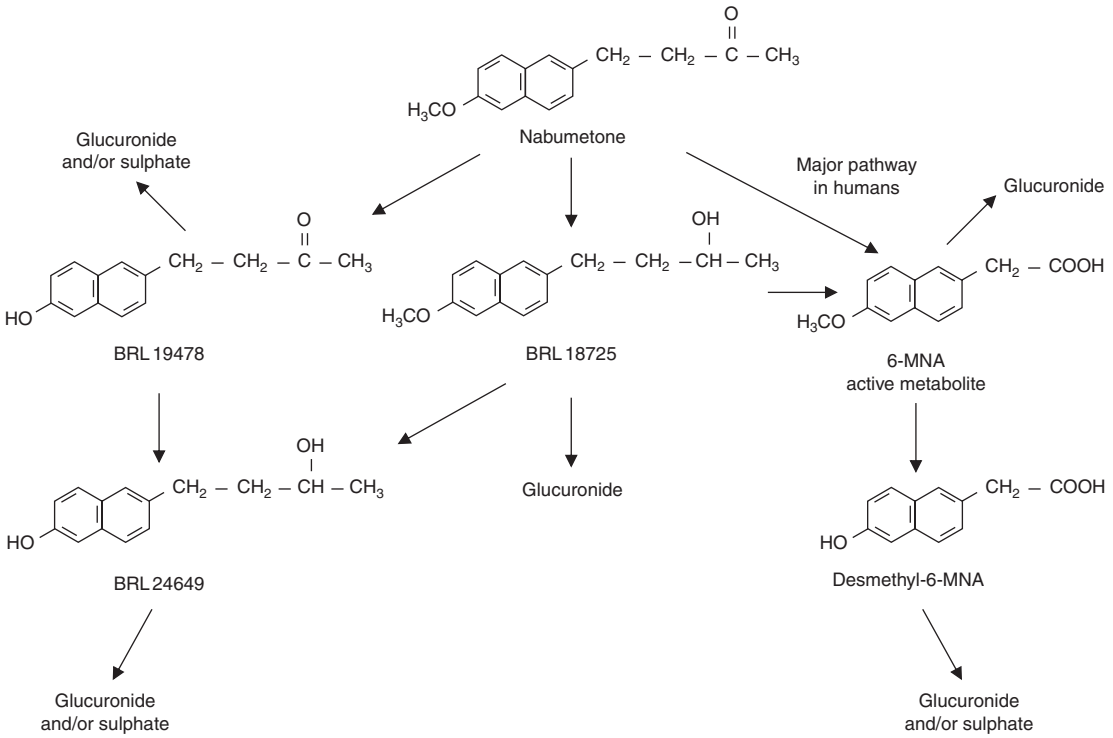

Fig. 1. Metabolic pathways of nabumetone. **6-MNA** = 6-methoxy-2-naphthylacetic acid.

the tolerability profile of COX inhibitors appear to be multifactorial and certainly more complex than previously understood.[25-28]

Several important factors have been identified for stomach ulcer development. These include, for example, the low disassociation constant (pKa) or acidic nature of most COX inhibitors as well as their ability to be absorbed in the stomach, which, together with biliary excretion, may result in vulnerability during secondary exposure of the stomach to the specific NSAID through a biliary reflux. Such factors are not applicable for nabumetone since it is a non-acidic prodrug that is poorly absorbed from the stomach and is not subject to biliary reflux.[21,27-29] Although nabumetone itself has no irritant effect on the gastric mucosa, the systemic effects of the active metabolite 6-MNA may, however, cause dyspepsia and nausea.

2. Pharmacokinetics

When taken orally, nabumetone is readily absorbed from the gastrointestinal (GI) tract to the presystemic circulation. Nabumetone is almost completely metabolised in the liver to produce a range of metabolites (figure 1). One of these metabolites, 6-MNA,[20,30] is the major pharmacologically active principle which accounts for the COX-1/COX-2 inhibitory activity. 6-MNA is the result of oxidative cleavage of the side-chain on the parent molecule. A number of additional metabolites are produced by demethylation processes and by reduction of the ketone moiety to an alcohol. The active 6-MNA metabolite is itself metabolised to desmethyl-6-MNA (figure 1), but this, as well as the other metabolites of nabumetone, appear to have minimal pharmacological activity compared with 6-MNA. Therefore, the parent compound nabumetone can be considered to be a non-acidic prodrug to 6-MNA.

Metabolism of orally administered nabumetone occurs through three interrelated metabolic pathways:[30,31] *O*-demethylation, reduction of the ketone to an alcohol and oxidative cleavage of the side-chain to yield acetic acid derivatives (figure 1 and figure 2).

After oral administration, plasma concentrations of unchanged nabumetone remain below the limit of detection in most individuals. The mean absolute bioavailability of the active metabolite 6-MNA was 38% after oral administration of nabumetone in six young healthy volunteers.[32-34]

After oral administration of a single nabumetone dose of 1.0g to patients with RA or OA, peak synovial fluid concentrations of the active 6-MNA metabolite range between 10 and 16 mg/L.[35] These concentrations are generally reached between 4 and 12 hours after the first administration of the drug. The active metabolite 6-MNA has a volume of distribution of around 7.5 L/kg. Essentially, no nabumetone is excreted unchanged in urine. Both free[30,31] and conjugated 6-MNA, as well as its *O*-demethylated metabolite are found in the urine (figure 1), but <1% of nabumetone reaches the urine as the major active 6-MNA metabolite.[33] Two non-acidic urinary metabolites account for another 16% of the dose. The remaining 45% is made up of numerous minor inactive metabolites resulting from further metabolism. Taken together, 80% of the administered dose of nabumetone is excreted in the urine and approximately 10% in the faeces.[20,32,33]

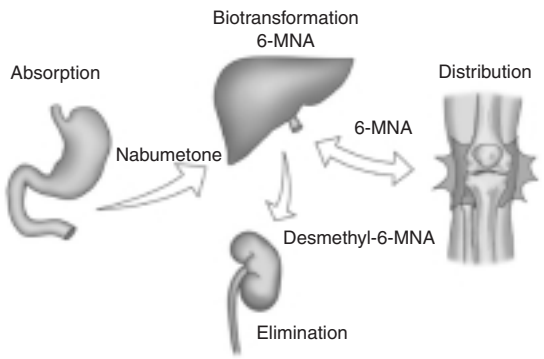

Fig. 2. Nabumetone disposition. Nabumetone is an inactive prodrug which is converted to its active metabolite 6-methoxy-2-naphthylacetic acid (6-MNA) in the liver.

Several metabolites of nabumetone other than 6-MNA have been found, mainly as conjugates in the urine, although in minor amounts.

2.1 Special Populations

2.1.1 Pregnancy and Neonates

In animal studies, 6-MNA crossed the placenta barrier[36] and was excreted in breast milk. Safety of nabumetone during pregnancy and lactation has not been established and, therefore, use is not recommended during this period.[36]

2.1.2 Children

Nabumetone has only been studied to a limited extent in groups of children and, therefore, its use is not recommended for children. However, in a recently performed open study in 99 patients with juvenile RA (aged 2–16 years), nabumetone was effective and safely used. The dose used was 30 mg/kg/day.[37] These findings are supported by data from two smaller studies including 10 and 15 patients with juvenile RA.[38,39]

2.1.3 Elderly

In the elderly, administration of nabumetone results in higher plasma 6-MNA concentrations compared with younger individuals.[20,40] However, this pharmacokinetic observation appears to be clinically insignificant[20] when comparing younger and elderly patients in terms of efficacy and adverse effects. Therefore, nabumetone dosages are generally not reduced when treating elderly patients.[32]

2.1.4 Patients with Liver and Renal Impairment

The pharmacokinetics of nabumetone have only been studied to a limited extent in patients with liver impairment. In a small study including patients with cirrhosis, nabumetone pharmacokinetics were similar to that in healthy volunteers,[41] while in another study[42] the excretion of 6-MNA appeared to be slightly delayed in the patients with liver dysfunction. Therefore, dose reduction may be necessary when treating patients with cirrhosis.

Both nabumetone and its metabolites show a high degree of protein binding. Glucoronidised metabolites are excreted renally but plasma 6-MNA concentrations are not altered during steady state in patients with reduced renal function despite of the fact that the renal elimination of 6-MNA is reduced.

This may be explained by a non-linear protein binding or that excretion may occur through other routes of elimination. Therefore, in practical terms the dose of nabumetone need not to be adjusted in patients with mild-to-moderate renal function.[43]

2.2 Drug-Drug Interactions

The active 6-MNA metabolite of nabumetone is >99% protein bound and it may, therefore, potentially displace other highly protein-bound drugs.[35] Although studies[44,45] have shown that coadministration of nabumetone with warfarin has no clinically significant effect on coagulation parameters, a case of abnormal bleeding complication has been reported.[46] Therefore, concomitant administration with warfarin and other anticoagulants should be undertaken with caution.

The following commonly available drugs do not affect nabumetone metabolism and bioavailability: paracetamol (acetaminophen), aspirin (acetylsalicylic acid), cimetidine, and aluminium hydroxide antacids.[47]

There are several reports of interactions between commonly used nonselective COX inhibitors as well as COX-2 selective inhibitors and antihypertensive drugs.[48] So far, there have been no such reports with nabumetone.[49]

2.3 Food-Drug Interactions

After oral nabumetone, the bioavailability of 6-MNA is largely unaffected by food. However, if nabumetone is administered orally together with milk, plasma 6-MNA concentrations increase.[20,49] Absorption of nabumetone is not affected by antacids, and alcohol (ethanol) does not appear to alter the kinetics of the drug.[49]

3. Therapeutic Efficacy

Similar to other COX inhibitors, nabumetone has been shown to be effective in reducing pain and inflammation in patients with OA, as well as pain, inflammation and stiffness in patients with RA. Furthermore, and like other COX inhibitors, nabumetone has not been shown to alter the progression of the disease process.

