Osteoarthritis and Cartilage

I C R S International Cartilage Repair Society

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

A 4-week randomized study of acetaminophen extended-release vs rofecoxib in knee osteoarthritis

T. J. Schnitzer M.D., Ph.D., Professor of Medicine†*, J. R. P. Tesser M.D.‡, K. M. Cooper M.S.§ and R. D. Altman M.D., Professor of Medicine‖

† Northwestern University Feinberg School of Medicine, Chicago, IL, United States
‡ Radiant Research, Phoenix, AZ, United States
§ McNeil Consumer Healthcare, Fort Washington, PA, United States
‖ David Geffen School of Medicine, University of California, Los Angeles, CA, United States

Summary

Objective: To compare the safety and efficacy of acetaminophen extended-release (APAP ER) with rofecoxib for the management of pain associated with knee osteoarthritis (OA).

Methods: Four hundred and three adult patients with moderate pain secondary to knee OA were randomized to receive APAP ER 1300 mg three times daily, rofecoxib 12.5 mg once daily, or rofecoxib 25 mg once daily. Primary end point was change from baseline at week 4 in the Western Ontario and McMaster Universities Osteoarthritis Index pain subscale score using a visual analog scale. This 4-week study was conducted at 23 US research sites from October 1999 to October 2000.

Results: APAP ER was noninferior to rofecoxib 12.5 mg because the upper 95% confidence limit (CL) for the least squares mean (LSM) change from baseline (35.27 mm at week 4) did not exceed the prespecified noninferiority limit of 50 mm. The upper CL (57.39 mm) exceeded the noninferiority limit for APAP ER compared with rofecoxib 25 mg at week 4. There were no significant differences among groups in the overall incidence of adverse events.

Conclusion: APAP ER 3900 mg daily was noninferior to rofecoxib 12.5 mg daily, but noninferiority was not established to rofecoxib 25 mg daily. APAP ER was well tolerated and no safety issues were identified. Based on the results of this study, APAP ER 3900 mg daily is an alternative to nonsteroidal anti-inflammatory drugs (NSAIDs), such as rofecoxib, in treating pain associated with knee OA.
© 2008 Published by Elsevier Ltd on behalf of Osteoarthritis Research Society International.

Key words: Acetaminophen extended-release, Knee, Osteoarthritis, Rofecoxib.

Introduction

The management of osteoarthritis (OA) remains challenging, despite greater awareness among primary care providers and rheumatologists of the importance of lifestyle modifications and the availability of new therapies. Nonpharmacologic interventions including exercise and bracing are commonly recommended but often not sufficient to adequately manage pain[1−3]. Thus, analgesic drug therapy is frequently required. Because OA is more prevalent in the elderly − many of whom have comorbidities − selection of an analgesic is often complicated[3,4]. Additionally, elderly patients are at greater risk for gastrointestinal (GI) bleeding secondary to use of nonsteroidal anti-inflammatory drugs (NSAIDs)[5].

Aspirin and other NSAIDs have been utilized for more than a century to effectively relieve musculoskeletal pain[6], although associated adverse GI side effects have long been recognized[5]. This has led to the development of analgesics with lower incidence of GI side effects[7]. Cyclooxygenase (COX)-2-selective inhibitors were introduced in 1999,

providing analgesia equivalent to older NSAIDs with markedly lower rates of GI ulcers and related complications[8]. Prophylactic use of misoprostol and proton pump inhibitors also may be appropriate for patients on chronic NSAID therapy who are at increased risk for upper GI adverse effects[1].

Peripheral edema, congestive heart failure, and increases in blood pressure have long been observed with traditional NSAID use[9,10]. More recent data suggest that COX-2-selective inhibitors are also associated with increased risk of myocardial infarction, stroke[11], and adverse renal and arrhythmia events[12]. This has resulted in a more detailed investigation of the cardiovascular risk of not only COX-2-selective inhibitors, but also traditional NSAIDs. A recent meta-analysis of all randomized, controlled trials of COX-2-selective inhibitors confirmed their increased cardiovascular risk compared with placebo[13]. The risk was similar to the increased cardiovascular risk seen with traditional NSAIDs, with the exception of naproxen, which was similar in risk to placebo. The mechanisms responsible are not well understood.

Controversy surrounding COX-2-selective inhibitors has prompted careful reevaluation of the risks and benefits of NSAID use[14]. Thus, an analgesic agent, such as acetaminophen (APAP), which has not been shown in randomized clinical trials to be associated with adverse GI or cardiovascular risks, provides an alternative that may be particularly

attractive for patients with OA at higher risk for complications[15]. APAP has been recommended by the American College of Rheumatology (ACR) as the first-line treatment for pain associated with OA[1]. An extended-release (ER) formulation permitting less frequent dosing has recently been introduced and has demonstrated efficacy in treating knee OA pain[16].

