ARTHRITIS & RHEUMATISM Volume 36
Number 9, September 1993, pp 1207–1213

EFFECT OF PIROXICAM ON GAIT IN PATIENTS WITH OSTEOARTHRITIS OF THE KNEE

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Objective. **To determine whether the use of a nonsteroidal antiinflammatory drug (NSAID) in patients with painful osteoarthritis (OA) of the knee would result in alterations in specific biomechanical parameters of gait.**

Methods. **Eighteen patients with symptomatic knee OA and varus knee deformity underwent initial clinical evaluation for pain and activities of daily living, and assessment of parameters of gait utilizing a well-described computerized system. All patients were then treated with piroxicam at 20 mg once daily, and clinical and gait analyses were repeated after 4 weeks.**

Results. **Fifteen of the 18 patients studied had a significant increase in the knee adduction moment after treatment. In the group as a whole there was a significant increase in knee adduction moment (mean percent body weight times height [%BWTH] 4.11 pretreatment versus 4.57 after 4 weeks of treatment; $P < 0.01$) and maximum quadriceps moment (mean %BWTH 2.13 pretreatment, 2.62 posttreatment; $P < 0.01$), as well as changes in other gait parameters that might be expected to be altered as a result of relief of pain. Sixteen of 18 patients experienced symptomatic relief, with a significant reduction in pain in the group as a whole after 4 weeks ($P < 0.001$).**

Conclusion. **NSAID treatment in patients with knee OA results in a reduction in symptomatic pain and an increase in loading of the knee. Whether the increased loading is due to the analgesic effects of the treatment is unknown, but if so, the development of agents capable of relieving pain while reducing loads at the knee may be desirable.**

Nonsteroidal antiinflammatory drugs (NSAIDs) are an accepted treatment for osteoarthritis (OA), with the goals of therapy being reduction of joint pain and inflammation and improvement of ability to carry out activities of daily living. The effects of NSAIDs are usually evaluated by subjective clinical assessment of pain and by patient satisfaction; fundamental biologic and pharmacokinetic data may also be available. The exact mechanism of action of these agents is unknown, but their analgesic properties in the setting of symptomatic OA of the knee might be expected to result in the loss of a protective pain reflex, leading to an increased load on the joint and more rapid progression of the disease. Clinical observations both supporting and refuting the occurrence of such a mechanism have been reported in the literature (1–5), without any definitive objective data regarding the long-term effects of therapy with either pure analgesic agents or NSAIDs.

Loading at the knee during walking has been shown to influence the outcome of surgical treatment (high tibial osteotomy) in patients with varus gonarthrosis (6,7). Patients who walked in a way that reduced loads on the medial compartment of the knee

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Supported in part by Pfizer International.

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Submitted for publication July 22, 1992; accepted in revised form February 11, 1993.

(adduction moment at the knee) prior to surgery had significantly better surgical results than did patients who had higher loads. These findings as well as findings of various analytic studies (8–10) suggest that the adduction moment during gait influences the load on the medial compartment of the knee joint. The findings further suggest that this loading can influence the progression of degenerative changes at the knee joint. It is not known at present why some patients modify their gait to reduce the loads and others do not. Furthermore, it is not known whether pain is a primary signal causing the reduction of loads, in which case the elimination of pain would cause an increase in loading.

To test the hypothesis that the use of analgesic agents affects loading on the knee and to define quantitative changes in gait, patients with knee OA were entered into an open-label study, and changes in gait parameters were analyzed before and after NSAID treatment. This investigation focused on the dynamic peak adduction moment at the knee, an important loading parameter and the major component of extrinsic load at the knee joint (9).

Actual loading of the knee joint can only be inferred indirectly from extrinsic measurement. However, the normal adduction moment is larger than the components of the moment tending to flex, extend, internally rotate, or externally rotate the knee. Thus, the magnitude of the adduction moment plays a substantial role in determining the total extrinsic loading at the knee joint. The adduction moment is probably the single component of load that is most directly responsible for the magnitude of total intrinsic compressive load on the medial side of the knee joint, since the intrinsic force-couple that would balance an isolated adduction moment consists of tension in the lateral soft tissue structures and a compressive force on the medial side of the knee joint (10). This loading would be superimposed on loading components due to muscular forces balancing the other moment components, as well as axial force due to extrinsic loading.

