ANALGESIC EFFICACY OF VALDECOXIB IN THE MANAGEMENT OF POST-ARTHROSCOPIC MENISECTOMY PAIN: A PLACEBO CONTROLLED AND ACTIVE COMPARATORS CLINICAL TRIAL.

ANWAR Z. ZEIDAN, MD*; MOHAMMED M. EL DAHISH, MD§
* Assistant Professor, Anaesthesia Department, Alexandria University
§ Assistant Professor, Anaesthesia Department, Cairo University

ABSTRACT

Objective: this randomized, double blinded, placebo-controlled and active comparators study aimed at evaluating the analgesic activity and tolerability of valdecoxib, a new cyclo-oxygenase (COX)-2 specific inhibitor, as compared with either etoricoxib or codeine/paracetamol combination. Methods: A total of 81 patients with moderate to severe pain following arthroscopic meniscectomy of the knee were randomly allocated to receive single oral doses of valdecoxib 40 mg (n=21), etoricoxib 120 mg (n=19), codeine/paracetamol 60/300 mg (n=21) or placebo (n=20). Efficacy was assessed by onset of analgesia, pain intensity difference (PID), pain relief (PR), time weighted sum of total pain relief (TOTPAR), sum of pain intensity difference (SPID), duration of analgesia (by time to rescue medication), percentage of patients requiring rescue analgesia and patients’ global evaluation. Patients were assessed for 24 hours and reported PID and PR scores at 14 pre-determined time points. Results: All active treatments were significantly superior to placebo for all efficacy measures (P<0.001 for all). Patients treated with valdecoxib or codeine/paracetamol experienced faster onset and longer duration of analgesia compared with those treated with etoricoxib (P<0.01). Patients receiving valdecoxib experienced significantly higher PI, PR, TOTPAR and SPID scores and greater satisfaction with their study medication compared with etoricoxib (P<0.01). Lower percentage of patients in valdecoxib group required rescue analgesia compared with etoricoxib group (P<0.01). Onset of analgesia with codeine/paracetamol group was comparable to that with valdecoxib group. Valdecoxib and codeine/paracetamol treatments provided a similar magnitude of analgesia up to 6 hours post-dose. Analgesia provided by valdecoxib was significantly superior to that of codeine/paracetamol from 8-24 hours post-dose (P<0.01). Codeine/paracetamol treatment resulted in more frequent overall adverse events (AEs) and drug related AEs compared with valdecoxib and etoricoxib treatments. Conclusion: Analgesia provided by 40 mg valdecoxib to patients with post-arthroscopic menisectomy pain is: rapid and sustained over 24 hours period, superior to that achieved by etoricoxib 120 mg, and comparable but longer lasting than that with codeine/paracetamol 60/300 mg. Valdecoxib and etoricoxib have a tolerability profile superior to that of codeine/paracetamol combination.

Keywords: COX-2 specific inhibitor, valdecoxib, etoricoxib postoperative, analgesia, arthroscopy.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit the synthesis of prostaglandins (PGs) both in the spinal cord and at the periphery, thus diminishing hyperalgesic state after surgical trauma(1). NSAIDs exert their pharmacological effect by acting on cyclooxygenase (COX) enzyme(2). COX exists as two distinct isoforms COX-1 and COX-2(3). COX-1 is constitutively active through-out the body and is responsible for mediating routine physiological functions and vascular haemostasis(2). In contrast, COX-2 is an inducible enzyme expressed by both polymorphnuclear leukocytes and macrophages after inflammatory stimuli(6). Conventional NSIDS (such as diclofenac, ibuprofen and naproxyn) non-specifically inhibit COX-1 and COX-2 isoforms(5). It is believed that the therapeutic activity of NSAIDs is primarily through inhibition of COX-2, whereas toxicity results mainly from inhibit-tion of COX-1(3). Clinical trials demonstrated that endoscopic ulceration is significantly reduced with COX-2 specific inhibitors(3). These data, combined with the lack of platelet effect by COX-2 specific inhibitors(3) may be responsible for the improved safety of administering these drugs in the peri-operative setting. Valdecoxib is a new COX-2 specific inhibitor developed for the treatment of pain and inflammation. Valdecoxib is approximately 28000 fold more selective...
against COX-2 than COX-1 in vitro. It is rapidly and completely absorbed after oral administration with an absolute oral bioavailability of 83%. Etoricoxib is another selective COX-2 inhibitor with an in vitro COX-1/COX-2 ratio of 344. At therapeutic concentrations, both of these coxibs inhibit the COX-2 isoenzyme without affecting the COX-1 isoform. Recent studies demonstrated valdecoxib to be an effective analgesic for the management of pain following various surgical procedures. However, there is limited information about the efficacy and safety profile of valdecoxib as compared with other COX-2 specific inhibitors or opioid-containing analgesics such as codeine/paracetamol combination. This study evaluated the analgesic efficacy and tolerability of valdecoxib 40 mg as compared with etoricoxib 120 mg and codeine/paracetamol 60/300 mg in patients who have undergone arthroscopic meniscectomy of the knee joint.