Few previous studies have been designed to directly compare NSAIDs with APAP, and their results have been inconsistent[17–19]. APAP ER has not been compared previously with a COX-2-selective inhibitor for knee OA. Therefore, this 4-week study was conducted to compare the safety and efficacy of APAP ER (given three times daily) with two standard doses of rofecoxib (12.5 mg and 25 mg given once daily) for the management of pain associated with knee OA.

Patients and methods

STUDY DESIGN AND SELECTION OF PARTICIPANTS

This multicenter, randomized, double-blind study compared treatment outcome with APAP ER or rofecoxib in patients experiencing pain associated with knee OA. Investigators at 23 centers in the US participated in the study from October 15, 1999 to October 27, 2000. The study protocol and amendments were reviewed by an ethics committee or received approval from an institutional review board (IRB), and written informed consent was obtained from each patient before enrollment.

Criteria for enrollment in the study included age ≥ 40 years and symptomatic idiopathic knee OA lasting at least six months and characterized by at least moderate pain requiring treatment three or more days per week with an analgesic or anti-inflammatory agent for at least three months. Patients also had to fulfill at least two of the five criteria established by the ACR for idiopathic knee OA[20]. Additionally, patients were required to have radiographic evidence of OA[21], normal laboratory test values, physical ability classified as ACR functional class I or II[22], and a historically positive response to the regular use of analgesics or anti-inflammatory agents for the treatment of knee OA pain. Patients must also have reported at least moderate pain when asked to evaluate their maximum pain intensity on a 5-point scale during a 24-h period. All women of childbearing potential were required to use an effective method of birth control, have negative serum pregnancy results, and not be lactating.

Patients were excluded from the study if they had a history of surgery, trauma, or arthroscopy of the study joint within the previous 12 months, any other type of arthritis, active malignancies, or any active GI, cardiovascular, renal, hepatic, neurologic, or psychiatric disease. Additionally, patients were excluded if they had been using anticonvulsants, tranquilizers, or antidepressants in the previous three months and had not been stabilized on therapy; had been using glucosamine or chondroitin sulfate in the previous six months without having been stabilized on therapy; had undergone treatment with hyaluronan in the previous six months; had used intra-articular or oral corticosteroids in the previous two months; or had required the use of concomitant medications that could have confounded the assessment of efficacy of study drug treatments (APAP, NSAIDs, aspirin, over-the-counter medications that may contain analgesics, narcotic analgesics, herbal preparations with potential analgesic qualities, and topical analgesics).

During the screening visit, patients received a physical examination, including a clinical laboratory profile and knee joint assessment. Patients also completed the Western Ontario and McMaster Universities OA Index (WOMAC) using a visual analog scale (VAS) to evaluate pain, stiffness, and physical function. Following the screening visit, potential study patients completed a washout period during which they were prohibited from taking their usual arthritis medications within five drug half-lives before randomization (ranged from three to five days, depending on the drug). Following the washout period, enrollment was limited to patients who experienced an arthritis flare, defined as an increase of the WOMAC pain subscale score of 20–80% relative to the screening visit. Those with signs of active inflammation of the study joint (i.e., redness, warmth, or bulging effusion) after the washout period were not eligible for randomization.

Patients were randomized in a 1:1:1 ratio to receive the following treatments in a double-blind, double-dummy fashion: APAP ER 3900 mg daily (1300 mg every 8 h), rofecoxib 12.5 mg once daily, or rofecoxib 25 mg once daily for four weeks. Patients randomized to receive APAP ER were instructed to dose every 8 h and received two APAP ER caplets and two rofecoxib−placebo capsules at each dosing interval. Patients randomized to receive rofecoxib 12.5 mg were instructed to dose every 8 h and received one rofecoxib capsule, one rofecoxib−placebo capsule, and two APAP ER−placebo caplets as the first dose in the morning, and two APAP ER−placebo caplets and two rofecoxib−placebo capsules at the second and third dosing intervals. Patients randomized to receive rofecoxib 25 mg were instructed to dose every 8 h and received two rofecoxib capsules and two APAP ER−placebo caplets as the first dose in the morning, and two APAP ER−placebo caplets and two rofecoxib−placebo capsules at the second and third dosing intervals.

STUDY ASSESSMENTS

Follow-up visits were conducted at 1, 2, and 4 weeks following the baseline visit or upon discontinuing participation in the study. At each visit, a joint examination was performed, and the patient's weight, blood pressure, adherence to the dosing regimen, and need for additional analgesia were assessed. The investigator recorded his or her impression of therapeutic response, and the patient recorded his or her own assessment of the medication as an analgesic for the study knee joint (both assessments rated on a 0−4 scale; 0 = poor and 4 = excellent). Each patient then completed the WOMAC by VAS to evaluate pain, stiffness, and physical function. At the final visit, the investigator recorded his or her global impression of the therapeutic response, and the patient recorded his or her overall impression of the study medication.

