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In vivo μελέτη της διαπερατότητας του αρθρικού υμένα από σελεκοξίμη και ετορικοξίμη και η επίδρασή της στον έλεγχο του πόνου σε ασθενείς με φλεγμονώδη αρθρίτιδα

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ΠΕΡΙΛΗΨΗ

ΣΚΟΠΟΣ: Η εκτίμηση του δείκτη διαπερατότητας του αρθρικού υμένα από τη σελεκοξίμη και την ετορικοξίμη σε ασθενείς με φλεγμονώδη αρθρίτιδα και η συσχέτιση του δείκτη αυτού με την οπτική αναλογική βαθμολογία πόνου (VAS). **ΜΕΘΟΔΟΙ:** Ασθενείς με συλλογή αρθρικού υγρού στην άρθρωση του γόνατος τυχαιοποιήθηκαν ανά ηλικία και το φύλο σε τρεις ομάδες (n=17) η καθεμία: την ομάδα της σελεκοξίμης, την ομάδα της ετορικοξίμης και την ομάδα ελέγχου. Οι δόσεις ήταν 100mg δύο φορές τη μέρα στην ομάδα της σελεκοξίμης, 90mg μια φορά την ημέρα στην ομάδα της ετορικοξίμης και ενώ η ομάδα ελέγχου δεν έλαβε καμία αγωγή. Οι συμμετέχοντες εκτίμησαν τη βαθμολογία VAS, και τα δείγματα αίματος και αρθρικού υγρού συλλέχθηκαν στη βασική γραμμή και επτά ημέρες αργότερα κατά τον χρόνο C_{max} για κάθε φάρμακο. Τα επίπεδα σελεκοξίμης και ετορικοξίμης προσδιορίστηκαν σε δείγματα ορού και αρθρικού υγρού από UPLC συζευγμένο με ICP-MS. Η ταυτοποίηση των ενώσεων διεξήχθη με QTOF-MS. **ΑΠΟΤΕΛΕΣΜΑΤΑ:** Μετά από προσδιορισμό συγκέντρωσης φαρμάκων ορού και αρθρικού υγρού, ο εκτιμώμενος δείκτης διαπερατότητας ήταν 23,3% (SD 32,8) για τη σελεκοξίμη και 49,5% (SD 21,1) για την etoricoxib, (p = 0,031). Στις 2 ομάδες ανιχνεύθηκε στατιστικά σημαντική μείωση του πόνου VAS (p < 0,001), αλλά μόνο οριακά στην ομάδα ελέγχου (p = 0.047). Η ετορικοξίμη ήταν ανώτερη σε σύγκριση με τη σελεκοξίμη στη μείωση του πόνου, όπως προσδιορίζεται από VAS (p = 0.02). Δεν βρέθηκε συσχέτιση μεταξύ του δείκτη διείσδυσης της αρθρικής μεμβράνης, ούτε στα φάρμακα, ούτε στη βελτίωση του πόνου. **ΣΥΜΠΕΡΑΣΜΑ:** Η ετορικοξίμη είχε καλύτερο δείκτη διείσδυσης στο αρθρικό υγρό και ισχυρότερη αναλγητική δράση από ότι η σελεκοξίμη στη δοσολογία που χρησιμοποιείται σε ασθενείς με ενεργή φλεγμονώδη αρθρίτιδα.

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In vivo study of the synovial membrane penetration index from celecoxib and etoricoxib and their impact on pain control in patients with inflammatory arthritis

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ABSTRACT

OBJECTIVES: To estimate the synovial membrane penetration index of celecoxib and etoricoxib, and determine their impact on pain visual analogue score (VAS). **MATERIAL AND METHODS:** Patients with inflammatory synovial fluid accumulation of the knee joint were randomized in three age- and gender-matched groups of 17 patients each: the celecoxib treated group, the etoricoxib treated group, and the control group. Dosages were 100mg b.i.d. for celecoxib, 90mg o.d. for etoricoxib, and no medication in the control group. The participants completed the pain VAS, and blood and synovial fluid samples were collected at baseline and seven days later at the time of C_{max} for each drug. Celecoxib and etoricoxib levels were determined in serum and synovial fluid samples by UPLC coupled to ICP-MS. Identification of compounds was performed by QTOF-MS. **RESULTS:** After serum and synovial fluid drug concentration determination, the estimated penetration index was 23.3% (SD 32.8) for celecoxib and 49.5 % (SD 21.1) for etoricoxib, (p=0.031). In the 2 coxib groups, statistically significant reduction of pain VAS was detected (p<0.001), but only marginally in the control group (p=0.047). Etoricoxib was superior compared to celecoxib in reducing pain, as determined by VAS (p=0.02). No correlation was found between the synovial membrane penetration index of either drug and pain improvement. **CONCLUSION:** Etoricoxib had a better penetration index in the synovial fluid and stronger analgesic effect than celecoxib in the dosage used in patients with active inflammatory arthritis.

