To test the hypothesis that delayed onset muscular soreness (DOMS) following intense eccentric muscle contraction could be due to increased production of prostaglandin E2 (PGE2), ten healthy male subjects were studied. Using a double-blind randomized crossover design, each subject performed two isokinetic tests separated by a period of at least 6 weeks: once with placebo, and once with piroxicam (Feldene®). They were given one capsule containing either placebo or piroxicam (20 mg) per day for 6 days with initial doses given starting 3 days prior to isokinetic testing. Exercise consisted of eight stages of five maximal contractions of the knee extensor and flexor muscle groups of both legs separated by 1 min rest phases, on a Kin Trex device at 60°/s angular velocity. The subjective presence and intensity of DOMS were evaluated using a visual analogue scale immediately after, and 24 and 48 h after each test. The mean plasma concentration of PGE2 measured at rest and after exercise was significantly lower in the group treated with piroxicam (p < 0.05). However, statistical analysis (two-way ANOVA test) revealed that exercise did not cause any significant change of mean plasma PGE2 over time in either of the two groups. Eccentric work was followed by severe muscle pain in extensor and flexor muscle groups. Maximal soreness was noted 48 h post-exercise. Serum creatine kinase activity and the serum concentration of myoglobin increased significantly, and reached peak values 48 h after exercise in both experimental conditions (p < 0.001). By paired t-test, it appeared that there were no significant differences in the serum levels of these two markers of muscle damage between the two groups at any time point. We conclude that: (1) oral administration of piroxicam fails to reduce muscle damage and DOMS caused by strenuous eccentric exercise; and (2) the hypothetical role of increased PGE2 production in eccentric exercise-induced muscle damage, DOMS, and reduced isokinetic performance is not substantiated by the present results.

Key words: Delayed onset muscle soreness, Eccentric contraction, Isokinetic exercise, Muscle damage, Non-steroidal anti-inflammatory agent, Prostaglandin

Introduction

Delayed onset muscle soreness (DOMS) refers to a dull, aching pain, frequently combined with tenderness and stiffness, localized to groups of previously active muscles. These symptoms are usually observed following strenuous, unaccustomed exercise, especially when eccentric contractions are involved. DOMS sensations develop in the first 24 h following muscular work and subside within 5 to 7 days after exercise. Despite the volume of data that have accumulated concerning DOMS during the last decade, the underlying mechanisms of this phenomenon remain poorly understood. Based on previous studies showing that strenuous exercise causes muscle and connective tissue damage, as well as an inflammatory response involving the release of algogenic inflammatory mediators such as prostaglandins (PG), it has been hypothesized that increased PG production by activated macrophages in injured areas could be one of the main
chemical stimuli responsible for DOMS. Histological and biochemical indices of exercise-induced muscle damage, the presence of leucocytes capable of producing arachidonic acid (AA) derived products in damaged muscles, and the increased production of these substances during exercise support this hypothesis. The results of a recent human study, where ibuprofen, a potent nonsteroidal anti-inflammatory drug (NSAID), reduced both DOMS and the decrease of muscle performance after strenuous eccentric contractions argued also for the involvement of PGs. It should be pointed out, however, that the effects of inhibitors of AA metabolism on DOMS is a matter of controversy. Several research groups have reported that anti-inflammatory agents inhibiting the production of AA-derived compounds failed to alleviate soreness after exercise. Among the possible factors responsible for these discrepancies are the administration protocol of NSAIDs and the effective doses that are absorbed. Therefore, in an attempt to address the question of whether metabolites of AA derived from the cyclooxygenase pathway, especially PGE₂, are involved in DOMS, we studied the effects of piroxicam (Feldene®), another potent NSAID, on perceived soreness, biochemical indices of muscle damage, and plasma levels of PGE₂ in subjects submitted to maximal eccentric isokinetic contractions. To optimize the potential effects of piroxicam on these variables, the drug was administered both before (prophylactically) and after (therapeutically) to each subject.

Methods

Subjects: Ten moderately active, healthy male subjects volunteered to take part in this study after giving informed consent. Their mean age (± S.E.M.) and body mass were 22 ± 0.4 years and 74 ± 1.5 kg, respectively. None was currently involved in lower body resistance or endurance training. They were requested to refrain from strenuous exercise and to abstain from the consumption of any form of medication during the study period. The experimental protocol was approved by the Ethics Committee of the University Hospital Center of Liège.