**METHODOLOGY**

**Selection of patients and study design:**

After approval of the local ethical committee and obtaining written informed consent, 81 patients (age>18 years) ASA physical status I-II scheduled for elective arthroscopic meniscectomy of the knee were enrolled. Selected patients had to experience post-surgical pain (within 4 hours of surgery) that was moderate to severe on pain intensity categorical scale. Patients were excluded from the study if they had received any analgesic medication within a 24 hours period before the operation, were pregnant or breast feeding, had a history of alcohol or drug abuse, or had clinically significant neurological, cardiovascular, or renal disease.

All surgical procedures were performed under local anaesthesia using 30 ml intra-articular bupivacaine 0.25%. Intra-operatively, patients received IV sedation with propofol (10-100 ug.Kg⁻¹.min⁻¹) and/or midazolam (1-3 mg bolus doses) as required. At the end of the procedure, an additional 30 ml bupivacaine 0.25% was injected through the arthroscope. Opioids were not a component of the intra-operative sedation.

The study design was randomized, double-blinded, and placebo-controlled with active comparators and was conducted over 24 hours period. A total of 81 patients were randomly allocated to receive single oral doses of valdecoxib 40 mg (Bextra, Searle & Co, Illinois, USA; n=21); etoricoxib 120mg (Arcoxia, Merck & Co., Hertfordshire, UK; n=19); codeine/paracetamol 60/300 mg (Tylenol 4, OrthoMcNeil, NJ, USA; n=21) or placebo (n=20). All study medications were administered within 4 hours of completion of surgery, when local anaesthetic effect had worn off and patients met minimum pain entry criteria. Rescue analgesic medication was available to any patient as needed throughout the study, and was in the form of codeine/paracetamol 60/300 mg. Once patients had taken rescue medication, they were excluded from further assessments and their last assessment before they took rescue medication was carried forward.

**Pain assessments**

Time to perceptible pain relief, time to meaningful pain relief, and time to onset of analgesia were measured using stopwatch technique. The study personnel started two stopwatches on the administration of study medication. Patients were instructed to stop the first stopwatch when they first experienced perceptible pain relief and the second when they experienced meaningful pain relief. Perceptible pain relief was defined as the point at which the patient first felt any pain-relieving effect from the study medication and meaningful pain relief was defined as the point at which the relief from pain was meaningful to the patient. Time to onset of analgesia was defined as the time to perceptible pain relief in patients who experienced both perceptible and meaningful pain relief. The number of patients experienced onset of analgesia in each group was recorded. Pain intensity and pain relief were assessed at 0 hour, at 0.25, 0.50, and 0.75 hours, and at 1, 1.5, 2, 4, 6, 8, 10, 12, 16, and 24 hours after administration of study medication or immediately before rescue medication.
Pain intensity (PI) was scored on a four-point categorical scale in which 0=none, 1=mild, 2=moderate, and 3=severe. Time specific pain intensity difference (PID) scores were calculated by subtracting the PI score at each time point from the baseline score. Pain relief (PR) was scored on a five point categorical scale in which 0=none, 1=a little, 2=some, 3=a lot, and 4=complete. Onset of analgesia was further assessed by the pain intensity difference at 0.50 and 0.75 hours. The highest PID and PR scores (peak PID and peak PR respectively) achieved at any time during the 24-hour evaluation period were determined for each treatment group. The magnitude of analgesic effect was assessed by the time weighted sum of total pain relief (TOTPAR) and the time weighted sum of pain intensity difference (SPID) at 6, 8, 10, 12, 16 and 24 hours following administration of study medication. The duration of analgesic effect (defined as time from administration of study medication to rescue analgesia, if required) and the percentage of patients taking rescue medication were monitored throughout the study period.