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Keywords: inflammatory arthritis, synovial fluid, penetration index, etoricoxib, celecoxib.

INTRODUCTION

Celecoxib was classified as the first generation coxib licensed in 1999, whilst the rest of coxibs were classified as second generation coxibs. Coxibs belong chemically to different chemical classes such as sulfonamides (celecoxib, parecoxib and valdecoxib), methylsulfones (etoricoxib) or products of phenyl acetic acid (lumiracoxib).^{1,2} All these compounds have structural similarities to classic non-steroidal anti-inflammatory drugs (NSAIDs). The differences in their physicochemical characteristics may affect their pharmacokinetics and the variety in their actions and adverse reactions.^{3,4} Data emerging from pharmacokinetic and pharmacodynamic studies helped in determining the dosage of a drug. Usually, pharmacokinetic and pharmacodynamic studies are performed using blood sera, although drugs act at the level of target tissues and not at the level of serum. The distribution of a drug in tissues has attracted less attention, mostly due to ethical reasons and difficulties in accessing the tissues, hence it is mentioned as the "forgotten relative" of clinical pharmacokinetics.⁵ The pharmacokinetic parameters of a drug depend on its absorption, bioavailability, tissue distribution and excretion. Its action and adverse reactions are correlated with plasma concentrations and tissue distribution.^{4,6} Most NSAIDs, even these with short half-lives, are distributed slower in joint fluid than in plasma, while synovial fluid concentrations are more steady with fewer fluctuations compared with plasma concentrations. This fact may explain the sustained action that these drugs exhibit in joints compared to the action expected based on their half life time.⁷⁻¹⁰ After p.o. administration, the less lipophilic Celecoxib has bioavailability 20-40%^{2,11} and maximum concentrations (C_{max}) at 3 hours. Steady state conditions are achieved after 5 days maximum using a bid dosage. Celecoxib is metabolized via cytochrome P450 enzyme CYP2C9 into 3 inactive to cyclooxygenase metabolites.^{12,13} There are CYP2C9 polymorphisms, with variable actions on celecoxib metabolism and adverse reactions.^{2, 14-16} Etoricoxib's pharmacokinetic is linear to its dosage. It is absorbed fast and its bioavailability reaches 100%.² C_{max} is achieved at 1 hour after p.o. administration and steady state conditions are reached in 7 days.^{10,17,18} The aim of this study was to determine serum and synovial fluid concentrations of celecoxib and etoricoxib in patients with inflammatory arthritis and synovial fluid accumulation in knee joint, and estimate their synovial membrane penetration index (PI). We will also compare celecoxib's and etoricoxib's impact on pain control, and determine the correlation of their PI of synovial membrane with pain reduction.

MATERIALS AND METHODS

Study population

Patients were invited to participate in the study during regular visit to the rheumatology clinics of our hospital. Ninety-eight patients were screened. The inclusion criteria were as follows: 1) age 18-80 years, 2) fluid accumulation in a knee joint (monoarthritis) of a patient with a diagnosis of an inflammatory arthritis, such as rheumatoid arthritis, psoriatic arthritis, seronegative spondyloarthritis, undifferentiated arthritis, or inflammatory osteoarthritis, 3) synovial fluids (SF) WBC $>2000/mm^3$. The exclusion criteria were: 1) septic arthritis diagnosed either at baseline or during follow up, 2) treatment with biologic agents and treatment changes of disease modifying anti-rheumatic drugs (DMARDs) in the last two months, 3) treatment with NSAIDs in the last 2 weeks before study entry, 4) any kind of inflammation in the body either this might be of infectious etiology or not, 5) intraarticular injections of any kind in the knee from which synovial fluid was drawn in the last two months, 6) history of hypersensitivity to aspirin, coxibs, or other NSAID. 7) Surgical intervention of the knee in particular the last 6 months before study entry, 8) knee trauma within the last six months, 9) SF values of WBC $\leq 2000/\mu L$ or $\geq 50.000/\mu L$ at the first study visit.

