ORIGINAL ARTICLE

Analgesia in ankle sprain: study with etoricoxibe*

Analgesia na entorse de tornozelo: estudo com etoricoxibe

Rogério Teixeira da Silva[1], Cristiano Frota Souza Laurino[2], Fábio Cesar Petri[3], Lidia Ferreira de Souza[4], Renata Botos da Silva Neves Petri[5]

** Received from the Nucleus of Sports and Orthopedics Studies (NEO) / Orthopedia Group, Samaritano Hospital, São Paulo, SP.*

SUMMARY

BACKGROUND AND OBJECTIVES: Ankle sprain is one of the most frequent diseases in orthopedic emergencies. In general, analgesics and anti-in‡ammatory drugs are prescribed. This study aimed at evaluating whether 60 mg daily etoricoxib is as effective as 90 mg daily etoricoxib to treat pain and in‡ammation in patients with ankle sprain grades I and II.

METHOD: This is a clinic, randomized, double-blind, prospective and controlled study which has evaluated 43 patients with ankle sprain grades I and II, with mean age of 32 years. Patients were randomly distributed in two groups: group I, made up of 23 patients treated with 90 mg daily bolus etoricoxib, and group II, made up of 20 patients under 60 mg daily bolus dose. Patients were evaluated by the visual analog scale (VAS) and by functional evaluation after 7 and 15 days of treatment.

RESULTS: There has been signifIcant pain improvement between visits before and after using the drug, with a mean of 4.1 VAS score ($p < 0.001$), however pain intensity improvement did not depend on therapeutic schedule. Drug was withdrawn from one patient due to tolerability, which was considered good for 90.7% of patients

CONCLUSION: Both 60 mg and 90 mg etoricoxib doses were effective and well tolerated to control acute pain in ankle sprain patients.

Keywords: Acute pain, Ankle, Etoricoxib, Treatment.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A torção de tornozelo é uma das doenças mais frequentes nas emergências ortopédicas. Normalmente prescrevem-se analgésicos e anti-in‡amatórios. O objetivo deste estudo foi avaliar se o etoricoxibe na dose diária de 60 mg é tão efetivo quanto à dose de 90 mg no tratamento da dor e in‡amação em pacientes com torções de tornozelo graus I e II.

MÉTODO: Estudo clínico aleatório, duplamente encoberto, prospectivo e controlado foram estudados 43 pacientes com diagnóstico de entorse de tornozelo graus I e II, com idade média de 32 anos. Os pacientes foram divididos em dois grupos aleatoriamente: grupo I, constituído por 23 pacientes tratados com 90 mg de etoricoxibe em dose única diária, e grupo II, constituído por 20 pacientes em uso de 60 mg em dose única diária. As avaliações pela escala analógica visual (EAV) e avaliação funcional foram feitas após 7 e 15 dias de tratamento.

RESULTADOS: Observou-se diminuição signifIcativa da dor entre as visitas pré e pós o uso do medicamento, com uma média de 4,1 pontos na EAV ($p < 0,001$), porém a diminuição da intensidade da dor não dependeu do esquema terapêutico utilizado. Um paciente teve

1. Master and Doctor in Orthopedics and Sciences, Federal University of São Paulo (UNIFESP); Coordinator of the Nucleus of Sports and Orthopedics Studies (NEO). Orthopedics Group. Samaritano Hospital, São Paulo, SP, Brazil.
2. Master in Sciences, Federal University of São Paulo (UNIFESP); Orthopedist of the Brazilian Confederation of Athletics. São Paulo, SP, Brazil.
3. Orthopedist – Military Hospital of São Paulo (HM-SP); Medical Coordinator of the Medical Orthopedic Cantareira Clinic. São Paulo, SP, Brazil.
4. Physical Therapist of the FisioEsporte Clinic. São Paulo, SP, Brazil.
5. Physical Therapist of the Nucleus of Sports and Orthopedics Studies (NEO) and Physical Therapy Coordinator of the Cantareira Clinic. São Paulo, SP, Brazil.

Correspondence to:
Rogério Teixeira da Silva, M.D.
R. Dr. Geraldo Campos Moreira 164 – cj 34 – Brooklin Novo
04571-020 São Paulo, SP.
E-mail: rgtsilva@uol.com.br

a medicação suspensa, devido à tolerabilidade, que foi considerada boa em 90,7% dos pacientes.
CONCLUSÃO: As doses de 60 e 960 mg de etoricoxibe foram efetivas e bem toleradas para o controle da dor aguda em pacientes com entorse do tornozelo.
Descritores: Dor aguda, Etoricoxibe, Tornozelo, Tratamento.

