Results from a patient survey to assess gastrointestinal burden of non-steroidal anti-inflammatory drug therapy contrasted with a review of data from EVA to determine satisfaction with rofecoxib

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Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) have frequently been linked with unpleasant gastrointestinal (GI) side-effects such as dyspepsia and ulcers. The present study investigated the burden of NSAID therapy from a patient perspective and also reviewed previously published data on satisfaction with a less gastrotoxic anti-inflammatory drug, rofecoxib. A questionnaire was sent to >6000 members of the Norwegian Rheumatism Association requesting information on use and toxicity of NSAID therapy and requirements for supplementary gastroprotective and analgesic medication. The questionnaire confirmed a high incidence of NSAID use. About two-thirds of users changed brands of NSAIDs at least once, usually because of adverse effects and poor efficacy. Supplementary over-the-counter (OTC) and prescription analgesics were required by 72 and 59% of patients, respectively, while OTC and prescription gastroprotective agents to treat NSAID toxicity were required by 35 and 30%. This new patient-focused survey showed that treatment with conventional NSAIDs was unsatisfactory in terms of GI toxicity and sub-optimal pain relief. Reviewing EVA (Experience with VIOXX in Arthritis) data showed that there was a high level of approval for rofecoxib, with >80% of 74192 osteoarthritis (OA) patients expressing a preference for continuing such therapy. Preference for rofecoxib was significantly higher among patients with prior experience of conventional NSAIDs or other OA-specific medication. In EVA, the reduced GI toxicity of rofecoxib previously reported in other studies appeared to translate into a strong preference to continue this therapy in a large sample of patients. This is not surprising, given the poor satisfaction with NSAIDs highlighted by the Norwegian survey.

KEY WORDS: Rofecoxib, NSAIDs, Survey, Review, Ulcer, Gastropathy, Osteoarthritis, Quality-of-life, Pain.

Introduction

Although non-steroidal anti-inflammatory drugs (NSAIDs) are the most widely used symptomatic remedies for rheumatic disorders [1], they are not ideal because many symptoms are incompletely controlled and their long-term use is associated with significant gastrointestinal (GI) toxicity. Adverse GI effects vary in severity and commonly include nausea, dyspepsia and ulceration; a small but important number of patients develop life-threatening complications such as perforations, obstruction and severe bleeding [2–4]. Estimates of the prevalence of NSAID-related GI toxicities vary, but data consistently demonstrate that such effects are likely to pose a significant problem for users of these drugs. There are more reports on NSAID-related adverse effects submitted to the Food and Drug Administration in the USA and the Committee on Safety of Medicines in the UK compared with any other form of drug treatment and most reports concern adverse reactions associated with the GI tract [5]. Gastric side-effects are costly in terms of human misery and expense to health-care services [1]; so-called ‘nuisance symptoms’ such as nausea and dyspepsia occur commonly and, although they may
not be life-threatening, they have a significant effect on quality of life, while events such as ulceration can be intensely painful and disruptive to normal functioning (P. A. Bjørke, personal communication). The present study investigated the burden of NSAID therapy from the perspective of patients themselves. A survey was performed in Norway which evaluated the consequences of long-term use of NSAIDs, focusing on toxicity and requirements for additional medication to provide adequate analgesia and to treat gastric side-effects. In addition, the preferences of 74 192 osteoarthritis (OA) patients given the opportunity to take a newer, less GI toxic anti-inflammatory drug, rofecoxib (VIOXX, Merck & Co., Inc.), were reviewed using data from the EVA study (Experience with VIOXX in Arthritis) recently carried out in Belgium [6].

Patients and methods

Target survey population

Of the 37 000 members of the Norwegian Rheumatism Association (NRF) sorted according to their postal codes, 6079 (every sixth member on the list) were randomly selected to participate. This ensured a representative geographic distribution of the survey population.

Survey methodology

This was a postal survey. Each selected recipient was sent a two-page questionnaire by direct mail, together with a covering letter from the NRF. Responses were anonymous and this was indicated clearly in the accompanying letter; there was no reward or other inducement offered to elicit a reply. A blanket reminder was sent out a week later, thanking those who had already responded, as a way of increasing response rate.

The period for collection of completed questionnaires was between 8 November and 3 December 1999. These forms were evaluated and the data were analysed by a professional market research organization in Norway.