Therapeutic activity has been assessed in patients with OA by symptom relief and analgesia. Efficacy parameters included physicians' and patients' global assessment of disease activity, pain relief and improvement in the Activities and Lifestyle Index.[50] In a large number of OA studies nabumetone has been compared with other traditional NSAIDs such as aspirin, diclofenac, indometacin (indomethacin) and naproxen in standard dosages.[47]

In patients with RA, nabumetone has been compared with aspirin, as well as with a number of other clinically available COX inhibitors. The parameters used to assess therapeutic activity in such trials commonly include the following: (i) Ritchie articular index; (ii) severity of pain; (iii) physician and patient global assessment of disease severity; (iv) duration of morning stiffness; (v) time to walk 50 feet (15.2 metres); (vi) grip strength; and (vii) improvement in the Activities and Lifestyle Index. In addition, outcome parameters may also include need for rescue analgesics and withdrawal rate for insufficient effect.[51]

In addition, a smaller number of studies are available in patients with juvenile RA, ankylosing spondylitis and soft tissue injuries.

3.1 Osteoarthritis

The majority of the early trials assessing the efficacy of nabumetone in OA were of short duration (2–8 weeks), but in four of the studies nabumetone and its reference treatments were given for periods of up to 1 year or longer.[52-55] In two of these early trials long-term nabumetone therapy was compared with placebo. In both studies[52,53] nabumetone 1g once and twice daily were statistically and clinically superior to placebo. Both treatment regimens were well tolerated, although nabumetone treatment was associated with more moderate adverse effects than placebo.

A 6-month, double-blind, controlled, randomised, parallel study of 40 patients compared the efficacy and tolerability of nabumetone (1g at bedtime) with naproxen (250mg twice daily) in the treatment of OA.[54] The results indicated that nabumetone and naproxen have comparable efficacy and tolerability at the dosage used. In another 6-month, multicentre, double-blind study of 332 patients with OA the efficacy and safety of nabumetone 1g as a single bedtime dose or aspirin 900mg in four divid-

ed doses was compared.[55] The result demonstrated that, at these dosages, nabumetone was as efficacious as aspirin and produced fewer adverse effects.

Short-term studies comparing nabumetone with traditional NSAIDs[47] have demonstrated similar efficacy to the comparative agents. The trials compared nabumetone with other COX inhibitors such as aspirin, diclofenac, indometacin and naproxen given in standard dosages.[47,50,51,56] In two studies some patients withdrew because of an unsatisfactory therapeutic effect of the 1 g/day dosage.[54,55] This indicates that the optimum therapeutic dose range may be between 1.0 and 2.0 g/day. In fact, in a multicentre trial where 868 patients with OA received open-label nabumetone at individually titrated doses ranging between 1.0 and 2.0g for up to 8 years, 70% of patients maintained or even further improved their initial response to therapy with time.[57]

3.2 Rheumatoid Arthritis (RA)

COX inhibitor therapy represents one of the cornerstones in the treatment of patients with RA. No formal dose-ranging studies have been performed for nabumetone in RA patients but 1.0g once daily in the evening remains the dosage schedule most frequently used,[58,59] although in some long-term RA studies, some patients required daily doses of 1.5–2.0g.[60] Nabumetone administered as an evening dose is considered to be more effective than a dose administered at other times of the day.[61]

Nabumetone 1.0 g/day or in the evening has an analgesic and anti-inflammatory effect in RA patients that is superior to placebo.[58,59] Furthermore, in comparative studies with other COX inhibitors, nabumetone appears to be better or equally well tolerated compared with most other COX inhibitors.[51,62] Compared with aspirin, nabumetone produced fewer GI and CNS complaints,[63] and compared with indometacin or diclofenac[64-66] nabumetone produced fewer GI adverse effects. In an open study of 1490 patients with RA or OA treated with nabumetone for up to 8 years, the withdrawal rate for lack of efficacy was 9.1% of patients.[57] In this study two-thirds of the 622 patients with RA maintained or even further improved short-term benefits during long-term nabumetone therapy.[57] A recent open-label study in patients with juvenile RA demonstrated a safety profile with no loss of efficacy compared with previous NSAID treatment.[67] Ninety-nine patients aged 2–16 years were enrolled and received nabumetone 30 mg/kg once daily (as a tablet or a slurry) for 12 weeks. The adverse event profile was similar to that reported for nabumetone in adults with RA.

3.3 Ankylosing Spondylitis

So far, nabumetone has only been evaluated in a limited number of small studies in patients with ankylosing spondylitis. In a double-blind, parallel-group trial including 29 patients, nabumetone 1.5 g/day was slightly less effective than indometacin given in dosages of up to 175 mg/day.[68] In an additional study, where 42 patients were receiving nabumetone 1g twice daily or indometacin 50mg three times daily, nabumetone demonstrated comparable efficacy to indometacin. There was also a similar profile of adverse events, although GI adverse effects appeared to be less frequent and less severe with nabumetone.[69]

3.4 Juvenile RA

In a recent open study, nabumetone was assessed in terms of safety and efficacy in patients with juvenile RA aged 2–16 years.[37] The authors concluded from this trial in 99 patients that treatment with nabumetone 30 mg/kg/day was safe and effective. These findings are further supported by data from two smaller studies including ten and 15 patients with juvenile RA.[38,39]

3.5 Soft Tissue Injuries

Studies in patients with soft tissue injuries, usually resulting from sporting accidents, seem to confirm that nabumetone is as effective as aspirin, ibuprofen and naproxen.[70-74]

4. Tolerability and Safety

Similarly to other COX inhibitors, safety issues for nabumetone and 6-MNA have been related to the GI and renal systems, as well as the cardiovascular system in relation to the platelet effects of 6-MNA.[75-77] Nabumetone has been extensively evaluated regarding GI adverse events in comparative studies as well as in large prospective safety

evaluations. Nabumetone therapy may cause salt and water retention and, therefore, patients with moderate or severe renal impairment may experience a reduction in glomerular filtration rate (GFR). In platelets, nabumetone inhibits thromboxane A_2 (TxA_2) production in a dose-dependent manner. Thus, nabumetone possesses anti-aggregatory properties, but the antiplatelet effect is less than that of naproxen and the bleeding time is not prolonged.[19,78] Nabumetone has also been evaluated in terms of its cardiovascular safety profile in patients at increased risk for thromboembolic events, as well as in patients at risk for heart failure and volume retention.[77,79,80]

Extended nabumetone safety data from both premarketing clinical trials and postmarketing surveillance studies has been published,[76] summarising the safety of nabumetone in 44 953 patients treated for periods between 3 weeks and 8 years. This surveillance report revealed a low incidence of serious GI, cardiovascular and renal adverse events related to nabumetone therapy. Furthermore, and importantly, the data collected[76] revealed no reports of bone marrow suppression, liver necrosis, serious CNS conditions or life-threatening dermatological reactions. In addition, there was no increase in toxicity in relation to increases in the dosage within the therapeutic range of 1–2 g/day or in relation to age. Withdrawal rates as a result of adverse events were between 3% and 13%, and varied among patients depending on the geographical location and duration of the treatment. As expected, most withdrawals for adverse effects in nabumetone treated patients occurred within the first year and after that the withdrawal rate was reduced.

A recent study investigated the extent to which nabumetone was tolerated by patients with verified hypersensitivity to aspirin or NSAIDs.[81] Twenty-four patients with a hypersensitivity reaction to aspirin or NSAIDs, which was verified by a physician, on at least two occasions were enrolled. Patients were exposed to nabumetone 1g orally and monitored for 4 hours, and further monitored after 3 and 12 months. Twenty-two of the exposed patients did not show any adverse reaction to nabumetone. One patient had urticaria and one had mild pruritus without objective signs, both of which resolved spontaneously. It should be noted that this was only single exposure, no long-term treatment was commenced. Hence, these findings indicate the possibility that nabumetone can be tried as an alternative in most patients with a hypersensitivity reaction to commonly used NSAIDs.

In a UK prospective surveillance study including 10 800 patients and conducted in a general practice setting, there was a low number of GI, cardio-

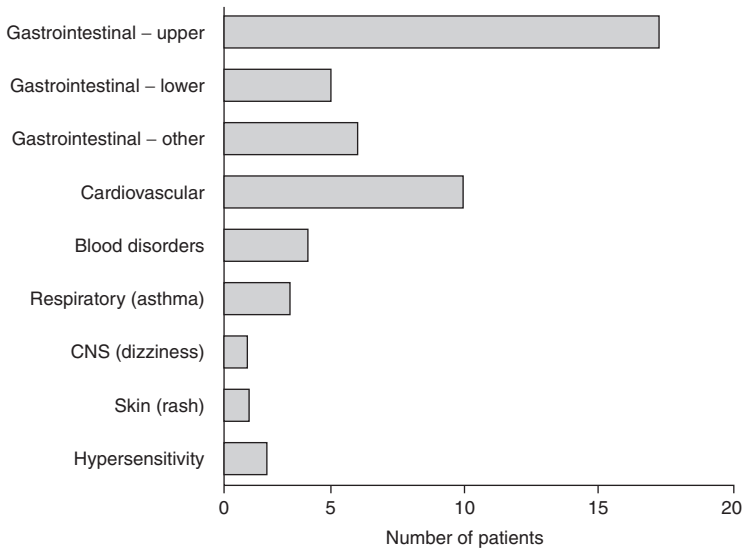

Fig. 3. Serious adverse events reported in 10 800 patients in a UK outpatient nabumetone safety surveillance study.[76]

vascular and renal events reported (figure 3 and figure 4).[76]

