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Effects of Ibuprofen and Vicoprofen® on Physical Performance After Exercise-Induced Muscle Damage

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Objective: To determine the effects of Vicoprofen® and ibuprofen on aerobic performance, agility, and pain after exercise-induced muscle damage. ***Design:*** Double-blind randomized, placebo-controlled, repeated-dose clinical trial. ***Setting:*** Human-performance and sports-medicine laboratory. ***Participants:*** 36 healthy men. ***Methods and Measures:*** Baseline testing was performed, 72 hours after which subjects performed eccentric exercise to induce muscle damage. They were evaluated for pain 24 hours postdamage and placed randomly into 3 groups: Vicoprofen (VIC), ibuprofen, or placebo (P). Postdamage testing was performed every day for 5 days. Subjects performed an economy run and a t-agility test to determine exercise performance. ***Results:*** The drugs had no significant effect on performance throughout the 5-day evaluation period. Pain was lower at days 4 and 5 in the VIC group than in P. ***Conclusions:*** It appears that Vicoprofen reduced pain after muscle damage, but the drug interventions did not enhance performance in aerobic and agility tasks. ***Key Words:*** agility, injury, medical therapy, running economy

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Exercise-induced muscle damage can negatively affect muscle performance. It is characterized by a dull, aching pain that occurs after strenuous or unusual activity.[1-4] The exercise-induced muscle damage results in soreness that typically increases during the 24 hours after exercise.[4,5] The pain and stiffness peak 24–48 hours postexercise and return to baseline approximately 5–7 days after the exercise bout. The symptoms can range from stiffness to debilitating pain that interferes with general movement activities.[2,3,6-8]

Various therapies have been employed in an attempt to diminish the discomfort associated with exercise-induced muscle damage, including topical ointments or thermal agents, ultrasound, and anti-inflammatory agents.[6,7] Ibuprofen is a typical anti-inflammatory drug used to relieve

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muscle pain and soreness. It reduces the production of prostaglandins and oxygen radicals but does not affect the loss of calcium after the injury.[7] The doses of ibuprofen associated with these effects, however, are greater than those used in the present study.

Although anti-inflammatory medications can provide pain relief in exercise-induced muscle damage, a combination treatment of opiate and anti-inflammatory agent might be more beneficial.[9] The analgesic effect of ibuprofen is augmented in this preparation, resulting in decreased pain throughout the recovery process. One preparation containing 7.5 mg hydrocodone bitartrate and 200 mg ibuprofen (Vicoprofen®) is similar to drugs used successfully in other clinical conditions. The beneficial effects of the combination drug could enhance both pain masking and muscle healing. Therefore, the purpose of our study was to examine the effects of 2 drug interventions (ibuprofen and Vicoprofen) on performance on physical work tasks and the perceived exertion associated with those tasks after eccentric muscle damage.

Methods and Materials

Subjects

Thirty-six moderately fit men, age 18–34 years, were recruited for the study. Table 1 shows the physical characteristics of the subjects. Each subject was randomly assigned to 1 of 3 experimental groups (n = 12/group; IBU = ibuprofen, VIC = Vicoprofen, P = placebo). The study protocol was approved by the University of Connecticut's Committee for the Protection of Human Subjects, and each subject gave informed consent before initiating the study protocol. Medical history, activity questionnaires, and physician clearance were completed before entry into the study. Each subject completed a 3-day food diary. Subjects who consumed more than 30% of their calories from protein were excluded from the study. The subjects were not athletes, nor had they been regular participants in organized competitive

Table 1 Physical Characteristics of Study Subjects*

	Age (y)	Height (cm)	Body mass (kg)	Body fat (%)
VIC	20 ± 0	173.6 ± 3.0	71.8 ± 2.1	14.8 ± 1.3
IBU	19 ± 0	164.5 ± 1.8	69.3 ± 2.4	16.6 ± 1.9
P	20 ± 0	178.4 ± 3.0	78.7 ± 3.9	17.6 ± 1.8

*Mean ± SEM. VIC indicates Vicoprofen®; IBU, ibuprofen; and P, placebo.

athletics for a period of at least 6 months before the study. They were allowed to participate in recreational activities such as swimming, jogging, or other aerobic activities, but they could not have participated in lower body resistance training during the preceding year.

