Influence of acetaminophen on performance during time trial cycling

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Mauger AR, Jones AM, Williams CA. Influence of acetaminophen on performance during time trial cycling. J Appl Physiol 108: 98–104, 2010. First published November 12, 2009; doi:10.1152/japplphysiol.00761.2009.—To establish whether acetaminophen improves performance of self-paced exercise through the reduction of perceived pain, 13 trained male cyclists performed a self-paced 10-mile (16.1 km) cycle time trial (TT) following the ingestion of either acetaminophen (ACT) or a placebo (PLA), administered in randomized double-blind design. TT were completed in a significantly faster time ($t_{12} = 2.55, P < 0.05$) under the ACT condition (26 min 15 s ± 1 min 36 s vs. 26 min 45 s ± 2 min 2 s). Power output (PO) was higher during the middle section of the TT in the ACT condition, resulting in a higher mean PO ($P < 0.05$) (265 ± 12 vs. 235 ± 15 W). Blood lactate concentration (B[La]) and heart rate (HR) were higher in the ACT condition (B[La] = 6.1 ± 2.9 mmol/l; HR = 87 ± 7%max) than in the PLA condition (B[La] = 5.1 ± 2.6 mmol/l; HR = 84 ± 9%max) ($P < 0.05$). No significant difference in rating of perceived exertion (ACT = 15.5 ± 0.2; PLA = 15.7 ± 0.2) or perceived pain (ACT = 5.6 ± 0.2; PLA = 5.5 ± 0.2) ($P > 0.05$) was observed. Using acetaminophen, participants cycled at a higher mean PO, with an increased HR and B[La], but without changes in perceived pain or exertion. Consequently, completion time was significantly faster. These findings support the notion that exercise is regulated by pain perception, and increased pain tolerance can improve exercise capacity.

Rating of perceived exertion (RPE) feedback model (41), propose that exercise intensity is preset before exercise in an anticipatory manner, based on experience. However, during exercise, intensity is regulated through the conscious perception of effort via the interpretation of afferent signals from the periphery (41). The CNS uses this information to regulate exercise intensity so that whole body homeostasis is protected and a metabolic “emergency reserve” is always present (40). Amann et al. (2) propose a similar system of central control, whereby peripheral fatigue is monitored by the CNS, which alters central motor drive (CMD) to limit the level of peripheral fatigue development, thus avoiding intolerable levels of effort/pain and/or excessive muscle dysfunction. If neuromuscular signals are consciously interpreted as pain, leading to pace or intensity regulation, then an individual with a higher tolerance for pain may be “allowed” a greater power output (PO) than an individual with a lower tolerance.

If pain is a moderator of allowed exercise intensity, then any mechanism that may either reduce the level of pain or raise the performer’s tolerance to it may theoretically serve to enhance performance by enabling an athlete to go above the normal protective threshold and into the metabolic reserve (41). One method in which this may be achieved is through the administration of analgesics, or “pain killers.” Analgesics are commonly used by athletes (17), but there has been relatively little research in this area, and that which does exist is often inconsistent. These studies have largely focused on the effect of drugs such as aspirin (11, 20), caffeine (20, 29), or amphetamines (10, 40) on exercise performance. However, these drugs elicit actions other than analgesia, such as anticoagulation, increased fat oxidation, or psychostimulation, such that any observed performance improvements cannot solely be attributed to the analgesic properties of the drug. Amann et al. (2) have previously shown that the peripherally acting analgesic fentanyl allowed cyclists to increase CMD during a self-paced time trial (TT). However, the observed increased PO during the first half of the TT caused severe peripheral muscle fatigue, leading to a reduced PO in the second half of the TT.