From the 98 patients screened, 66 fulfilled inclusion and exclusion criteria. Out of the 66 patients, only 51 completed the study (1 patient had septic arthritis two days after first visit, 2 were lost to follow-up, and 12 did not have enough synovial fluid at second visit). No change of concomitant medications was allowed to patients of all groups and use of paracetamol as a rescue drug was only allowed to group C patients, and was discontinued 48 hours before the second visit. During the first visit, a detailed medical history was taken and a physical examination of the patients was performed. Also, a VAS for knee pain was completed by the patients. Then, knee joint aspiration was performed and 10ml blood was collected from every patient, using 21g needle syringes. The knee aspiration was diagnostic at first visit (differential diagnosis from septic arthritis in all cases). Immediately after aspiration, SF was cultured, a cell count and differential was carried out, and at least 5ml of synovial fluid were centrifuged in heparinized tube and were stored at -70. Blood serum was also stored at -70. After that, every patient randomized into three age- and gender-matched groups: In group A, patients received celecoxib 100 mg b.i.d; in group B, patients received etoricoxib 90 mg o.d; and in group C, patients received no NSAID, and started the appropriate treatment. Control group received no NSAID or drug other than allowed by protocol; whereas paracetamol was allowed as a rescue drug, only to be discontinued 48 hours before second visit. Patients came back for the second visit 7 days later so that steady

state conditions could be achieved. We repeated the same procedures as during the first visit, 3 hours after the morning dose of celecoxib and one hour after the daily dose of etoricoxib, in order to have C_{max} of the study drugs according to their known pharmacokinetics. The serum and joint fluid collection were done in steady state conditions in all cases.

This protocol was approved from our hospital Ethical Committee. Patients were seen during scheduled visits, were fully informed and had consented, according to the ethical principles of the declaration of Helsinki.

METHODS

Determinations of Celecoxib and Etoricoxib Concentrations in Joint Fluid and Serum were performed as analytically described in our previous paper.¹⁹ Briefly, High Performance Liquid Chromatography was coupled to Inductively Coupled Plasma Mass Spectrometry for the measurement of Sulphur-containing compounds such as both drug compounds. Ultra Performance Liquid Chromatography was coupled to Quadrupole Time of Flight Mass Spectrometry for quantitative determinations and detection of drug metabolites.²⁰⁻²²

Penetration index of the study drugs was determined in every patient according to the following form: penetration index=joint fluid concentration/serum concentration x100.

Statistical analysis

For data presentation, descriptive tests like mean value and standard deviation were used. When comparison was between the 3 study groups, Kruskal-Wallis was used, and when comparison was between the first and second visit, the measurement of the same variable of a particular study group by Wilcoxon test was used for statistic control. For correlations analysis, Pearson's cor-

relation coefficient was used. Analysis of data was processed by SAS 9.1.3 software (SAS Institute Inc., Cary, NC, USA). Level of significance was determined at 0.05.

RESULTS

Patients were equally distributed to the 3 groups according to gender ($p=0.165$) and age ($p=0.19$). There were statistically significant differences between the 3 groups according to the BMI ($p=0.01$), with the control group having BMI 28.1 compared to the BMIs of the celecoxib and etoricoxib groups, which were 25.91 and 24.77, respectively (**Table 1**).

Determination of serum and synovial fluid concentrations and penetration index of celecoxib and etoricoxib

All patients in all groups had 1 blood and 1 synovial fluid sample from both first and second visits. Celecoxib was determined in all 17 serum samples in concentrations varying from 0.346 to 1.855 $\mu\text{g/mL}$, and in only 6 of the 17 synovial fluid samples in concentrations varying from 0.333 to 0.789 $\mu\text{g/mL}$. Etoricoxib was determined in all 17 serum samples and in all 17 synovial fluid samples in concentrations varying from 1.023 to 3.301 $\mu\text{g/mL}$ and from 0.494 to 2.292 $\mu\text{g/mL}$, respectively. A statistically significant difference between the two drugs was found regarding the penetration index of the synovial membrane, with etoricoxib having the better penetration (**Table 2**).