Study Design and Muscle-Damage Protocol

The study design was a double-blind randomized, placebo-controlled, repeated-dose trial. All subjects completed a series of initial assessments including maximal oxygen consumption, body composition, and history and physical screening. These assessments were used both as screening evaluations and as descriptive data regarding the subject group. After the screening evaluations (day V3), each subject completed a series of baseline tests (including each of the dependent variables: running economy, t-agility performance, pain scores, and creatine kinase [CK]; Figure 1). The baseline testing allowed the subjects to familiarize themselves with the testing protocols and served to reduce the potential confounding learning or training effects associated with test performance.

The following day (V4), each subject performed an eccentric-exercise protocol to induce muscle damage. The protocol consisted of seated knee flexion, starting with a straight leg, followed by flexion of the knee. The contractions were performed on an isotonic leg-extension machine that allowed for the resistance to remain constant while the speed of the contraction could change. The protocol was completed with single-leg contractions using the dominant leg. Approximately 100 contractions were performed against a resistance of 120% of the 1-repetition-maximum concentric load.[10]

Twenty-four hours after the damage protocol (V5), the subjects were evaluated for pain after a single-leg (damaged leg), unweighted squat using a visual analog scale (VAS). Subjects with mild or greater pain levels were randomized into 1 of the 3 experimental groups (VIC, IBU, or P). Treatment was administered (as per protocol in following section) for the

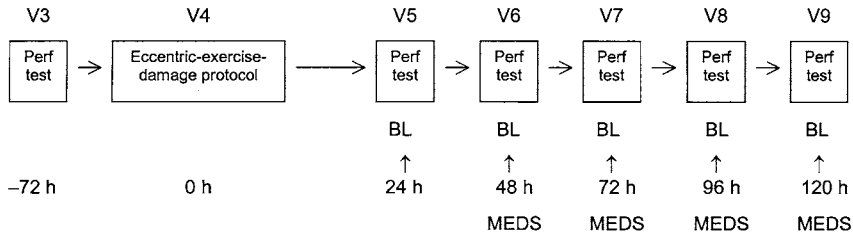

Figure 1 Study design timeline including visits to the laboratory (V), performance and cognitive testing (Perf), blood draws (BL) and corresponding hours before or after the eccentric-exercise damage protocol. The administration of study medications is also included (MEDS).

subsequent 4 days (V6–V9). All dependent variables were measured under similar conditions (ie, time of day, room temperature, and test order) for each of the remaining days of the protocol (V6–V9).

Drug Administration

All subjects were required to take their medication 4 times per day (every 4–6 hours). The IBU group took one 200-mg tablet per dose, which allowed for comparison with the ibuprofen content in the VIC dosage. The VIC group consumed tablets containing 7.5 mg hydrocodone bitartrate with 200 mg ibuprofen (Vicoprofen, Knoll Pharmaceutical Co, Mt. Olive, NJ). The P group was given a placebo medication. Dosing began after testing on day 5 of the protocol (24 hours after damage) and was administered in the presence of a member of the research team. The remaining 3 doses of the drug were taken over the following day, the final dose immediately before the testing session on day 6. From day 6 forward (through day 9), the subjects would receive a bottle containing 4 pills, 1 of which was taken in the presence of a study investigator, and the final pill was taken just before the subsequent day's testing session. The subjects were not allowed to take any additional medications during the study period.

Aerobic Performance

The running-economy profile was performed in 4 continuous stages on a motorized treadmill at 0% incline. Five-minute stages began at 2.5 mph, followed by additional stages at 5, 6, and 7 mph. Oxygen consumption (VO_2) and respiratory-exchange ratio were measured for the final 3 minutes of each running speed. During the last minute of each stage, the subjects selected a rating of perceived exertion (RPE) according to the Borg scale.[11] RPE was determined for each leg and for the total body. Heart rate was recorded during the last minute of each stage by a heart-rate monitor. The protocol was designed to assess running economy in such a manner that moderately fit individuals could perform the task.

t-Agility Test

The t-agility test was used to determine the agility of the subjects before and after the damage protocol. The subjects sprinted in a straight line from a standing start to a cone 9 m away, followed by a side-shuffle left (without crossing the feet) to a cone 4.5 m away. After touching the cone, the subjects side-shuffled right to a cone placed 9 m away and then side-shuffled back to the middle cone. A final backpedal motion to the starting line completed the test. Each subject performed 2 trials of the test, with the fastest time recorded.

Pain Assessment

A VAS was used to determine subjects' pain. Pain was assessed after a single-leg (damaged leg), unsupported, unweighted squat. The VAS was a 10-cm linear scale with labels *no pain* and *pain as bad as can be* on either end. Each subject would subjectively mark his pain rating on the scale, and the distance (cm) from the *no pain* point was measured as the raw pain score. A daily pain score was recorded after the single-leg (damaged leg) squat performance, and this value served as a baseline pain measure each day of the protocol.