Acetaminophen, also known as paracetamol, is a commonly used nonprescription analgesic and antipyretic and is considered one of the safest nonopioid analgesics at therapeutic doses (4, 30). Its main mechanism of action is the inhibition of cyclooxygenase (COX), similar to that of nonsteroidal anti-inflammatories (NSAIDs) (3), which is responsible for the production of prostaglandins. As prostaglandins sensitize nociceptors, this effectively means that acetaminophen relieves pain by elevating the pain threshold, that is, by requiring a greater amount of pain to develop before it is felt (21). Despite acetaminophen’s action on COX, its mechanism of action is different from that of NSAIDs, as acetaminophen has only a minor peripheral effect (18). Instead, acetaminophen’s primary action is central, namely on the serotonergic descending pain pathways (3). The pharmacokinetics of acetaminophen are unaf-
fected by exercise (39), it has little anti-inflammatory action (38), and other than analgesia, it has no other effects that might be expected to alter exercise capacity (27). The use of acetaminophen in research therefore appears to be preferable to other previously used drugs investigating pain relief and exercise performance.

The purpose of the present study was to establish whether the ingestion of acetaminophen would reduce perceived pain and RPE during a 10-mile (16.1 km) cycle TT, resulting in improved completion times. It was hypothesized that acetaminophen would reduce RPE and pain and improve completion time compared with that of a placebo.

**METHODS**

*Participants.* Thirteen trained [peak oxygen consumption ($\dot{V}O_{2peak}$) = 65 ± 5 ml · kg⁻¹ · min⁻¹] competitive male cyclists, aged 26 ± 9 yr, were recruited from local cycling clubs to participate in this study. These participants were selected because they participated in regular, structured training (13.4 ± 3 h/wk) and competed frequently (~1 competition/wk) in distances the same as, or similar to, that performed in the present study. Before selection for the study, all participants were asked to fill out an acetaminophen risk assessment questionnaire that was developed following consultation with a Lead Clinician in Pain Management and Consultant Anaesthetist. Where this questionnaire was not satisfactorily completed and consumption of acetaminophen was judged unsafe, the participant was not permitted to participate in the study. The study was conducted with approval of the Institutional Ethics Committee, and participants read and signed a form of written informed consent. Before the testing conditions all participants were given a period of familiarization in the laboratory, including a 10-mile TT. All exercise tests were conducted on a Computrainer cycle ergometry system (RacerMate Computrainer, Seattle WA), which allows each cyclist to ride his own bicycle in the laboratory. Previous research has shown these ergometers to provide a reliable measure of power output (PO) compared with standard laboratory ergometers (12), and similar devices are now being widely used in research (6, 9, 26). Before each test, the Computrainer was calibrated in accordance with the manufacturers’ recommendations.

$\dot{V}O_{2peak}$ test. After the familiarization period, all participants completed a maximal incremental exercise test (MIE) to exhaustion during which oxygen consumption ($\dot{V}O_2$) (Cortex Metalyser 11R, Cortex GmbH, Lepzig, Germany), PO, RPE, pain, and heart rate (HR) (Polar) were recorded for the duration of the test. After a 10-min warm-up at a self-selected intensity, the test commenced at a PO of 150 W. Thereafter, the PO increased by 20 W/min until the subject could no longer maintain the required PO (44). RPE and perceived pain were recorded every minute (8). The researcher gave verbal encouragement throughout each MIE. Peak PO (POmax) was defined as the highest PO attained during the MIE.

*Time trials.* Each participant returned to the laboratory on two more separate occasions to perform a 10-mile TT. The first TT was completed within 7 days of the MIE. These TT were separated by 2–7 days to allow the participant full recovery and were completed at the same time of day (~2 h). Before each TT, participants were asked to refrain from drinking alcohol (48 h abstinence) or caffeine (8 h abstinence) and instructed not to perform any exhaustive exercise in the 48 h preceding the TT. Participants were also asked to keep their preexercise meal the same. On entry to the laboratory, participants orally ingested either three (500 mg) capsules of acetaminophen (1.5 g total) (ACT) or a placebo control (PLA) (1.5 g dextrose). The capsules were administered in a randomized, double-blind design. After ingestion participants were given a period of 45 min during which they were allowed to sit quietly, stretch, or warm-up on their bike. This time period was chosen as peak plasma concentrations of acetaminophen occur 30–60 min after ingestion (27). Participants were asked to perform the same activities during this time in both conditions. TT commenced ~1 h following ingestion of the acetaminophen or placebo. For each TT a laptop computer was placed in front of participants, which displayed the Computrainer software program. Participants could see a computer-projected image of themselves, the distance that they had cycled, and the distance remaining on a continuum scale. Each TT began with a starting stand after a numerical countdown appeared on the computer screen. Participants were given no indication of completion time and received no feedback on performance during or after either TT. A fan was positioned in front of the participants throughout testing. The Computrainer ergometry system continuously recorded PO, speed, and time. $\dot{V}O_2$ and HR were recorded continuously as previously described. Blood lactate concentration (B[La]) was measured halfway through and 4 min after (End B[La]) completion of each condition. A fingertip blood sample was taken using an automated lancet (Hemocue, Angelholm, Sweden) and then immediately analyzed for B[La] with an YSI 2300 Stat Plus Analyzer (Yellow Springs Instruments). In both conditions, participants were asked their RPE and perceived pain for every kilometer completed of the TT. On completion of both conditions and following a debriefing all participants stated that they could not tell the difference between the administered capsules on ingestion.