Evaluation of pain VAS

Table 3 shows the mean values of pain VAS at visit 1 and visit 2 (before and after study drug treatment). A statistically significant pain VAS reduction was detected in the celecoxib ($p<0.001$) and etoricoxib ($p<0.001$) group and in the control group ($p=0.047$). **Table 4**

Table 1. Demographic Data

Parameter		Celecoxib group	Etoricoxib group	Control group	p
Gender	male	5 (29.41)	9 (52.94)	4 (23.53)	0.165
	n (%) female	12 (70.59)	8 (47.06)	13 (76.47)	
Age		56.18 (17.4)	57.18 (19.2)	67.35 (9.9)	0.19
Mean value (SD)					
BMI		25.91 (6.5)	24.77 (3.1)	28.51 (2.7)	0.010
Mean value (SD)					

n: number, BMI: body mass index, SD: standard deviation

Table 2. Celecoxib's and etoricoxib's concentrations and penetration index.

Parameter	Celecoxib group (n=17)	Etoricoxib group (n=17)	
Concentrations of drug	No of patients with drug detection/ total No of patients (range of concentrations)	No of patients with drug detection/ total No of patients (range of concentrations)	
Serum	17/17 (0.346-1.855 µg/mL)	17/17 (1.023-3.301 µg/mL)	
Joint fluid	6/17 (0.333-0.789 µg/mL)	17/17 (0.494-2.292 µg/mL)	
Penetration index	Mean value (SD)	Mean value (SD)	p
Values on %	23.3 (32.8)	49.5 (21.1)	0.031

Table 3. Mean values of visual analogue scale (VAS) in mm, according to study group, in the first and second visit (before and after drug treatment).

parameter	Celecoxib group ^α	Etoricoxib group ^β	Controls ^γ
pain Vas	mean value (SD)	mean value (SD)	mean value (SD)
1st visit	60 (25.09)	62.76 (19.25)	50.47 (18.29)
2nd visit	42.65 (29.45)	36.71 (20.10)	46.82 (16.98)

$\alpha: p < 0.001$, $\beta: p < 0.001$, $\gamma: p = 0.047$.

Values are in mm.

Table 4. Changes of pain VAS from 1st to 2nd visit and comparison between groups.

Change of VAS of pain (values on mm)	Celecoxib group	Etoricoxib group	Controls	
	mean value (SD)	mean value (SD)	mean value (SD)	
	17.4 (15)	26.1 (13.8)	3.6 (7.0)	
Comparison between groups	Celecoxib /etoricoxib	Celecoxib /controls	Etoricoxib /controls	Celecoxib/Etoricoxib /Controls
p	0.02	0.002	<0.001	p<0.001

Table 5. Correlation between changes of pain VAS from 1st to 2nd visit and synovial fluid penetration index in celecoxib and etoricoxib groups. Negative values correspond to reduction of pain VAS on second visit.

Parameter	Celecoxib group penetration index		Etoricoxib group penetration index	
	correlation coefficient r	p	correlation coefficient r	p
Pain VAS changes	-0.23	0.91	-0.01	0.65

shows changes of pain VAS from the first to the second visit in all the 3 study groups. Statistically significant differences in pain reduction were found in the celecoxib or etoricoxib groups compared with the control group ($p=0.002$ and <0.001 , respectively). Pain VAS reduction was more pronounced in the etoricoxib than celecoxib group ($p=0.02$).

Correlation of synovium penetration index with pain VAS change

As shown in **Table 5**, no correlation between pain VAS changes and synovial fluid penetration index for celecoxib ($p=0.91$) and etoricoxib ($p=0.65$) was detected.