INTRODUCTION

Ankle strain is a very frequent disease seen by orthopedic emergency sectors. International data from 1997 have shown that approximately 1 million people were annually affected by this problem in the United States[1]. A different North-American study has reported incidence of approximately 6 out of 1 thousand people/year, which in population terms is a high number. Most current recommendations favor early mobilization as an important aid for patients' recovery[3], and for this to be effective, both pain control and adequate immobilizing devices are necessary measures.

In spite of new advances in ankle immobilizers' manufacture, the gain of the painless movement arch is still an important factor for patients to more rapidly recover joint function and to have adequate tissue healing. For such, physicians have analgesic and anti-in‡ammatory drugs which are routinely used by orthopedic departments.

There are several criteria for measuring treatment evolution, being the most important pain improvement when ambulating during both active and passive ankle mobilization[1,4]. A good analgesia is necessary to meet such objective.

Many drugs may be useful to decrease pain and tissue in‡ammation, ranging from those purchased over-the-counter to more potent analgesics. Since most sprains are part of Leach classifIcation grades I and II (mild and moderate)[5], in general non-opioid analgesics such as paracetamol, and non-steroid anti-in‡ammatory drugs (NSAIDs) are the most widely used. These, although safe for most cases, may lead to gastrointestinal and cardiovascular complications depending on usage time and patients' profIle[6].

In the late 1990s, studies were aimed at the development of selective cycloxygenase-2 inhibitor NSAIDs, called coxibs. These drugs proved to be safe for the gastrointestinal tract when compared to traditional NSAIDs[7], and started to be widely used worldwide.

More recently there has been concern with the chronic use of these drugs, especially due to cardiovascular adverse events. Although the literature has published studies supporting the safety of such drugs[8], several studies appeared in recent years deeply discussing coxibs-related complications.

Due to these studies, several international regulatory agencies have determined that these coxibs should be limited to specifIc cases, and that further studies should confIrm the lowest effective dose possible, to prevent complications.

Taking into consideration that all patients suffering ankle sprain have to be immobilized as part of their treatment, it is believed that this, by itself, is a major aid to treat joint pain of these patients, allowing supposing that analgesia may be effective with decreased routine coxib analgesic doses, when patients are adequately immobilized. In the specifIc case of etoricoxib, recommended daily dose is 120 mg for acute pain and there are no studies about the effIcacy of a lower dose in analgesia and joint mobility improvement. Another important point is that acute pain studies have evaluated dental pain models, which is not necessarily the best comparison for the acute orthopedic pain model.

Given this premise, we decided to study other doses of this drug to check the effIcacy of decreasing the recommended drug dose to control acute orthopedic pain.

This pilot study primarily aimed at testing the hypothesis that 90 mg daily etoricoxib is as effective as 60 mg to treat initial pain and in‡ammation in patients with ankle sprain grades I and II. Secondarily, we have observed the tolerability of such drug when used for two weeks.

METHOD

This is a clinical, double blind, randomized and prospective study with two active treatment arms, including 50 patients with ankle sprain grades I and II, seen by the emergency sector of a tertiary hospital of the city of São Paulo, from August 2009 to February 2010. After initial contact with the evaluator, who was a physician, patients were invited to read and sign the free and informed consent term for voluntary participation in the study.

Patients' age varied from 18 to 50 years with mean age of 32 years. Inclusion criteria were history of acute ankle sprain during sports practice, with time interval less than 24 hours between the injury and the flrst evaluation.

Exclusion criteria were patients with less than 18 years of age and more than 50 years of age, with history of previous ankle sprain submitted or not to treatment, in one or both ankles; patients with foot and/or ankle fractures previous or simultaneous to current sprain; patients under anti-in‡ammatory drugs or chronic steroids; pa-

tients with heart diseases, vascular failure, previous or current deep venous thrombosis, vascular diseases being treated, congenital deformities with lack of limb, amputations, hypertension, rheumatic diseases, wounds and scars with deformities, cardiovascular diseases such as angina, acute myocardial infarction, heart failure, renal diseases, kidney diseases, allergic reaction to acetylsalicylic acid or other anti-in‡ammatory drugs, history of stroke or transient ischemic attack.