Blood Collection and Creatine-Kinase Analysis

Blood was collected daily (V5–V9; see Figure 1) via venipuncture from an antecubital vein. Blood was centrifuged and the serum placed into aliquots and stored at –85°C for later analysis. CK concentrations were determined in duplicate using a colorimetric assay (Sigma Chemical Co, St. Louis, Mo). Intra-assay and interassay variances were less then 5% and 10%, respectively.

Data Analysis

Analysis of variance (ANOVA) with repeated measures was used to statistically evaluate the data set. When appropriate, Fisher least-significant-difference post hoc tests were used for pairwise comparisons. Statistical significance was chosen as $P \leq .05$.

Results

Data were analyzed for the period of time that both passive recovery and medications were employed (48–120 hours postdamage). This time period was used because it resembles the care that many athletes experience after muscle damage.

Serum CK was significantly elevated in all groups after the muscle-damage protocol. Comparisons between the groups indicated that there were no significant differences at any time point measured. The CK values were similar to data reported previously using the same damage protocol.[12]

Figure 2 illustrates the response in oxygen consumption to running at the 6-mph stage in the 3 experimental groups over time. VO_2 was significantly greater in the VIC group than in IBU at 24 hours postdamage. All other comparisons were not significantly different between the groups in oxygen consumption. For heart rate (Figure 3), the P group was significantly higher (179 ± 3 beats/min) than both VIC (169 ± 5 beats/min) and IBU (167 ± 4 beats/min) at 24 hours postdamage. Heart rate also was not significantly different between groups at any of the remaining time points measured in this study.

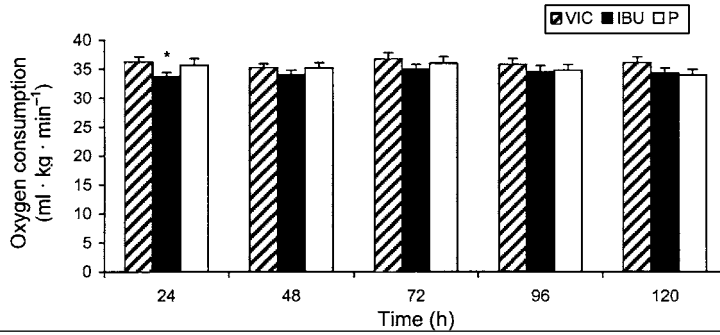

Figure 2 Oxygen-uptake response at 24, 48, 72, 96 and 120 hours after muscle-damage protocol for the 3 experimental groups. Values are mean ± SEM.
*vs P ($P \leq .05$).

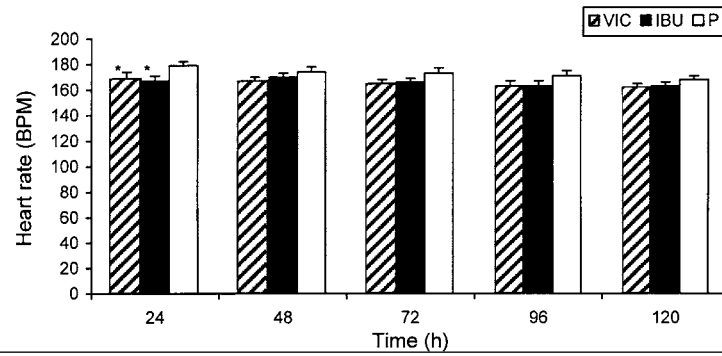

Figure 3 Heart-rate response at 24, 48, 72, 96 and 120 hours after muscle-damage protocol for the 3 experimental groups. Values are mean ± SEM.
*vs P ($P \leq .05$).

RPE varied slightly during the aerobic-performance (running economy) test for each group and was not shown to be different between groups throughout the recovery period. RPE data for each group in the dominant (injured) and nondominant (uninjured) legs were also not different between groups, but there was a trend for the injured leg (dominant) to have somewhat higher RPE values in both the P and IBU groups at 24 (P = 14 ± 1, VIC = 12 ± 1, IBU = 14 ± 1) and 48 (P = 13 ± 1, VIC = 12 ± 1, IBU= 13 ± 1) hours after the damage protocol.