PATIENTS AND METHODS

Patients. Eighteen patients (10 women and 8 men) were selected from among the clinical research database of the Section of Rheumatology at Rush–Presbyterian–St. Luke's Medical Center. Entry criteria consisted of willingness to participate in the study, age 30–75 years, radiographic evidence of grade II or grade III OA of the knee (11), symptomatic disease for more than 6 months, mild-to-moderate disease symptoms in only 1 knee, varus deformity of the knee determined by long leg radiograph, treatment with NSAIDs for at least 2 weeks prior to the first visit, weight within 20% of standard range adjusted for age and height, and ability to perform 2 gait analysis procedures within 4 weeks. All patients met the American College of Rheumatology (formerly, the American Rheumatism Association) criteria for OA of the knee (12).

Table 1. Characteristics of the osteoarthritis patients studied*

Males/females	8/10
Age, years	61.5 ± 8.4
Weight, kg	81.5 ± 14.6
Height, cm	170.0 ± 0.1
Mechanical axis, degrees	5.3 ± 2.2

* Except for the number of males/number of females, values are the mean ± SD.

Patients were excluded from the study if they had anemia or any other hematologic disorder, active liver disease, active peptic ulcer disease or gastrointestinal bleeding within the preceding 12 months, known or suspected allergy to the study medication or other NSAIDs, significant renal disease (creatinine level >2 mg/dl), or treatment with oral, parenteral, or intraarticular steroids within 1 month prior to the study. Patients with a history of knee trauma or knee surgery, including arthroscopic surgery, were also excluded, as were pregnant women and women of childbearing potential who were not practicing contraception.

Characteristics of the patient population are presented in Table 1.

Protocol. All patients underwent a physical and laboratory examination and were then entered into a 3–7-day NSAID washout period. Those patients who had a disease flare (defined as a 2-compartment increase in pain using a 21-compartment visual analog scale [VAS] [13] and/or worsening of the patient's global assessment of the knee by 1 point on a 5-point scale) underwent physician assessment, patient self-assessment, and weight-bearing long leg radiography with measurement of mechanical axis of the knee (14). The 21-compartment VAS was used in all VAS determinations in this study.

Patient self-assessment included determination of the severity of nighttime pain and the severity of daytime pain by VAS, and similar measurement by VAS of the difficulty in performing the following functional activities: rising from a chair, walking on flat ground, walking up stairs, reaching (picking items up from the floor), and ability to do daily chores, collectively referred to as activities of daily living (ADL). The patient's global assessment of the knee was rated on a 5-point scale (1 = very good, 2 = good, 3 = fair, 4 = poor, and 5 = very poor). Physician assessment included determination of pain on passive movement (4-point scale: 1 = none, 2 = mild, 3 = moderate, and 4 = severe), knee joint tenderness on pressure (5-point scale: 1 = none, 2 = very slight, 3 = definite, 4 = tenderness with wincing, and 5 = wincing with withdrawal), and global assessment of the knee (5-point scale: 1 = very good, 2 = good, 3 = fair, 4 = poor, and 5 = very poor). Gait analysis was then undertaken, and patients were begun on a treatment regimen of piroxicam at 20 mg/day in a single daily dose. Drug compliance during the study was monitored by pill counts. At the end of the 4-week