The primary efficacy end point in this study was change from baseline in the WOMAC pain subscale score at week 4. Secondary efficacy end points included change from baseline in the WOMAC pain subscale score at weeks 1 and 2; change from baseline in the WOMAC stiffness and physical function subscale scores at weeks 1, 2, and 4; the investigator's impression of the therapeutic response and the patient's impression of the medication as an analgesic at weeks 1, 2, and 4; the investigator's global impression of the therapeutic response at week 4 or the final visit; and the patient's overall impression of the study medication at week 4 or the final visit.

Safety was assessed by careful monitoring of adverse events (AEs) throughout the course of the study, which was based on signs and symptoms reported by the patient or observed by the investigator. In addition, each patient was asked the nonspecific question: "Have you experienced any unusual signs or symptoms since your last visit?" All responses were recorded using standard medical terminology. Details regarding the AEs, including information about medication used to treat the AEs, were recorded. All serious AEs were reported to the sponsor, and the study investigators analyzed the potential relationship to study medication.

STATISTICAL METHODS

A sample size of at least 100 patients per treatment group was chosen to provide 90% power to detect a difference between rofecoxib and APAP ER of 50 mm in improvement from baseline in the WOMAC pain subscale score at week 4 assuming a common standard deviation of 120. The changes from baseline in the WOMAC subscale scores for pain, stiffness, and physical function were analyzed with analyses of variance (ANOVA), with treatment, investigator, and treatment by investigator as interaction terms in the model. Noninferiority was established if the upper one-sided 95% confidence limit (CL) for the difference in least squares mean (LSM) change from baseline was ≤50 mm. A difference of 50 mm represents 10% of a maximum score of 500 mm on the pain subscale. If noninferiority was established, statistical superiority was tested by determining if the upper one-sided 95% CL of the difference excluded zero. Statistical superiority was not tested if noninferiority was not established.

Similar testing procedures were used for the secondary efficacy end points obtained from the WOMAC. Although not specified explicitly in the protocol, a difference of 170 mm represents 20% of an expected baseline score of approximately 850 mm in the physical function subscale, and a difference of 20 mm represents 20% of an expected baseline score of 100 mm on the stiffness subscale. The remaining secondary efficacy end points were analyzed similarly, although there were no prespecified noninferiority limits.

The analyses of the primary efficacy end point were based on the per-protocol (PP) population. Patients were included in the PP population if they had taken at least 80% of assigned doses, returned to the study center for follow-up visits, and complied with study restrictions. Patients who had taken at least one dose of medication and completed at least one post-baseline efficacy assessment were included in the intent-to-treat (ITT) population. A safety evaluation was completed for all patients who had taken at least one dose of blinded study medication. AE rates were compared using Fisher's exact tests. All statistical analyses were performed with SAS version 8.2 Software (SAS Institute Inc; Cary, NC, USA).

Results

CHARACTERISTICS OF STUDY PATIENTS

Of 403 patients randomized in this study, 136 were assigned to the APAP ER group, 138 to the rofecoxib
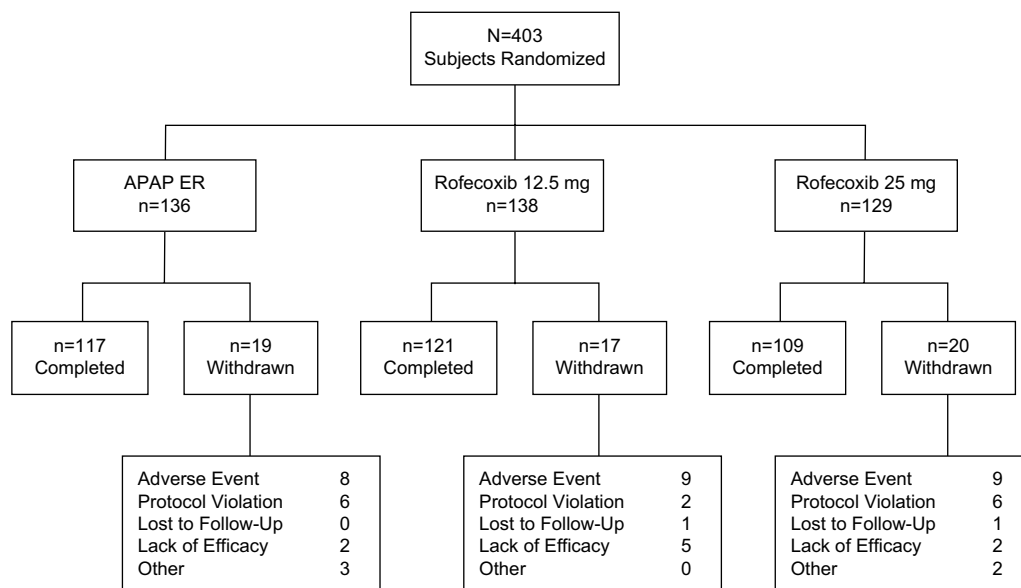
Fig. 1. Patient disposition.