The questionnaire was divided into two parts. Part A comprised four sections containing a series of questions about direct and indirect costs of the respondent’s rheumatic disease. Part B comprised seven sections focusing on the use of prescribed analgesic/anti-inflammatory agents, with respect to type/brand, frequency, efficacy and toxicity, and contained a series of detailed questions about these parameters, as well as about patterns of usage of both over-the-counter (OTC) and professional market research organization in Norway.

Results

Response rates and demographics

There were 1823 valid replies to the 6079 mailed surveys, giving an overall inclusion rate of ~30%. The majority of responders were adults of middle age and above: 0.7% were 0–10 yr; 0.7% were 11–20 yr; 2.8% were 21–30 yr; 8.7% were 31–40 yr; 16.3% were 41–50 yr; 28.3% were 51–60 yr; 24.8% were 61–70 yr; 15.5% were 71–80 yr; and 2.3% were older than 80 yr.

Current use and efficacy of NSAIDs

A total of 81% of responders to the questionnaire used NSAIDs. Twenty-six different brands were cited, with 9.7% of users currently taking Voltaren (diclofenac, Novartis), 8.9% Napren-E (naproxen, Nycomed Pharma), 8.3% Orudis (ketoprofen, Aventis), 8.3% Arthrotec (diclofenac plus misoprostol, Pharmacia/Searle), 8.0% Ibux (ibuprofen, Weifa), 7.1% Relifex (nap- umetone, GlaxoSmithKline), 7.1% Brexidol (piroxicam, Nycomed Pharma), 5.1% Naprosyn Entero (naproxen, Roche), 4.3% Brufen (ibuprofen, Knoll), 3.7% Naproxen NM (naproxen, NM Pharma), 3.7% Felden (piroxicam, Pfizer), 3.7% Confortid (indomethacin, Alpharma) and 2.9% Pirox (piroxicam, Alpharma), with a combined total of 19.3% using 13 other brands. A total of 68.3% of users took NSAIDs every day, 4.9% took them every 2nd day, 4.6% every 3rd day, 3.5% every 4–5th day, 2.8% every 6–7th day and 16.3% more seldom (n = 1470; Table 1). Efficacy of treatment was rated as excellent in 10% of cases, good in 57%, neutral in 29%, poor in 4% and ineffective in 1% (rounded to nearest whole number).

Previous NSAID usage and reasons for switching

Patients were asked how many different NSAID brands they had used in addition to their current NSAID during the previous 2 yr; 34% used no other brand, but 19% used one other brand, 23% used two others, 15% used three others, 5% used four others and 4% used five or more. The main reasons for switching brands were adverse effects in 52% of cases, poor efficacy in 30%, cost in 2%, other reasons in 9% and unknown in 7% (n = 875; Fig. 1). Among the 1444 patients responding to the question about side-effects, only 18% reported no adverse reactions while taking conventional NSAIDs. Among the reported adverse events, 68% were GI toxicities including abdominal pain, dyspepsia, diarrhoea and ulcers; 36% of all patients reported abdominal pain and 12% reported ulcers (Fig. 2). Other toxicities included headache, dizziness, nausea, itching, rashes and oedema.

<p>| TABLE 1. Frequency of need to use NSAIDs, rescue analgesics and gastroprotective drugs |</p>
<table>
<thead>
<tr>
<th>Frequency of requirement</th>
<th>% of patients needing NSAIDs (n = 1470)</th>
<th>% of patients needing rescue analgesics (n = 1277)</th>
<th>% of patients needing gastroprotective agents (n = 725)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Every day</td>
<td>68.3</td>
<td>30</td>
<td>38</td>
</tr>
<tr>
<td>Every 2nd day</td>
<td>4.9</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Every 3rd day</td>
<td>4.6</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Every 4–5th day</td>
<td>3.5</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Every 6–7th day</td>
<td>2.8</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>More seldom</td>
<td>16.3</td>
<td>37</td>
<td>31</td>
</tr>
</tbody>
</table>

The data are expressed as percentages of users of each type of medication.
Current use of additional rescue analgesic medication

