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Review Article

Review On Analytical Method Development and Validation of Etoricoxib Using UV Spectroscopy

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ABSTRACT

Chronic pain is a debilitating condition with a growing prevalence both in the USA and globally. The complex nature of this condition necessitates a multimodal approach to pain management that extends beyond the established pharmaceutical interventions currently employed. A variety of devices comprising both invasive and noninvasive approaches are available to patients, serving as adjuvants to existing regimens. The benefits of these interventions are notable for their lack of addiction potential, potential for patient autonomy regarding self-administration, minimal to no drug interaction, and overall relative safety. However, there remains a need for further research and more robust clinical trials to assess the true efficacy of these interventions and elucidate if there is an underlying physiological mechanism to their benefit in treating chronic pain or if their effect is predominantly placebo in nature. Etoricoxib is a selective cyclooxygenase-2 inhibitor, with a lower risk of gastrointestinal toxicity compared to traditional nonsteroidal anti-inflammatory drugs (NSAIDs). We evaluated the effectiveness and tolerability of etoricoxib in extremely elderly patients with chronic pain due to osteoarthritis (OA). A prospective, single-center, single-arm study was conducted, enrolling 19 extremely elderly men with OA (mean age 85.9, range 79-96 years), who responded inadequately to NSAIDs or other analgesics. Regardless, the field of device-based intervention and treatment remains an evolving field with much promise for the future chronic pain management.


INTRODUCTION

Chronic pain is a complex problem that places a significant burden on the patients affected by it. In contrast to acute pain, which provides a survival benefit, chronic pain continues to persist after

healing from an injury or disease has taken place, or pain that occurs in the absence of prior tissue damage. Although commonly a product of injury or disease, it is imperative to consider chronic pain as a unique and separate condition given the variety of

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treatment modalities available to clinicians and patients [1, 2]. The prevalence of pain both worldwide and in the USA demonstrates the need for myriad approaches to chronic pain management. The National Health Interview Survey data indicate a prevalence in the USA of approximately 20.5% (50.2 million) American adults being affected by chronic pain [3, 4]. Globally, approximately 1.9 billion people display common symptoms of chronic pain, such as tension-type headaches [2]. The allostatic load hypothesis postulates that individuals who endure persistent daily exposure to poor socioeconomic conditions are predisposed to the development of numerous diseases, including chronic pain, due to the elevation and accumulation of stress hormones such as cortisol. In essence, a steady-state, sympathetic fight-or-flight state of existence results in an accumulated stress on the body that eventually manifests in a variety of disease states. Furthermore, patients with lower socioeconomic status (SES) were found to have greater disability secondary to chronic pain and experience more intense pain compared with individuals from higher SES classes [5–7]. The complex nature of chronic pain necessitates a multimodal approach to its management, with therapies designed to target various aspects of its biopsychosocial composition in a stepwise escalating manner. Initial interventions are comprised of oral analgesics, ranging from nonsteroidal anti-inflammatory (NSAIDs) to weak and strong opioids. Topical formulations of both opioids and nonopioids are viable alternatives, especially given their improved safety profile in comparison to the oral formulations [8–10]. Additionally, the aforementioned medications can be supplemented with adjuvant therapies designed to address neuropathic pain in particular: antiepileptics and antidepressant therapies. Furthermore, antidepressants serve a multi-pronged approach given their primary function of treating the

commonly associated comorbidities of depression and insomnia with chronic pain [11]. Patients with persistent or progressive pain despite oral and transdermal analgesic interventions are often candidates for interventional management. These therapies include nerve blocks, denervation procedures, implantable devices such as infusions pumps and neurostimulators, and transcutaneous electrical nerve stimulation (TENS). New approaches to chronic pain management include mobile applications and virtual reality (VR), both of which have shown promise in meta-analyses as potential primary interventions given their safety profiles [12, 13]. One of the main symptoms accompanying the majority of rheumatic diseases is pain. This is why a non-steroidal anti-inflammatory drug (NSAID) is prescribed by rheumatologists or primary care physicians to most patients with rheumatoid diseases. Etoricoxib belongs to the class of non-steroidal anti-inflammatory drugs. It is an oral selective inhibitor of cyclooxygenase-2 (COX-2). Cyclooxygenase is an enzyme responsible for the production of prostaglandins. It occurs as two isoenzymes: COX-1 and COX-2. COX-2 is an inflammation-induced isoenzyme responsible for the synthesis of prostanoid mediators of pain, inflammation and fever. Pharmacological studies show that etoricoxib, similarly to other coxibs, causes dose-dependent inhibition of COX-2 activity, without affecting COX-1 activity. Based on clinical trial results, etoricoxib was approved for the treatment of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis and pain caused by gout attack.

