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Etodolac: An overview of a selective COX-2 inhibitor

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Abstract—Etodolac is a non-steroidal anti-inflammatory drug (NSAID) which has been shown to be effective in the treatment of rheumatoid arthritis and osteoarthritis and a selective COX-2 inhibitor in a wide range of clinically relevant assays in direct comparisons with other NSAIDs. Studies have shown etodolac to have no overall suppression of gastric or duodenal prostaglandins and endoscopic analysis with etodolac showed placebo level scores in comparison with ibuprofen, which showed inducement of gastro-intestinal (GI) side effects. This high degree of gastric tolerability was further demonstrated by microbleeding studies. The favourable GI tolerability profile of etodolac has been shown in long-term and large-scale trials and by routine clinical observation. In summary, etodolac is a well established selective COX-2 inhibitor that has been shown not to suppress gastric or duodenal prostaglandins, to have minimal hepatic or renal effects and to have favourable GI tolerability in comparison with ibuprofen.

Key words: NSAIDs; etodolac; COX-2.

1. INTRODUCTION

Non-steroidal anti-inflammatory drugs used for the treatment of arthritic conditions, are the most commonly prescribed group of drugs world wide. In essence, they are derived from aspirin and have been shown to induce their therapeutic effects by decreasing biosynthesis of prostaglandins and other anti-inflammatory agents. Further work in this area have shown that NSAIDs decrease the production of pro-inflammatory prostaglandins by the inhibition of prostaglandin synthetase (cyclooxygenase), which catalyses the conversion of arachidonic acid to prostaglandin H_2 (PGH_2). This is the biochemical precursor for the synthesis of prostaglandins, prostacyclins and thromboxanes. Recent studies have shown that cyclooxygenase exists in two isoforms.

Cyclooxygenase-1 (COX-1) is expressed in most tissues (i.e. it is constitutive) and is described as a 'housekeeping' enzyme regulating normal cellular processes

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being stimulated by hormones and growth factors. The level of expression of the COX-1 gene, as detected by quantitative mRNA studies, shows little change during the inflammatory process. Activation of COX-1 leads to prostaglandin production in the stomach mucosa (desirable gastroprotectant action), thromboxane production in the platelets and prostaglandin production in the kidney (maintenance of renal function).

Cyclooxygenase-2 (COX-2) expression is nearly undetectable in unstimulated cells though constitutive expression is seen in the brain and kidney. The gene encoding for COX-2 is induced on binding of proinflammatory factors, inducing increased expression of COX-2 in areas of inflammation, resulting in some unpleasant effects such as pain.

The adverse effects of NSAIDs on the GI tract, particularly gastric irritation and ulceration, are the most common side effects, and the presence of the two COX isozymes and their interaction with NSAIDs may help to explain the varying profiles of NSAIDs. This has led to the postulation that GI side effects of NSAIDs are mediated by inhibition of COX-1 and that the therapeutic effects seen are mediated by inhibition of COX-2. Thus an NSAID with selectivity for COX-2 over COX-1 would potentially have an improved GI tolerability profile. However, as yet the correlation between COX-2 inhibition and GI tolerability has not been fully established. Also, there are other biochemical pathways that probably are involved such as the free radical pathway, immunological pathways and maybe even the apoptotic pathway. Factors such as the plasma half-life and enterohepatic recirculation of an NSAID play important roles. However, other side effects such as skin rashes that are not COX-1 mediated should not be overlooked when determining the profile of an NSAID. As a result, an NSAID that exhibits selective COX-2 inhibition may have potential undesired effects in other areas induced by other mechanisms. This has already been seen in the form of hepatotoxicity and oedema with certain NSAIDs.

Etodolac is an NSAID that has been available since 1985, and is indicated for the chronic treatment of rheumatoid arthritis (RA) and osteoarthritis (OA). It is a pyranocarboxylic acid, and the chemical nomenclature is 1,8-diethyl-1,3,4,9-tetrahydropyrano-[3,4-b]indole-1-acetic acid (Fig. 1). Etodolac has been shown to be a selective COX-2 inhibitor with a well-documented profile in terms of efficacy and safety. In light of recent interest in the whole COX-2 area, this review will give an insight into an already well established selective COX-2 inhibitor, etodolac.