Patients were asked which supplemental OTC rescue medications they used in addition to their currently prescribed NSAID in order to provide adequate analgesia; 62% used paracetamol, 16% used OTC NSAIDs, 12% used aspirin and 28% used no OTC rescue medication ($n = 1643$). Patients were also asked which prescription rescue medications they used in addition to their prescribed NSAID: 50% used Paralgin Forte, Paralgin Major, Paralgin Minor, Pinex Forte (all paracetamol plus codeine, Weifa) or Aorex (dextropropoxyphene plus paracetamol, Alpharma); 4% used Temgesic (buprenorphine, Schering-Plough), Ketodur, Ketorax (both ketobemidone, Pharmacia/Searle) or Nobilan (tramadol, Gruenenthal); 12% used other medications; and 41% used no prescription rescue medication ($n = 1503$). Among users of rescue analgesic medications, 30% used them every day, 8% took them every 2nd day, 7% every 3rd day, 10% every 4–5th day, 9% every 6–7th day and 37% more seldom ($n = 1277$; Table 1).

Current use of additional gastroprotective medication

Patients were asked which OTC gastroprotective medications they used in addition to their NSAID: 26% used Titralac (calcium carbonate, Nycomed Pharma) or Novalucid (antacid mixture, AstraZeneca); 7% used Pepcidin (famotidine, Merck & Co., Inc.) or Zantac (ranitidine, GlaxoSmithKline); 6% used others; and 65% used no OTC gastroprotective agents ($n = 1426$). Patients were also asked which prescription gastroprotective medications they used in addition to their NSAID: 15% used Losec (omeprazole, AstraZeneca), Somac (pantoprazole, Byk Gulden) or Lanzo (lansoprazole, Wyeth-Lederle); 13% used Cimal (cimetidine, Alpharma) or Cimetid (cimetidine, Nycomed Pharma); 1.4% used Cytotec (misoprostol, Pharmacia/Searle); 0.3% used Antepsin (sucralfate, Orion) or De-Nol (bismuth subcitrate, Yamanouchi Pharma); 5% used others; and 70% used no prescription gastroprotective agents ($n = 1100$).

Among users of gastroprotective agents, 38% used them every day, 10% used them every 2nd day, 8% every 3rd day, 7% every 4–5th day, 6% every 6–7th day and 31% more seldom ($n = 725$; Table 1).

Discussion

In this patient-oriented study, the efficacy of NSAIDs such as diclofenac, ketoprofen, diclofenac, nabumetone and naproxen was generally rated as good or better in 67% of patients, but 72% of patients required supplemental OTC analgesics and 59% required supplemental prescription analgesics to control the pain of arthritis adequately and among these, almost a third needed to use such medication every day. Among the 875 patients switching brands of NSAIDs, 30% did so because of poor efficacy. The phenomenon of 'preparation-hopping'
is known to be higher with NSAIDs than with any other class of drugs and this may be related to their inability to control most symptoms of OA completely [1]. Overall, 66% of patients attempted treatment with at least one other brand of NSAID and 47% tried two or more. Most brand-switching in the present study occurred as a result of adverse effects; more than half of all patients trying a different brand of NSAID did so because they had experienced toxicity. Eighty-two per cent of NSAID-users reported adverse effects and about two-thirds of these were GI in nature, ~1 in 5 patients reporting GI effects suffered with ulcers. These toxicities were all assumed to be symptomatic, since patients would be presumed to report only symptomatic events and as such, would have a consequent impact on quality of life, but it is important to consider that many patients also probably developed asymptomatic GI effects that would not have been picked up in this survey. Endoscopically observed ulcers, for example, commonly occur in patients treated with NSAIDs, but are usually asymptomatic [2]. The impact of GI side-effects on quality of life was indicated by the frequency with which patients needed to take medication to stop gastric pain: 35% of patients used OTC gastroprotective agents and 30% used prescription gastroprotective agents, and among these, nearly half used them at least every other day (38% used them every day).

The results of the Norwegian survey suggest that patients receiving long-term NSAIDs face a compromise between taking doses high enough to control the pain of arthritis while low enough to minimize gastric toxicity, but the observed requirements for supplemental analgesic and gastroprotective medications suggested that in many cases a satisfactory compromise was not reached. The results are complemented by findings that 44% of general practitioners sampled in the UK reported that their main aim when prescribing NSAIDs for OA was not to eradicate pain completely, but to minimize GI-related adverse effects by using low doses, indicating that patients were likely to experience inadequate pain control [7].

