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Tramadol effects on physical performance and sustained attention during a 20-min indoor cycling time-trial: A randomised controlled trial

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ABSTRACT

Objectives: To investigate the effect of tramadol on performance during a 20-min cycling time-trial (Experiment 1), and to test whether sustained attention would be impaired during cycling after tramadol intake (Experiment 2).
Design: Randomized, double-blind, placebo controlled trial.
Methods: In Experiment 1, participants completed a cycling time-trial, 120-min after they ingested either tramadol or placebo. In Experiment 2, participants performed a visual oddball task during the time-trial. Electroencephalography measures (EEG) were recorded throughout the session.
Results: In Experiment 1, average time-trial power output was higher in the tramadol vs. placebo condition (tramadol: 220 W vs. placebo: 209 W; $p < 0.01$). In Experiment 2, no differences between conditions were observed in the average power output (tramadol: 234 W vs. placebo: 230 W; $p > 0.05$). No behavioural differences were found between conditions in the oddball task. Crucially, the time frequency analysis in Experiment 2 revealed an overall lower target-locked power in the beta-band ($p < 0.01$), and higher alpha suppression ($p < 0.01$) in the tramadol vs. placebo condition. At baseline, EEG power spectrum was higher under tramadol than under placebo in Experiment 1 while the reverse was true for Experiment 2.
Conclusions: Tramadol improved cycling power output in Experiment 1, but not in Experiment 2, which may be due to the simultaneous performance of a cognitive task. Interestingly enough, the EEG data in Experiment 2 pointed to an impact of tramadol on stimulus processing related to sustained attention.
Trial registration: EudraCT number: 2015-005056-96.

1. Introduction

There is an increasing tendency to treat minor sporting injuries with the use of analgesic drugs in order that an athlete is able to continue training and competing. One of these "trending" analgesics is tramadol that is an opioid agonist and is used in the treatment of moderate to severe pain. Tramadol has a dual mechanism of action, being both an μ-opioid receptor agonist, and a serotonin and norepinephrine reuptake inhibitor.[1] Activation of the μ-opioid receptor agonist can cause analgesia and sedation. Likewise, by inhibiting serotonin and norepinephrine reuptake, tramadol seems to reduce pain perception.[1] Given the negative association between pain and exercise capacity, the prophylactic use of analgesic medication (also known as "painkillers") is relatively common to reduce pain in order to enhance sport performance.[2] Similar to other painkillers,[3] it is therefore possible that tramadol could improve

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exercise performance via its effect on effort, pain perception, or mood. However, little is known about the effect of tramadol in sporting performance, with the literature being limited to non-athletic populations.[4] Of the limited research to date, results are conflicting with some suggesting beneficial effects of reduced pain perception and improved effort based exercise performance,[4] some reporting uncertain effects on cognitive function,[5] and some proposing a negative effect on cognitive function and chemosomatosensory evoked potentials.[6]

Informal reports from professional World-Tour cyclists and staff suggest that there may be some abuse of tramadol for potential performance enhancement reasons.[7] Indeed, results of a recent study involving young elite cyclist suggested that they identified tramadol as a potential doping agent.[8] Despite a significant media interest surrounding tramadol,[9] little is known of its ergogenic effect in cycling. Currently, tramadol is not included on the list of banned substances by the World Anti-Doping Agency (WADA) but, it is placed on WADA's monitoring program from 2012 to 2017 to detect potential patterns of abuse.[10] According to the WADA monitoring program, 71–82% of the tramadol use between 2012 and 2015 in globally monitored sports occurred in cycling.[11] Of particular concern is the drowsiness reported following tramadol administration, which could lead to reduced perception, attention and vigilance causing possible falls in the pro-cycling peloton.[12]

In this study, we aimed to test the potential ergogenic effect of tramadol during cycling, and whether it reduces sustained attention (i.e. the ability to keep focused on a particular task over the time). Sustained attention was investigated at the behavioural and brain level, by asking participants to perform a cognitive task while performing the cycling exercise and by recording electroencephalography (EEG). Specifically, we tested the hypothesis that acute oral administration of tramadol would improve 20-min cycling time-trial performance (Experiment 1). We hypothesised that information processing and behavioural responses in a sustained attention task would be influenced by tramadol during the 20-min time-trial (Experiment 2). Given the aforementioned effect of painkillers on perceptual variables,[3] we also investigated subjective measures of the participants' mood, perceived effort and mental fatigue. We hypothesised that tramadol would affect mood at rest and reduce perceived effort and fatigue during the 20 min TT.