12.5-mg group, and 129 to the rofecoxib 25-mg group (Fig. 1). Overall, 56 patients (13.9%) withdrew from the study; withdrawal number was comparable among groups. Demographic and baseline characteristics for the ITT population were similar among groups (Table I). The mean age of patients was 59.8 years, and 37.5% of the patients were male. Fifty-six percent of patients treated with APAP ER, 55% treated with rofecoxib 12.5 mg, and 52% treated with rofecoxib 25 mg were 100% compliant with study medication. Study medication compliance was at least 80% for 98%, 99%, and 98% of patients in the APAP ER, rofecoxib 12.5-mg, and rofecoxib 25-mg groups, respectively.

EFFICACY RESULTS

When the primary end point was tested, APAP ER was therapeutically noninferior to rofecoxib 12.5 mg in the

Table I
Demographic and baseline characteristics for subjects included in the ITT analysis by treatment group

Characteristics	APAP ER 3900 mg TID ($n = 126$)	Rofecoxib 12.5 mg QD ($n = 129$)	Rofecoxib 25 mg QD ($n = 121$)
Gender, n (%)			
Men	51 (40.5)	48 (37.2)	42 (34.7)
Women	75 (59.5)	81 (62.8)	79 (65.3)
Age (years)			
Mean (SD)	60.9 (10.8)	60.8 (10.2)	57.5 (11.5)
Body mass index (kg/m^2)			
Mean (SD)	32.4 (7.7)	33.0 (7.2)	33.7 (9.0)
Race, n (%)			
Caucasian	101 (80.2)	107 (82.9)	96 (79.3)
African American	20 (15.9)	20 (15.5)	14 (11.6)
Other	5 (4.0)	2 (1.6)	11 (9.1)
Baseline knee pain, n (%)			
Moderate	40 (31.7)	49 (38.0)	39 (32.2)
Moderately severe	73 (57.9)	69 (53.5)	70 (57.9)
Severe	13 (10.3)	11 (8.5)	12 (9.9)
Concomitant medication, n (%)	110 (87.3)	109 (84.5)	105 (86.8)
Concomitant use of glucosamine or chondroitin	15 (11.9)	22 (17.1)	16 (13.2)
WOMAC pain subscale			
Mean (SD)	290.3 (101.2)	285.9 (102.8)	310.7 (107.2)
WOMAC stiffness subscale			
Mean (SD)	117.8 (43.5)	122.2 (44.0)	130.5 (45.0)
WOMAC physical function subscale			
Mean (SD)	972.3 (341.8)	987.2 (335.6)	1066.4 (377.8)

QD = once daily; TID = three times daily.

Table II
LSM change from baseline in WOMAC pain, physical function, stiffness subscales, patient's overall impression of study medication, and investigator's global impression of therapeutic response (PP population)

Study week	Statistic	APAP ER 1300 mg TID	Rofecoxib 12.5 mg QD	Rofecoxib 25 mg QD
Pain subscale*				
Baseline	*n*	123	125	117
	Mean	288.64	288.08	311.82
1	*n*	119	122	114
	Mean	185.33	180.55	175.52
	Change from baseline	102.22	107.17	136.26
	LSM change	103.18	109.77	128.65
	Difference in LSM†	—	6.59	25.48
	95% CL‡	—	−13.39, **26.56**	5.01, **45.94**
2	*n*	109	112	102
	Mean	163.17	154.05	142.36
	Change from baseline	122.82	132.72	166.14
	LSM change	126.52	134.74	159.20
	Difference in LSM†	—	8.23	32.68
	95% CL‡	—	−14.84, **31.29**	9.01, **56.36**
4	*n*	103	109	100
	Mean	150.35	136.25	127.98
	Change from baseline	140.89	147.64	184.42
	LSM change	143.46	154.43	175.93
	Difference in LSM†	—	10.97	32.46
	95% CL‡	—	−13.34, **35.27**	7.54, **57.39**
Physical function subscale*				
Baseline	*n*	121	125	116
	Mean	970.55	990.34	1071.26
1	*n*	119	122	112
	Mean	627.46	638.91	616.43
	Change from baseline	338.42	355.54	457.97
	LSM change	334.03	349.40	424.18
	Difference in LSM†	—	15.37	90.14
	95% CL‡	—	−54.17, **84.91**	18.29, **162.00**
2	*n*	109	112	102
	Mean	573.18	561.53	526.65
	Change from baseline	385.96	424.44	527.35
	LSM change	420.99	442.90	534.44
	Difference in LSM†	—	21.91	113.45
	95% CL‡	—	−53.86, **97.68**	35.39, **191.50**
4	*n*	103	107	99
	Mean	530.63	513.36	465.84
	Change from baseline	448.32	470.95	598.74
	LSM change	438.49	468.86	557.40
	Difference in LSM†	—	30.37	118.91
	95% CL‡	—	−51.37, **112.12**	34.68, **203.14**
Stiffness subscale*				
Baseline	*n*	123	125	117
	Mean	117.28	123.06	131.30
1	*n*	119	122	114
	Mean	75.45	82.59	73.77
	Change from baseline	41.06	41.06	56.78
	LSM change	41.61	38.85	50.86
	Difference in LSM†	—	−2.76	9.25
	95% CL‡	—	−11.89, **6.37**	−0.12, **18.61**
2	*n*	109	112	102
	Mean	67.26	66.46	62.27
	Change from baseline	50.94	55.80	66.99
	LSM change	55.97	57.31	66.30
	Difference in LSM†	—	1.34	10.33
	95% CL‡	—	−8.44, **11.12**	0.30, **20.37**
4	*n*	103	108	100
	Mean	65.63	60.36	55.01
	Change from baseline	54.97	59.61	75.88
	LSM change	55.48	60.19	70.72
	Difference in LSM†	—	4.71	15.23
	95% CL‡	—	−5.35, **14.77**	4.89, **25.57**