Patients were blindly and randomly distributed in two groups being group I made up of 25 patients treated with 90 mg daily etoricoxib in bolus dose for 14 days, and group II, made up of 25 patients with 60 mg daily bolus. To assure randomization, 50 numbers of 3 digits were generated by a computer program and only the chief researcher, who had no contact with patients would have information about the therapeutic schedule.

Clinical evaluation protocol

The study was divided in four visits and a telephone call, being the flrst visit on day zero, that is, the day patients would enter the emergency sector. In this visit, a questionnaire was fllled with personal data, clinical data and ankle sprain history, followed by additional tests: total blood count, biochemistry, beta-HCG for female patients, urine test I and simple ankle X-rays to rule out the possibility of fractures.

After collecting additional tests, the protocol was started with visit I on day zero. In this visit, patients were submitted to physical evaluation where blood pressure was measured, edema was generally inspected and measured by volumetry and perimetry in 8. Visual analog pain scale (VAS) was used to evaluate pain intensity, where 0 = no pain and 10 = maximum pain ever experienced by patients. Pain was evaluated in three situations: at rest, during ankle passive and active mobilization. After this, ligament stability was checked with speciflc tests and movement amplitude was evaluated with a goniometer.

Finally, patients were oriented to stay in orthostatic position on both feet, in orthostatic position on the injured foot and in orthostatic position on the tip of the injured foot. In each position, the researcher would ask patients about pain intensity according to VAS. At the end of visit I, patients were immobilized with Aircast® and the flrst drug dose was administered.

Visit II could be simultaneous to visit I day zero because the protocol applied to visit I was repeated in visit II, plus pain evaluation with VAS during counter-resistance evaluation and drug control item.

Visit III was carried out on the 8th day after injury and the evaluation protocol was the same used during visit II, plus the following items: adverse reactions, drug eflcacy and tolerability.

Visit IV was on the 15th day, the protocol was maintained and the chief researcher requested patients to repeat complementary tests.

A telephone call was made by the chief researcher 45 days after the injury, when patients were asked about the presence of pain and edema, and about the subjective flnal result of the treatment.

Statistical analysis

SPSS 15.0 software was used for statistical analysis and the following variables were calculated for descriptive analysis: mean, standard-deviation, minimum, median, maximum and frequency.

Numeric variables were compared by visits and by group. ANOVA for repeated measures was used for variables with normal distribution. Non-parametric Wilcoxon test p-value was used for numeric variables without normal distribution where signiflcance level was equal 0.05 divided by the number of comparisons of each variable.

Non-parametric Nc Nemar test was used to compare categorical variables by visits and by group, with signiflcance level of 0.05 divided by the number of comparisons of each variables

In comparisons between visits I and III, I and IV and III and IV for numeric variables not meeting normality assumptions, p-value of non-parametric Wilcoxon test at signiflcance level of 0.0167. Divisions were made by the number of comparisons.

In comparisons between visits I and III, I and IV and III and IV for categorical variables, the p-value of non-parametric Wilcoxon test was signiflcant at the level of 0.0167.

This study was approved by the Institution's Ethics Committee, process 25000.188.520/2007-41.

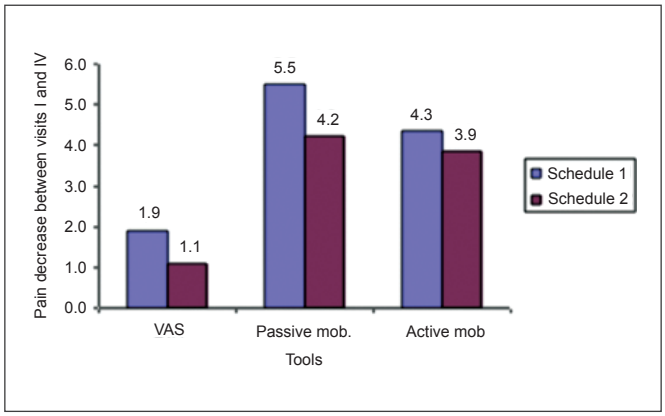
RESULTS

From 50 patients starting the protocol, 43 were included in the flnal analysis. Seven patients were excluded because they missed the 3rd and/or 4th visit.

From 43 patients included in the flnal evaluation, 23 (GI) (53.5%) used the therapeutic schedule 1 – 90 mg etoricoxib; 20 patients (GII) (46.5%) used the therapeutic schedule 2 – 60 mg etoricoxib. From all 43 patients, 9.3% were females and 90.7% were males.

