Tramadol Does Not Improve Performance or Impair Motor Function in Trained Cyclists

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ABSTRACT

BEJDER, J., A. BREENFELDT ANDERSEN, T. C. BONNE, J. F. PIIL, L. C. H. HAGEN, Y. DEHNES, K. H. EIBYE, L.NYBO, and N. B. NORDSBORG. Tramadol Does Not Improve Performance or Impair Motor Function in Trained Cyclists. *Med. Sci. Sports Exerc.*, Vol. 52, No. 5, pp. 1169–1175, 2020. **Purpose:** To investigate the hypothesis that a therapeutic oral dose of Tramadol improves cycling time trial performance and compromises motor-cognitive performance in highly trained cyclists. **Methods:** Following two familiarization trials, 16 highly trained cyclists completed a preloaded time trial (1 h at 60% of peak power followed by a 15-km time trial) after ingestion of 100 mg Tramadol or placebo in a double-blind placebo-controlled counterbalanced crossover design separated by at least 4 d washout. Visuomotor tracking and math tasks were completed during the preload ($n = 10$) to evaluate effects on cognition and fine motor performance. **Results:** Time trial mean power output (298 ± 42 W vs 294 ± 44 W) and performance (1474 ± 77 s vs 1483 ± 85 s) were similar with Tramadol and placebo treatment, respectively. In addition, there were no differences in perceived exertion, reported pain, blood pH, lactate, or bicarbonate concentrations across trials. Heart rate was higher ($P < 0.001$) during the Tramadol time trial (171 ± 8 bpm) compared with placebo (167 ± 9 bpm). None of the combined motor-cognitive tasks were impaired by Tramadol ingestion, in fact fine motor performance was slightly improved ($P < 0.05$) in the Tramadol trial compared with placebo. **Conclusions:** In highly trained cyclists, ingestion of 100 mg Tramadol does not improve performance in a 15-km cycling time trial that was completed after a 1-h preload at 60% peak power. Additionally, a therapeutic dose of Tramadol does not compromise complex motor-cognitive or simple fine motor performances. **Key Words:** PAIN, OPIOID, ENDURANCE, COGNITIVE, ATHLETES, EXERCISE

Frequent prescription and addictive use of opioids is a major general health concern (1,2). The extent of opioid medication in elite sport is unclear (3) but evident from antidoping analyses (4).

Concern has been raised that prescription opioids used either to treat injury or reduce pain may provide an unfair performance advantage. Additionally, harm to athletes may occur by compromising cognitive performance or suppressing signals that help maintain motor control which for example could cause crashes in cycling. Clinical doses of Tramadol have been shown to increase mean power output approximately 5% during 20 min maximal cycling in moderately trained males and females with an average maximal oxygen uptake (VO_{2peak}) of approximately 49 mL $O_2 \cdot min^{-1} \cdot kg^{-1}$ (5). Of concern for athlete health and sport integrity, the Union Cyclist International banned the use of Tramadol in cycling from March 2019 (6), whereas the World Anti-Doping Agency monitors the drug but has not yet banned the use (7). If Tramadol enhances athletic performance a general ban in sport must be considered. However, Tramadol's impact on human exercise performance has only been examined in moderately trained participants (5). In comparison, well-trained athletes exhibit a higher pain tolerance (8), possibly as a consequence of training (9). Moreover, training desensitizes μ-opioid receptors (10) and reduces sensitivity to morphine-induced analgesia (11). Therefore, whether opioids exerts performance enhancing effects in highly trained athletes is unknown.

Opioid side effects include dizziness, vomiting, nausea, somnolence, and constipation (12), which may increase the risk of accidents in sports like road cycling. Indeed, more attentional resources are allocated to a cognitive task during exercise although behavioral performance is unaffected when participants receive Tramadol (5). Thus, investigation of Tramadol's effect on motor-cognitive task performance and physical capacity appear to be of importance not only for professional cyclists but for all

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occupations and activities where altered attention may impose a risk.

Finally, detection of Tramadol is possible for 24 to 48 h after ingestion of 50 to 100 mg in untrained humans (13,14), but the detection remains unknown for highly trained subjects following exercise.

In the present study, 16 highly trained individuals completed a randomized double-blind placebo-controlled counterbalanced cross-over design to investigate the hypothesis that a therapeutic dose of Tramadol 1) increase mean power output during a 15-km cycling time trial and 2) compromises motor-cognitive task performance and 3) is detectable for 24 h in highly trained men.

PATIENTS AND METHODS

Sixteen males (ten cyclists, six triathletes) were enrolled in the study. Subjects were Caucasian, highly trained and non-smokers. Their characteristics are presented in Table 1. The participants competed at a national sub-elite and elite level. The local ethics committee of Copenhagen, Denmark approved the study (H-17028397), which was performed in accordance with the Declaration of Helsinki and registered on www.clinicaltrials.gov (NCT03934411). All subjects received oral and written information regarding potential risks and discomforts associated with participation before providing written informed consent.