Etoricoxib in the treatment of osteoarthritis

Our study showed that after switching to etoricoxib, the pain, joint function, quality of life, and treatment satisfaction improved significantly in the extremely elderly patients with OA. On average, both pain and disability scores decreased as determined using the WOMAC index and BPI-SF. The TSQM results showed a higher perception



of overall satisfaction with the treatment among the patients. The quality of life scores measured by the SF36 and EQ-5D VAS also significantly improved after switching to etoricoxib. No adverse events were reported during the 4-week treatment or 2-month follow-up. This study is the first analysis of the efficacy of etoricoxib in treating OA in the extreme elderly population. The extreme elderly are a growing population, often not adequately represented in epidemiological studies [12]. To the best of our knowledge, there were no previous cohort studies investigating the effect of medication on relieving pain due to OA in the extreme elderly. According to the World Health Organization, an aging society is one in which 7% of the population is ≥ 65 years old, while in an “aged society” or “hyper-aged society” this proportion reaches 14% and 20%, respectively [38]. Accommodating the aging population is a global challenge [39] and the real-world experience is becoming more and more important. In a number of trials, the clinical efficacy of etoricoxib in the symptomatic treatment of OA pain has been well documented [6,19,25-34]. The efficacy of etoricoxib treatment of 6-12 weeks was significantly more higher than placebo in improving pain symptoms in patients with OA, and as effective as diclofenac, ibuprofen, naproxen, or celecoxib [26]. Similar to our findings, an analysis of the extreme elderly in a paired design showed reductions in scores for WOMAC pain and physical function and patient’s global assessment that were equivalent for 30 mg etoricoxib once daily versus 800 mg ibuprofen 3 times daily, as well as for 60 mg etoricoxib once daily versus 50 mg diclofenac 3 times daily and versus 500 mg naproxen twice daily, and met the criteria for noninferiority for etoricoxib versus celecoxib [26]. Furthermore, efficacy with etoricoxib was maintained for up to 4.5 years in extension studies [40]. Also, etoricoxib was generally well tolerated in clinical trials of patients with OA and other types of arthritis [26].

We observed an improvement of the quality of life in the extremely elderly patients, with the given treatment dose and period that was shorter compared to the other trials. In addition to the improvement of the quality of life, drug safety is another important issue. Regarding the risk of thrombotic cardiovascular (CV) events, the multinational etoricoxib and diclofenac arthritis long-term program, including a pooled analysis of >34,000 patients with OA or rheumatoid arthritis, showed that, in terms of the overall rate of arterial and venous thrombotic CV events, etoricoxib was noninferior to diclofenac [19]. Similarly, in a pooled analysis of 12 trials no difference between etoricoxib and non-naproxen NSAIDs was evident regarding thrombotic events [26]. In addition, MI resulting from etoricoxib was reported in only one trial (relative risk 1.58, 95% confidence interval 0.06 to 38.66) [41]. On the other hand, Savage [4] suggested that, due to their thrombotic potential, COX-2 inhibitors are contraindicated in patients with ischemic heart disease or stroke as well as in patients that are at high risk of developing those conditions [4], which was also suggested in another study [42]. Currently, there are several families of drugs clinically recognized as pain therapeutics, which have varying degrees of efficacy and adverse events, often limiting their utility. The management of inflammatory conditions typically includes NSAIDs, inhibitors of COXs (COX-1 and/or COX-2) [43-45], and opiates [43,46]. Significant effort and investment have been made in the development of novel therapeutics for managing pain [43,47,48], including COX inhibiting nitric oxide donors and the dual COX/lipoxygenase (LOX) inhibitor, licofelone. Initial results suggest that those therapies may be more tolerable compared to NSAIDs and selective COX-2 inhibitors [49]. Future clinical trials evaluating the efficacy of new therapeutics in comparison with etoricoxib are warranted, especially in the frail and extremely elderly patients who are at increased risk for side



effects and reduced drug tolerance. Our study has several limitations, including the small number of, only male, patients (n = 19) and single-center design. We included only male patients because the study was conducted at the Yunlin Veterans Nursing Institution where all residents are male veterans. In addition, improvement in health-related quality of life was assessed using only the SF36 and EQ-5D. Other scales, such as the instrumental activities of daily living (IADL) scale [50], could have been used to reflect improvement in daily functioning. Our results showed that, in this extreme elderly population, etoricoxib could relieve pain effectively, but significant improvements in function and ability to do normal work could not be expected due to the impact of patient age and advanced degenerative changes. Other assistance and therapies should be considered, in addition to pharmacologic treatment, in an effort to further aid the patients in this age group.