4.1 Upper Gastrointestinal (GI) Adverse Effects of COX Inhibition

A major drawback associated with long-term use of COX inhibitors relates to GI complications such as perforation, ulcer or bleedings (PUBs).[82] In general, the incidence of serious PUBs due to long-term COX inhibition by a variety of agents is about 2–4% per year, but rates increase when specific risk factors are present.[83,84]

The prevailing hypothesis that nonselective COX inhibitors induce GI injury, primarily by inhibiting the mucosal COX-1 isoenzyme, predicts that a COX-1 selective inhibitor should be very toxic to the GI mucosa and that COX-1 mice deficient in the isozyme would be susceptible to spontaneous mucosal ulcer development and also more sensitive to COX inhibition than their wild-type littermates. However, this is not the case. Furthermore, it has been reported that a highly selective COX-1 agent (SC-560) induces no GI injury in rats when administered alone, whereas GI toxicity develops when given together with a COX-2 selective inhibitor.[85] Furthermore, Langenbach et al.[86] reported that COX-1-deficient animals had no detectable GI ulcer disease and, if anything, were more resistant to indometacin-induced ulcer development. To make matters even more confusing, Morham et al.[87] found in a subsequent study that COX-2 knockout mice were not viable, and developed peritonitis and renal disease. The notion that COX-2 inhibition has negative consequences is also supported by animal studies indicating that ulcer healing in the proximal and distal part of the gut was retarded in animals treated with selective COX-2 antagonists.[88-91]

These findings demonstrate that the prevailing concept, that COX-related GI mucosal injury is predominantly related to inhibition of mucosal COX-1 activity, needs to be reassessed since laboratory as well as clinical studies demonstrate that the injurious actions of COX inhibitors are not always linked to their ability to inhibit COX-1 in the gastric mucosa. Thus, there is a possibility that these drugs may cause injury of the gastric mucosa by mechanisms other than COX inhibition. A rather strong case can be made that nonspecific COX inhibitors induce GI

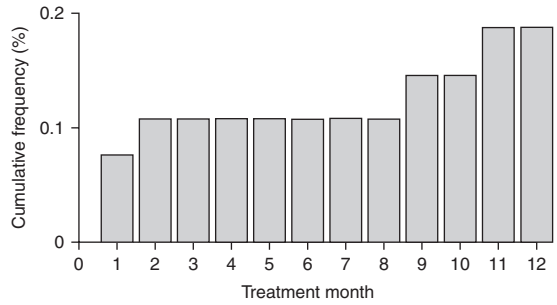

Fig. 4. The cumulative frequency of gastrointestinal perforations, ulcers and bleeds in relation to treatment duration (12 months) in a UK outpatient nabumetone safety surveillance study (n = 10 800).[76]

ulceration and bleeding primarily by topically injuring the mucosa, since they can enter the GI lumen via oral intake, secretion into the bile or both. Lichtenberger[92] has put forward the hypothesis that zwitterionic phospholipids (e.g. phosphatidylcholine) secreted into either the mucus gel layer or bile may protect the GI epithelium from the toxic effects of a variety of noxious agents such as hydrochloric acid or bile salts present in the lumen. An alternative hypothesis may, therefore, be that COX inhibitors induce GI ulceration and bleeding by diminishing the availability of phosphatidylcholine and related phospholipids, which normally protects the GI mucosa against a variety of luminal ulcerogenic agents.

There is also evidence from clinical studies suggesting that mucosal COX inhibition may not be directly involved in the pathogenesis of the enteropathy induced by COX inhibitors. In fact, several studies in humans have reported that intravenous administration of aspirin does not cause any detectable histological injury to the gastric mucosa, which is in contrast to oral administration of the COX inhibitor in the same dose range.[93,94] Moreover, after 2–4 weeks of COX inhibitor treatment, the human gastric mucosa becomes resistant to the injurious actions of oral aspirin or indometacin. Furthermore, this adaptive response was not linked to a recovery of COX activity, which remained fully blocked during the study period.[95,96]

Various animal laboratory studies have compared the COX inhibitory efficacy and the GI toxicity of several COX inhibitors when given by different routes of administration (intragastric vs rectal or

parenteral).[97,98] Interestingly, such studies demonstrate that the GI damaging effect of several nonselective COX inhibitors, such as sulindac, ibuprofen and aspirin, was dependent on the intragastric delivery of these drugs. This was evident despite the fact that they all induced maximal mucosal COX inhibition, regardless of the route of administration. An interesting characteristic for some of the COX inhibitors is that GI mucosal injury may also appear when agents are administered systemically. Indometacin, diclofenac or ketoprofen are all secreted into the bile and enter the enterohepatic transport system.[99-101] From such data in animals it may be demonstrated that there is a highly significant association between the percentage of the administered dose of a COX inhibitor that is secreted into the bile and the ability of the COX inhibitor to induce GI ulceration.[99] Further evidence supports the possibility that these drugs may induce topical injury to the mucosa by being secreted into the bile. Results from a number of laboratories indicate that mucosal injury which occurs with systemic administration of COX inhibitors can be prevented by bile duct ligation.[100,101] Also worth noting is the fact that some of the animal studies that have demonstrated that systemic aspirin administration induces gastric injury, purportedly by gastric COX inhibition, have been performed exclusively on cats,[102-104] a species that is highly sensitive to the GI toxic effects of aspirin.

Thus, COX inhibitor-induced GI mucosal injury is not easily explained, and an interesting case can be made to investigate other mechanisms by which COX inhibitors may induce GI mucosal injury. Importantly, such information could be used to develop alternative strategies to reduce or prevent the GI toxicity of COX inhibitors. Other potential targets of COX inhibitor-related enteropathy may be related to reduced mucosal blood flow and enhanced leucocyte adherence to the vascular wall,[105] uncoupling of mitochondrial oxidative phosphorylation,[106] induction of cellular acidification due to their protonophore characteristics,[107] or attenuation of the hydrophobic, non-wettable characteristics of the mucosa, which would increase the susceptibility of the tissue to luminal acid.

However, a number of questions remain about the putative the role of COX-1 inhibition in the pathogenesis of NSAID-induced gastropathy, and the potential influence of COX-2 inhibition in mucosal integrity and the ulcer healing process. The initial and prevailing hypothesis states that nonselective COX inhibitors induce GI injury by inhibiting COX-1, which leads to a depletion of 'cytoprotective' prostaglandins in the mucosal tissue. Indeed, there is considerable support for the concept that nonselective COX inhibitors primarily induce GI injury by inhibiting COX-1 activity of the gastric mucosa.[103,108-113] Several studies have demonstrated, in both animals and humans, that COX inhibitor-related gastroduodenal PUBs are frequently associated with a decrease in the mucosal prostaglandin content and/or COX activity. Furthermore, the exogenous administration of prostaglandin analogues such as, for example, misoprostol can either partially or completely reverse the deleterious effects of COX inhibitors on the GI mucosa. However, such findings related to substitution therapy cannot be considered as definitive proof since prostaglandin administration has a general protective effect on the GI mucosa against a number of damaging stimuli or conditions that do not cause tissue prostaglandin depletion.[108,109]

Although much debated, it is now evident that in the clinical setting, COX-1-induced inhibition of prostaglandin synthesis does not entirely explain NSAID-induced gastroduodenal toxicity. For example, mice lacking the COX-1 gene still develop ulcers on COX inhibitor therapy.[86] Furthermore, in clinical studies, replacement of mucosal prostaglandin with misoprostol does not fully prevent COX-related ulcer development.[113,114] In addition, in patients with healed COX inhibitor-induced ulcers, 27% relapsed during 1 year of continuous misoprostol treatment to prevent COX inhibitor ulcer recurrence.[114] From such examples, it is apparent that other factors are involved, which may also be related to the multifunctional roles of COX-2 in the GI mucosa. COX-2 is widely expressed in epithelial cells of the gastric mucosa at the margin of ulcers. It seems to participate in epithelial regeneration,[89,115] which may be relevant to gastric ulcer healing. As indicated by Stenson,[116] inflammation and wound healing are dependent on similar mechanisms and, therefore, drugs that inhibit inflammation may also retard gastric ulcer healing. However, an effect of COX-2 inhibition on gastric ulcer heal-

ing may not be detectable in short-term gastric ulcer studies. In studies extending over longer time periods, however, the effect might be evident because an increased ulcer prevalence can result from either induction of ulcers or delaying their spontaneous healing. Therefore, it is clear that only long-term outcome studies correctly assessing gastric ulcer incidence that compare COX-2-selective inhibitors with other COX inhibitors such as nabumetone will provide clinically useful data.