DISCUSSION

Generally the synovial fluid concentration of most NSAIDs in steady state conditions is 60% of its plasma concentration due to the lower albumin concentration in synovial fluid.²³ Human studies on determination of synovial fluid PI of NSAIDs²⁴ have been performed for oxyphenbutazone (PI, $57,1 \pm 13,4\%$), phenylbutazone (PI, 55-100% in rheumatoid arthritis patients and 50% in osteoarthritis patients), meloxicam (PI, 47% after just a single dose), piroxicam (PI, 39%) and tenoxicam (PI, 42-71%).²⁵⁻³⁰ Human pharmacokinetic studies using other parameters have been performed in the synovial fluid with thiaprofenic acid,³¹ alminoprofen,³² indomethacin,³³ loxonolac,³⁴ meloxicam,³⁵ salicylic acid³⁶ and from the coxib lumiracoxib,⁹ with excellent results, especially for lumiracoxib, regarding the diffusion of the drugs in the synovial fluid. Soren reported³⁶ that the diffusion of salicylic acid in the synovial fluid differs depending on the histopathology of the synovial membrane. Regarding celecoxib, the only pharmacokinetic study on synovial fluids to our knowledge is that of Hunter et al.,³⁷ who determined celecoxib's penetration in greyhounds' joints. Celecoxib was determined in all synovial fluids one hour after per os administration, while synovial concentrations of the drug were constantly less than those in serum except in synovial fluid samples drawn 24 hours after the last p.o.

dose.³⁷ To our knowledge, there are no studies either on etoricoxib's penetration in synovial fluid or celecoxib's and etoricoxib's estimation of penetration index in synovial fluid in humans. Moreover, in none of these studies correlations of penetration or pharmacokinetics in synovial fluid, with NSAIDs effect on pain VAS have been reported.

In the present study, the presence of target molecules in the clinical sample was certified with the analysis of samples by Q-TOF-MS. Analysis in QTOF-MS provides full scan MS and MS-MS data which offers additional information about the analyzed samples and enhances the identification potential of the method. Recent developments in this technology offer features that enhance drug metabolism and pharmacokinetic analysis, providing full product spectra, high specificity and sensitivity.¹⁹⁻²² Using this highly specific and sensitive method, we found that etoricoxib was detected in all synovial fluid samples whereas celecoxib only in 6, and the PI of etoricoxib was statistically significantly higher than that of celecoxib. This diversity in the penetration capability can be attributed to their different chemical structure as mentioned in the introduction.

Regarding celecoxib, an interesting study of Hunter et al. in greyhounds³⁷ hypothesized that the decrease in C_{max} and area under the curve (AUC) of celecoxib that was noticed after the 10th day of treatment was attributed to a reduction of drug absorption from the intestine due to competitive absorption of a recirculated metabolite, or to a change in the capsule solubility in the stomach and small intestine, or to a change in drug metabolism during its first pass from the liver. During first pass from the liver a proportion of the drug is metabolized by the respective enzyme and the rest, which is the active part, enters the systemic circulation. In an in vitro study it has been found that there are two different cytochrome P450 (CYP450) phenotypes in humans: the one that metabolizes slowly and the one that metabolizes fast,¹⁶ and several polymorphisms of the CYP2C9 which is the main enzyme that metabolizes celecoxib.¹⁴ Thus, diversions on phenotype CYP450

between people or probably the ability of celecoxib to induce the CYP450 enzyme, explain the lower bioavailability of this drug the 10th day of administration compared with the 1st day in Hunter's study. Celecoxib has been reported to inhibit isomorphous CYP2D6 in humans.³⁸ The theory of CYP450 polymorphism or of the induction of a CYP450 isomorph from celecoxib, could possibly explain the fast metabolism during its pass from the liver and its fast removal from the circulation before it enters in the joint compartment in some individuals who participated in our study. Etoricoxib is metabolized by a different enzyme. Moreover, it could be that an unknown celecoxib metabolite contributes to its penetration in the joint fluid. Our finding that celecoxib was not detected in all synovial fluids, probably relates either to the lower ability of its molecule to penetrate the synovial membrane, or a property of its molecule to penetrate it on a delayed fashion. We measured the concentrations of the study drugs, both in serum and synovial fluid, at a time point respectively to their C_{max} in blood according to their known pharmacokinetics³⁹ which are: 1 hour after etoricoxib dose, and 3 hours after the morning dose of celecoxib. It is possible that celecoxib and/or etoricoxib synovial fluid levels increase later. In most patients suffering from rheumatic diseases, clinical response to most NSAIDs has little correlation with their plasma concentration. It has been reported in some studies that synovial fluid of patients with arthritis may behave as a peripheral compartment and thus there is a lag of time between NSAIDs' systematic distribution.^{7,9,23,40} Understanding the pharmacokinetic and possible distribution of an NSAID in the synovial tissue is important, keeping in mind that this is an important target for these drugs. Scott et al.⁹ in their pharmacokinetic study with lumiracoxib have noted that there was a lag time between plasma drug maximum concentration and pain remission. They hypothesized that either a significant proportion of the drug was distributed in another compartment related to pain, such as the joint, or that an active metabolite was delayed in plasma. In this same study it was found that synovial fluid C_{max} were gained 3-4 hours later than plasma C_{max} , and surpassed plasma C_{max} 5 hours after p.o. drug administration. Thus, synovial fluid concentrations were higher than plasma concentrations for 28 hours and therapeutic results of lumiracoxib lasted more than that expected from its plasma pharmacokinetics.^{9,41,42} Moreover, other studies noted that C_{max} of some classic NSAIDs, especially those with short half-life, is reached in synovial fluid later than that in plasma, and in some cases synovial fluid C_{max} reached higher levels and maintained them for a longer period.^{6,43-45} Additionally, the inter-individual diversity in synovial fluid NSAIDs pharmacokinetics and concentration is great.⁶