Table II (*continued*)

Study week	Statistic	APAP ER 1300 mg TID	Rofecoxib 12.5 mg QD	Rofecoxib 25 mg QD
Study assessment				
Patient's overall impression of study medication§				
	n	103	109	100
	Mean	1.89	2.31	2.54
	LSM change	1.87	2.29	2.53
	Difference in LSM†	—	0.43	0.67
	95% CL‡	—	0.19, **0.67**	0.42, **0.92**
Investigator's global impression of patient's therapeutic response§				
	n	103	108	100
	Mean	1.99	2.31	2.63
	LSM change	1.99	2.32	2.62
	Difference in LSM†	—	0.32	0.63
	95% CL‡	—	0.08, **0.56**	0.38, **0.87**

*Using a VAS, maximum pain ranged from 0 to 500 mm, maximum physical function ranged from 0 to 1700 mm, and maximum stiffness ranged from 0 to 200 mm.

†Treatment difference (rofecoxib − APAP ER) in LSM change.

‡APAP ER noninferiority = upper CL ≤ 50 mm for pain subscale, upper CL ≤ 170 mm for physical function subscale, and CL ≤ 20 mm for stiffness subscale; CL reported as (lower, **upper**).

§Scores range from 0 to 4; 0 = poor, 1 = fair, 2 = good, 3 = very good, 4 = excellent.

treatment of pain associated with knee OA, because the upper one-sided 95% CL for the difference between APAP ER and rofecoxib 12.5 mg in the LSM change from baseline WOMAC pain subscale score at week 4 did not exceed the predefined limit of 50 mm (Table II, Fig. 2). For APAP ER and rofecoxib 25 mg, the upper one-sided 95% CL for the LSM change from baseline WOMAC pain subscale score at week 4 exceeded 50 mm. These results did not provide sufficient evidence to establish the noninferiority of APAP ER to rofecoxib 25 mg (Fig. 3). Primary efficacy results from the ITT population were consistent with those obtained from the PP population.

Results from the secondary end points correlated with those from the primary end points. The upper one-sided 95% CL for the difference between APAP ER and rofecoxib 12.5 mg in the LSM change from baseline WOMAC physical function and stiffness subscale scores did not exceed 170 and 20 mm, respectively, establishing noninferiority of APAP ER to rofecoxib 12.5 mg (Table II). Because the upper one-sided 95% CLs exceeded the limits in the rofecoxib 25-mg analysis, noninferiority of APAP ER to rofecoxib 25 mg could not be established for physical function and stiffness. All other secondary end point results were consistent with conclusions from the WOMAC pain, physical function, and stiffness tests (Table II). Results obtained from the ITT population for the secondary efficacy end points were consistent with the PP population.

SAFETY RESULTS

All study medications were well tolerated, with no significant differences in the overall nature or severity of AEs, drug-related AEs, or discontinuations because of AEs among treatment groups (Table III). Numerically, more drug-related AEs were reported in the APAP ER group. One patient in the APAP ER group and three patients in the rofecoxib 12.5-mg group experienced serious AEs. The patient in the APAP ER group had larynx edema, considered possibly related to study medication. Two of the serious AEs in the rofecoxib 12.5-mg group were myocardial infarctions, which were deemed unrelated to study medication. There were no myocardial infarctions or strokes reported in the other treatment groups.

Discussion

This study established the noninferiority of APAP ER 3900 mg daily to rofecoxib 12.5 mg daily in relieving pain associated with knee OA, as measured by the WOMAC pain subscale. Results from the secondary efficacy end points correlated well with those from the primary end point, and established the noninferiority of APAP ER 3900 mg daily to rofecoxib 12.5 mg daily in improving physical function and relieving stiffness. In the population studied, the noninferiority of APAP ER to rofecoxib 25 mg daily could not be established. The AEs reported were similar among treatment groups, and both study drugs were well tolerated.