2. Methods

The study involved a randomized, double blind, placebo controlled trial. The trial was approved by the Spanish Agency of Medicines and Medical Devices (AEMPS), EudraCT number: 2015-005056-96, and the Ethical Committee of Clinical Research in Granada. All experimental procedures were designed to comply with the Declaration of Helsinki and Good Clinical Practice (GCP). The randomization process, the audit and verification of compliance of GCP rules were performed by an external clinical research organization (CRO; Delos Clinical, Seville, Spain). The sample sizes were based on power calculations using G*Power Software[13] and assuming a 0.8 power and an alpha error of 0.05. Only cyclists and triathletes with a high-medium level of physical fitness were included in the study. Exclusion criteria were the presence of symptomatic cardiopathy, metabolic disorders such as obesity (BMI >30) or diabetes, chronic obstructive pulmonary disease, epilepsy, therapy with ß-blockers and medications that would alter cardiovascular function, hormonal therapy (and estrogen–progestogen contraception for females participants) and smoking. Participants were asked to refrain from drinking alcohol (48 h abstinence) and caffeine (24 h abstinence), to keep their pre-exercise meal the same, and not to perform any exhaustive exercise in the 48 h before each experimental visit.

In Experiment 1, we recruited 30 cyclists, 20 males and 10 females. Two participants could not complete Experiment 1: one male due to nausea and drowsiness after tramadol ingestion (approximately 90 min), and one female due to an ankle injury not related with the experiment. The final sample was 28 participants, 19 males and 9 females, (mean (SD) age 25.6 (5.9) years, weight 69.07 (10.3) kg; VO_{2max}: 49.17 (7.29) ml/min/kg for Experiment 1. For male participants, tramadol dose corresponded to 1.35 mg/BM, with a dose of 1.77 mg/BM given to females. Participants visited the research laboratory on three separate occasions at the Mind, Brain and Behaviour Research Centre of the University of Granada, firstly for an assessment of their cardiorespiratory fitness, with two further visits for the experimental manipulation. At initial visit participants performed a maximal incremental exercise test to establish their maximal oxygen uptake following a standard laboratory protocol.[14] During the test, participants' VO_2 was measured on a breath-by-breath basis using an online gas analyser (JAEGER MasterScreen; CareFusion GmbH, Germany). After completing the maximal incremental test, participants performed a 10-minutes time-trial in order to familiarised with protocol. The shorter duration of the familiarization test (with respect to the proper experimental time-trial) might be seen as a limitation of our study. However, two reasons motivated our choice: (1) our participants were experienced cyclists used to performing this type of (sustained) physical effort, and given their expertise, the purpose was that of familiarize them with the laboratory setting testing procedure, (2), we were mindful that the 10′ test was performed after the maximal incremental exercise test from which participants were already fatigued.

On arrival at the laboratory for visits 2 and 3 (Supplementary material Fig. S1 in the online version at DOI: 10.1016/j.jsams.2017.10.032 for protocol schematic), participants completed a Profile of Mood States Questionnaire (POMS), and a visual analogue scale (VAS) concerning perceived activation, mental and physical fatigue. After completing the questionnaires, participants consumed either tramadol or placebo as outlined below. The experimental sessions were completed at the same time of the day (±1 h). The time-trial commenced 120 min following ingestion of the tramadol or placebo capsule (*see experimental manipulation below*). Before the beginning of the time-trial, the participant's EEG was recorded as a baseline measure and throughout the session. Next, participants performed a 10 min warm-up at 100 W, followed immediately by a 20-min cycling time-trial on a cycle ergometer (SRM, Julich, Germany). Participants adjusted saddle and handle bar height and length, and it was kept for all sessions. The time-trial was conducted in a dimly-illuminated, sound-attenuated faraday cage. Convective cooling was provided by one fan (2.5 m/s wind speed) located 100 cm from the ergometer. Participants were instructed to maintain the highest average power possible during the time-trial and were freely able to change gearing and cadence throughout. Participants were aware of the elapsed time, but did not have feedback on performance (wattage and heart rate) during, or after the time-trial. Heart rate was measured continuously throughout the protocol (V800, Polar Electro, Finland). Immediately after the time-trial participants were asked to rate their average perceived exertion during the preceding exercise. Then, participants completed 10 min cool-down (60 W), following which another EEG recording was taken. Finally, the POMS and VAS were completed again.

As we did not find any effect of gender in Experiment 1, and given the difficulty of finding a large enough samples of females, we only recruited and tested males and in Experiment 2. One participant only completed visit 1, and data from another was removed due to data acquisition issues, meaning that the final sample for Experiment 2 was n = 28: age 25 (5) years, weight 73.2 (7.7) kg;

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