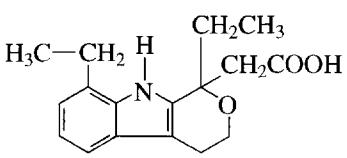

Figure 1. Chemical structure of etodolac (1,8 diethyl-1,3,4,9-tetrahydropyrano-[3,4-b]indole-1-acetic acid).

2. COX-2 INHIBITION OF ETODOLAC

Owing to the postulation that the COX-2 selectivity profile of an NSAID may reflect the GI tolerability, many studies have been undertaken in varying assay systems. These have ranged from intact cells expressing human COX isozymes, isolated purified enzymes, time dependent microsomal enzyme assays and isolated human cells such as the human whole blood assays. The inhibitory activities are usually expressed as IC_{50} values (the concentrations, which inhibit activity by 50%) and the indices of selectivity are expressed as the ratios of the IC_{50} values for COX-1 and COX-2. As such, COX-2 inhibition data is very dependent on the assay system used, which over time has seen progressive evolution in terms of sensitivity and clinical relevance.

Etodolac has shown consistent selective COX-2 inhibition across a wide range of assays in direct comparisons with other NSAIDs. A study reported that in direct comparison with other NSAIDs, etodolac showed 1000-fold selectivity for COX-2 over COX-1 in chinese hamster ovarian cells (CHO) expressing recombinant human COX isozymes (Riendeau *et al.*, 1997a). Etodolac was three times more COX-2 selective than meloxicam, another COX-2 inhibitor, and the active metabolite of nabumetone, 6-MNA showed no COX-2 selectivity. A recent study (Kawai *et al.*, 1998) reported that etodolac demonstrated 179-fold selectivity for COX-2 as compared with COX-1 in direct comparison with other NSAIDs (Table 1). This was conducted in an assay system comprised of isolated human platelets taken from healthy human volunteers to assess COX-1 activity and synovial cells isolated from patients with active RA to assess COX-2 activity.

A paper published recently looked at various NSAIDs in a direct comparison using an *in vitro* modified human whole blood assay (Warner *et al.*, 1999). Etodolac was shown to be more COX-2 selective than meloxicam, nimesulide and celecoxib. Indeed the COX-2 selectivity was not far removed than that of rofecoxib, which has been classed as a highly selective COX-2 inhibitor. The study showed that at 80%

Table 1.
Comparison of IC_{50} values of various NSAIDs using human platelet COX-1 and synovial cell COX-2

NSAID	Ratio COX-1 : COX-2
Aspirin	0.12
Diclofenac	38.00
Etodolac	179.00
Ibuprofen	0.86
Indomethacin	0.30
Loxoprofen-SRS	3.20
NS-398	1263.00
Oxaprozin	0.061
Zaltoprofen	3.80

Modified from Kawai *et al.*, 1998.

inhibition of COX-2, etodolac showed 25% inhibition of COX-1, which was not far removed from the 17% inhibition shown by rofecoxib. Of interest in this particular assay was the lower COX-2 selectivity of celecoxib, which had previously been shown to be highly COX-2 selective in an assay consisting of recombinant human COX-1 and COX-2 from broken insect cells.

An earlier study (Riendeau *et al.*, 1997b) examined the effect of a wide range of NSAIDs including test drugs such as 5,5-methyl-3-(3-fluorphenyl)-4-(4-methylsulphonyl)phenyl-2-(5H)-furanone (DFU) on the COX-1 enzyme. Etodolac showed significantly less inhibition of COX-1 than a number of tested NSAIDs including celecoxib, which was also later seen in the Warner study. Again, this affirms the awareness required when interpreting comparative data from varying assays.

Hence, the evidence for etodolac as a highly selective COX-2 inhibitor is very strong.

3. GASTRIC MUCOSAL PROSTAGLANDINS

It has been well documented that prostaglandins have been shown not only to play major roles in the pathogenesis of pain and inflammation but also in the maintenance of gastric protection. It was recently postulated that gastric prostaglandin sparing NSAIDs may become the gold standard and suggested that the GI tolerability profile of etodolac may be due in part to this. A study was carried out over 4 week periods in patients with active RA, assessing etodolac (600 mg/day) against naproxen (1000 mg/day) and measuring suppression of prostaglandins by biopsies along with endoscopy (Russell, 1990). This, together with other studies showed etodolac to have no overall suppression of gastric or duodenal prostaglandins.