**Perceived pain.** A category-ratio scale was used to assess perceived pain during conditions (11). This scale uses 0–10 scores, accompanied by verbal descriptors (“no pain at all” to “extremely intense pain”). An option to select a number above 10 (“unbearable pain”) is available when necessary. This scale has been shown to be a reliable and valid measure of pain during cycling exercise (11). Before testing, participants were given an introduction to and explanation of the pain scale.

**Statistical analysis.** Descriptive data are presented as means ± SD. Due to the lack of previous literature investigating acetaminophen during exercise, two studies using similar methods and dependent variables were selected to provide power calculations (7, 34). It was estimated that a sample size of ~14 was required to achieve a statistical power of 80% at an alpha level of 0.05 (37). Differences in completion time, mean PO, B[La], $\dot{V}O_2$, and HR were assessed using a one-way ANOVA and appropriate Student’s paired t-tests. Values for mid-$\dot{V}O_2$ and mid-HR were taken during the first 30 s of the 8th kilometer in each TT and were calculated as a percentage of $\dot{V}O_{2peak}$ and maximum HR recorded during the MIE test. Values for end-$\dot{V}O_2$ and end-HR were taken during the final 30 s of the final kilometer and were calculated as a percentage of $\dot{V}O_{2peak}$ and maximum HR recorded during the MIE test. Changes in PO, RPE, and pain over each condition were examined using a two-way ANOVA with repeated measures. For analysis of PO, the first 1.5 km was not included in the ANOVA to accommodate for the part of the riders pacing strategy which, according to Ulmer (43), would not be dictated by afferent feedback due to “lag-time” associated with the onset of exercise. The 95% confidence intervals were calculated for completion time, mean PO, B[La], and HR for each condition. PO was recorded every 10 s in each condition, and averaged for every half-kilometer completed to create the graphed PO profiles. Statistical tests were conducted using SPSS version 15.0 (Chicago, IL), and significance was accepted when $P < 0.05$.

**RESULTS**

**Completion time.** A significant difference in completion time between conditions was found ($t_{12} = 2.54$, $P < 0.05$) (95% CI of the difference = 4.3–55.8), with participants completing the TT in significantly less time during the ACT condition (26 min 15 s ± 1 min 36 s) than during the PLA condition (26 min 45 s ± 2 min 2 s), as shown in Fig. 1.

**Power output.** A significant difference in the mean PO (MPO) achieved by participants between conditions was observed ($F_{1,12} = 4.79$, $P < 0.05$) (95% CI of the difference =
In the ACT condition participants rode at a higher MPO (265 ± 12 W, 95% CI = 239–292 W) than in the PLA condition (255 ± 15 W, 95% CI = 222–287 W) (see Fig. 2). Paired-samples t-tests showed a significant difference in PO between the ACT and PLA conditions during the 7th kilometer ($t_{12} = -2.6, P < 0.05$) (95% CI of difference = -44.5 to -1.0) and the 10th kilometer ($t_{12} = -2.2, P < 0.05$) (95% CI of difference = -37.2 to -3.3).

**Blood lactate, $\tilde{V}_O_2$, and heart rate.** Group mean data are shown in Table 1. A significant difference in B[La] between conditions was found ($P < 0.05$), with participants reaching a greater B[La] concentration in the ACT condition than in the PLA condition. A significant difference in mid-HR between conditions was observed ($P < 0.05$), with a higher percentage of maximum HR reached in the ACT condition. No significant differences between conditions were observed for end-B[La], mid-$\tilde{V}_O_2$, end-$\tilde{V}_O_2$, or end-HR ($P > 0.05$).