Final results were not statistically different between

both therapeutic schedules in any time and for any variable: pain evaluation at rest (VAS), passive mobilization, active mobilization and counter-resistance mobilization (Graph 1).

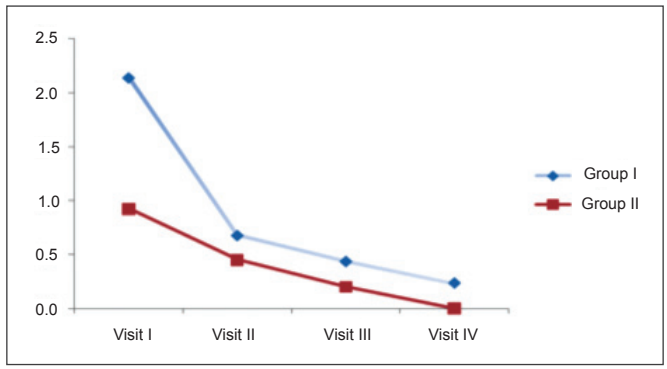


Graph 1 – Decreased pain intensity by the visual analog scale between visits 1 and 4 by measurement tools (clinical outcomes) and therapeutic schedule.
Schedule 1 = 90 mg etoricoxib; Schedule 2 = 60 mg etoricoxib

Signiflcant pain decrease was observed between visits I and IV according to VAS during pain evaluation at rest. This improvement was either general, regardless of the therapeutic schedule, or when considered each therapeutic schedule separately. There has been a higher trend for pain decrease in group I, using 90 mg etoricoxib, but difference was not statistically signiflcant.
There has been signiflcant pain decrease during visits I and IV with mean of 4.1 points ($p < 0.01$), being interesting to stress that this decrease was not therapeutic schedule-dependent.
From 43 studied patients, only one patient had the drug withdrawn following medical orientation because he presented stomach discomfort and diarrhea after starting the protocol. The protocol was maintained until study completion, even after drug withdrawal.
Both groups had tolerability of 90.7%, considered good, and just 4.7% had poor tolerability.

DISCUSSION

This study has shown that 90 and 60 mg etoricoxib doses were effective for analgesia of immobilized patients after ankle sprain. There was a trend of patients under 90 mg dose to report further pain decrease measured by VAS, however this difference was not signiflcant. In addition, both doses were well tolerated by patients. The analysis of this study has shown that there is still a very interesting research fleld in the area of sports orthopedics and traumatology, especially in acute pain models.
It is known that patients with acute contusions and traumas should be treated with pain killers, but some studies do not report different manners to induce analgesia, such as affected joint immobilization[9-11]. What can be observed in sprain patients is that reported pain is not that severe as compared to pain at rest. VAS measures for ankle movement pain were signiflcantly higher than those reported at rest (Graph 2).



Graph 2 – Pain intensity at rest.

Studies showing the benefits of orthosis to treat acute ankle sprain do not mention the coadjuvant treatment with analgesic or anti-inflammatory drugs, leaving these data as secondary for patients' analgesia[11]. It is known that most patients looking for orthopedic services after ankle sprain will have some type of immobilization, even if for a short period. Peripheral nociceptive pain in these cases may also be controlled by joint immobilization, which acts as a factor to promote analgesia.
All studied pain models and analgesic therapies take into account the extent to which chemical pain mediators may be blocked. For acute injuries, analgesics and NSAIDs are widely used. NSAIDs have a very good analgesic potential for the acute phase because they block the production of prostaglandin (PG) which induces tissue in‡ammation. Studies have shown that at least 80% of PG production should be blocked to obtain a satisfactory analgesic effect in the acute phase and this depends on the drug, usage time and on the dose[12]. This blockade should be constant, and for such it is necessary to know the adequate dose of a certain anti-in‡ammatory substance[12-14].
Traditional NSAIDs and coxibs are major examples of this group of drugs used during the acute phase of such sprains to control pain. Even simple analgesics, such as paracetamol and ibuprofen have already

been studied for acute orthopedic pain. A study with 260 ankle sprain patients has shown that 3.9 mg/day extended release paracetamol in three doses of 1.2 g a day has good analgesic efficacy, comparable to 1.2 g ibuprofen in three doses of 400 mg. The major problem of this study was the dose, since it is known that paracetamol has a maximum allowed dose of 4 g a day and that possibly 1.2 g ibuprofen could have been insufficient to control acute pain. Since in this study patients were also immobilized and ankle sprains were limited to grades I and II, it might be that in patients with high pain intensity these drugs may have limited effects.