4. GASTRIC TOLERABILITY

As stated before, the most common adverse events seen with NSAIDs are GI related. The most serious GI events result in perforation, ulcers and bleeds (PUBs) requiring hospitalisation and sometimes resulting in death. To this end, NSAIDs remain a significant social and economic problem owing to the sheer number of prescriptions for chronic use. They are not only used in the treatment of OA and RA but also for soft tissue injuries, which potentially increases the number of adverse events seen with NSAIDs owing in part to over-zealous prescribing. The reduction of NSAID mediated PUBs remains an area of concern for health care professionals, to which other agents have been used to counteract their injurious effects on the GI tract. Prophylactic agents such as proton pump inhibitors, H_2-antagonist and prostaglandin analogues have been used alongside NSAIDs with varying degrees of success.

Whilst prostaglandin analogues have been shown to reduce GI side-effects with NSAIDs that are known to lower gastric prostaglandins levels, there is no evidence to suggest any advantage when used in conjunction with etodolac which has been

shown not to lower gastric prostaglandins. Furthermore, reports have shown that use of exogenous prostaglandins can induce a reduction in endogenous prostaglandin levels, with possible deleterious effects. Some of the side effects induced by the prophylactic agents have resulted in patient's discontinuing treatment. Another factor for consideration is the increased cost of co-prescribing.

Owing to the severity of GI events induced by NSAIDs, their GI profile is of paramount importance though how this is assessed has been an area of controversy. Endoscopic and microbleeding studies allow an insight into this though interpretation of the data is dependent on the methodology. To this end, etodolac has shown a favourable GI profile in comparison with other NSAIDs.

A study by Lanza *et al.*, 1987 assessed the effects of various NSAIDs on the GI mucosa by endoscopy. 72 healthy volunteers with a gastroscopy Lanza score of 0 were randomly assigned to one of 6 study groups (12 subjects/group) and received maximal dosages of etodolac, ibuprofen, naproxen, indomethacin or placebo for 7 days following 8 day predrug period. The Lanza scale, depending on the severity of GI erosions, expressed the gastroscopy results of all tested NSAIDs. Etodolac showed no significant increase in GI erosion compared to placebo even at the highest dosage of 1000 mg/day (40% above therapeutic dose in the UK), whereas ibuprofen, naproxen and indomethacin showed significant increases (Fig. 2).