4.1.1 COX-1/COX-2 Inhibition

The risk of developing severe GI adverse events varies between patients as well as between COX inhibitors. Numerous epidemiological studies demonstrate that the use of COX inhibitors increases the overall risk (expressed as the odds ratio [OR]) of peptic ulcer bleeding (OR 2.7–3.3), perforation (OR 5.9–6.1) and GI adverse event-related death (OR 4.79–7.62).[117-121] Among risk factors that predispose COX inhibitor users to a greater risk of developing a severe GI event are age >60 years (OR 2.86), a history of ulcer or ulcer bleeding (OR 4.76–9.5), high-dose or use of multiple COX inhibitors (OR 4.0–23.3), concomitant corticosteroid therapy (OR 1.83–4.4) and concomitant anticoagulation therapy (OR 2.1–16.0).[117-121] Since GI safety has been a major concern with the use of COX-1/COX-2 inhibitors for decades, many preparations have been developed to minimise COX inhibitor-induced GI adverse events by using different drug formulations, including enteric coating or encapsulation[122] or by offering different routes of administration.[123] Unfortunately, none of these approaches have reduced the occurrence of long-term GI ulcer complications to any major extent.[117-121]

4.1.2 Nabumetone

From a mechanistic point of view, nabumetone has several pharmacological properties that may contribute to its low GI toxicity. Such beneficial properties include the nonacidic prodrug formulation, lack of enterohepatic recirculation and possibly a preferential inhibition of COX-2.[124,125] These properties reduce the direct influence of nabumetone and its metabolite 6-MNA on the GI mucosa and minimise the risk of mucosal injury caused by the agent.[126] Interestingly, early studies evaluating the effect of nabumetone on GI blood loss with ^{51}Cr-tagged red blood cells did not show any significant difference in faecal blood loss between nabumetone 1g given at bedtime and placebo, whereas aspirin 3.6 g/day caused substantial GI microbleeding.[127] The likely explanation for this is that long-term use of nabumetone, in contrast to conventional nonselective COX-inhibitors, did not cause intestinal inflammation or mucosal injury, and further that intestinal permeability remained normal.[128]

Although COX-related damage to the upper GI tract has been extensively investigated, small bowel adverse events are less studied reflecting the relative inaccessibility of that part of the GI tract for endoscopic studies. New techniques for investigating the small bowel are emerging including increased use of enteroscopy and the recently described wireless endoscopic capsule that produce endoscopic images of the entire small intestine.[129] These techniques will focus on the COX-related enteropathies in the future. However, different approaches including intestinal permeability assessment, enteroscopy, markers of inflammation in the stools, surgery and postmortem studies have been undertaken. The rate of small bowel damage related to nonselective COX inhibitors differs (8–65%) according to which diagnostic methods are used. The highest prevalence is found using the faecal markers.[130] Whether the highly selective COX-2-inhibitors are associated with small bowel damage needs to be further studied.

Nabumetone use seems to be less related to these enteropathies than other nonselective COX inhibitors. In patients with RA the intestinal permeability measured with ^{51}CrEDTA was unchanged during treatment with nabumetone 1 g/day compared with a significant increase of permeability during treatment with indometacin 150 mg/day.[131] Because nabumetone, in contrast to indometacin, is a prodrug it is a poor inhibitor of the prostaglandin synthesis until it is converted to its active form. Therefore, nabumetone would have little effect on the mucosa during the absorption phase and as, in contrast to most other COX inhibitors, it is not secreted into the bile, it would have little effect via this route. The difference between nabumetone and indometacin suggests that COX inhibitors cause small bowel damage during absorption or after biliary excretion, and that systemic effects are less important.

Lichtenberger[92] has recently provided an explanation as to how COX inhibitors secreted into the bile possibly induce GI injury. Biliary phosphatidylcholine plays an important role in intestinal mixed micelle formation, which reduces the cytotoxic effects of bile salts. Phosphatidylcholine can protect rats from a number of ulcerogenic agents including NSAIDs. There is also evidence that COX inhibitors have a strong ability to chemically associate with phosphatidylcholine, which transforms the mixed micelles into cytotoxic bile salt micelles.[92] Since nabumetone is not secreted into the bile, it should not be affected by this interaction with phosphatidylcholine.

Individual studies have suggested that nabumetone has a safety profile which is superior to comparator NSAIDs as expressed by PUBs, especially in long-term studies.[47,76] The cumulative incidence of nabumetone-induced PUBs in the early premarketing and postmarketing studies varied from 0.02% to 0.95%. The low incidence of PUBs observed in those surveys in the nabumetone-treated patients may be due to patient selection as well as the fact that nabumetone is a prodrug. When administered to patients, the conversion of the inactive parent drug (nabumetone) to the active 6-MNA metabolite takes place after absorption. Thus, the non-acidic structure of nabumetone, the fact that it does not inhibit COX until after conversion to 6-MNA and the lack of enterohepatic circulation[28,132] may be important explanations to the low incidences of PUBs reported after nabumetone therapy.

The early nabumetone studies including 1677 patients with RA or OA showed that there were 17 patients who developed ulcers, although the majority were regarded as being uncomplicated.[133] A Kaplan-Meier life table analysis from this nabumetone-treated cohort showed that the nabumetone-associated risk of ulcer formation was 0.3% (95% CI 0, 0.6) at 6 months; 0.5% (0.1, 0.9) at 1 year; 0.8% (0.3, 1.3) at 2 years; and 2.35% (1.1, 3.59) at 6 years. Expressed as a yearly incidence over the 6 years, the mean calculated ulcer development rate was approximately 0.4% per year, with the upper 95% confidence limit being 0.6% per year. Moreover, and as shown in figure 5, the cumulative life table rate of ulcer formation in nabumetone-treated patients is essentially linear over 5 years, which allows the event rate to be expressed in terms of events per 100 patient-years of nabumetone exposure. Of the 17 ulcers related to nabumetone, there were only four clinically significant bleeding episodes and no perforations, providing an incidence a rate of complicated PUB events of only 0.1 per 100 patient-years.

4.1.3 Nabumetone versus Other COX Inhibitors

The comparative GI safety of nabumetone has been evaluated in a meta-analysis of randomised trials which compared the GI safety of nabumetone with other COX inhibitors in patients with RA or OA. The 4411 patients assessed in these trials were randomised to either nabumetone or a comparator COX inhibitor such as diclofenac, naproxen, ibuprofen or piroxicam. Patients were given recommended starting dosages of their respective medication, and the investigator increased these dosages, depending on clinical response and tolerability. Notably, only one ulcer occurred in the 3287 patients in the nabumetone group (681 patient-years), whereas six ulcers occurred in the 1077 patients receiving the reference COX inhibitor therapy (221 patient-years). There was a significant difference between the nabumetone and reference COX inhibitor strategies, whether based on cumulative incidence (Kaplan-Meier life table) or events per 100 patient-years of exposure[133] (figure 5).

Huang et al.[75] evaluated the difference in GI adverse events, such as the rate of PUBs, in comparative trials of nabumetone and conventional COX-1/COX-2 inhibitors. This meta-analysis identified 13 studies consisting of 29 treatment arms and 49 501 patients that met the criteria predefined in the protocol. Tests for heterogeneity found no significant difference between the individual studies included in the meta-analysis. Overall, dyspeptic symptoms of flatulence, constipation and diarrhoea were the most commonly reported adverse events, accounting for 98.6% of the total GI adverse events. Significantly more patients treated with comparator nonselective COX inhibitors experienced GI adverse events compared with patients treated with nabumetone ($p = 0.007$). In fact, after adjustment for patient-exposure years, PUBs were 10 to 36 times more likely to develop in patients treated with a comparator nonselective COX inhibitor than with nabumetone.

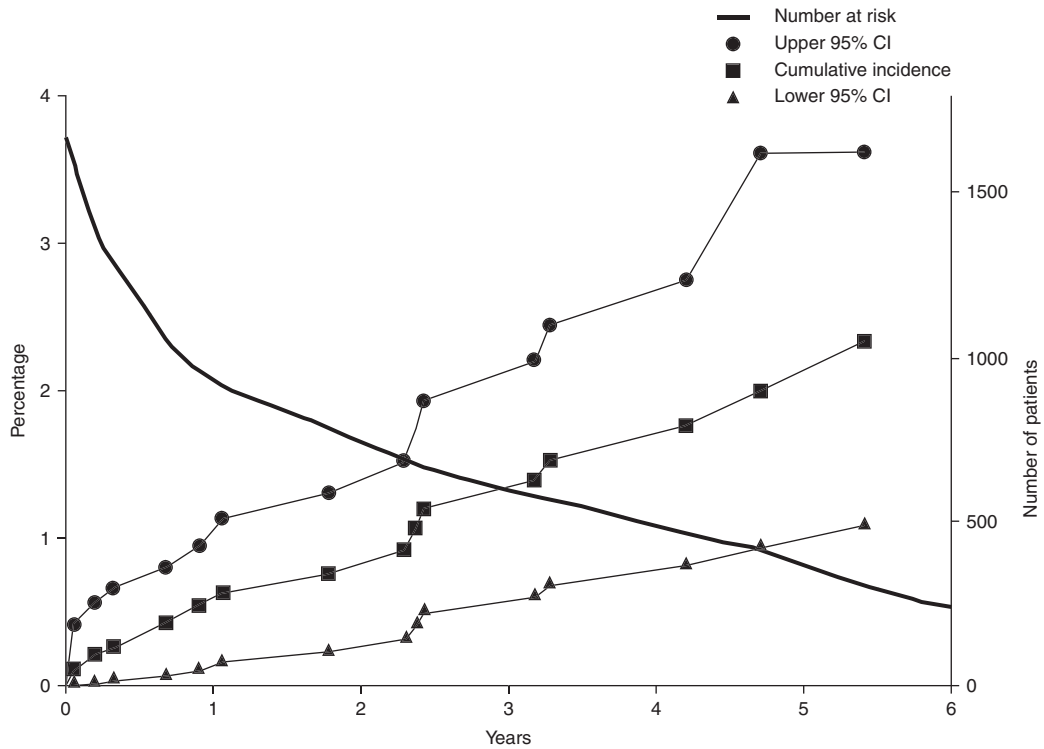

Fig. 5. Gastrointestinal events over 6 years in patients treated with nabumetone. Shown is the cumulative incidence, expressed as a percentage which raises the number of patients at risk in a linear fashion. The population at risk declines, as indicated by the dotted line (reproduced from Freston,[133] with permission from Excerpta Medica, Inc.). **CI** = the 95% confidence interval for the cumulative incidence.