Other authors[13] have described the beneflts of other NSAIDs, such as diclofenac and piroxicam and even pain improvement of acute orthopedic injuries with the use of dermal patches with diclofenac[16] and ketoprofen[17] as active substances. By the time, little was known about gastrointestinal complications, but today we know that even with the short term use of these drugs, which do not selectively inhibit COX-2, there might be severe gastric complications[16].

A study carried out from 1999 to 2001 in the Canadian public system[18] has evaluated 726 admitted patients (first visit) from a sample of 1,054,532 people/year. This population was compared to 20,002 controls to perform a regression logistic analysis to estimate odds ratio (OR) with 95% confidence interval (CI-95) to evaluate the risk of confirmed upper gastrointestinal (GI) complications and their association with NSAIDs. Rofecoxib and naproxen users had higher GI risk with adjusted OR of 3.6 (CI-95 from 2.2 to 5.7) and 3.4 (CI-95 from 1.8 to 6.7), respectively. No association was found between GI risk and celecoxib (OR 1.1 with CI-95 from 0.7 to 1.8) or diclofenac associated to misoprostol, a gastric protector widely used in the USA and Canada (OR 0.7 with CI-95 from 0.3 to 1.8).

No study was found in the literature with etoricoxib, used in our study, and because it is a more selective Cox-2 inhibitor we believe that it would be interesting to evaluate results with doses lower than 120 mg, recommended for acute pain. This drug had already recommended doses for more chronic pain: 90 mg for rheumatoid arthritis and 60 mg for osteoarthritis, and these doses, associated to immobilization, could be effective to control pain, which has been proven.

Clinical coxibs utilization has been shown to be effective to handle GI complications, for leading to a selective blockade of arachidonic acid cascade inhibition. This is interesting because it prevents upper GI complications, common with non-selective NSAIDs. But there has been also concern with cardiovascular events[19], and major regulatory agencies have indicated that further studies are needed and that the lowest most effective dose should be looked for in this group of drugs[20]. In addition, drugs should be used for the shortest possible time after obtaining the desired clinical effect.

In our study, patients have greatly benefited from both therapeutic schedules with a mild trend to further pain decrease with 90 mg etoricoxib. This shows the extent to which acute orthopedic pain models should be studied because immobilization itself has helped local ankle pain improvement, which probably has helped analgesia of patients under 60 mg to the point that there was no statistical difference between both doses. Recommended etoricoxib dose for acute pain is 120 mg[21-23], and with this study it is also possible to include at least the dose of 90 mg to this indication spectrum.

Another important aspect of this study is that it is the flrst to prove the efflcacy of this drug in a model of acute orthopedic pain, since all other studies have proven its efflcacy in models of dental pain and postoperative pain in general[20].

A limitation of this study was the number of patients, since the analysis of just 50 individuals may lead to some bias, which could be avoided with a larger sample. We have also not studied the anatomic level of ligament and capsule injury, deciding to consider the practical part of pain control, which is a major factor during sprain acute phases. As from the results of this pilot study, we intend to carry out a larger study to improve the understanding of this acute orthopedic pain control model.

This study may encourage further studies in this area because we were able to prove with this drug, and also with other drugs, that a lower dose is effective for acute pain and may prevent major clinical complications.

CONCLUSION

This study has shown that 60 and 90 mg etoricoxib doses are effective and well tolerated to control acute pain in patients with ankle joint sprain.

ACKNOWLEDGMENTS

We acknowledge Adriana Greggio and Adriana Barros,

who helped with the administrative part; to PSG Estatísticas Médicas, which has coordinated this clinical trial in an exemplary manner. And we thank once more the flnancial and scientiflc support of MSD.