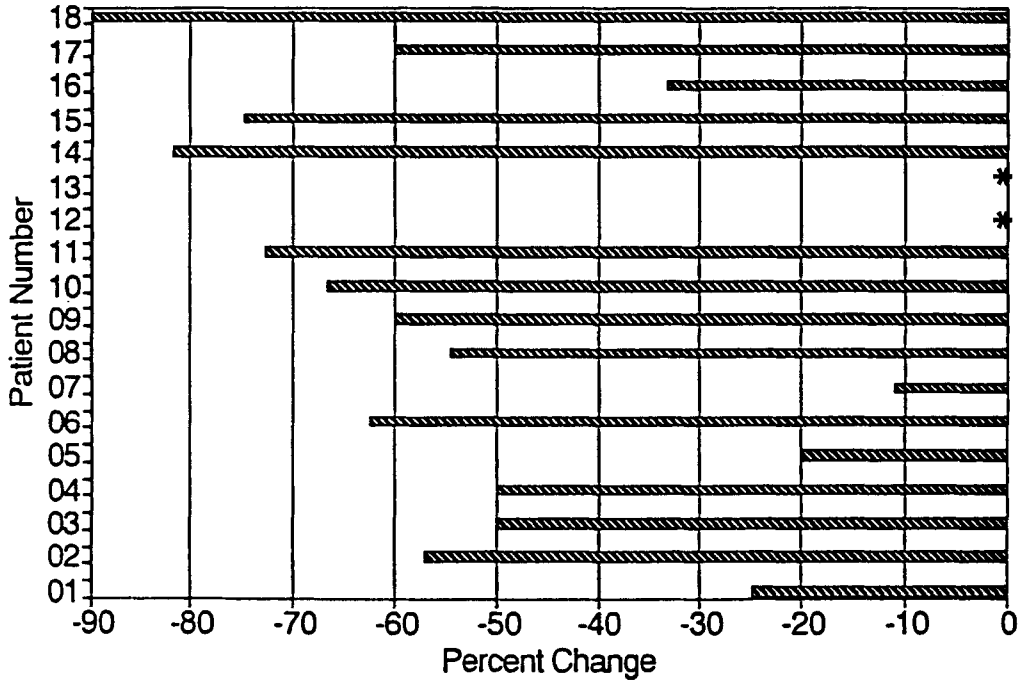

Figure 1. Percent change from baseline in reported daytime pain, measured after 4 weeks of piroxicam treatment in patients with knee osteoarthritis. Each bar represents 1 of the 16 patients who had a change in the pain score; asterisks represent the 2 patients with no change in the pain score.

treatment period another gait analysis was performed, as were physician and patient assessments.

Gait analysis. Motion and force were recorded using a video-based motion measuring system (Gait Link; Computerized Functional Testing, Chicago, IL) and multidimensional force platform (BERTEC, Columbus, OH) for measurement of foot-ground reaction force (15). During level walking, 6 strides were evaluated (2 at slower-than-normal, 2 at normal, and 2 at greater-than-normal walking speed). External reflective markers were placed with 2-sided stick tape on the leg at the anterior superior iliac spine, greater trochanter, lateral joint line at the knee, lateral malleolus, lateral aspect of the calcaneus, and base of the fifth metatarsal bone. Markers were placed on the bony prominences to minimize artifacts due to skin movement. The positions of joint centers at the hip, knee, and ankle on the sagittal plane were located relative to the positions of the reflective markers at the greater trochanter, lateral knee joint, and lateral malleolus, respectively. The position of joint center of the knee joint in the frontal plane was located by identifying the midpoint of a line between peripheral margins of the medial and lateral plateaus at the level of joint surfaces. The hip joint was located 1.5 cm distal to the midpoint of a line from the anterior superior iliac spine to the pubic symphysis. The ankle joint was estimated to be at the midpoint of a line from the tip of the lateral malleolus to the tip of medial malleolus. The joint centers were located and marked on each subject prior to observation of gait.

The 3-dimensional position of each reflective marker was sampled 60 times per second. Ground reaction force measurements were acquired simultaneously with the measurement of limb position. The force platform provided the 3 components of ground reaction force, vertical twisting moments, and location of resultant forces at the foot.

To calculate the moments (16), each segment of the limb (thigh, shank, and foot) was idealized as a rigid body with a coordinate system chosen to coincide with anatomic axes. Angular velocity and acceleration about longitudinal segments were assumed to be negligible. The inertial properties of the limb segment were approximated as previously described by Andriacchi and Strickland (16). That report also described an analysis of the sensitivity of the moment calculated to artifactual marker movement. It was assumed that the flexion–extension axis remained perpendicular to the plane of progression, that abduction–adduction and internal–external rotation axes at the hip joint moved with thigh segment, that axes of the knee joint moved with the shank segment, and that the ankle joint moved with the foot. The components of the moment vector were resolved into directions such that moments producing flexion–extension, abduction–adduction, and internal–external rotation at each joint could be identified. Values were normalized to percent body weight times height (%BWTH).