Several guidelines committees for the management of OA recommend APAP as a first-line therapy[1,15]. In a 2006 Cochrane review involving the pooled data of five randomized controlled trials that compared APAP with placebo, APAP demonstrated a modest improvement in pain relief compared with placebo[19]. Patient compliance with a dosing regimen may be improved with an ER formulation because fewer daily doses are required[23]. In addition, ER formulations may maintain more constant drug levels in the blood[23,24]. APAP ER 1300 mg administered three times daily effectively managed pain in a 12-week, randomized, placebo-controlled study involving patients with hip or knee OA[16]. The availability of an ER formulation of APAP may be more convenient for patients who require consistent analgesia to manage OA pain.

Previous OA trials have suggested that patients experience superior pain relief with NSAIDs compared with APAP[19,25–28]. A study conducted by Geba *et al.*[18] showed that the pain relief afforded by rofecoxib 12.5 mg and 25 mg daily was greater than that observed with APAP in patients with knee OA. Unlike the previous study, however, this study established that APAP ER 3900 mg daily was noninferior to rofecoxib 12.5 mg daily in treating knee OA pain. However, consistent with Geba's study, noninferiority of APAP to rofecoxib 25 mg daily could not be demonstrated. In another trial, patients with mild to moderate OA pain experienced comparable pain relief with APAP 4000 mg daily and ibuprofen 1200 mg daily[29]. A more recent study evaluating APAP for hip or knee OA established that APAP 4000 mg daily was well tolerated and had efficacy similar
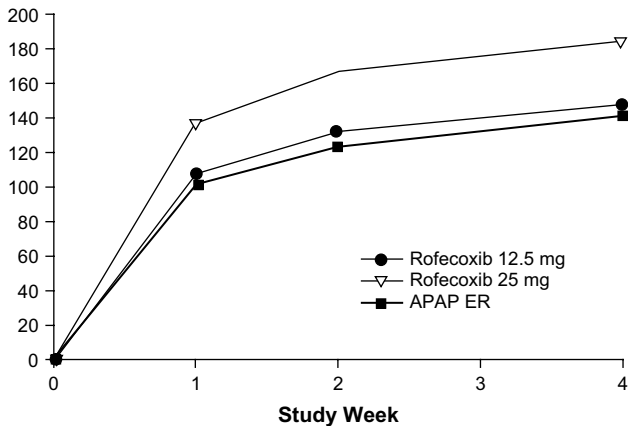
Fig. 2. Mean change from baseline WOMAC pain subscale in the PP population at weeks 1, 2, and 4.

to that of naproxen 750 mg daily for up to 1 year[30]. Based on the findings in the present study and those of other studies, APAP may be an effective alternative to rofecoxib and other NSAIDs for relief of mild to moderate pain.

In this relatively short trial, few AEs were reported. Although there have been concerns regarding abnormal liver function demonstrated even in short-term trials of APAP at the maximum recommended dose of 4000 mg daily[31], a retrospective review of seven studies involving 1530 patients taking APAP for up to 12 months at 1950–4000 mg daily showed only low-level, transient alanine aminotransferase elevations that either resolved or decreased with continued APAP therapy[32]. In the retrospective review, no clear risks of GI bleeding, cardiovascular events, or renal failure with APAP were identified. Although overdosage with APAP can result in hepatic toxicity, it is also the drug of choice in individuals with renal and hepatic insufficiency who require an analgesic agent for mild to moderate pain. There were no hepatic abnormalities noted in the present study.

Limitations of the present study include the lack of a placebo group, relatively short duration, lack of liver enzyme testing, and the exclusion of patients with active inflammation of the study joint after the washout period. It should be noted that the inclusion of a placebo group often makes
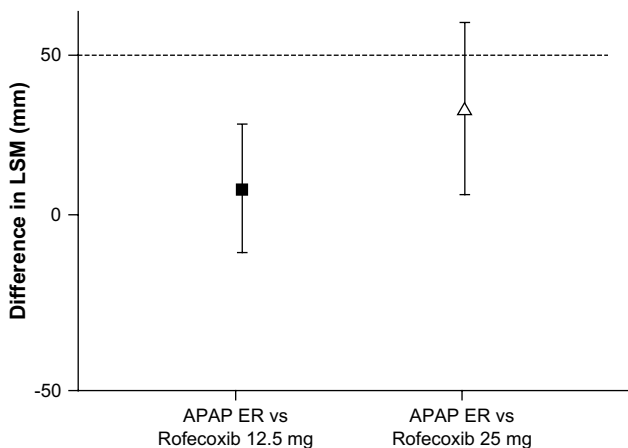

Fig. 3. LSM change from baseline in WOMAC pain subscale in the PP population at week 4.