**Rating of perceived exertion and perceived pain.** No significant difference between conditions was observed for RPE ($F_{1,12} = 0.71, P > 0.05$), and no interaction in RPE scores over time between each condition was found ($F_{15,180} = 1.26, P > 0.05$). There was no significant difference between conditions for perceived pain ($F_{1,12} = 1.30, P > 0.05$), and no interaction in pain scores over time between conditions was observed ($F_{15,180} = 0.15 = P > 0.05$) (Fig. 3).

**DISCUSSION**

The purpose of this study was to ascertain whether the ingestion of 1.5 g of acetaminophen would influence completion time, physiological responses, perceived exertion, and perceived pain during a 10-mile TT. It was hypothesized that the ingestion of acetaminophen would improve the completion time of the TT through the reduction of perceived exertion and pain. Our principal and novel finding was that after ingestion of acetaminophen, TT completion time was reduced, but in the absence of any reduction in perceived pain or perceived exertion. This is an important finding as it confirms the previously unsupported suggestion that acetaminophen can be used as an ergogenic aid in sport. This practice is prevalent in a number of sports, particularly cycling and sprinting (17), and the present findings suggest this could be beneficial to performance. Despite the incidence of acetaminophen use among athletes, to our knowledge this is the first study to directly test its effects on self-paced exercise performance.

The average of 2% (30 s) improvement in completion time observed in the ACT condition appears to be the result of a significantly reduced drop in PO during the middle section of the TT (see Fig. 2). This reduced drop in PO with the ingestion of ACT occurred alongside no change in perceived pain or exertion between conditions (see Fig. 3). It therefore appears that the ingestion of ACT before exercise allows an athlete to exercise at a greater intensity for the same level of perceived pain and exertion. Swart et al. (40) have previously shown that the amphetamine methylphenidate allowed cyclists to sustain higher work rates and greater levels of “metabolic and cardiorespiratory stress for longer,” while perceiving the exercise “stress” to be identical to a placebo condition. The authors concluded that methylphenidate allowed cyclists access to a “metabolic and cardiorespiratory reserve” that is normally prohibited by a CNS regulator. Although they could not pinpoint what change in the CNS “allowed” this access, it was surmised that methylphenidate altered the manner in which the central regulator interpreted afferent feedback from the homeostatic sensors in the body. In the present study, a similar effect...
on PO and perceived exertion was found. However, because acetaminophen is an analgesic rather than a stimulant and has no side effects that may alter exercise capacity, the change in performance observed in the present study can be solely attributed to the analgesic properties of acetaminophen. This finding provides support to the notion that pain tolerance is one of the possible variables that is utilized by a CNS regulator, or governor, to limit exercise intensity to prevent physiological harm. Acetaminophen presumably reinforced participants’ descending inhibitory pain pathways (35), thereby blunting the pain response to exercise. This would cause the putative CNS regulator to “think” that the physiological demands of exercise were less than they actually were, consequently allowing a higher work rate to be maintained [or access to a “metabolic reserve” (40)].

In addition to the improved completion time and increased PO associated with acetaminophen ingestion, a higher HR and an increase in B[La] was observed in the ACT condition. The observed increase in HR and B[La] is likely due to the energy supply from oxidative and nonoxidative sources being elevated as a consequence of the increased PO (23). The increased work rate and associated increase in HR and B[La], in the absence of increased effort or perception or pain, provides further evidence that during the placebo trial, participants were somehow prevented from, or were reluctant to, exercise at an intensity that was still within their physiological capacity. This conclu-

Table 1. B[La], VO$_2$, and HR in the ACT and PLA conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>B[La], mmol/l</th>
<th>End B[La], mmol/l</th>
<th>Mid-V$_O$2, %max</th>
<th>End V$_O$2, %max</th>
<th>Mid-HR, %max</th>
<th>End HR, %max</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACT</td>
<td>6.1 ± 2.9</td>
<td>7.1 ± 2.4</td>
<td>79 ± 9</td>
<td>94 ± 5</td>
<td>87 ± 7</td>
<td>95 ± 4</td>
</tr>
<tr>
<td>PLA</td>
<td>5.1 ± 2.6*</td>
<td>7.0 ± 2.4</td>
<td>76 ± 10</td>
<td>91 ± 6</td>
<td>84 ± 9*</td>
<td>93 ± 5</td>
</tr>
</tbody>
</table>

Values are means ± SD. B[La], blood lactate concentration; VO$_2$, oxygen consumption; HR, heart rate, ACT, acetaminophen; PLA, placebo. *Significantly different between ACT and PLA conditions (P < 0.05).