Interestingly, the meta-analysis of the incidence of ulcers and ulcer complications associated with the therapeutic use of nabumetone by Huang et al.[75] suggests that the GI and other safety of this agent is superior to that of nonselective comparator COX inhibitors. This was a consistent finding in patients participating in non-endoscopic (n = 7468) as well as endoscopic studies (n = 244). Furthermore, in postmarketing or open-label studies of nabumetone there was only one PUB reported per 500 patient-exposure years over 17 502 treatment years (n = 39 389). Moreover, GI adverse event-related study withdrawals and hospitalisations were 1.3- and 3.7-fold higher in patients treated with a comparator COX inhibitor compared with nabumetone, respectively.[47]

In addition to the direct comparative studies and meta-analyses, the incidence of PUBs with nabumetone has been assessed and compared with other COX inhibitors in database studies.[75,134-137] Two large database studies have compared the rates of GI events occurring during treatment with nabumetone and a variety of other COX inhibitors. In both studies the lowest rates of GI complications were observed in nabumetone treated patients.[134,136,137]

The Tayside Medicines Monitoring Unit Study[134,136] provided data for the rate of upper GI toxicity in 53 293 patients aged ≥50 years receiving COX inhibitors during the 3-year period from 1 January 1989 to 31 December 1991 compared with 73 792 subjects who did not receive a COX inhibitor during the same period. In the study groups, 382 ulcers or complications (163 ulcers or erosions and 219 complications) occurred during 29 700 patient-years of COX inhibitor exposure, that is, a rate of 1.29 per 100 patient-years. In the reference group, there were 1005 events (495 ulcers or erosions and 510 complications) during 220 540 years of follow-up, that is, an incidence rate of 0.46 per 100 patient-years. Interestingly, the point estimate for nabume-

tone was the lowest within the group, which is consistent with the experience from the nabumetone clinical trials' data.

In another large study, the ARAMIS (Arthritis, Rheumatism, and Aging Medical Information System) database was surveyed[137] providing data on 3883 patients with RA, including COX inhibitor treatment and complication rates. Data have been collected from 1976 and the study is still ongoing. In this large cohort, nabumetone had the lowest absolute rate of hospitalisation for PUBs among all COX inhibitors surveyed, which is consistent with the results achieved in the early controlled trials for this agent.

An important rationale for the development of COX-2 inhibitors, that is, the premise that they would cause fewer GI adverse effects than available nonselective COX inhibitors, seems unlikely to apply to nabumetone, which has the lowest incidence of GI toxicities among the agents. The incidence of 0.4% GI ulcers and 0.1% serious complications for nabumetone (e.g. GI perforations or bleeds) is approximately one-tenth of that for the comparator nonselective COX-1/COX-2 inhibitors and constitutes the current standard of comparison for the COX-2 inhibitors.

4.2 Platelet Effects of COX Inhibition

Over the past few decades, multiple clinical evidence has emerged on the antithrombotic effect of aspirin in cerebrovascular and coronary disease.[138] TxA_2 is generated and released by platelets in response to a number of stimuli such as collagen, thrombin and adenosine diphosphate (ADP). These events may result in irreversible platelet aggregation and vascular contraction. In this sense, TxA_2 enhances the ability of platelets to react with an aggregatory response to a number of diverse stimuli. By this mechanism, platelet-derived TxA_2 may initiate sequences of biological responses resulting in an occlusive thrombotic disease event.[139]

RA patients have an increased risk for cardiovascular events.[140] Thus, it is of major importance in any therapeutic regimen to evaluate and consider effects on platelet function.

4.2.1 COX-1 and COX-1/COX-2 Inhibition

The COX-1 isoform of COX, which is produced in human platelets,[141,142] has been crystallised[143] and the structural basis of enzyme inhibition by aspirin[15] as well as traditional COX-1/COX-2 inhibitors[144] has been elucidated. The aspirin- and the COX inhibitor-binding sites both lie within a narrow hydrophobic channel within the core of the enzyme.[144] Thus, there may be a structural basis for a competitive interaction between aspirin and other COX inhibitors, which is also supported by evidence from recent studies.[145]

TxA_2 is the predominant product of COX in platelets.[146] The anucleate platelet represents a unique target for aspirin because once COX is acetylated by aspirin, substrate access to the active site of the enzyme is blocked for the remaining lifespan of the platelet. Thus, normal and continuous TxA_2 formation requires new platelets, which are formed at a daily rate of approximately 10%.[147,148] The only isoform of COX in platelets is COX-1.[148] Aspirin irreversibly inhibits platelet COX-1 by acetylating the amino acid serine in position 529 within the active site of the COX-1 enzyme, which results in a reduced production of TxA_2.[141] Aspirin also irreversibly inhibits the inducible COX-2 enzyme in a similar way. The platelet COX-1 inhibitory properties of aspirin have been evaluated *in vitro* by analysing the amount of TxB_2 generated during blood coagulation, that is, analysis of serum TxB_2, which is a stable metabolite of TxA_2. Single doses of aspirin 5–100mg dose-dependently inhibit platelet COX-1 and a dose of 100mg induces an almost complete inhibition of platelet COX-1, that is an almost total inhibition TxA_2 generation. This inhibitory effect has been studied in healthy volunteers[149] and in patients with atherosclerotic vascular disease.[150] The effect is very rapid and present before aspirin enters the systemic circulation. Thus, the therapeutic effect of aspirin is probably the result of an acetylation of platelet COX-1 already in the presystemic portal circulation. Moreover, and as a result of the irreversible effect of aspirin on COX-1, when the daily intake of aspirin is stopped, the COX activity in the platelets will very slowly resume full activity. This process is dependent on *de novo* generation of platelets from the bone marrow and their appearance in the circulation.[151] Because of the

irreversible nature of the aspirin-induced platelet COX-1 inhibition, the inhibitory effect of aspirin doses <100mg is cumulative.[148,149] Administration of aspirin 30–50 mg/day will result in an almost complete blockade of platelet COX-1 after approximately 7–10 days, resulting in a maximal inhibition of thromboxane-dependent platelet aggregation as well as a slight to intermediate prolongation of bleeding time.[152,153] Biochemical,[154] pharmacological[155] and clinical studies[156] unanimously support the concept that aspirin-induced inhibition of platelet COX-1 is the mechanism that is mainly responsible for its antithrombotic effect.

The irreversible blockade of COX-1 and COX-2 is specific for aspirin, while other COX inhibitors induce reversible and dose-dependent blockade of these enzymes. Most COX inhibitors, which have no distinct COX-1/COX-2 selectivity inhibit both isoenzymes to a similar and clinically significant extent. The clinical consequences of the different platelet inhibitory properties of COX-2 selective agents compared with the nonselective COX-1/COX-2 inhibitors have been considerably debated during recent years.[157-159]

In light of these novel findings on the putative role of COX-2 related to platelet-vessel wall interactions, the question has been raised as to whether or not COX-2-specific inhibitors confer an increased risk of arterial thrombosis. Looking at the current evidence, the majority of the early efficacy studies of COX-2 inhibitors in arthritis patients were of short duration, and not designed or powered to reveal an altered incidence of arterial thrombotic events (e.g. cardiovascular events). However, in some recent large studies examining the efficacy and safety profiles of the COX-2-selective inhibitors celecoxib and rofecoxib, sufficiently large numbers of patients were included allowing for an analysis of cardiovascular outcomes.[160,161]

Four large outcomes studies (VIGOR [Vioxx Gastrointestinal Outcomes Research],[160,162,163] ADVANTAGE [Assessment of Difference Between Vioxx and Naproxen to Ascertain Gastrointestinal Tolerability and Effectiveness] trial,[164] CLASS [Celecoxib Long-term Arthritis Safety Study][161-163] and SUCCESS [the Successive Celecoxib Efficacy and Safety Studies]),[165,166] examined the GI and overall safety of rofecoxib and celecoxib compared with established COX-1/COX-2 inhibitors (naproxen, ibuprofen or diclofenac) in >39 000 patients with OA or RA. Some data from these trials may indicate that patients taking COX-2 inhibitors (rofecoxib or celecoxib) had lower rates of PUBs compared with the reference COX-1/COX-2 inhibitors naproxen, ibuprofen or diclofenac. However, more debated has been the fact that the VIGOR trial, where patients were not allowed low-dose aspirin, showed a significantly increased occurrence of severe adverse events, preferentially related to cardiovascular and thrombotic endpoints. One potential explanation behind this could be the lack of platelet inhibitory effects of the COX-2 inhibitor in comparison with the reference therapy, the COX-1/COX-2 inhibitor naproxen.

4.2.2 Nabumetone

Cipollone and coworkers[167] studied the effect of nabumetone 0.5–1 g/day on prostaglandin synthesis in nine healthy volunteers.[167] Platelet COX-1 activity was investigated by determination of serum TxB_2 at steady state during day 7, and there was a dose-dependent 50–70% inhibition of TxB_2 metabolites and serum TxB_2. After cessation of 7-day nabumetone treatment, serum TxB_2 was normalised at a rate that corresponded to the half-life of the active nabumetone metabolite 6-MNA. The authors concluded that nabumetone inhibited platelet COX-1-dependent TxA_2 synthesis in a dose-dependent manner.[167] Several COX inhibitors (indometacin, naproxen, 6-MNA and nabumetone) were investigated by Jeremy and coworkers[168] by assessing their effects on platelet aggregation and TxA_2 synthesis. In their work, platelet aggregation and TxA_2 generation was inhibited in the following sequence; indometacin > naproxen > 6-MNA > nabumetone. From these results it was also concluded that 6-MNA effectively inhibits platelet prostaglandin synthesis, as opposed to the prodrug nabumetone, which did not demonstrate any platelet inhibitory properties in its own right.[168]

The effect of nabumetone on platelet activity was studied by Nunn and Chamberlain[78] in six healthy volunteers and compared with the effect elicited by naproxen. Nabumetone had a demonstrable inhibitory effect on collagen-induced platelet aggregation

and the 'second wave' effect by ADP-induced aggregation.[78]

Jennings et al.[46] studied the effect of nabumetone in patients undergoing lower extremity surgery. There was no difference in bleeding time between the 15 patients who were randomised to nabumetone 1 g/day and the 15 randomised to placebo. In addition, the results from a study where arthroscopic knee surgery was performed[169] showed that nabumetone had little or no effect on haemostasis and it was suggested that this drug could be used safely in the perioperative setting.