The EVA study was a nation-wide survey carried out in Belgium in 2000 [6]. A total of 5986 physicians participated, including 5265 primary care physicians (38% of all Belgian-registered general practitioners) and 721 specialists, including rheumatologists, orthopaedic surgeons and specialists in the areas of physical medicine and rehabilitation. A total of 74 192 OA patients were recruited, none of whom had recognized contraindications to the use of rofecoxib. NSAID therapy was suspended and patients received treatment with rofecoxib 12.5 or 25 mg once daily as appropriate. Treatment at inclusion comprised analgesics in 50% of patients, conventional NSAIDs in 63% and corticosteroids in 4%, while 8% of patients were taking no therapy. Gastroprotective or antulcer agents were used at study entry by 18% of patients recruited by general practitioners and 21% recruited by specialist physicians. After a mean treatment period of 30 days, there was high patient satisfaction with rofecoxib therapy for all main efficacy parameters (pain relief, general satisfaction and mobility) measured using five-point visual analogue scales (1 = poor and 5 = excellent; Fig. 3), and >80% of patients expressed a preference for continuing treatment with rofecoxib (Fig. 4). Preference for continuing rofecoxib was significantly higher (P = 0.001) among the 45 453 patients who had received conventional NSAIDs or other OA-specific medication prior to the study compared with the 3575 patients who had not previously used drugs for their OA (83 vs 77%, respectively).

In view of the drawbacks associated with conventional NSAID therapy, it is likely that alternative treatments offering comparable efficacy but significantly reduced GI toxicity would be welcomed. The EVA study specifically examined patient satisfaction with the newer anti-inflammatory drug rofecoxib, which acts via selective inhibition of cyclooxygenase-2. Rofecoxib has a reduced likelihood of causing gastric side-effects because it has little effect on cyclooxygenase-1 (which has an important role in generating cytoprotective prostaglandins in the gastric mucosa) while producing its anti-inflammatory effects via inhibition of cyclooxygenase-2 (which is up-regulated during inflammation); in contrast, conventional NSAIDs non-selectively inhibit both cyclooxygenase-1 and cyclooxygenase-2, leading to gastric toxicity as well as anti-inflammatory effects [8]. Current data consistently demonstrate that rofecoxib has efficacy comparable to conventional NSAIDs, but with significantly reduced GI toxicity [9–12]. In some studies, the gastric effects...
of rofecoxib are indistinguishable from placebo, even when using maximum clinically recommended doses [13]. Results from the Belgian EVA study showed that there was a strong preference for continuing to use rofecoxib compared with previous therapy, which was probably a consequence of its good efficacy and excellent GI safety profile. Given the large sample size (>74 000 patients), the results were likely to be representative of the real-life situation among the patient population of Belgium. Preference was significantly higher among previously treated patients, perhaps indicating that drawbacks experienced with prior therapy increased the appreciation of rofecoxib. The high patient satisfaction scores in the EVA study were in line with previous studies showing comparable efficacy of rofecoxib and conventional NSAIDs.

Combined findings from the Norwegian and Belgian surveys strongly suggest that current NSAID therapy is frequently associated with undesirable sequelae and that alternative treatment with rofecoxib is preferable for most patients questioned. Treatments that reduce the risk of GI-related side-effects have the potential to transform the prospects of patients requiring long-term anti-inflammatory therapy for OA. As well as producing more readily perceived benefits to quality of life by reducing common but intrusive GI toxicities, rofecoxib may also have benefits relating to more serious GI complications such as perforations and massive bleeding that have been associated with conventional NSAIDs. NSAID-related GI effects represent the second greatest threat to life in patients with rheumatic diseases [14]. In the USA, it has been estimated that every year ~107 000 patients are potentially hospitalized because of serious NSAID-related GI complications and 16 500 NSAID-related deaths occur annually among patients with definite or probable rheumatoid arthritis (RA) or OA [15]. Any treatment capable of decreasing such toxicity while maintaining clinical efficacy should be highly beneficial for patients and health-care resources; rofecoxib appears to be a major step in this direction. In contrast to the situation with conventional NSAIDs, where many physicians are reluctant to prescribe optimally therapeutic doses because of GI toxicity [7], the considerably reduced risk of GI adverse events associated with rofecoxib may increase confidence to prescribe doses providing fully effective pain relief. It is also likely that a reduction in the high level of dependence on concomitant medications would be appreciated by patients and may encourage adherence to therapy. Patients are clearly suffering from the burden of conventional NSAIDs and more widespread use of newer treatments such as rofecoxib, which are likely to significantly improve quality of life, should be strongly considered.

References