Table III
Adverse Events*

Evaluation	APAP ER 1300 mg TID (n = 136)	Rofecoxib 12.5 mg QD (n = 138)	Rofecoxib 25 mg QD (n = 129)
Summary of all AEs			
Patients with AEs	59 (43.4)	58 (42.0)	55 (42.6)
Patients with serious AEs	1 (0.7)	3 (2.2)	0 (0.0)
Patients with drug-related AEs	43 (31.6)	36 (26.1)	38 (29.5)
Patients who discontinued because of AEs	8 (5.9)	9 (6.5)	9 (7.0)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)
Drug-related AEs that occurred in at least 3% of any subgroup			
Abdominal pain	5 (3.7)	2 (1.4)	0 (0.0)
Constipation	5 (3.7)	1 (0.7)	0 (0.0)
Diarrhea	10 (7.4)	4 (2.9)	4 (3.1)
Dizziness	2 (1.5)	2 (1.4)	5 (3.9)
Dyspepsia	7 (5.1)	4 (2.9)	3 (2.3)
Flatulence	4 (2.9)	2 (1.4)	4 (3.1)
Nausea	4 (2.9)	8 (5.8)	6 (4.7)
Headache	9 (6.6)	1 (0.7)	7 (5.4)
Pain	8 (5.9)	3 (2.2)	0 (0.0)
Peripheral edema	2 (1.5)	3 (2.2)	4 (3.1)

*All values shown as *n* (%).

accrual into such studies more difficult, despite the availability of escape therapy for escalating pain. Additionally, a placebo arm requires the enrollment of many more patients into the study to account for the anticipated high number of dropouts who fail on placebo therapy. In a 12-week study evaluating APAP ER for knee OA pain, the superiority of APAP ER compared with placebo was demonstrated as early as 4 weeks[16]. Because the intent of the present study was to determine efficacy comparable to a COX-2-selective inhibitor, a longer study was deemed unnecessary. Although liver enzyme testing was not performed in this study, it has been extensively studied, as described earlier[31,32]. Another limitation of this study is that the effect of multimodal therapy (e.g., combined analgesic, anti-inflammatory, topical, and intra-articular agents) was not assessed. It is not known if combined therapy would be more effective than separate therapies. Finally, the exclusion of patients who had signs of active inflammation of the study joint limits the generalizability of these results.

APAP ER 3900 mg daily was well tolerated and noninferior to rofecoxib 12.5 mg daily for the treatment of mild to moderate pain associated with knee OA, but noninferiority could not be established to rofecoxib 25 mg daily. Adverse GI and cardiovascular events associated with traditional NSAIDs and COX-2-selective inhibitors warrant a reevaluation of their risks and benefits and highlight the need for a safer analgesic alternative. Based on the results of this study, and consistent with published guidelines, APAP ER should be considered as an alternative to NSAIDs for the treatment of mild to moderate pain associated with knee OA.