However, in slight contrast to these data, Giuliano and coworkers[170] used an *in vitro* system to evaluate the COX-1 and COX-2 antagonising effect in plasma from healthy volunteers after intake of different COX inhibitors such etodolac 200 or 400mg twice daily, meloxicam 7.5 or 15 mg/day, nabumetone 0.5 or 1g twice daily, nimesulid 100 or 200mg twice daily or naproxen 500mg twice daily.[170] The plasma from etodolac-treated patients demonstrated a slight COX-2 preferential effect. This COX-2 preference was more pronounced after intake of meloxicam or nimesulid. The plasma from nabumetone-treated patients, however, showed no or slight preference for COX-1 and naproxen had a greater effect on COX-1 compared with COX-2.[170]

Regarding nabumetone and its active metabolite 6-MNA, it is clear that there is a significant effect on COX-1 resulting in a platelet inhibitory effect as shown by reduced aggregatory activity *in vitro* and reduced TxA_2 synthesis. Thus, it is reasonable to conclude that nabumetone in such test systems appears as a COX-1/COX-2 inhibitor.[170] Furthermore, it is difficult to make a reasonable comparison from available *in vitro* data of the capacity of the different COX inhibitors to block COX-1 and inhibit platelet TxA_2 production *in vivo*. It is likely that a single dose of aspirin 100mg as well as aspirin 30–75 mg/day for 1 week both induce a more effective platelet COX-1 inhibition than a therapeutic dose of nabumetone. Proper comparative studies have not yet been performed, but based on current evidence it would not be surprising if such studies should demonstrate a largely similar inhibitory effect on platelet COX-1 of the two agents.

4.2.3 COX-2 Inhibitors

Leese and coworkers[171] investigated the effect of a supratherapeutic dose of celecoxib 600mg twice daily compared with a standard dose of naproxen 500mg twice daily in 24 healthy volunteers. Platelet activity was evaluated by bleeding time, aggregometry and serum TxB_2. The study demonstrated that even at these high doses, celecoxib did not interfere with normal platelet activity, providing evidence for a high degree of COX-2 selectivity for celecoxib and consequently the lack of platelet effects of such therapy.[171]

The results from the recent VIGOR study have led investigators to speculate whether naproxen has a cardioprotective effect.[160,162,163] If such an effect is present during naproxen therapy, a similar effect should also be present after long-term nabumetone treatment since the two agents seem to inhibit platelet COX-1 to a similar extent.[20,21] However, such an effect is not present with the selective COX-2 inhibitors celecoxib and rofecoxib.

Hennan et al.[172] studied the effect of aspirin and celecoxib on thrombogenic mechanisms experimentally in the dog. Mechanisms of coronary thrombosis and coronary vasodilatation were investigated in their experimental model. The authors found that celecoxib counteracted the anti-thrombotic preventive effect of aspirin. Moreover, celecoxib inhibited arachidonic acid-induced vasodilatation in coronary arteries, which led the authors to conclude that: "The results indicate important physiological roles for COX-2-derived prostacyclin and raises concerns regarding an increased risk of acute vascular events in patients receiving COX-2 inhibitors. The risk may be increased in individuals with underlying inflammatory disorders, including coronary artery disease".[172]

In another recent work by Konstam et al.[173] a pooled analysis was made of all studies with the COX-2 inhibitor rofecoxib regarding Antiplatelet Trialists' Collaboration adverse events (cardiovascular death, death from bleeding, sudden death, nonfatal myocardial infarction [MI] and nonfatal stroke).[173] The authors stated that: "This analysis provides no evidence for an excess of [cardiovascular] events for rofecoxib relative to either placebo or the non-naproxen COX inhibitors that were studied. Differences observed between rofecoxib

and naproxen are likely to be the results of the antiplatelet effects of the latter agent". There have been several comments on this work, emphasising that alternative interpretations are possible. Also, from a methodological point of view, this is a retrospective meta-analysis pooling different patient groups. For example, results from 6-week studies were mixed with studies of 15 months' and 4 years' duration. In addition, studies were mixed regarding when aspirin was and was not allowed.[173]

In a recent, very interesting study, Catella-Lawson and coworkers[145] found that ibuprofen inhibited the irreversible acetylation of platelet COX-1 induced by aspirin. Such an effect was not present for celecoxib.[145] The authors concluded that in order to obtain a cardioprotective effect, aspirin should be taken 2 hours before ibuprofen and that ibuprofen by itself could reduce the cardiac protective effect by aspirin if this interaction is not considered. Thus, given these results, there are reasons to perform detailed studies on platelet COX-1 acetylation for a number of COX-1/COX-2 inhibitors as well as selective COX-2 inhibitors when combined with aspirin.[145,174] Van Solingen et al.[175] studied the effect of ketoprofen 200 mg/day with and without coadministration of aspirin 325 mg/day on platelet aggregation as well as serum TxB_2.[175] After a daily intake during 1 week, ketoprofen alone reduced serum TxB_2 by 85% compared with an 84% reduction during concomitant medication with ketoprofen and aspirin.[175]

Taken together, the current clinical data are relatively consistent regarding the effect of highly selective COX-2 inhibitors on platelets, of which there are few. However, it remains unclear what impact the platelet effects of the COX inhibitors may have on cardiovascular morbidity and mortality. Clearly, several studies on nonselective COX-inhibitors demonstrate cardioprotective effects, while other studies on selective COX-2 inhibitors have shown an interference with the cardioprotective effects of nonselective COX-inhibitors.

4.3 Cardiovascular Adverse Effects of COX Inhibition

As discussed in section 4.2, COX-2 inhibitors lack major effects on platelet function and, thus, cardioprotective effects. The potential of COX-2 inhibitors to increase the risk of cardiovascular events in patients with arthritis/musculoskeletal pain has emerged as a major concern in comparison with treatment with conventional COX-1/COX-2 inhibitors.[157] The reasons for this concern are that any beneficial effects of the selective COX-2 inhibitors related to GI safety could potentially be outweighed by this potential increased cardiovascular risk of these novel agents or indeed compared with the cardioprotective effects of aspirin or several conventional nonselective COX inhibitors.

4.3.1 COX-1/COX-2 Inhibition

Aspirin has been shown to be effective in the secondary prevention of vascular disease in hypertensive patients.[176] However, the effectiveness of traditional COX-1/COX-2 inhibitors in this respect is largely unknown, since prospective, controlled trials are, as yet, limited.[177,178] Data from an initial case-control analysis may suggest that COX-1/COX-2 inhibitors may not reduce the risk of a first MI.[179] COX-1/COX-2 inhibitors, unlike aspirin, bind in a reversible manner to the active site of the COX enzyme, usually depressing COX-1-dependent platelet thromboxane formation to the degree that platelet function is inhibited only for a portion of the dose administration interval.[180]

According to current dogma, COX-1 is constitutively expressed in cultured endothelial and vascular smooth-muscle cells while the expression of COX-2 is increased by a number of agents, such as cytokines, growth factors, phorbol esters and lipopolysaccharide in endothelial and vascular smooth muscle cells, and by injury to the vasculature. On the basis of these observations it has been suggested that COX-2 is involved in the increase of prostacyclin formation during clinical syndromes related to platelet activation.[181] COX-2, as well as COX-1, expression is upregulated in foam cells and smooth-muscle cells in atherosclerotic plaques.[14] COX-2 inhibitors decrease urinary excretion of prostacyclin metabolites in healthy individuals, [182,183] which is indicative of a decreased prostacyclin production.[184] An important function of COX-2 in endothelial cells is that laminar shear forces increase prostacyclin expression *in vitro*[185] and may do so also in endothelial cells in healthy individuals.[183] Therefore, prostacyclin, as well as vascular COX-2,

may be a part of a homeostatic defence mechanism limiting the consequences of platelet activation *in vivo*.[181]

In support of this, *in vivo* biochemical studies suggest that selective COX-2 inhibition could alter the platelet-blood vessel wall homeostasis mediated by a balance between TXA_2 and prostacyclin effects, where TXA_2 acts as a vasoconstrictor and promotes platelet aggregation, while prostacyclin acts as a vasodilator and inhibits platelet aggregation. Administration of COX-2-selective inhibitors such as celecoxib or rofecoxib to healthy volunteers resulted in a suppression of *in vivo* prostacyclin production as measured by its urinary metabolite, while there was no effect on platelet TXA_2 production.[182,183] This is in contrast to the effects of low-dose aspirin, which induces suppression platelet TXA_2 production while it has relatively minor effects on vascular prostacyclin production.[150,186]

4.3.2 Nabumetone

Nabumetone has been compared with indometacin with regards to the cardiovascular and renal responses to exercise in healthy volunteers.[187] Neither compound, given as a daily dose of nabumetone 1g or indometacin 100mg during rest or exercise, had any effect on arterial blood pressure (BP), cardiac output, renal responses or plasma catecholamines.

COX inhibitors have frequently been reported to interfere with the BP-lowering effects of a number of antihypertensive drugs.[188] In a study by Thakur et al.,[189] nabumetone did not influence the antihypertensive response of a fosinopril and hydrochlorothiazide combination in hypertensive women with arthritis.