Experimental procedures: All isokinetic measurements were performed on a Kin Trex device (Medtronic Instruments SA, Ecublens, Switzerland) at 60°/s angular velocity. During these experiments, the subjects performed isokinetic exercise in a seated position at approximately 105° of hip flexion. Belts placed across hips, chest and thigh were used to stabilize their position.

On their first visit to the laboratory, the subjects volunteered to take part in this study. They were requested to refrain from strenuous exercise and to abstain from the consumption of any form of medication during the study period. The experimental protocol was approved by the Ethics Committee of the University Hospital Center of Liège.

Perception of muscle soreness and indirect evaluation of muscle damage: The subjective presence and intensity of DOMS were evaluated using a visual analogue scale graded from 0 (no pain) to 10 (very severe, intolerable pain) immediately after, and 24 and 48 h after eccentric testing. Increased serum levels of creatine kinase (CK) and myoglobin (Mb) were used as indirect indices of exercise-induced muscle damage.

Blood sampling: Before each test, an indwelling catheter was inserted into an antecubital vein and sealed. Venous blood samples (10 ml) were collected into sterile tubes immediately before isokinetic test, 10 min after catheter insertion; immediately after exercise, and after 30 min recovery. Two additional blood samples were taken by venipuncture 24 and 48 h after exercise, respectively. The venous blood samples were
divided in two aliquots: 5 ml whole fresh blood into a plain plastic tube, and 5 ml of whole blood into a vial containing EDTA as anticoagulant. The first portion was allowed to clot at room temperature, and the serum phase was used for the measurement of creatine kinase (CK) activity and myoglobin (Mb) concentration. The second portion was immediately centrifuged. The supernatants were kept at −70°C until plasma PGE2 assay.

**Biochemical assays:** Plasma PGE2 levels were assessed using an enzyme immunoassay (Cayman Chemical, Kit 514016). Routine spectrophotometric techniques used in the Dept of Clinical Biology were applied to measure serum CK activity and Mb concentrations.

**Statistical analysis:** Values in the text and figures are expressed as group means ± S.E.M. For each variable, differences between mean values obtained at each time point in the two groups were evaluated using a paired Student’s t-test. For the variables listed above, a two-way analysis of variance for repeated measures design (two-way ANOVA test) was used to assess changes over time. The level of statistical significance was set to p < 0.05.

**Results**

Mean peak torque produced by the quadriceps and hamstring muscle groups during pre- and post-test exercise sessions in the two experimental conditions are shown in Fig. 1. Pre-test mean PTmax of knee flexor and extensor muscle groups were 157 ± 9 and 339 ± 17 Nm, respectively. Maximum eccentric contractions were not followed by any significant change of this variable after two days of recovery.

As shown in Fig. 2, eccentric exercise caused marked soreness, reaching peak levels 2 days after isokinetic testing. The pattern of change of mean soreness scores over time, as well as mean soreness scores at each time point were not significantly changed by piroxicam. The effects of this agent on mean plasma PGE2 concentrations are illustrated in Fig. 3. When compared to the placebo group, this variable was significantly decreased at four time points in the piroxicam group (p < 0.05). By the two-way ANOVA test, it appeared that exercise did not cause any significant change of plasma PGE2 concentration over time in either experimental condition.

The effects of exercise on serum levels of CK and Mb are shown in Fig. 4 and 5, respectively. Beginning on the day after the isokinetic test, marked release of CK was observed in both groups, reaching a maximum on day 2 of recovery (p < 0.001). Serum Mb concentration also demonstrated a delayed peak after 48 h recovery in both experimental conditions (p < 0.001). Piroxicam did not significantly change the mean serum levels of these biochemical markers of muscle damage at any time point.