We need more studies on NSAID pharmacokinetics to establish an understanding of celecoxib and etoricoxib metabolism in plasma and synovial fluid.

The results of pain VAS showed that in the second visit all the study groups had a statistically significant reduction of the VAS (**Table 3**). Comparing the 2 drugs (**Table 4**), we found a statistically significant ($p=0.020$) superiority of etoricoxib over celecoxib, in the doses used, in reducing the pain of patients with inflammatory arthritis. These results are in agreement with Bingham et al.^{46,47} Their work is a head-to-head comparison of etoricoxib 30 mg daily versus celecoxib 200 mg daily in humans. In these studies, there was no statistically significant difference on pain control between the 2 drugs. In our study, we used the same dose for celecoxib (200 mg daily) but a triple dose for etoricoxib (90mg daily) which is the recommended dose for inflammatory arthritis and this might explain our results. In a recent study on etoricoxib, celecoxib and non-selective NSAIDs for the treatment of ankylosing spondylitis, etoricoxib was found to be associated with more quality adjusted life years (QALYs) compared with the other NSAIDs.⁴⁸ In our study, the difference on pain control between celecoxib and etoricoxib may be not only due to their different capacity on COX-2 inhibition (etoricoxib is a stronger inhibitor of COX-2) and the different chemical structure,² but also due to the different pharmacokinetic properties. As mentioned in the introduction, etoricoxib has better bioavailability than celecoxib, the celecoxib metabolites are totally inactive, whereas etoricoxib metabolites may have a weak activity as COX-2 inhibitors. Moreover, the enzymes that metabolize these two coxibs are different.¹⁰⁻¹³

We found no statistically significant correlation between VAS changes and the penetration index of the synovial fluid for the 2 study drugs. A correlation between VAS change and PI could be anticipated. A possible reason for not doing so was that the drug concentrations correspond to the total of the drug and not the free/active proportion in the synovial fluid that is higher than in serum. Moreover, we measured concentrations of the drugs in synovial fluid and serum from only one time point, respective to the theoretical serum C_{max} , which it is known that is different from the synovial fluid C_{max} . On the other hand, PI was calculated based on the concentrations of the original compound and not its metabolites. Celecoxib metabolites are inactive on COX-2, but etoricoxib metabolites have a weak action. Additionally, we don't know their actions on substance P, cytokine and other pain-related mediators. We should keep in mind that VAS although easy, and popular is a subjective pain measure,⁴⁹ and, therefore, correlations of pain VAS with PI are not objective. To our knowledge there is no published study on any NSAID cor-

relating its PI with its effect on pain.

To our knowledge, this is the first study that measures the penetration index of celecoxib and etoricoxib in synovial fluid and the correlation between the penetration index of these and the reduction in pain. Also to the best of our knowledge, this is the first clinical study that utilizes QTOF-MS and ICP-MS analytical methods¹⁹ for the determination or for a pharmacokinetic study of etoricoxib and celecoxib.¹⁹

In conclusion, our study demonstrated that during steady state conditions etoricoxib 90 mg daily has

greater penetration index than celecoxib 100 mg bid. Both etoricoxib 90 mg od, was superior to celecoxib 100 mg b.i.d on pain VAS reduction in patients with knee inflammatory arthritis.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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