In another larger study involving 1042 patients with OA of the knee, rofecoxib 12.5mg or nabumetone 1g was given over a 6-week treatment period.[79,162] The primary objective was to compare the therapeutic efficacy of the two treatment alternatives. In this trial, there were similar proportions of patients in the nabumetone and rofecoxib groups that experienced hypertension or increased BP. However, there were more patients who reported oedema-related adverse events in the rofecoxib group, which led the evaluator to conclude that: "An increase in cardiovascular events at higher doses of rofecoxib cannot be excluded".[79,162]

In another similar trial (n = 978),[79,162] nabumetone 1g was compared with rofecoxib 12.5mg or placebo, also in patients with OA of the knee, for 6 weeks. In this study there were significantly more patients discontinuing rofecoxib treatment because of clinical adverse experiences (7.4%) compared with nabumetone (3.8%) or placebo (3.6%). There were no deaths in the study, but significantly more serious adverse experiences were reported on rofecoxib therapy (2.3%) compared with nabumetone (0.5%) or placebo (0.5%).[79,162] Furthermore, in this study there were significantly more reports with one or more adverse experiences in rofecoxib patients (56.4%) compared with nabumetone (49.2%) or placebo (42.9%). In addition, there were six serious cardiovascular adverse experiences (MI, cerebrovascular accident, atrial fibrillation) in the rofecoxib-treated patients compared with two such experiences (congestive heart failure, MI) in patients treated with nabumetone and one (coronary artery occlusion) in the placebo group.

A recent study by Palmer and coworkers[190] showed that nabumetone therapy was well tolerated in patients with antihypertensive therapy and on a par with COX-2 therapy.[190] They performed a double-blind study in which 385 hypertensive patients were stabilised on an ACE inhibitor and concomitantly treated with nabumetone, celecoxib, ibuprofen or placebo for 4 weeks. This was an experimental study in patients without RA or OA. Ibuprofen caused significantly greater increases in systolic ($p < 0.001$) and diastolic ($p < 0.01$) BP compared with placebo, but not nabumetone or celecoxib. The proportion of patients with systolic BP increases of clinical concern at endpoint was significantly higher ($p < 0.001$) for the ibuprofen group (16.7%; 15 of 90), but not for the nabumetone group (5.5%; 5 of 91) or the celecoxib group (4.6%; 4 of 87) compared with the placebo group (1.1%; 1 of 91).

4.3.3 COX-2 Inhibitors

Specifically, since the COX-2-selective agents rofecoxib and celecoxib lack antiplatelet properties, one could anticipate that there would be an increased risk of cardiovascular events in high-risk

patients compared with COX-1/COX-2 inhibitory agents. In the VIGOR study, which included 8076 patients, rofecoxib was compared with naproxen.[160] In this study there were an increased number of MIs in the patient group receiving rofecoxib. In the rofecoxib group 0.4% (n = 111) of patients had a MI compared with 0.1% (n = 50) in the patient group receiving the nonselective COX-1/COX-2 inhibitor naproxen over the follow-up period.[160] The increased incidence of MIs in the patient group randomised to rofecoxib has been ascribed to the lack of platelet effects[159] of the COX-2 selective agent rofecoxib.

Although there was a 4-fold increase in MI in patients on the COX-2 inhibitor in the VIGOR study,[160] in the CLASS study which compared celecoxib with ibuprofen or diclofenac, the rate of MI did not differ between groups.[161] One difference between the two studies was that low-dose aspirin was allowed when indicated in the CLASS study, where approximately 20% of patients took low-dose aspirin. This was not permitted in the VIGOR study, although a further and later analysis of the VIGOR study cohort showed that 4% of patients met clinical criteria for low-dose aspirin treatment but were not taking it. Interestingly, 38% of patients who had a MI event were in this subgroup. These results have been interpreted as showing that selective COX-2 inhibition may provoke MI clinical events in patients at risk and that low-dose aspirin or nonspecific COX inhibition may be protective in these patients.[73,157,176,177]

In the VIGOR study, the increased cardiovascular risk seen with rofecoxib relative to naproxen may be explained by the actions of COX-2 inhibition or the lack of platelet COX-1 inhibition. This effect is likely to have been absent or reduced in the CLASS study, where low-dose aspirin was allowed in those patients who had indications for such therapy. Therefore, one may argue that an increased cardiovascular risk, if confirmed, may be a class effect of COX-2 inhibitors and not specific for rofecoxib only. On the basis of these findings and arguments, there has been speculation as to whether an increase in cardiovascular risk of COX-2 inhibition would balance estimates of lives lost as a result of COX-1-/COX-2-related major upper GI events.[161]

In Australia, calculated COX-1-/COX-2-induced upper GI haemorrhage- and bleeding-related deaths has amounted to 100–200 patients each year.[191] If there was an increase in ischaemic heart disease deaths of 100–200 per annum this would amount to an increase of only 0.34–0.68% of deaths per year.[192] Thus, only a very small proportionate increase in ischaemic heart disease death related to COX-2-selective inhibitors would outweigh any advantage of reduced upper GI mortality compared with conventional platelet inhibitory COX-1/COX-2 inhibitors.

In addition to this, British as well as Australian committees on safety of medicines have reported that the spectrum of adverse effects for the selective COX-2 inhibitors includes morbidity as well as mortality related to PUBs.[192,193] Moreover, there were also significant numbers of cardiovascular and renal adverse events among the spectrum of adverse effects reported.

Additional evidence from case reports may also indicate that use of COX-2 inhibitors could exacerbate thrombotic disease. Two patients with connective tissue diseases and medical histories suggestive of antiphospholipid syndrome both developed arterial occlusions after celecoxib.[194] Thus, on a population level, deaths from upper GI toxicity related to nonselective COX-1/COX-2 inhibitors or preferential COX-2 inhibitors may well be balanced by their cardiovascular protective effects in patients at high risk.[178] Thus, the previous focus on safety of COX-2-specific inhibitors in relation to upper GI events may have overlooked the obvious and clinically important fact that COX-1/COX-2 inhibitors have beneficial cardiovascular actions, which do provide sizeable reductions in cardiovascular morbidity and mortality.

4.4 Renal Adverse Effects of COX Inhibition

In the kidneys, prostaglandins maintain a normal renal blood flow (RBF) and normal GFR by balancing a number of vasoconstrictor stimuli.[195-199] Renal COX-1 is constitutionally expressed in endothelial cells, in smooth muscle cells, in glomeruli and in the cells of the tubular collecting duct system.[200-202] The location of COX-1 in the kidneys indicate that prostaglandins are of local haemodynamic importance as well as having a direct effect on the salt-

water excretion.[201,202] Renal COX-1 is responsible for prostaglandin synthesis under normal conditions but, in contrast to several other tissues, there is also a relatively pronounced constitutive expression of COX-2 under normal physiological conditions.[199,201,203,204] In experimental animals, this expression takes place in the renal medulla and macula densa.[202,205,206] In addition, COX-2 activity is increased during conditions of salt and water restriction,[201,202] which indicates that prostaglandin synthesis via COX-2 plays a role in the regulation of the salt-water balance and renal haemodynamics during normal physiological as well as pathophysiological conditions.

4.4.1 COX-1/COX-2 Inhibition

COX-mediated inhibition of prostaglandin synthesis via COX-1 results in a reduction of RBF and GFR, as well as salt and water retention since there is an inhibition of the vasodilatory effect of the prostaglandins on the renal vascular bed.[207,208] The effects of COX-1 inhibition are largely dose related and a 20–50% reduction of RBF and GFR can be seen within 24–48 hours after drug administration.[207] In some patients or individuals at high risk, acute renal failure may develop.[209] Patients at particular risk for adverse effects affecting renal function are those who have an activated renin-angiotensin system, such as during salt and water restriction or individuals who already have a reduced RBF and GFR through other mechanisms or diseases.[207-209] In such individuals, maintenance of an intact renal haemodynamic function is critically dependent on intact prostaglandin synthesis and homeostasis. However, the risk of renal adverse events by COX-mediated prostaglandin inhibition is minimal in individuals with a normal renal function.[208] When symptoms do appear in individual patients, they vary from moderate weight increase, peripheral oedema, increased BP or precipitation of hyperkalaemia to overt congestive heart failure or even acute renal failure.[207-209] The negative effects on RBF and GFR become apparent within a few days after initiation of treatment with COX inhibitors, while symptoms related to an increased salt and water retention usually appear after a longer time on therapy.[207-209] In order to detect untoward renal effects by COX inhibitors, it is important to closely monitor patients who are at an increased risk for developing renal adverse effects. This can be done by simple tests reflecting renal function, such as control of serum creatinine 1 week after start of treatment with a COX inhibitor.

Apart from functionally related adverse effects on the renal function, COX-1 inhibitors may also exert direct nephrotoxic effects, which may lead to interstitial renal damage and pronounced proteinuria.[207,208,210] However, this type of adverse effect is relatively uncommon. The time span to its development may vary from days to months after exposure to COX inhibitor treatment and the renal damage does not appear to be directly related to the inhibition of prostaglandin synthesis. In most patients the renal damage is fully or partially reversible after cessation of the COX-1 inhibitor therapy.[207]

4.4.2 Nabumetone

After hepatic conversion from nabumetone, 6-MNA inhibits COX-2 as well as COX-1 in a COX-2 preferential manner. Several well controlled studies have investigated the renal effects of nabumetone in humans.[77,211-213] In these studies, nabumetone was compared with placebo, indometacin, sulindac and ibuprofen, but none of the studies investigated the renal effects of nabumetone compared with a COX-2-selective inhibitor such as rofecoxib or celecoxib. However, most studies have investigated relatively small patient groups during short durations of therapy, commonly between 1 and 4 weeks. Moreover, the studies have generally not included patients with known renal disease, congestive heart failure or patients with a negative salt-water balance, but rather included patient groups at low risk for renal adverse events. Results from such studies show that patients with a low risk for renal adverse effects from COX inhibition have had no apparent untoward effects of nabumetone on renal function. Furthermore, there are no reports of interstitial renal damage during therapy with nabumetone as yet.