Etoricoxib in the treatment of rheumatoid arthritis

Etoricoxib showed similar efficacy to a high dose of the non-selective NSAID naproxen, supporting results from studies with other selective COX-2 inhibitors in RA which also showed similar efficacy to non-selective NSAIDs [7,8]. The results differed from those in the replicate study of etoricoxib in RA [9] which found that etoricoxib was more effective than naproxen. The reason for the difference in results between the two studies is unclear since the studies had identical designs, including entry criteria, doses of study medication, and outcome measures. However, although patient enrollment criteria were identical, more patients in the present study were using concomitant corticosteroids (approximately 57% versus 32%) and disease modifying antirheumatic drugs, including methotrexate (approximately 82% versus 68%). It is conceivable that the increased concomitant RA medication use may have

obscured the ability to detect small, but perhaps meaningful differences between active treatments. Interestingly, in this study as compared to the replicate etoricoxib RA study [9], the placebo response rate was higher (ACR20-responders were 40.9% in the current study versus 20.8% in the replicate study) and the discontinuations due to lack of efficacy were lower in the placebo group (25.2% in the current study vs 54.5% in the replicate study), and this may also have influenced the results. Although unproven, other potential explanations may relate to the fact that the present study was conducted largely outside the United States and the previous study inside the United States [9]. Therefore, differences in underlying disease characteristics and/or cultural differences in perceptions of efficacy may have also contributed to the difference in the results. Others have reported different findings for RA studies with similar designs which were conducted in the United States versus other countries. Serum C-reactive protein levels were noted to be elevated compared to placebo in the etoricoxib group. This was not observed in other etoricoxib RA studies [19,9]; in one study no difference was seen from placebo [19], and in the other study a lowering in serum C-reactive protein was observed [9]. It is generally not believed that changes in serum C-reactive protein are substantially influenced by NSAID treatment. Therefore, this was not felt to represent a clinically meaningful finding. Etoricoxib was generally well tolerated by the patients in this study, consistent with results from prior clinical trials of etoricoxib for RA and other indications [9,11-13]. There was a significantly higher number of patients with drug-related clinical adverse events for etoricoxib versus placebo. However, the difference was small and should be interpreted with caution since more patients on placebo discontinued early (primarily due to lack of efficacy) and therefore had less chance of experiencing an adverse event. The findings may therefore overestimate adverse event



rates for the active treatments compared with placebo. Particular attention was paid to the typical NSAID-related renal effects of edema and hypertension since data with both selective COX-2 inhibitors and non-selective NSAIDs have suggested that they have an effect on renal physiology [14,15]. Etoricoxib and naproxen showed a small increase in hypertension adverse events compared with placebo. Mean changes in blood pressure among the treatment groups was small, and both etoricoxib and naproxen treatment groups showed only small increases in mean systolic blood pressure compared to baseline. Among patients who had hypertension adverse events on etoricoxib, no patient discontinued from the study. The incidences of lower extremity edema adverse events for etoricoxib were similar to placebo and no patient treated with etoricoxib discontinued as a result. The main proposed advantage for selective COX-2 inhibitors is reduced gastrointestinal toxicity. However, a thorough and adequate assessment of this can only be made either in very large long-term trials or pooled analyses because of the relatively low incidence of clinically significant gastrointestinal PUBs [6,16]. In fact, only one confirmed PUB was reported in the present study. It has also been suggested [6,17,18] that the use of selective COX-2 agents may be associated with a higher incidence of cardiovascular thrombotic events than naproxen (a potent and sustained inhibitor of platelet aggregation at therapeutic doses). As with upper GI clinical events (PUBs), these events are rare and conclusive data can only be adequately amassed in large data sets. The incidence of confirmed cardiovascular thrombotic events in the present study was low (3 events), therefore no meaningful conclusions about the overall cardiovascular safety of etoricoxib can be determined from this single study.