**Discussion**

The marked increase of serum CK activity and Mb concentration following isokinetic eccentric
Piroxicam and delayed muscle soreness

Despite the large number of studies currently available concerning DOMS, little is known about its underlying mechanisms. Based on literature data showing that eccentric muscular work is the most effective way to cause muscle damage associated with humoral and cellular indices of an inflammatory response, it has been suggested that algogenic substances derived from arachidonic acid metabolism, especially PGE2, could play a pivotal role in the production of the delayed sensation of pain, a cardinal symptom of DOMS. The increase of muscle AA levels accompanying static contraction, the production of prostaglandins during strenuous muscular work, as well as reports of the beneficial effects of NSAIDs on exercise-induced injuries in mouse skeletal muscle fibres and certain manifestations of DOMS in man, lend support to this hypothesis. However, previous studies suggesting that other factors could also be involved in exercise-induced pain, as well as the discrepancies concerning the effects of drugs known to inhibit the AA metabolism on DOMS, led us to verify whether piroxicam could effectively help to manage pain, reduced muscle performance and muscle damage following maximal isokinetic eccentric contractions.

The protein leakage from skeletal muscle has been widely used to estimate the severity of exercise-induced skeletal muscle damage. In accordance with this view, the data presented in Figs 4 and 5 indicate that the present exercise protocol caused severe myocellular injury. Surprisingly, when compared to the PTmax measured before isokinetic exercise, the ability of the knee flexor and extensor muscle groups to produce force was unaffected 2 days after the damage induced by the two experimental conditions. This suggests that muscle injury was not severe enough to alter PTmax and/or that motor units containing non-damage fibres were recruited.

FIG. 3. Plasma concentration of prostaglandin E2 as a function of time in the two experiments. Vertical bars are S.E.M. * Pre-exercise; 30 min: immediately after exercise; 60 min: after 30 min recovery; 24 h, 48 h: 24 h and 48 h after exercise.

FIG. 4. Mean serum activity of creatine kinase (logarithmic scale) as a function of time in the placebo and piroxicam groups (see Fig. 5).

FIG. 5. Mean serum concentration of myoglobin (logarithmic scale) as a function of time in the placebo and piroxicam groups (see Fig. 5).
metabolism via the cyclooxygenase pathway do not play a major role in the pathogenesis of DOMS nor in exercise-induced damage. Nevertheless, the hypothesis that larger doses of piroxicam or lowering the plasma levels of PGE2 below 200 pg/ml could reduce DOMS in subjects submitted to damming exercise of longer duration deserves to be tested experimentally.

In contrast with previous studies where strenuous exercise was found to increase plasma and muscle levels of AA-derived products,4–7 there was no significant change in plasma PGE2 concentration over time in the two experimental conditions. The reasons for this discrepancy are unclear. One possibility is that we measured plasma levels of PGE2 in venous blood samples drawn at a site distant from the active muscles in which this compound has been shown to accumulate.7 Because of the short half-life of PGE2 in blood, it is possible that regional changes of this variable in the venous effluent of skeletal muscle have been shown to accumulate.7 Because of the short half-life of PGE2 in blood, it is possible that regional changes of this variable in the venous effluent of skeletal muscles are not detectable in blood from a forearm vein. Another factor that could act in concert with the sampling site effects is the limited muscle mass involved in the isokinetic exercise. The isokinetic device used in the present study does not allow simultaneous contraction of limb muscles on both sides. It is therefore possible that the amount of PGE2 released from the active muscles was too low to be reflected by changes in venous PGE2 concentrations measured in blood samples drawn from a forearm vein. For ethical and technical reasons, we did not measure the arterio-venous difference of PGE2 at the lower limbs. Therefore, increased production of this compound induced by exercise in the active muscles cannot be definitively ruled out. Nevertheless, the significant difference of resting and post-exercise plasma concentrations of PGE2 between the two groups demonstrates that the dose of piroxicam used in this study effectively inhibited the production of this compound. As mentioned above, because the failure to find a significant difference in either the serum levels of the biochemical markers of muscle injury or in the intensity of DOMS between the two groups, despite piroxicam-induced reduction of plasma PGE2 concentrations, argues against the hypothesis that cyclooxygenase-derived AA metabolism are involved in exercise-induced damage and DOMS. Based on these results, it would appear that the activation of pain afferents after eccentric contractions is caused by other noxious stimuli. It has been suggested that increased intramuscular pressure,2 and/or production of algogenic substances such as serotonin, histamine, acetylcholine and kinins could be involved in the production of DOMS.8 To our knowledge, these hypotheses remain to be tested experimentally.

References

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