Pain-rating data are presented in Table 2. There were no significant differences between groups in VAS after the unloaded single-leg squat. VAS scores were significantly lower in the VIC group at 48 and 72 hours than in P after both the aerobic-performance test and the t-agility test. There were no differences reported at any other time point measured.

Table 2 Pain Assessments During Aerobic-Exercise Bout (6 mph), t-Agility Test, and Squat Using a Visual Analog Scale (VAS) After an Eccentric Muscle-Damage Protocol*

	Time Postdamage				
	24 h	48 h	72 h	96 h	120 h
Squat VAS					
VIC	4.23 ± 0.59	3.08 ± 0.70	2.00 ± 0.40	1.78 ± 0.34	0.83 ± 0.28
IBU	4.42 ± 0.69	2.97 ± 0.46	2.06 ± 0.51	1.22 ± 0.25	1.40 ± 0.83
P	5.05 ± 0.68	4.25 ± 0.63	3.01 ± 0.59	1.94 ± 0.49	1.28 ± 0.49
Aerobic VAS					
VIC	5.23 ± 0.51	3.23 ± 0.50†	2.80 ± 0.44†	2.48 ± 0.51	1.90 ± 0.69
IBU	6.10 ± 0.68	4.08 ± 0.70	3.64 ± 0.76	2.35 ± 0.73	1.55 ± 0.54
P	5.87 ± 0.79	5.75 ± 0.81	4.40 ± 0.76	2.70 ± 0.67	2.26 ± 0.78
t-Agility VAS					
VIC	4.68 ± 0.61	3.02 ± 0.68†	2.37 ± 0.45†	1.99 ± 0.46	1.35 ± 0.53
IBU	5.51 ± 0.53	3.58 ± 0.48	2.62 ± 0.60	1.55 ± 0.26	0.98 ± 0.23
P	6.14 ± 0.78	5.13 ± 0.85	3.92 ± 0.79	2.33 ± 0.59	1.90 ± 0.72

*Mean ± SEM. VIC indicates Vicoprofen®; IBU, ibuprofen; and P, placebo.
†vs P.

Figure 4 depicts the t-agility test results. Although the P group's times appeared to be somewhat slower than those of either VIC or IBU throughout the entire recovery period, there were no significant differences between groups at any point in the recovery process. The findings were driven by the large variability in the P-group data at each time point measured.

Discussion

The present study was designed to test the effect of 2 drug interventions on measures of physical performance after exercise-induced muscle damage. We hypothesized that the VIC condition would provide significant perceptual alterations during the recovery period and that the benefits would be seen in more rapid return to baseline.

Eccentric exercise causes substantial muscle damage[2,13] that can be measured, indirectly, by evaluating CK in the blood.[10,14,15] In the present study, CK was significantly increased in all groups after the muscle-damage protocol. The drug interventions did not appear to have a significant effect on the delayed onset of muscle soreness or the CK values over the 5-day recovery

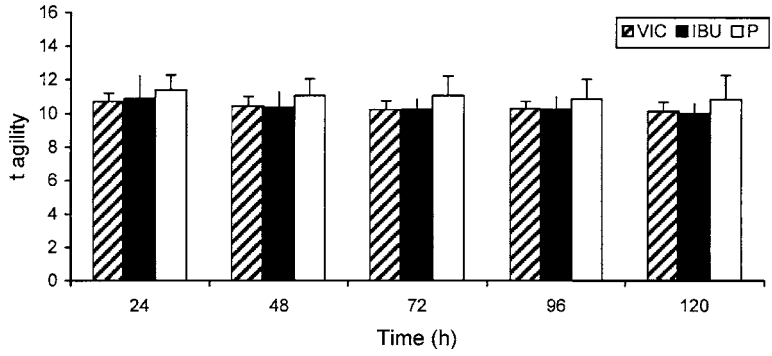

Figure 4 t-Agility response at 24, 48, 72, 96 and 120 hours after muscle-damage protocol for the 3 experimental groups. Values are mean ± SEM.

period. The CK values indicated that muscle damage was present in these subjects (24 hours after the damage protocol).

The study protocol resulted in a pattern of elevated CK values in the VIC group, in which they were significantly elevated over predamage values at days 3 through 5. It is probable that the subjects in the VIC group did not feel the level of discomfort associated with the treadmill running and agility testing because of a more effective pain medication including an opiate. Therefore, they might have run somewhat more aggressively, resulting in additional damage. The damage could have been increased because of the nature of the running protocol (ie, relatively greater eccentric component) in all groups tested; therefore, the CK values remained elevated throughout the protocol. A similar phenomenon has been reported in marathon runners.[16] The potential pain masking in the VIC group could be a risk for injured athletes, who could further injure their muscles while recovering from an initial muscle injury.