REFERENCES

1. Renström PA, Konradsen L. Ankle ligament injuries. Br J Sports Med 1997;31(1):11-20.
2. Bridgman SA, Clement D, Downing A, et al. Population based epidemiology of ankle sprains attending accident and emergency units in the West Midlands of England, and a survey of UK practice for severe ankle sprains. Emerg Med J 2003;20(6):508-10.
3. Kerkhoffs GM, Rowe BH, Assendelft WJ, et al. Immobilisation and functional treatment for acute lateral ankle ligament injuries in adults. Cochrane Database Syst Rev. 2002;(3):CD003762
4. Wolfe MW, Uhl TL, Mattacola CG, et al. Management of ankle sprains. Am Fam Physician 2001;63(1):93-104.
5. Liu SH, Nguyen TM. Ankle sprains and other soft tissue injuries. Curr Opin Rheumatol 1999;11(2):132-7.
6. Graham DJ. COX-2 Inhibitors, other NSAIDs, and cardiovascular risk: the seduction of common sense JAMA 2006;296(13):1653-6.
7. McAdam BF, Catella-Lawson F, Mardini IA, et al. Systemic biosynthesis of prostacyclin by cyclooxygenase (COX)-2: the human pharmacology of a selective inhibitor of COX-2. Proc Natl Acad Sci U S A 1999;96(1):272-7.
8. Laine L, Curtis SP, Cryer B, et al. Assessment of upper gastrointestinal safety of etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. Lancet 2007;369(9560):465-73.
9. 9. Man IO, Morrissey MC. Relationship between ankle-foot swelling and self-assessed function after ankle sprain. Med Sci Sports Exerc 2005;37(3):360-3.
10. Ivins D. Acute ankle sprain: an update. Am Fam Physician 2006;74(10):1714-20.
11. Boyce SH, Quigley MA, Campbell S. Management of ankle sprains: a randomized controlled trial of the treatment of inversion injuries using an elastic support bandage or an Aircast ankle brace. Br J Sports Med 2005;39(2):91-6.
12. Zeilhofer HU, Brune K. Analgesic strategies beyond the inhibition of cyclooxygenases. Trends Pharmacol Sci 2006;27(9):467-74.
13. Bahamonde LA, Saavedra H. Comparison of the analgesic and anti-inflammatory effects of diclofenac potassium versus piroxicam versus placebo in ankle sprain patients. J Int Med Res 1990;18(2):104-11
14. Vane JR, Botting RM. Anti-inflammatory-drugsandtheir mechanism of action. Inflamm Res 1998;47(Suppl 2):S78–S87.
15. Dalton JD Jr, Schweinle JE. Randomized controlled noninferiority trial to compare extended release acetaminophen and ibuprofen for the treatment of ankle sprains. Ann Emerg Med 2006;48(5):615-23.
16. Galer BS, Rowbotham M, Perander J, et al. Topical diclofenac patch relieves minor sports injury pain: results of a multicenter controlled clinical trial. J Pain Symptom Manage 2000;19(4):287-94.
17. Mazieres B, Rouanet S, Velicy J, et al. Topical ketoprofen patch (100 mg) for the treatment of ankle sprain: a randomized, double-blind, placebo-controlled study. Am J Sports Med 2005;33(4):515-23.
18. Castellsague J, Holick CN, Hoffman CC, et al. Risk of upper gastrointestinal complications associated with cyclooxygenase-2 selective and nonselective nonsteroidal antiinflammatory drugs. Pharmacotherapy 2009;29(12):1397-407.
19. Kearney PM, Baigent C, Godwin J, et al. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. BMJ 2006;332(7553):1302-8.
20. Mehallo CJ, Drezner JA, Bytomski JR. Practical management: nonsteroidal antiinflammatory drug (NSAID) use in athletic injuries. Clin J Sport Med 2006;16(2):170-4.
21. Rasmussen GL, Malmstrom K, Bourne MH, et al. Etoricoxib provides analgesic efficacy to patients after knee or hip replacement surgery: a randomized, double-blind, placebo-controlled study. Anesth Analg 2005;101(4):1104-11.
22. Chang DJ, Desjardins PJ, King TR, et al. The analgesic efficacy of etoricoxib compared with oxycodone/acetaminophen in an acute postoperative pain model: a randomized, double-blind clinical trial. Anesth Analg 2004;99(3):807-15.
23. Malmstrom K, Kotey P, Coughlin H, et al. Randomized, double-blind, parallel-group study com-

paring the analgesic effect of etoricoxib to placebo, naproxen sodium, and acetaminophen with codeine using the dental impaction pain model. Clin J Pain 2004;20(3):147-55

Submitted in January 30, 2012.
Accepted for publication in June 06, 2012.
Con‡ict of interests: None – Sponsorship source: Merk Sharp Dohme Laboratory (MSD).