Patients’ global evaluation of study medication
Patients completed the patients’ global evaluation of study medication at the end of the study, or immediately prior to taking rescue analgesia. Patients’ global evaluation was assessed on a four-point scale in which 1=poor, 2=fair, 3=good, and 4=excellent.

Safety
The general clinical safety of the study medications were assessed by monitoring the number and frequency of treatment emergent adverse events (AEs) during the 24 hour assessment period.

Statistical analysis
Unless otherwise specified, data are presented as mean ± SD. Baseline characteristics were compared across treatment groups using analysis of variance (ANOVA), Fisher exact test or Pearson’s χ² test as appropriate. The last observation carried-forward approach was used to account for missing data due to patients taking rescue medication. The median times to perceptible/meaningful pain relief and to onset of analgesia were measured, and the 95 percent confidence interval was calculated according to the method of Simon and Lee. The overall and between group treatment comparisons were carried out using the long-rank test and the pair-wise long rank test respectively. The time specific PR and TOTPAR were analyzed with ANOVA. The time specific PID, SPID and patient’s global evaluation were analyzed by analysis of covariance (ANCOVA). The safety data were analyzed with Fisher exact test. A P value <0.05 was considered statistically significant.

RESULTS
There were no significant differences between treatment groups regarding demographics or baseline characteristics (Table 1).

Times to perceptible/meaningful pain relief and to onset of analgesia
All active treatments were associated with significantly shorter times to perceptible/meaningful PR and to onset of analgesia compared with placebo (P<0.001, Table 2). Similarly a significantly greater proportion of patients in the active treatment groups experienced onset of analgesia compared with placebo (P<0.001). Patients treated with valdecoxib or codeine/paracetamol experienced significantly faster times to perceptible/meaningful PR and to onset of analgesia compared with patients treated with etoricoxib (P<0.01, Table 2).

Pain assessments
Mean PID and PR scores were significantly higher in all active treatment groups compared with placebo group at all scheduled time points (P<0.001, Figures 1,2). Patients in valdecoxib and codeine/paracetamol groups experienced higher PID and PR scores compared with either etoricoxib or placebo groups at 30 minutes following study drug administration (P<0.01 and P<0.001 respectively). PID and PR scores for etoricoxib group were significantly higher than those for placebo group at 45 minutes following administration of study medication (P<0.001). These differences in PID and
Table 1: Demographics and baseline characteristics.

<table>
<thead>
<tr>
<th>Demographic/baseline characteristic</th>
<th>Valdecoxib (no=21)</th>
<th>Etoricoxib (no=19)</th>
<th>Codeine/Paracetamol (no=21)</th>
<th>Placebo (no=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>24.3 ± 4.12</td>
<td>23.6 ± 3.91</td>
<td>24.7 ± 4.82</td>
<td>22.1 ± 3.64</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>74.6 ± 16.1</td>
<td>72.3 ± 18.2</td>
<td>75.1 ± 17.4</td>
<td>74.8 ± 16.9</td>
</tr>
<tr>
<td>Sex. no (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>18 (86)</td>
<td>16 (84)</td>
<td>19 (90)</td>
<td>18 (90)</td>
</tr>
<tr>
<td>Female</td>
<td>3 (14)</td>
<td>3 (16)</td>
<td>2 (10)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Baseline PI no (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate PI</td>
<td>9 (43)</td>
<td>7 (37)</td>
<td>9 (43)</td>
<td>8 (40)</td>
</tr>
<tr>
<td>Severe PI</td>
<td>12 (57)</td>
<td>12 (63)</td>
<td>12 (57)</td>
<td>12 (60)</td>
</tr>
<tr>
<td>Mean PI</td>
<td>68.2 ± 11.29</td>
<td>71.4 ± 10.35</td>
<td>69.1 ± 12.36</td>
<td>67.8 ± 10.83</td>
</tr>
<tr>
<td>Time from end of surgery to</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>administration of study medication</td>
<td>132 ± 31</td>
<td>129 ± 33</td>
<td>134 ± 30</td>
<td>130 ± 29</td>
</tr>
</tbody>
</table>