Muscle damage should cause a decrease in the person's ability to perform steady-state aerobic work (a decrease in economy and efficiency). As the individual begins to heal, he or she should return to baseline values. Any pharmacological agent that facilitates healing or masks pain or discomfort could positively affect running economy. Furthermore, if the drug intervention reduced the perception of pain or discomfort, the subject should report lower perceived exertion than would individuals not receiving the treatment.

The 2 measures used in this study to evaluate steady-state running performance were oxygen uptake and heart rate. Each group remained fairly constant in VO_2 during the 6-mph stage of the test throughout the study. HR was reduced, however, in the VIC group at its highest value (24 hours postdamage) throughout the protocol (Figure 3), and it returned more

rapidly to baseline than in the other 2 treatment groups. The medication taken by the VIC group has been shown to produce centrally mediated effects.[7,9,17] Potential influence of the VIC drug on central-nervous-system-mediated autonomic control of heart rate might have been evident in these subjects throughout the study. Further exploration of these phenomena is warranted.[7,9,17]

The impact of the drug interventions on the perception of physical exertion both globally and in each leg separately followed many of the trends hypothesized. Total-body RPE was initially elevated after the damage protocol (24 hours) and gradually returned to baseline in all 3 groups. The VIC group, as expected, showed the smallest increase in RPE values after the damage protocol, followed by the IBU group. It is clear that the pain- or discomfort-masking properties of these agents were evident in this group of subjects.

Dominant-leg RPE response (the damaged leg) was similar to the global RPE response, with the VIC and IBU groups reduced in response over time. These findings support the work of Hasson et al,[7] who examined the influence of ibuprofen on muscle soreness. Perception of muscle soreness after a therapeutic dose of ibuprofen (24-hour TID) was significantly diminished compared with placebo 48 hours after exercise. Nondominant-leg findings were consistent with the a priori hypothesis of no change throughout the protocol.

Agility during the muscle-damage period should be reduced because of the physical damage to skeletal-muscle fibers. Although there might be functional motor units throughout the muscle, motor units should be damaged after the eccentric-exercise protocol in specific regions of the muscle. It is possible that the drug interventions reduce the perception of pain or discomfort, thereby allowing the subjects to return to baseline agility measures more readily. Results from the present study do not support this hypothesis. All 3 experimental groups improved in agility from the baseline measure. In addition, the P group was slower than either the IBU or the VIC group during every visit (including baseline). IBU subjects returned to baseline values more rapidly than either the P or the VIC group. This suggests that the effects of IBU on the cellular reconstruction of skeletal muscle during recovery might influence an individual's ability to perform rapid physical tasks requiring coordinated movements.

It appears that the pain data do not directly relate to either of the performance tests. Pain was reduced at 48 and 72 hours in the VIC group after both the economy run and the agility test, but it was not accompanied by a significant improvement in performance. Coupled with the elevated CK data in this group, however, it could be speculated that the masked pain might result in increased damage with these types of running activities. It could be postulated that these tests are not limited by the single-leg damage that each subject endured. Performance of running economy is influenced by multiple factors, many of which are central (ie, cardiorespiratory function).

The single-leg damage would only account for a small additional demand placed on these subjects. Similarly, the t-agility test evaluated the subjects' neuromuscular ability and coordination. The impact of the single-leg damage might not have been a large enough stimulus to significantly disrupt overall performance on this test.

The present study is the first to examine the influence of Vicoprofen treatment on the recovery of running economy and agility tasks similar to those required in many sport activities. Recreational and competitive athletes are often plagued with soft-tissue injuries that include muscle damage. Sports-medicine physicians often prescribe pharmacological agents to decrease both inflammation and pain from these injuries. It appears that combination medications (ie, opiate and ibuprofen) can be effective in reducing pain and discomfort after exercise-induced muscle damage. Furthermore, the impact of ibuprofen alone on perception of pain was similar to the combination treatment, although not as significant in magnitude. The influence of these agents on recovery in terms of physical performance on either aerobic or agility tasks remains unremarkable. Athletes who experience muscle pain caused by training damage might benefit perceptually from the medications evaluated in this study, but the influence of these drugs on the inflammatory and healing processes remains unclear. Further research is necessary to determine the influence of these drug interventions on the factors involved in the muscle-healing and -regeneration processes.

Acknowledgment

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