Statistical analysis. Comparison of pre- and posttreatment gait data and clinical data was performed using Student's *t*-test. Pearson correlation coefficients were determined for the regression analyses reported.

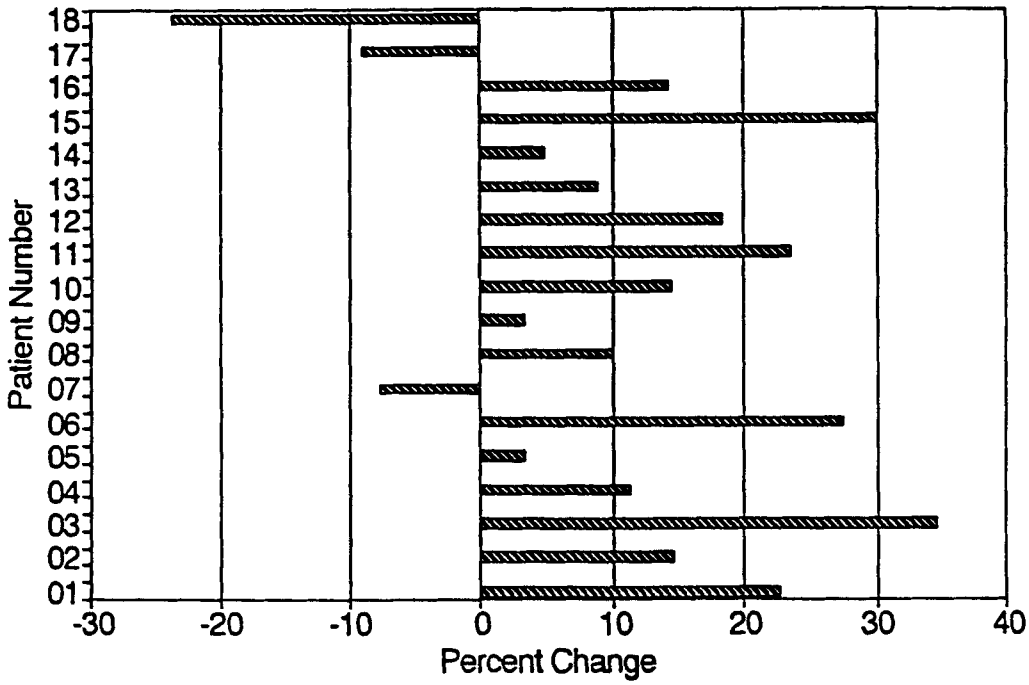

Figure 2. Percent change from baseline in knee adduction moment, measured after 4 weeks of piroxicam treatment in patients with knee osteoarthritis. Each bar represents an individual patient.

RESULTS

Clinical assessment. Improvement after NSAID treatment was noted in the group as a whole, in degree of pain, nighttime pain, arising from a chair, walking, walking up stairs, reaching from the floor, and ADL ($P < 0.001$ for each parameter). Evaluation of individual patients indicated that 16 of 18 patients receiving NSAID treatment reported a decrease in pain on the VAS (Figure 1), and 17 of 18 had an increase (i.e., less difficulty) in ADL parameters. Patient and physician global assessment of the knee demonstrated improvement over baseline in 16 of 18 patients and 17 of 18 patients, respectively, after 4 weeks of therapy ($P < 0.01$ for both, by sign test). No patient had a palpable knee effusion during the study.

Table 2. Results of gait analysis before and after piroxicam treatment in the 18 osteoarthritis patients studied*

	Pretreatment	Posttreatment	*P*
Walking speed, msec	0.98 ± 0.16	1.14 ± 0.15	<0.001
Maximum knee flexion, degrees	54.98 ± 5.6	56.44 ± 4.8	<0.02
Maximum quadriceps moment, %BWTH	2.13 ± 0.95	2.62 ± 0.92	<0.01
Midstance knee flexion, degrees	10.57 ± 6.5	12.50 ± 5.4	<0.02
Hip adduction moment, %BWTH	5.45 ± 0.3	5.77 ± 1.02	<0.05
Knee adduction moment, %BWTH	4.11 ± 1.20	4.57 ± 1.38	<0.01
Knee abduction moment, degrees	0.16 ± 0.18	0.21 ± 0.22	<0.05
Heel-strike knee flexion, degrees	6.32 ± 3.44	5.77 ± 2.85	<0.05
Toeing out, degrees	18.52 ± 9.47	18.01 ± 11.63	NS

* Values are the mean ± SD. %BWTH = percent body weight times height; NS = not significant.