Thus, the renal effect profile of nabumetone appears to be qualitatively similar to the type of renal adverse event profile seen with nonselective COX-1/COX-2 inhibitors. Available documentation for nabumetone further indicates that there is a low incidence of such renal adverse events in individuals with a normal renal function without any other

known risk factors for renal damage by COX inhibition.[77,211-213]

4.4.3 COX-2 Inhibitors

While the renal consequences of nonselective COX inhibition are well characterised, the effects of selective COX-2 inhibition on renal function and structure are to date less well known. Brater and coworkers[204] reviewed the renal effects of selective COX-2 inhibitors and concluded that COX-2-selective inhibitors and nonselective COX inhibitors induce similar reductions in urinary prostaglandin excretion and GFR as well as similar degrees of salt-water retention. Thus, it is unlikely that selective COX-2 inhibition would result in a different spectrum of renal adverse events compared with nonselective COX inhibitors. Indeed, current research and clinical experience show that selective COX-2 inhibitors as well as nonselective COX-1/COX-2 inhibitors share a similar renal adverse event profile.[201,202,214] Thus, COX-2-selective inhibitors should be used with similar restrictions as nonselective COX-1/COX-2 inhibitors in patient groups at increased risk for renal adverse events, that is, patients with reduced renal function, diabetes mellitus or congestive heart failure. Current postmarketing experience and adverse event or side effect reporting also indicate that COX-2-selective inhibitors may induce interstitial renal damage as expected as a result of the presence of COX-2 in the renal medulla.[201,215,216]

As mentioned in section 4.4.1, selective COX-2 inhibitors seem to share a similar renal adverse event profile to the nonselective COX-1/COX-2 inhibitors or a preferential COX-2 inhibitor. Thus, from a renal point of view it is questionable whether or not COX-2 inhibitors provide any advantage over conventional COX-1/COX-2 inhibitors.

5. Hepatic Adverse Effects of COX Inhibition

Elevations in serum transaminase levels may occur with nabumetone therapy, which is similar to other COX-inhibitors. Thus, there are some reports of elevations in alanine transaminase (ALT) and aspartate transaminase (AST) in patients receiving nabumetone, but the incidence of marked elevations of serum transaminase levels in major clinical trials was <1%.[31,80] In patients with symptoms and/or signs suggestive of liver dysfunction, or in whom an abnormal liver function test has occurred while receiving COX inhibitor treatment, an evaluation for evidence of a more severe hepatic reaction should be performed.

In long-term safety studies of nabumetone, marked elevations in ALT and AST were observed in only 0.4% of treated patients.[80] Similar results were also reported by Jackson et al.[31] in a study cohort of more than 1900 patients from which ten patients withdrew because of liver function test abnormalities. No clinically important changes or trends were apparent in the remaining patients as assessed by the predefined abnormal test definition (AST and ALT >100% of normal range). However, in this patient cohort there was a trend toward an elevation of lactate dehydrogenase.[31] In another large patient study comparing the safety experience of nabumetone and four other COX-1/COX-2 inhibitors, patients were randomised to one of the following groups: nabumetone 1–2 g/day (n = 3315); diclofenac 100–200 mg/day (n = 296); naproxen 500–1000 g/day for OA patients or 1500 g/day for RA patients (n = 279); ibuprofen 1.2–3.2 g/day (n = 235); or piroxicam 10–20 mg/day (n = 286). Of the five COX-1/COX-2 inhibitors studied, diclofenac was the only agent associated with significant elevations of transaminases (at least two to three times the upper limit of normal).[217] With diclofenac therapy, the incidence of AST elevation was 1.1% compared with 0.2% with nabumetone ($p < 0.01$). For the other three COX inhibitors the incidence of ALT elevation was 0% for piroxicam and 0.4% for naproxen and ibuprofen, respectively. In another study investigating patients aged 65 years or more, the incidence of abnormal hepatic function related or probably related to nabumetone therapy was 0.4% (n = 1392) compared with 3.3% (n = 174) of patients treated with diclofenac ($p < 0.04$).[218]

Thus, from a hepatic point of view, nabumetone appears to be a safe alternative in a wide range of patients.

6. Comparison of Adverse Events Spectrum Between COX-1/COX-2 and COX-2 Selective Inhibitors

The optimal ratio of COX-2 to COX-1 inhibition for obtaining an anti-inflammatory response and an acceptable safety profile of an anti-inflammatory agent is not yet settled. While COX-1 previously was thought to be important in maintaining cellular homeostasis (e.g. in the GI tract, kidney and platelets), COX-2 was considered to be induced during inflammatory states.[219] However, more recent evidence in COX-1 knockout mice suggests that COX-1 may also play a role in the inflammatory process. Langenbach et al.[86] showed a reduced inflammatory response to arachidonic acid in such animals, while COX-2 knockout mice were still able to show inflammatory responses.[220] There is also evidence suggesting that COX-2 may play an important role in GI epithelial integrity and GI ulcer healing,[89,90,221] bone and cartilage repair,[222] renal haemodynamics and function[223,224] and ovarian function.[225] These studies, except the one by Stichtenoth et al.[223] which was performed in healthy volunteers and demonstrated that COX-2 is responsible for the prostaglandin synthesis-mediated renin release, were all performed in animal models. In 40 healthy salt-depleted volunteers, Rossat et al.[226] showed that a selective COX-2 inhibitor at higher doses reduced GFR and renal plasma flow compared with baseline. It is possible that COX-1 and COX-2 have overlapping functions in inflammatory states and during normal physiological conditions.[227,228] In order to determine the physiological roles of COX-1 and COX-2 and the possible clinical relevance of such findings, well controlled clinical trials are needed to properly assess the relative inhibition of COX-1 and COX-2 with respect to safety as well as efficacy.

The efficacy, safety and tolerability of nabumetone were compared with rofecoxib and placebo in 341 OA patients aged ≥80 years.[229] In this trial, the primary efficacy endpoint, Patient Global Assessment of Disease Status, was similarly reduced for the two active treatments versus placebo. Secondary endpoints, including the three Western Ontario and McMaster Universities OA Index (WOMAC) subscales (pain, stiffness and disability) and the Investigator Global Assessment of Disease Status, were consistent with the primary endpoint. There were no significant between-group differences in the proportions of patients who discontinued treatment as a result of clinical adverse events or abnormal laboratory values. Renal adverse experiences such as oedema and hypertension were similar for rofecoxib and nabumetone. There were no gastroduodenal ulcers reported in the trial. From these data, the authors concluded that in OA patients ≥80 years, clinical efficacy for rofecoxib 12.5 and 25mg once daily was similar to that of nabumetone 1.5g. Moreover, and importantly, both the selective COX inhibitor rofecoxib and the COX-1/COX-2 prodrug nabumetone were well tolerated in this elderly study cohort.

7. Conclusion

Since the start of clinical use of aspirin more than a century ago,[230] there has been a quest for agents with anti-inflammatory properties equal or better than aspirin but with decreased toxicity. As a result of this, a wide range of COX inhibitors have been developed and become clinically available over the past five decades. Although the anti-inflammatory efficacy of these agents has remained largely similar, there has been a focus on finding COX inhibitors with a more beneficial adverse effect profile, in particular related to GI ulcers or bleeding complications as well as cardiovascular, haematological and renal adverse events. Importantly, in spite of the fact that many promising agents from the COX inhibitor class have been developed over the years, the true and complete adverse event profile for any individual agent only becomes apparent after many years of clinical use in large patient populations the clinic. The choice of a specific COX inhibitor for patients with OA, RA or other inflammatory disorders should ideally be based on such critical evaluations of therapeutic benefit versus individual risks.

Nabumetone is a chemically distinct COX inhibitor prodrug that is converted to its active metabolite, 6-NMA, which acts prostaglandin synthase inhibitor by a dual blockade of COX-1/COX-2. In clinical use nabumetone exhibits an anti-inflammatory efficacy that is similar to a wide range of other COX-1/COX-2 as well as selective COX-2 inhibitors. In terms of safety, nabumetone has been extensively evaluated in large postmarketing surveillance stud-

ies showing that it is well accepted by patients with a very low incidence of liver or kidney damage and bone marrow suppression as well as precipitation of heart failure or oedema. Interestingly, there is also a low incidence of cardiovascular complications, which may be due to the fact that the 6-MNA metabolite of nabumetone provides a dose-dependent inhibition of platelet aggregation.

A major clinical drawback associated with the long-term use of a COX inhibitor is that of GI PUBs.[82] For most COX inhibitors, the incidence of PUBs ranges between 2% and 4% per year, and increases significantly in the presence of certain risk factors.[83] For nabumetone, the cumulative incidence of PUBs in large clinical trials and postmarketing surveillance studies is considerably less, and ranges between 0.02% and 0.95%. The reason behind this lower incidence of PUBs is considered to be due to the nonacidic nature of the parent nabumetone compound as well as the lack of enterohepatic circulation.[28] These properties of nabumetone are thought to be the main reasons for the improved GI safety profile of this agent. In recent studies on a comparatively small number (341) of elderly OA patients, nabumetone 1.5g has been compared with rofecoxib 12.5 and 25mg in terms of efficacy and safety,[229] in particular, GI or cardiovascular/renal adverse experiences. These studies did not demonstrate any differences in the GI/cardiovascular/renal safety profile between the agents, nor were there any differences in the clinical efficacy in elderly OA patients. These data provide evidence that nabumetone may offer a similar degree of GI safety as the COX-2-selective agent rofecoxib. In addition to that, nabumetone may, in contrast to a COX-2 inhibitor, offer platelet inhibitory properties by an action on COX-1.

In conclusion, nabumetone is a COX-1/COX-2 inhibitor prodrug that has been clinically available for the management of RA, OA and other rheumatic disorders for approximately two decades. Current evidence shows that long-term nabumetone treatment of such disorders may also offer patients a GI safety profile that is superior to nonselective COX-1/COX-2 inhibitors and seems to be similar to that of a COX-2 selective inhibitor, albeit with preserved cardiovascular preventive properties.

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