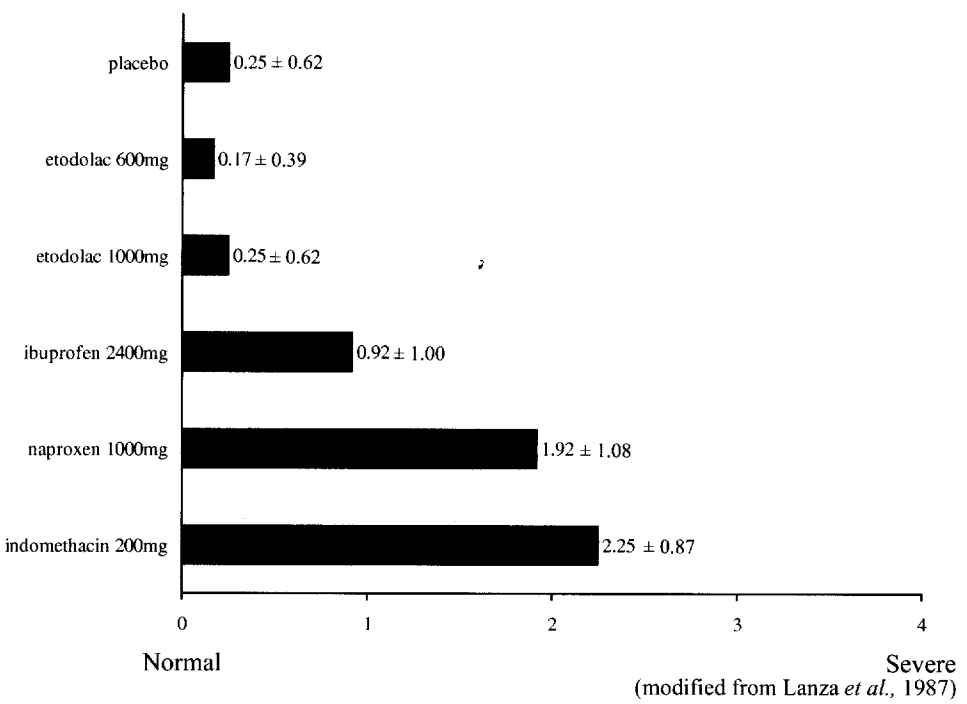

Figure 2. Mean endoscopy scores of various NSAIDs. Open-label, analyst blind, parallel endoscopy study of 72 healthy subjects following seven days of treatment. The Lanza Scale was used to assess gastroscopy scores.

A microbleeding study compared faecal blood loss associated with the use of maximal dosages of etodolac, ibuprofen, indomethacin and naproxen in normal healthy volunteers (Arnold *et al.*, 1985). This study was undertaken as a randomised parallel, placebo-controlled, double-blind study over 21 days ($n = 9-12$ per study group). Etodolac even at the high dose of 1200 mg/day showed no significant increase in microbleeding compared to placebo in comparison with the other NSAIDs which all showed significant increases.

In general the GI profile of an NSAID can be assessed through long-term and large-scale clinical trials alongside routine clinical observation. A three-year study (Neustadt, 1997) compared the long-term efficacy and safety of 2 doses of etodolac (300 mg and 1000 mg/day) with that of ibuprofen (2400 mg/day) in 1446 patients with active RA and was conducted as a double-blind, parallel, multicentre study. The incidences of most side effects were comparable, although dyspepsia and rash occurred less frequently with 300 mg/day etodolac than with ibuprofen. In each treatment group, about 50% of all patients enrolled completed one year, 30% completed 2 years and 20% completed 3 years of the study. A clinically significant higher incidence of GI ulcers and bleeding was seen with ibuprofen compared with etodolac, even at 1000 mg/day, over the three year study. In both etodolac dosage groups, GI ulceration and bleeding occurred fairly early in the study, within 100–140 days, whereas with the ibuprofen group, they occurred throughout the study period. No perforations occurred in any treatment group.

Two large-scale, open-label studies were performed in France to assess the efficacy and safety of etodolac (Benhamou, 1990). The studies were conducted as a 6 week, multicentre study undertaken by 974 rheumatologists, and as a postmarketing study undertaken by 9000 general practitioners, comprising of over 55 000 patients with various arthritic conditions. The incidence of serious GI events was only 0.04% in the post-marketing study, which were fully investigated and treated favourably. No drug-related deaths were reported. In these studies, etodolac was shown to be effective in the treatment of OA and RA, and only 11% of patients reported one or more adverse reactions.

According to data from the Arthritis, Rheumatism, and Ageing Medical Information System (ARAMIS), there were two agents that gave rise to no serious GI bleeds or other clinically significant events requiring hospitalisation, etodolac and nabumetone (Singh *et al.*, 1997). This data base has been recently expanded. Singh stated that in general, NSAIDs with poor COX-2 selectivity appeared to be more toxic than those with better COX-2 selectivity, and that clinical decisions about NSAIDs should be based primarily on documented GI incidence rates.

5. CONCLUSION

GI toxicity is the primary concern relating to NSAID use. The data would suggest that selective COX-2 inhibitors show a reduced toxicity in comparison with non-COX-2 selective NSAIDs. Etodolac has been shown to have a high degree of

selective COX-2 inhibition in a wide range of assays. However, to fully ascertain an NSAID's profile, not only with GI toxicity but also in other areas of concern such as hepatic and renal effects, one needs to look carefully at the clinical data. Clinical trials enable one to gauge the clinical profile of an NSAID, though this is dependent on the trial's criteria. Etodolac has demonstrated good efficacy along with favourable gastric tolerability in various clinical trials in comparison with other NSAIDs. The data available would also suggest that in general etodolac has minimal hepatic and renal effects. However, how this relates to patients with hepatic or renal impairments is currently unclear.

In summary, an NSAID's profile should be determined by large-scale, long-term studies and a proven track record through routine clinical observation over a number of years. Etodolac is a selective COX-2 inhibitor that has been shown to fulfil such criteria.

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