Fig. 3. Group mean rating of perceived exertion (RPE; A) and perceived pain (B) responses over both PLA and ACT time trial conditions. Participants showed a similar linear increase in RPE and perceived pain across both conditions that were not significantly different.
tion is in line with the study of Amann et al. (2). The absence of any significant change in \( \dot{V}O_2 \) between conditions, coupled with an increased B[La] in the ACT condition, indicates that the performance improvement observed was not due to a decrease in peripheral fatigue, but rather to an increased tolerance to a higher work rate. An interesting addition to this point is that on completion of both conditions the majority of participants revealed that they found the ACT condition “easier” or “better,” despite there being no difference in their recorded pain or RPE scores. As the participants were all highly trained cyclists, this may be due to their knowledge of the gearing and cadence selected (and thus PO).

Amann et al. (2) have previously shown that the injection of intrathecal fentanyl to impair cortical projection of opioid-mediated muscle afferents allowed cyclists to endure a higher development of peripheral locomotor muscle fatigue. However, in that study, no performance improvement was observed as the blocking of lower limb afferent feedback caused participants to induce peripheral muscle fatigue substantially beyond their “critical threshold” (1, 14). As a result, participants rode at a significantly higher PO during the first half of the TT, but a significantly lower PO during the second half of the TT in the fentanyl condition. The findings of the present study support the conclusions of Amann et al. (2) that central motor drive restricts the development of peripheral locomotor fatigue to an individual critical threshold, and that this level of restriction is at least partly based on muscle afferent feedback. It is interesting to note that in the present study, a performance improvement was associated with the attenuation of afferent feedback, whereas in the study of Amann et al. (2) it was not. This may be due to fentanyl attenuating ascending activity of nociceptive and metaboreceptive fibers below T1-T3 (peripheral action), whereas acetaminophen acted on serotoninergic descending pain pathways. The central action of acetaminophen therefore may have depressed the CNS perception of pain, whereas fentanyl simply prevented signals of pain from reaching the CNS. Therefore, acetaminophen may allow at least some level of interpretation of afferent feedback and pain to occur. This is reflected by the differences in pacing strategy adopted in the study of Amann et al. (2) and in the present study. In the fentanyl condition, participants adopted a highly aggressive positive pacing strategy (different from their control condition), whereas in the ACT condition in the present study, participants displayed a classic U-shape or linear pacing strategy that was similar to the PLA condition. The significantly higher PO in the first half of the fentanyl condition may have forced the adoption of a positive pacing strategy, due to significantly higher development of peripheral locomotor fatigue that could not be endured. The absence of this effect in the ACT condition of the present study suggests that after ingestion of acetaminophen some level of central regulatory system could be maintained. However, acetaminophen did reduce the restraint on central motor drive, allowing work rate to increase to a level that increased TT performance, but not to a point where peripheral fatigue developed such that PO was severely affected, as with fentanyl. Gandevia et al. (15) showed that in the complete absence of afferent feedback from the hand, participants could still complete simple motor tasks to the same level as when full feedback was available. This contrasting finding suggests that peripheral and central aspects of control may differ depending on the task and the muscle group.