no= number, PI= pain intensity

Table 2: Time to onset related assessments.

<table>
<thead>
<tr>
<th>Study medication</th>
<th>Time to perceptible pain relief hr : min (95% CI)</th>
<th>Time to meaningful pain relief hr : min (95% CI)</th>
<th>Time to onset of analgesia hr : min (95% CI)</th>
<th>Number (%) of patients experiencing analgesia onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valdecoxib (no=21)</td>
<td>0.24* (0.20, 0.28)</td>
<td>0.47* (0.44, 0.53)</td>
<td>0.36* (0.32, 0.41)</td>
<td>19 (90)</td>
</tr>
<tr>
<td>Etoricoxib (no=19)</td>
<td>0.38 (0.30, 0.41)</td>
<td>1.06 (0.56, 1.24)</td>
<td>0.51 (0.47, 0.59)</td>
<td>17 (89)</td>
</tr>
<tr>
<td>Codeine/paracetamol (no=21)</td>
<td>0.25* (0.22, 0.29)</td>
<td>0.45* (0.42, 0.52)</td>
<td>0.35* (0.33, 0.42)</td>
<td>18 (86)</td>
</tr>
<tr>
<td>Placebo (no=20)</td>
<td>1.08† (0.48, 1.24)</td>
<td>&gt;24 hours†</td>
<td>&gt;24 hours†</td>
<td>3 (15)†</td>
</tr>
</tbody>
</table>

no= number, CI= confidence interval; * P < 0.01 for valdecoxib or codeine/paracetamol versus etoricoxib treatment; † P < 0.001 for placebo versus all active treatments.

PR scores provide further evidence for the faster onset of analgesia in valdecoxib and codeine/paracetamol groups compared with etoricoxib group. Valdecoxib and etoricoxib treated patients experienced highest PID and PR scores at 4 and 6 hours post-dose respectively (Figures 1,2). Peak PID and PR scores attained in valdecoxib and etoricoxib groups were sustained throughout the 24-hours evaluation period. In contrast, peak PID and PR scores for patients receiving codeine/paracetamol occurred earlier (two hours post-
dose) than it did with valdecoxib or etoricoxib treatment groups, but they were not sustained. PID and PR scores in codeine/paracetamol group decreased significantly between 2 and 10 hours post-dose.

Mean PID and PR scores for valdecoxib group were significantly higher than those for etoricoxib group at all scheduled time points from 0.5 to 24 hours (P<0.01). Patients receiving valdecoxib had PID and PR scores similar to those in codeine/paracetamol group between 0 and 6 hours post-dose. The PID and PR scores for valdecoxib group were significantly higher compared with those for codeine/paracetamol group beginning 8 hours after administration of study medication and until the end of 24 hours assessment period (P<0.01). Patients treated with codeine/paracetamol experienced significantly greater PID and PR scores compared with those treated with etoricoxib between 0.5 and 6 hours post-dose (P<0.05). The PID and PR scores for etoricoxib group were significantly higher compared with codeine/paracetamol group at all time points between 10 and 24 hours post-dose (P<0.05, Figures 1,2).

The mean SPID and TOTPAR scores were significantly higher in all active treatment groups compared with placebo group at all scheduled time intervals i.e. at 6,8,10,12,16, and 24 hours (P<0.001, Figures 3,4). Patients in valdecoxib group had significantly higher SPID and TOTPAR scores compared with those in etoricoxib group at all scheduled time intervals (P<0.01). SPID and TOTPAR scores for valdecoxib and etoricoxib groups were significantly higher compared with those for codeine/paracetamol groups at all time points between 10 and 24 hours post-dose. SPID-6 and TOTPAR-6 were significantly higher, while SPID-8 and TOTPAR-8 were not statistically different between etoricoxib and codeine/paracetamol groups.