Conflict of interest

References

1. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. Arthritis Rheum 2000;43: 1905–15.
2. AGS Panel on Persistent Pain in Older Persons. The management of persistent pain in older persons. J Am Geriatr Soc 2002;50(Suppl): S205–24.
3. Felson DT, Lawrence RC, Hochberg MC, McAlindon T, Dieppe PA, Minor MA, et al. Osteoarthritis: new insights. Part 2: treatment approaches. Ann Intern Med 2000;133:726–37.
4. Felson DT, Zhang Y. An update on the epidemiology of knee and hip osteoarthritis with a view to prevention. Arthritis Rheum 1998;41:1343–55.
5. Gabriel SE, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs: a meta-analysis. Ann Intern Med 1991;115:787–96.
6. Andermann AAJ. Physicians, fads, and pharmaceuticals: a history of aspirin. MJM 1996;2:115–20.
7. FitzGerald GA, Patrono C. The coxibs, selective inhibitors of cyclooxygenase-2. N Engl J Med 2001;345:433–42.
8. Langman MJ, Jensen DM, Watson DJ, Harper SE, Zhao P-L, Quan H, et al. Adverse upper gastrointestinal effects of rofecoxib compared with NSAIDs. JAMA 1999;282:1929–33.
9. Frishman WH. Effects of nonsteroidal anti-inflammatory drug therapy on blood pressure and peripheral edema. Am J Cardiol 2002;89(Suppl): 18D–25D.
10. Page J, Henry D. Consumption of NSAIDs and the development of congestive heart failure in elderly patients: an underrecognized public health problem. Arch Intern Med 2000;160:777–84.
11. Bresalier RS, Sandler RS, Quan H, Bolognese JA, Oxenius B, Horgan K, et al, for the Adenomatous Polyp Prevention on Vioxx (APPROVe) Trial Investigators. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med 2005;352:1092–102.
12. Zhang J, Ding EL, Song Y. Adverse effects of cyclooxygenase 2 inhibitors on renal and arrhythmia events: meta-analysis of randomized trials. JAMA 2006;296:1619–32.
13. Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomized trials. BMJ 2006;332:1302–8.
14. Fendrick AM. COX-2 inhibitor use after Vioxx: careful balance or end of the rope? Am J Manag Care 2004;10:740–1.
15. Jordan KM, Arden NK, Doherty M, Bannwarth B, Bijlsma JWJ, Dieppe P, et al. EULAR recommendations 2003: an evidence based approach to the management of knee osteoarthritis: report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). Ann Rheum Dis 2003;62: 1145–55.
16. Altman RD, Zinsenheim JR, Temple AR, Schweinle JE. Three-month efficacy and safety of acetaminophen extended-release for osteoarthritis pain of the hip or knee: a randomized, double-blind, placebo-controlled study. Osteoarthritis Cartilage 2007;15:454–61.
17. Bradley JD, Katz BP, Brandt KD. Severity of knee pain does not predict a better response to an antiinflammatory dose of ibuprofen than to analgesic therapy in patients with osteoarthritis. J Rheumatol 2001;28: 1073–6.
18. Geba GP, Weaver AL, Polis AB, Dixon ME, Schnitzer TJ, for the Vioxx, Acetaminophen, Celecoxib Trial (VACT) Group. Efficacy of rofecoxib, celecoxib, and acetaminophen in osteoarthritis of the knee: a randomized trial. JAMA 2002;287:64–71.
19. Towheed TE, Maxwell L, Judd MG, Catton M, Hochberg MC, Wells G. Acetaminophen for osteoarthritis. Cochrane Database Syst Rev 2006;1:CD004257.
20. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, et al. Development of criteria for the classification and reporting of osteoarthritis: classification of osteoarthritis of the knee. Arthritis Rheum 1986; 29:1039–49.
21. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957;16:494–502.
22. Steinbrocker O, Traeger CH, Batterman RC. Therapeutic criteria in rheumatoid arthritis. JAMA 1949;140:659–62.
23. Talan DA, Naber KG, Palou J, Elkharrat D. Extended-release ciprofloxacin (Cipro XR) for treatment of urinary tract infections. Int J Antimicrob Agents 2004;(Suppl):S54–66.
24. Van Kerrebroeck P, Kreder K, Jonas U, Zinner N, Wein A, for the Tolterodine Study Group. Tolterodine once-daily: superior efficacy and tolerability in the treatment of the overactive bladder. Urology 2001;57: 414–21.
25. Case JP, Baliunas AJ, Block JA. Lack of efficacy of acetaminophen in treating symptomatic knee osteoarthritis: a randomized, double-blind, placebo-controlled comparison trial with diclofenac sodium. Arch Intern Med 2003;163:169–78.
26. Lee C, Straus WL, Balshaw R, Barlas S, Vogel S, Schnitzer TJ. A comparison of the efficacy and safety of nonsteroidal antiinflammatory agents versus acetaminophen in the treatment of osteoarthritis: a meta-analysis. Arthritis Rheum 2004;51:746–54.
27. Pincus T, Koch GG, Sokka T, Lefkowith J, Wolfe F, Jordan JM, et al. A randomized, double-blind, crossover clinical trial of diclofenac plus misoprostol versus acetaminophen in patients with osteoarthritis of the hip or knee. Arthritis Rheum 2001;44:1587–98.
28. Schnitzer TJ, Weaver AL, Polis AB, Petruschke RA, Geba GP, for the VACT-1 and VACT-2 (Protocols 106 and 150) Study Groups. Efficacy of rofecoxib, celecoxib, and acetaminophen in patients with osteoarthritis of the knee: a combined analysis of the VACT studies. J Rheumatol 2005;32:1093–105.
29. Altman RD, the IAP Study Group. Ibuprofen, acetaminophen, and placebo in osteoarthritis of the knee: a six-day double-blind study. Presented at the Annual Meeting of the American College of Rheumatology; November 13–17, 1999; Boston, MA.
30. Temple AR, Benson GD, Zinsenheim JR, Schweinle JE. Multicenter, randomized, double-blind, active-controlled, parallel-group trial of the long-term (6–12 months) safety of acetaminophen in adult patients with osteoarthritis. Clin Ther 2006;28:222–35.
31. Watkins PB, Kaplowitz N, Slattery JT, Colonese CR, Colucci SV, Stewart PW, et al. Aminotransferase elevations in healthy adults receiving 4 grams of acetaminophen daily: a randomized controlled trial. JAMA 2006;296:87–93.
32. Kuffner EK, Temple AR, Cooper KM, Baggish JS, Parenti DL. Retrospective analysis of transient elevations in alanine aminotransferase during long-term treatment with acetaminophen in osteoarthritis clinical trials. Curr Med Res Opin 2006;22:2137–48.