Etoricoxib in the treatment of ankylosing spondylitis

In this study, both etoricoxib 90 and 60 mg were non-inferior to naproxen 1000 mg on the primary endpoint of time-weighted average change from baseline in the SPI score of a 6-week period. These results were further validated by other endpoints, including PGART and discontinuations due to lack of efficacy. An analysis was done for the secondary objective comparing the effect of etoricoxib 90 mg vs. etoricoxib 60 mg on the time-weighted average change from baseline SPI score; the difference in the effect did not meet the prespecified MCID. All other secondary and tertiary endpoints supported similar efficacy between the doses in Part I. Among the subset of subjects who did not have an adequate response to the 60 mg dose during Part I, those who received the 90 mg dose in Part II demonstrated an additional average improvement of ~3 mm in SPI score from Week 6 over Weeks 10 and 12 as compared to subjects who continued receiving the 60 mg dose in Part II. This result was identified as being statistically significant in this study; however, the results were not supported by PGART results. The 3-mm average improvement with the 90 mg dose vs. the 60 mg dose also did not meet the predefined MCID of 6 mm. Further research evaluating MCID on an individual patient level rather than as an average measure may be useful in determining if the numerically greater improvement from the 90 mg dose provides clinically important effects for some AS patients. Overall, while etoricoxib previously demonstrated efficacy in subjects with AS at a dose of 90 mg [16], our results indicate that etoricoxib 60 mg is a clinically relevant dose that provides efficacy for a majority of patients similar to that achieved with 90 mg. An effective lower dose of medication may decrease a patient's potential adverse effects, and treatment interruptions. In the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) study, which was a large outcome trial that was designed to evaluate safety parameters among osteoarthritis (OA) and rheumatoid arthritis



patients who received etoricoxib 60 mg, etoricoxib 90 mg, and diclofenac 150 mg, the 60 mg dose (received by OA patients) was associated with fewer discontinuations due to AEs or serious AEs compared with OA patients who received etoricoxib 90 mg. Additionally, a lower rate of congestive heart failure and discontinuations due to edema were observed with etoricoxib 60 mg vs. etoricoxib 90 mg in the MEDAL trial [18, 19]. In the current study, all treatments were generally well tolerated with no new or unexpected safety findings. There were no significant differences in AEs between treatment groups; however a small numeric increase in SAEs was noted in Part II in 90 and 60 mg/90 mg treatment arms as compared to 60 mg treatment arm. Due to the cardiovascular and gastrointestinal risks associated with NSAIDs [20], these events were adjudicated by an external committee of experts in this trial. Further, it should be noted that CV risk is elevated in AS patients [21]. The proportion of subjects who experienced thrombotic CV or upper GI events was relatively low and not unexpected in this study. The thrombotic CV events that occurred in this study were in the etoricoxib groups with none occurring in the naproxen group; however, the incidence was too low to adequately assess risk. Previous analyses have suggested that NSAIDs, including COX-2 selective NSAIDs such as etoricoxib, have a similar increased risk of CV events, although with the possible exception of naproxen which is not associated with an increased risk [20]. A large outcome program (the MEDAL program) demonstrated a similar rate of thrombotic CV events with etoricoxib (60 or 90 mg) and diclofenac 150 mg; the MEDAL program also demonstrated a reduced risk of uncomplicated upper GI events with etoricoxib vs. diclofenac [22]. This study demonstrated that etoricoxib 60 and 90 mg are clinically important doses in the treatment of AS and are non-inferior to naproxen 1000 mg with regard to reduction of spinal pain intensity.

However, the limitation of this study was that assessments of the efficacy of these doses on an individual patient level were not studied. Additionally, these treatments were only assessed based on clinical endpoints. Previous research demonstrated radiographic improvement in AS patients treated with NSAIDs, COX-2 selective NSAIDs in particular, presumably due to inhibition of osteoblast activity [9]. Though not assessed in this study, the effect of etoricoxib and other COX2 inhibitors on radiographic disease progression in AS patients is a potentially important area for future research.

CONCLUSION

In extremely elderly patients with OA, the pain, joint function, quality of life and treatment satisfaction improved significantly with etoricoxib administration. The sum of the evidence from this study suggests that etoricoxib 60 and 90 mg effectively control pain and a choice of two effective doses (60 mg or 90 mg) has now been described for patients with AS, with 60 mg once daily as the lowest effective dose for most patients. This choice of two effective doses provides healthcare providers with an additional option to optimize AS treatment based on individual patient response. Action of etoricoxib shows that the former is a beneficial therapeutic option in patients with osteoarthritis, rheumatoid arthritis, ankylosing spondylitis or gout who have few cardiovascular risk factors and, at the same time, a relatively high risk of gastrointestinal complications.

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