Gait changes. Changes in gait occurred following NSAID treatment in the majority of the patients. Fifteen of the 18 patients tested had an increased peak adduction moment at the knee (Figure 2). The increase in the average moment for the group as a whole (~10%) was statistically significant (Table 2). A similar increase in the maximum net moment sustained by the quadriceps was observed in 14 of the 18 patients tested (Figure 3). The average increase in the quadriceps moment for the patient population as a whole was >20%, which was statistically significant.

There were also a number of changes in other parameters of gait (Table 2). Values for all of these gait variables after treatment tended to return toward

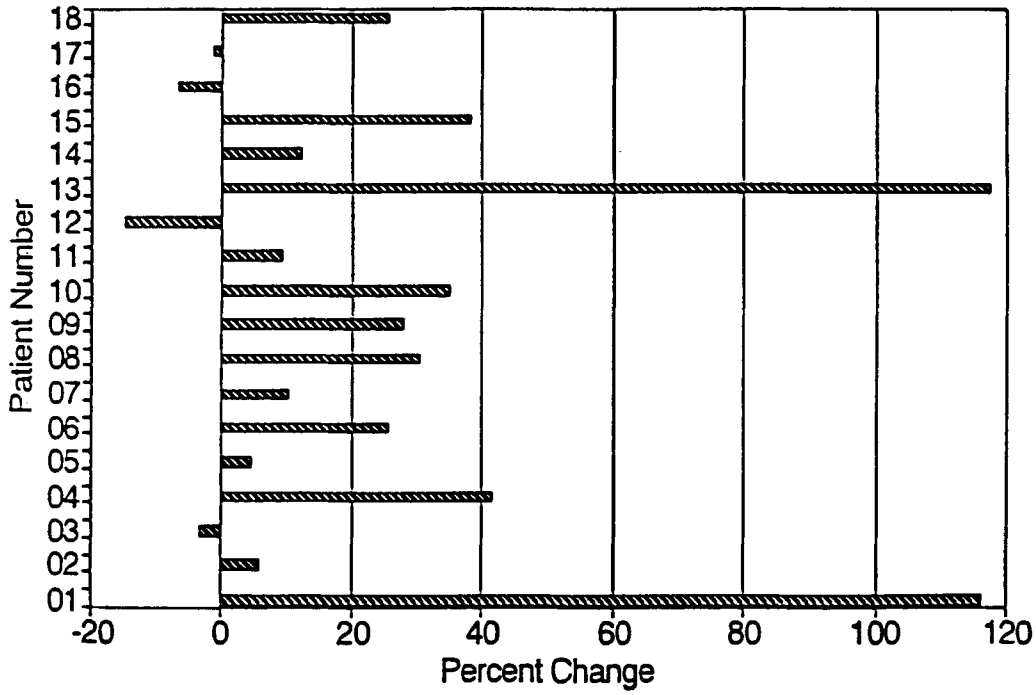

Figure 3. Percent change from baseline in maximum quadriceps moment, measured after 4 weeks of piroxicam treatment in patients with knee osteoarthritis. Each bar represents an individual patient.

values measured in individuals with no knee disease. The variables that changed significantly included maximum knee flexion, midstance knee flexion, and heelstrike knee flexion. Typically, patterns of abnormality in these parameters are indicative of pain, and following a reduction of pain the parameters approach normal values. These results tend to confirm the initial hypothesis that reduction in pain will tend to normalize gait, but at the same time will increase several of the parameters that can be associated with loading of the knee joint.

Regression analysis was undertaken to investigate the relationship between pain relief and changes in gait parameters. The only significant correlation found was between pretreatment report of knee pain and pretreatment report of ease of walking on flat ground ($r = 0.5251$, $P = 0.025$). The degree of change in pain and the degree of change in this walking parameter were also closely associated ($r = 0.4445$, $P = 0.06$). There was no statistically significant correlation of change in knee adduction moment or quadriceps moment and change in pain on VAS (either daytime or nighttime pain), although though the analysis was limited by the small sample size.

