Gastrointestinal Safety of Nabumetone

a report by
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Non-steroidal anti-inflammatory drugs (NSAIDs) are the most widely used agents for the treatment of painful conditions in which the physiopathological basis is an inflammatory process. Nevertheless, owing to the array and intensity of their side effects, NSAIDs have garnered considerable controversy both within the scientific community as well as in society in general. Notable among these side effects are several gastrointestinal maladies such as ulcers, perforations and bleedings in different areas of the digestive tract, as well as hepatic and renal toxicity. Moreover, the past decade has witnessed reports on the cardiovascular side effects of these drugs. A representative example of these reports is a publication by Wolfe et al. in which the number of deaths attributed to NSAIDs in the US in 1997 was reported as 16,500, nearly the same as that reported for HIV (16,685), and considerably higher than that reported for multiple myeloma (10,503). Hence there is a need to develop NSAIDs that are safe and that provide analgesic, anti-inflammatory and anti-pyretic efficacy.

Nabumetone is an NSAID with a good hepatic and renal safety profile and an excellent gastrointestinal safety profile, making it a sound choice for the treatment of chronic conditions such as rheumatoid arthritis (RA) and osteoarthritis (OA). Given the age, pluripathology and polymedication of the patients that suffer these conditions, their treatment demands a strong analgesic that is very safe for the gastrointestinal (GI) tract.

Pharmacological Characteristics of the Molecule

Nabumetone is a non-acidic, non-steroidal pro-drug whereby the active metabolite is 6-methoxy-2-naphthylacetic acid (6-MNA), which is formed after absorption through first-pass metabolism, and which is a more potent specific inhibitor of cyclooxygenase 2 (COX-2) than is the parent compound. Nabumetone is metabolised in three primary pathways: O-demethylation, reduction of the ketone to an alcohol and oxidative cleavage of the side-chain to afford acetic derivatives. No unmetabolised compound. Nabumetone is metabolised in three primary pathways: O-demethylation, reduction of the ketone to an alcohol and oxidative cleavage of the side-chain to afford acetic derivatives. No unmetabolised 6-MNA is excreted and <1% of unmetabolised 6-MNA is excreted, of which 80% can be recovered from urine and another 10% from faeces.

Gastric Safety

Early pre-marketing individual studies suggested that nabumetone had a better gastrointestinal safety profile than do other NSAIDs. These studies were based on the incidence of serious GI events such as perforations, ulcers and bleeding. The incidence of these effects in pre- and post-marketing studies ranges from 0.02% to 0.95%.

In one analysis on nabumetone safety, based on 1,677 patients with either RA or OA, 17 patients developed ulcers, although the majority of these patients did not present any major complications. The Kaplan-Meier curve for the entire group of nabumetone-treated patients revealed that the risk of suffering a gastric ulcer was 0.3% (95% confidence interval [CI], 0.0, 0.6) at six months; 0.5% (95% CI 0.1, 0.9) at one year; 0.8% (95% CI 0.3, 1.3) at two years; and 2.35% (95% CI 1.1, 3.59) at six years. For the studied period of six years, the calculated annual risk was 0.4% per year (95% CI, 0.6 upper limit).

To evaluate the safety and efficacy of nabumetone a large randomised controlled multicentre trial was conducted in 450 rheumatology offices. Each investigator performed his own two-arm study and could choose from ibuprofen, piroxicam, diclofenac or naproxen. Three thousand, three hundred and fifteen patients were randomised to nabumetone, 279 to naproxen, 296 to piroxicam, 296 to diclofenac and 235 to ibuprofen. The nabumetone group had one detected ulcer. The comparators had a total of six ulcers (p= 0.001).

Combined data of seven randomised studies and this last trial give a total of 6,732 patients with OA and RA treated. This analysis showed that nabumetone use was associated with a significant lower incidence of perforations, ulcers and bleedings than a group of conventional NSAIDs including diclofenac, indomethacin, piroxicam, naproxen and ibuprofen (0.03%; 95% CI: 0.0%-0.08% versus. 1.4%; 95% CI: 0.5%-2.4% – see Figure 1).

Huang et al. performed another meta-analysis of various clinical trials in which they analysed the differences in GI events as well as the incidence of perforations, ulcers and bleedings among patients treated with either nabumetone or conventional COX-1/COX-2 inhibitors. The authors identified 13 studies comprising 29 treatment arms and a total...
Relifex® produced 36 times less symptomatic perforations, ulcers and bleedings than the comparator NSAIDs (OR 35.5; 95% CI: 5.756)³

Recommended dose in osteoarthritis is 1-2 g/day given as a single daily dose⁴

Abbreviated Prescribing Information Please refer to your local full Summary of Product Characteristics when prescribing.