**Figure 1.** Mean pain intensity difference scores over time. P<0.01 for valdecoxib versus codeine/paracetamol from 8 to 24 hours and versus etoricoxib from 0.5 to 24 hours. P<0.05 for codeine/paracetamol versus etoricoxib from 0.5 to 6 hours and for etoricoxib versus codeine/paracetamol from 10 to 24 hours. Error bars represent standard error of means.
Figure 2. Mean pain relief scores over time. P<0.01 for valdecoxib versus codeine/paracetamol from 8 to 24 hours and versus etoricoxib from 0.5 to 24 hours. P<0.05 for codeine/paracetamol versus etoricoxib from 0.5 to 6 hours and for etoricoxib versus codeine/paracetamol from 10 to 24 hours. Error bars represent standard error of means.

Figure 3. Sum of pain intensity difference (SPID). P<0.01 for valdecoxib versus etoricoxib at all scheduled time intervals. P<0.05 for valdecoxib and etoricoxib versus codeine/paracetamol at 10,12,16, and 24 hours. Error bars represent standard error of means.
Figure 4. Time weighted sum of total pain relief (TOTPAR). P<0.01 for valdecoxib versus etoricoxib at all scheduled time intervals. P<0.05 for valdecoxib and etoricoxib versus codeine/paracetamol at 10,12,16, and 24 hours. Error bars represent standard error of means.

**Rescue medication**

Significantly fewer patients receiving active treatments required rescue medication compared with those receiving placebo (P<0.001, Table 3). Significantly fewer patients in valdecoxib group required rescue analgesia compared with those in either etoricoxib or codeine/paracetamol group (P<0.001). The percentage of patients requiring rescue medication in etoricoxib group was significantly lower compared with those in codeine/paracetamol group (P<0.01).

All active treatments were associated with significantly longer duration of analgesia (i.e. longer time to rescue medication) compared with placebo (P<0.001, Table 3). The median time to rescue analgesia observed with valdecoxib was significantly longer than those recorded after etoricoxib or codeine/paracetamol treatment (P<0.001). Patients in etoricoxib group experienced a longer time to rescue medication than those in codeine/paracetamol group (P<0.01).

**Safety**

There were no serious AEs during the study, and no patient discontinued the study as a result of AEs. The incidence of AEs observed with valdecoxib or etoricoxib was not significantly different from those recorded with placebo treatment (P>0.05, Table 4). Significantly more AEs were experienced by patients treated with codeine/paracetamol (81%) compared with those receiving valdecoxib, etoricoxib or placebo (24%, 31% and 30% respectively; P<0.001 for all). Most of AEs reported with codeine/paracetamol were opioid related and were in the form of nausea, vomiting, dizziness and somnolence.

**Patients’ global evaluation of study medication**

Significantly more patients in the active treatment groups rated their study medication as good or excellent compared with those in placebo group (P<0.001, Figure 5). Significantly more patients who received valdecoxib rated their study medication as good or excellent compared with those who received etoricoxib or codeine/paracetamol. Similarly, a significantly higher percentage of patients in etoricoxib group described their medication as good or excellent compared with codeine/paracetamol group (P<0.05).
Table 3: Number (%) of patients taking rescue medication and time to rescue analgesia

<table>
<thead>
<tr>
<th>Study medication</th>
<th>Number (%) of patients receiving rescue medication</th>
<th>Median time to rescue analgesia in hr : min (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valdecoxib (no=21)</td>
<td>4(19)*</td>
<td>20:18* (18:32- &gt;24.00)</td>
</tr>
<tr>
<td>Etoricoxib (no=19)</td>
<td>9(47)†</td>
<td>13:47† (11:37-16:48)</td>
</tr>
<tr>
<td>Codeine/paracetamol (no=21)</td>
<td>13(62)</td>
<td>07:13 (04:31-13:26)</td>
</tr>
<tr>
<td>Placebo (no=20)</td>
<td>18(90)§</td>
<td>01:08§ (01:03-01:41)</td>
</tr>
</tbody>
</table>

no=number, CI=confidence interval; * P<0.001 for valdecoxib versus etoricoxib or codeine/paracetamol; † P<0.01 for etoricoxib versus codeine/paracetamol; § P<0.001 for placebo versus all active treatments.