The PO selected by participants in both conditions was very similar during the first 3–4 km of the TT. However, after this point, differences increased between the conditions, as illustrated by an average of 5% higher PO in the ACT condition between the 6th and 12th kilometer (see Fig. 2). This reduced drop in PO during the middle period of the trial is a finding that is consistent with Swart et al. (40), who observed that during a cycling exercise at fixed RPE, the amphetamine methylphenidate did not affect initial selection of PO but did cause PO to fall less rapidly following exercise onset. Ulmer (43), in his original proposition of teleoanticipation, identified a period of lag-time at the onset of exercise, where afferent feedback from the periphery is yet to reach, or be interpreted by, a central regulator. As a result, this initial pacing strategy at the start of an exercise bout is often different from the middle section, where a greater emphasis is placed on afferent feedback as an exercise regulator. In the present study, if a pacing strategy was set in an anticipatory and feedforward manner, then in the absence of afferent feedback the similar PO between conditions at the start of the TT is not unexpected. Once afferent feedback becomes a contributory factor to the regulation of a pacing strategy, differences in PO between the conditions become apparent. This is due to acetaminophen reducing the perception of pain for a given intensity, and therefore lessening the stringency of the central regulator, allowing exercise to continue at a higher level despite increased metabolic and cardiorespiratory demands. If the performance improvement elicited by acetaminophen is only apparent during the part of the exercise where afferent feedback is used as the primary information for exercise regulation, then the observed performance improvement is likely to be less clear in exercise of shorter duration but might be more pronounced in exercise of longer durations.

A further observation of the study is the unchanged RPE profile between conditions, despite changes in PO, completion time, B[La], and HR. RPE showed a linear increase in both conditions that was not found to be significantly different. This finding supports the main notion of the RPE-anticipatory model that RPE mediates pacing strategy (41) and that in self-paced exercise, RPE is scaled proportionally to the exercise time remaining (13).

Despite the observed improvement in performance produced by acetaminophen in the present study, previous research investigating the efficacy of analgesics in exercise has produced equivocal results. Garcin et al. (17) reported that the incidence of acetaminophen use among young subelite athletes was greater than that in the normal population, with the greatest use reported in sprinters and cyclists. Garcin et al. (16) found that young (age = 19 yr old), high-level athletes who consumed acetaminophen had a lower perceived exertion response at a running velocity at lactate turnpoint. The authors concluded that athletes may have consumed acetaminophen in an attempt to better tolerate the pain associated with training and competition. Although B[La] responses to exercise were not measured continuously in the present study, participants did cycle with greater blood lactate concentrations for the same level of pain in the middle section of the ACT condition, which is consistent with the results of Garcin et al. (16). The inges-
tion of aspirin (11, 24, 36) and various NSAIDs before, and following, exercise (19) has produced equivocal results. Differences between present and previous findings are likely to be due to differences in protocol or dose. However, the differing mechanism of action between different analgesics may influence their impact on exercise performance. This is particularly apparent when comparing the present study with that of Amann et al. (2). Future research should focus on isolating mechanisms of action for analgesics during exercise, as this will provide further insight into which afferent pathways are of primary importance for central regulation of exercise.

The use of pharmacological methods to reduce pain during exercise in an attempt to improve exercise performance raises a number of ethical concerns. Athletes who ignore pain, or are more tolerant to it through the ingestion of analgesics, are potentially at greater risk of injury, as pain may be an important warning of impending or actual tissue damage. Large or chronic doses of pain relief medication can also be dangerous, causing liver, kidney, and gastrointestinal damage (4, 27, 30). International and national sport organizations have banned many pain medications, yet several over-the-counter medications (such as acetaminophen) are not regulated. We wish to point out that we do not condone or recommend the chronic use of analgesics for the enhancement of athletic performance and stress the importance for a greater awareness among coaches and athletes of the potential dangers for the use of nonprescribed pain-relief medication in sport.

In conclusion, this study has shown that the ingestion of acetaminophen improves the performance of a 10-mile cycle TT through an increased PO, in the absence of a change in perceived pain or exertion. The 2% (30 s) improvement in TT performance is highly meaningful in performance terms in trained cyclists. We speculate that the increased tolerance of pain with acetaminophen allowed exercise intensity to be set closer to the actual physiological limit, or critical threshold (1, 14), which would otherwise be limited by a central regulator. These findings provide support for the notion that exercise is centrally regulated through the provision ofafferent feedback from the periphery and is, to the authors’ knowledge, the first study to provide evidence for a direct link between moderation of pain perception and an improved exercise performance.

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DISCLOSURES

No conflicts of interest are declared by the authors.

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