DISCUSSION

Some patients with varus deformity of the knee have been shown in this and previous studies to walk with a gait characterized by a higher-than-normal external adduction moment (6,7). One consequence of this type of gait is an increase in force across the medial aspect of the knee. This increased force has been hypothesized to result in a more rapid progression of the osteoarthritic process and has been shown in studies by Prodromos and colleagues (6) and Wang et al (7) to be associated with poorer outcomes in patients undergoing high tibial osteotomy for treatment of knee OA. Additionally, the elevated external adduction moment must be balanced dynamically by muscle forces and/or soft tissue tension in order to keep the joint stable and closed laterally. This is demonstrated by a significant elevation of the knee flexion moment. Although resulting in joint stability, this increase in flexion moment likewise adds to the forces directed medially at the joint and may play a role in hastening the progression of OA.

In the present study, at the time of the initial gait analysis when patients were not receiving analge-

sic therapy, they were found to have a higher-than-normal external adduction moment, consistent with the observations in previous investigations (6,7,15). With the subsequent introduction of analgesic therapy and concomitant attainment of symptomatic pain relief, the adduction moment increased yet further. This increase in external adduction moment was associated with a marked increase in the flexion moment, resulting in increased compressive forces in the affected knee. Other parameters of gait also changed in a manner expected in the clinical setting of decreased pain after analgesic therapy: there were statistically significant increases in stride length, walking speed, and maximum knee flexion. A more compelling correlation between these changes in gait parameters and relief of pain might be demonstrated in an investigation using a double-blind, placebo-controlled study design.

It is important to understand the mechanism by which patients alter their gait in response to pain, in order to evaluate their response to analgesic agents. With pain, there is inhibition of contraction of the quadriceps muscle (17), often an early manifestation of knee disease. The consequent reduction in the flexion moment, unless offset by a reduction in the adduction moment, would result in a dynamically unstable knee (10). Thus, as shown in the present study, patients would be expected to reduce the external adduction moment to maintain knee stability under such conditions. The mechanism by which this occurs is not known, although "toeing out," or external rotation of the foot, has been shown to be one mechanism that can be used (7).

In this study, no rotation at the foot was seen. Thus, the alteration in the pattern of gait may be a consequence of quadriceps inhibition, with the need to maintain knee stability a primary factor. With the relief of pain brought about by analgesic agents, the quadriceps is able to effect a larger flexion moment, maintain knee stability, and allow a return toward more "normal" gait characteristics (stride length, speed, knee maximum flexion), with a consequent return to higher adduction moments and larger compressive loads on the knee.

Ideally, one would like to be able to develop an intervention strategy whereby pain relief would not be associated with an increase in the adduction moment. This could be accomplished by reducing the adduction moment arm, reducing the axial load, or increasing the lateral balancing forces across the joint (10). Altering the adduction moment may be accomplished either by means of gait training (teaching "toeing out") or more simply, by the development of appropriate foot orthoses. Weight loss itself will reduce axial force and has been shown to result in slower progression of OA (18). Finally, an increase in the strength of the knee flexors might result in a gait adaptation that reduces the adduction moment, thus reducing the net force across the medial aspect of the knee and retarding progression of the osteoarthritic process.

All of these interventions warrant serious consideration since they are noninvasive and their cost-effectiveness, though not yet established, could make them attractive alternatives to the use of either pure analgesic agents or NSAIDs and ultimate surgical treatment. Preliminary studies have indicated that there is merit to all 3 approaches, at least in terms of symptom relief, in patients with OA (6,18,19). Biomechanical analysis of these interventions should help provide us with a means of assessing and understanding the mechanisms by which OA develops, progresses, and responds to therapy and should facilitate the development of yet more effective approaches to treatment.

Finally, it must be noted that, although increases in parameters of knee loading were seen after treatment with piroxicam, an NSAID, in the present study, the use of pure analgesic agents has been associated with similar changes (15). It is not known whether changes in the loading parameters differ among different classes of analgesic agents or among different NSAIDs, whether such differences are clinically significant, or whether there might be some threshold of drug concentration that would permit analgesia without adversely affecting knee joint loading during gait. These questions warrant further investigation.

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