Table 4: Number (%) of patients with adverse events.

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Valdecoxib (no=21)</th>
<th>Etoricoxib (no=19)</th>
<th>Codeine/paracetamol (no=21)</th>
<th>Placebo (no=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event</td>
<td>5(24)</td>
<td>6(31)</td>
<td>17(81)*</td>
<td>6(30)</td>
</tr>
<tr>
<td>Headache</td>
<td>2(9)</td>
<td>2(11)</td>
<td>1(5)</td>
<td>2(10)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1(5)</td>
<td>1(5)</td>
<td>5(24)*</td>
<td>1(5)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>0(0)</td>
<td>1(5)</td>
<td>4(19)*</td>
<td>1(5)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1(5)</td>
<td>1(5)</td>
<td>4(19)*</td>
<td>1(5)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0(0)</td>
<td>0(0)</td>
<td>3(14)*</td>
<td>1(5)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1(5)</td>
<td>1(5)</td>
<td>0(0)</td>
<td>0(0)</td>
</tr>
</tbody>
</table>

no=number; * P<0.001 for codeine/paracetamol versus all other groups.

DISCUSSION

Arthroscopy of the knee joint is a common procedure that is usually performed on an outpatient basis. Although the degree of trauma associated with arthroscopic procedures is less compared with conventional open techniques, yet the surgical sites of repair including the anterior fat pad, the joint capsule, and the synovial tissue, have free nerve endings that are capable of sensing painful stimuli and producing severe pain. Arthroscopic meniscectomy of the knee may cause enough pain and swelling to delay rehabilitation and return to normal daily activities for up to 2 weeks after surgery. In addition, uncontrolled pain can lead to hyperalgesia where nociception is upregulated through both peripheral and central mechanisms and resulting pain becomes increasing difficult to treat. Therefore, an analgesic agent with a fast onset of action and high magnitude of pain relief can enhance post-arthroscopic convalescence and may prevent the development of neuronal plasticity in these patients.
In the present study valdecoxib was effective in the treatment of moderate to severe pain following arthroscopic meniscectomy of the knee. Valdecoxib was superior to placebo for all efficacy measures throughout the 24-hours post-dose assessment period. Compared with etoricoxib, valdecoxib was associated with faster onset and greater magnitude of analgesia. This was demonstrated by significantly better PID and PR scores with valdecoxib compared with etoricoxib at all measured time points from 0.5 to 24 hours post-dose, and by the lower percentage of patients requiring rescue analgesia with valdecoxib. Results for all other time-specific measures (SPID and TOTPAR) were generally consistent with the results of PID and PR. The faster and greater analgesia for valdecoxib compared with etoricoxib may be explained by the tighter binding and the greater inhibitory effect exhibited by valdecoxib on COX-2 enzyme compared with other COX-2 specific inhibitors (9).

Patients treated with valdecoxib in the present investigation experienced onset of analgesia comparable to those treated with codeine/paracetamol. The degree of pain relief provided by the two drugs was similar up to six hours post-dose. However, the degree of analgesia attained in valdecoxib group was statistically superior to that achieved by codeine/paracetamol from 8 to 24 hours post-dose. The sustained analgesic effect of valdecoxib over 24 hour period is considerably larger than that predicted by its elimination half life of 8.11 hours (11). The difference between the duration of the pharmacodynamic effect and the pharmacokinetic half life of valdecoxib may be attributed to the slow dissociation from its binding site on COX-2 enzyme (9).