Name and composition: Relifex® film-coated tablets and dispersible tablets containing 500 mg or 1 g of nabumetone (country-specific).

Indications: Osteoarthritis and rheumatoid arthritis.

Dosage: 1-2 g taken as a single dose at bedtime or as directed by the physician.

Contraindications: Hypersensitivity to nabumetone or any of its excipients.

Warnings: Avoid use in patients with a history of severe hepatic impairment. High blood pressure may be the first sign of acute pancreatitis.

Precautions: Use with caution in patients with impaired renal function.

Adverse effects: Common side effects include dizziness, drowsiness, nausea, vertigo, and gastrointestinal symptoms. Rare side effects include gastrointestinal bleeding, ulceration, and perforation. Headache, dizziness, drowsiness, confusion, sedation, depression, insomnia, dizziness, tinnitus, abnormal vision, chest pain, nausea, vomiting, haematemesis, ulcerative stomatitis, gastritis, hypotension, gastrointestinal bleeding, ulceration, and perforation.

of 49,501 patients that met their pre-defined criteria. No significant differences among the individual tests were found by heterogeneity testing. The most prevalent side effects were the dyspeptic symptoms of flatulence, constipation and diarrhoea, which accounted for 98.6% of total adverse GI effects. Of greatest importance is the fact that the patients treated with conventional COX inhibitors suffered significantly more side effects than those treated with nabumetone (p=0.007); incidence of perforations, ulcers and bleedings were 10 to 36 times higher in the former group when the values were adjusted for patient-exposure years.

**Intestinal Safety**

Studies on GI safety are focused on major events observed in the oesophagus and stomach. For several years, some researchers have pursued research on the small intestine, an area relatively inaccessible by conventional studies. In fact, certain inflammatory phenomena in the small intestine that are traditionally associated with minor bleeding and protein loss can lead to iron deficiencies and/or hypoproteinaemia.10 Sighothorson et al. performed an elegant study11 in which they demonstrated for the first time that intestinal permeability test dose composition and osmolarity must be taken into account when predicting the consequences of a given NSAID on intestinal integrity. They went on to report that ingestion of conventional NSAIDs caused inflammatory changes in the small intestine, but that ingestion of aspirin or of nabumetone did not lead to these changes.

**Nabumetone**

Nabumetone is an NSAID with a good hepatic and renal safety profile, and an excellent gastrointestinal safety profile, making it a sound choice for the treatment of chronic conditions such as rheumatoid arthritis and osteoarthritis.

**Why Does Nabumetone Have a Good Gastrointestinal Safety Profile?**

The low incidence of perforations, ulcers and bleedings observed in the aforementioned clinical trials of nabumetone are most likely the result of its unique pharmacological profile. In contrast with conventional NSAIDs, which are primarily acidic, nabumetone is non-acidic, hence it does not readily dissociate in the gastric lumen. As nabumetone is a pro-drug, even if it does penetrate the mucosal gel layer to enter the gastric epithelium, it remains inactive and thus has no effect upon prostaglandins.12

Conventional NSAIDs (e.g. indomethacin, diclofenac, naproxen, piroxicam, meloxicam, sulindac and etodolac) are repeatedly exposed to the gastric mucosa because they undergo enterohepatic circulation, which occurs upon absorption of the drug in the duodenum, processing by the liver and secretion in bile. Part of the bile refluxes back into the stomach, carrying with it some of the secreted NSAID, thus creating a continuous cycle between the bile and the stomach and, consequently, causing an ever-increasing amount of NSAID to be absorbed by the stomach. Repeated exposure of the NSAID to the hepatic parenchyma amplifies its hepatotoxic effects.

Nabumetone undergoes first-pass hepatic metabolism. It is converted to its active metabolite 6-MNA, and inactive metabolites, in the liver. 6-MNA is eliminated in the urine as a conjugate or as a dimethylated metabolite. Most importantly, 6-MNA does not undergo enterohepatic recirculation, and thus is not re-exposed to the gastric mucosa.13

Since its approval by the US Food and Drug Administration (FDA) in 1991, the NSAID nabumetone has consistently proven its efficacy and safety, especially in terms of GI side effects. It offers an excellent risk/benefits ratio, making it the treatment of choice for chronic pain and inflammatory rheumatic diseases suffered by older patients with pluripathology and polymedication.