Previous clinical trials have studied the analgesic efficacy of valdecoxib following dental, general surgery, and orthopedic operations (11,16, 24-26). In post-operative dental pain model, valdecoxib 20 or 40 mg was significant-
ly better than placebo, based on onset of analgesia, 6- and 24- hours TOTPAR scores and time to rescue medication. Similarly, when administered pre-operatively to patients undergoing bunionectomy or oral surgery, valdecoxib 10-80 mg was significantly better than placebo in terms of PID scores for 24 hours, time to rescue medication and percentage of patients requiring rescue analgesia. In laparoscopic cholecystectomy patients, pre-operative intra-venous parecoxib 40 mg (parenteral form of valdecoxib) plus post-operative valdecoxib 40 mg/day for 4 days resulted in significantly fewer patients reporting moderate to severe pain on post-operative day 1 compared with placebo. Additionally, valdecoxib recipients in the same study used significantly less supplementary analgesia than placebo recipients over days 1-4 post-operatively. In Christensen et al. report, valdecoxib was significantly superior to rofecoxib (another COX-2 specific inhibitor) with respect to mean time specific pain intensity difference and pain relief scores for up to 1.5 hours post-dose. Moreover, times to onset of analgesia observed for valdecoxib (30 minutes) and placebo (>24 hours) in Christensen et al study are consistent with those recorded in the present investigation. Valdecoxib also demonstrated opioid sparing effects in patients undergoing joint arthroplasty. In two trials, the patient controlled cumulative dose of morphine over the first 24 hours was reduced by 24% after knee arthroplasty and by 43% after hip arthroplasty.

Both valdecoxib and etoricoxib were well tolerated in this trial, and there were no significant differences in the incidence of AEs between valdecoxib, etoricoxib and placebo treatments. Valdecoxib and etoricoxib administration resulted in significantly fewer opioid-related AEs, such as dizziness, nausea, vomiting, and somnolence, than did codeine/paracetamol administration. Previous studies have also shown that combination of paracetamol with codeine or oxycodone resulted in a greater incidence of AEs than either COX-2 specific inhibitors or conventional NSAIDs.

Reduced opioid consumption in the present study (demonstrated by significantly less need for codeine/paracetamol as a rescue analgesic) and improved analgesia may be partially responsible for the lower incidence of post-operative nausea and vomiting in valdecoxib and etoricoxib treated patients. COX-2 specific inhibitors alone can also prevent pharmacologically induced emesis in animals. Previously published studies have shown that COX-2 specific inhibitors, owing to their COX-1 sparing nature, demonstrated an incidence of gastro-duodenal ulceration that is significantly lower than that observed with conventional NSAIDs and comparable to placebo. In addition, valdecoxib does not negatively impact platelet function, a characteristic of all COX-2 specific inhibitors. This lack of effect on platelets makes valdecoxib and other COX-2 specific inhibitors suitable for administration in the peri-operative period, thereby providing an opportunity to reduce post-operative pain without significantly increasing the risk of bleeding. No cardiovascular AEs were found in this trial. However, administration of parecoxib/valdecoxib combination for 14 days in patients undergoing coronary artery bypass grafting resulted in greater (though statistically insignificant) incidence of cardiovascular thrombotic complications.

Analysis of patients’ global evaluation of safety medication showed that the proportion of patients giving a rating of good or excellent in this study was highest in valdecoxib group followed by etoricoxib, codeine/paracetamol and placebo. Overall, patient’s satisfaction with valdecoxib was statistically superior to all other treatment groups. Consistent with other data, reduction of post-operative nausea and vomiting together with the better quality of analgesia could be the predominant determinant of higher patient satisfaction scores in valdecoxib treated patients compared with either etoricoxib or codeine/paracetamol treated patients.

In conclusion, analgesia provided by 40 mg oral valdecoxib in patients with postarthroscopic menisectomy pain was rapid and sustained over 24 hours period, superior to that achieved with etoricoxib 120 mg, and comparable but longer lasting than that with codeine/paracetamol 60/300 mg. Valdecoxib and etoricoxib have a tolerability profile superior to that of codeine/paracetamol combination. Larger scale trials are required to investigate the cardio-renal safety issues associated with COX-2 specific inhibitors.
REFERENCES