Design

One screening and two familiarization trials were completed before execution of the randomized double-blind placebo-controlled counter-balanced cross-over trial (Fig. 1). Randomization was algorithm generated (www.randomizer.org). Participants ingested either 100 mg Tramadol (Tramadol Actavis, Actavis Group PTC ehf, Hafnarfirdi, Iceland), corresponding to (mean ± SD) 1.4 ± 0.2 $mg \cdot kg^{-1}$ bodyweight with a range of 1.1–1.9 $mg \cdot kg^{-1}$ bodyweight, or $CaCO_3$ placebo contained in visually indistinguishable capsules. Trials were separated by at least 4 d.

Experimental protocol. To maximize ecological validity, participants performed all testing on their own race bike, which was mounted in an electromagnetic braked resistance generator (Tacx Neo Smart; Tacx BV, Wassenaar, Holland) and controlled by commercially available software (Tacx Trainer Software v4; Tacx BV).

TABLE 1. Subject characteristics.

Age (yr)	26 ± 5
Height (cm)	181 ± 7
Weight (kg)	73 ± 9
$\dot{V}O_{2peak}$ (L $O_2 \cdot min^{-1}$)	4.61 ± 0.48
$\dot{V}O_{2peak}$ (mL $O_2 \cdot min^{-1} \cdot kg^{-1}$)	64 ± 6
Peak power (W)	404 ± 45
Endurance training history (yr)	6 ± 3
Endurance training volume ($h \cdot wk^{-1}$)	14 ± 4
Cycling distance ($km \cdot wk^{-1}$)	332 ± 141
Creatinine ($\mu mol \cdot L^{-1}$)	83 ± 11
Alanine aminotransferase ($U \cdot mmol^{-1}$)	24 ± 7

Values are means ± SD for $n = 16$, except for endurance training volume ($n = 15$) and cycling distance ($n = 12$).

The protocol is illustrated in Figure 1. Briefly, on day A, the highest 30 s average VO_{2peak} was determined from expired O_2 and CO_2 fractions and ventilation (Masterscreen CPX, CareFusion, Rolle, Switzerland) during exhaustive incremental cycling (6 min at 90 W, 6 min at 150 W followed by increments of 25 $W \cdot min^{-1}$). Peak power (PPO) was calculated as 25 W × $t/60 + P_{compl}$ (t, time at last work load before exhaustion (s); P_{compl}, last workload completed [W]). After the maximal test, familiarization to the 'testing protocol' was completed, which consisted of 6 min bouts at 90 W and 150 W, 5 min recovery and a preload (60 min at 60% of PPO), 5 min rest and a 15-km simulated time-trial including 2% inclines from 5.0 to 6.5 km and 10.5 to 12.0 km. Visual feedback of covered distance and current incline was provided. A large fan behind the subjects induced cooling. On day B, familiarization to the "testing protocol" was repeated. On day C and D the treatment was administered 90 min before initiating the preload to ensure a maximal analgesic effect (13) (see Table 2 for timing of the treatment). Oxygen uptake was determined at 6 to 8 min and from 58 to 60 min of the preload. Carbohydrate drinks (500 mL H_2O mixed with 47 g of High5 Energy Source, which per 100 g contain 94 g carbohydrate, including maltodextrin and fructose, and 510 mg Na^+) were administered during the preload (at 8–10 + 50–52 min, 1.5 $mL \cdot kg^{-1}$ bw; at 30–35 min, 3.0 $mL \cdot kg^{-1}$ bw) and water *ad libitum* was provided. At the midpoint and end of the preload as well as every 2nd km and at time trial finish, RPE (15) and quadriceps femoris pain (16) were assessed. Finally, blinding efficiency was evaluated by the Bang Blinding Index (17) by letting participants guess their treatment. The index ranges from −1 or 1, representing that all guessed false or true, respectively. If the 95% confidence interval (CI) of the index included null, treatment-arm blinding was interpreted as maintained. The subjects were instructed to refrain from caffeine and alcohol intake on the day of testing and to prepare similarly for all test days.

Blood and urine samples. Blood samples (<2 mL) were collected from an antecubital vein before, at the midpoint and end of the preload and the time trial in all subjects. Lactate, pH, bicarbonate (HCO_3^-), glucose, K^+, and Na^+ concentrations were determined on an ABL 800 blood gas analyzer (Radiometer; Brønshøj, Denmark) in duplicate.

Urine was collected from 10 participants before and after the "testing protocol" as well as at 6 and 24 h after treatment. Collected urine was stored at −20°C until analysis at the World Anti-Doping Agency accredited Norwegian Doping Control Laboratory. A volume of 0.5 mL of urine was added to an internal standard solution (50 µL, 1 $ng \cdot \mu L^{-1}$ d_6-Tramadol (Alsachim, C404, France) prior to liquid-liquid extraction in tert-butyl methyl ether (pH 8–8.3). The organic phase was evaporated and derivatized by adding MSTFA:NH4I:etanthiol (1000:2:6) and heated for 20 min at 65°C to 75°C. For urine samples with high concentrations of Tramadol, the analysis was repeated with a reduced urine volume (50 or 25 µL) to obtain measurements within the linear range of the validated method.

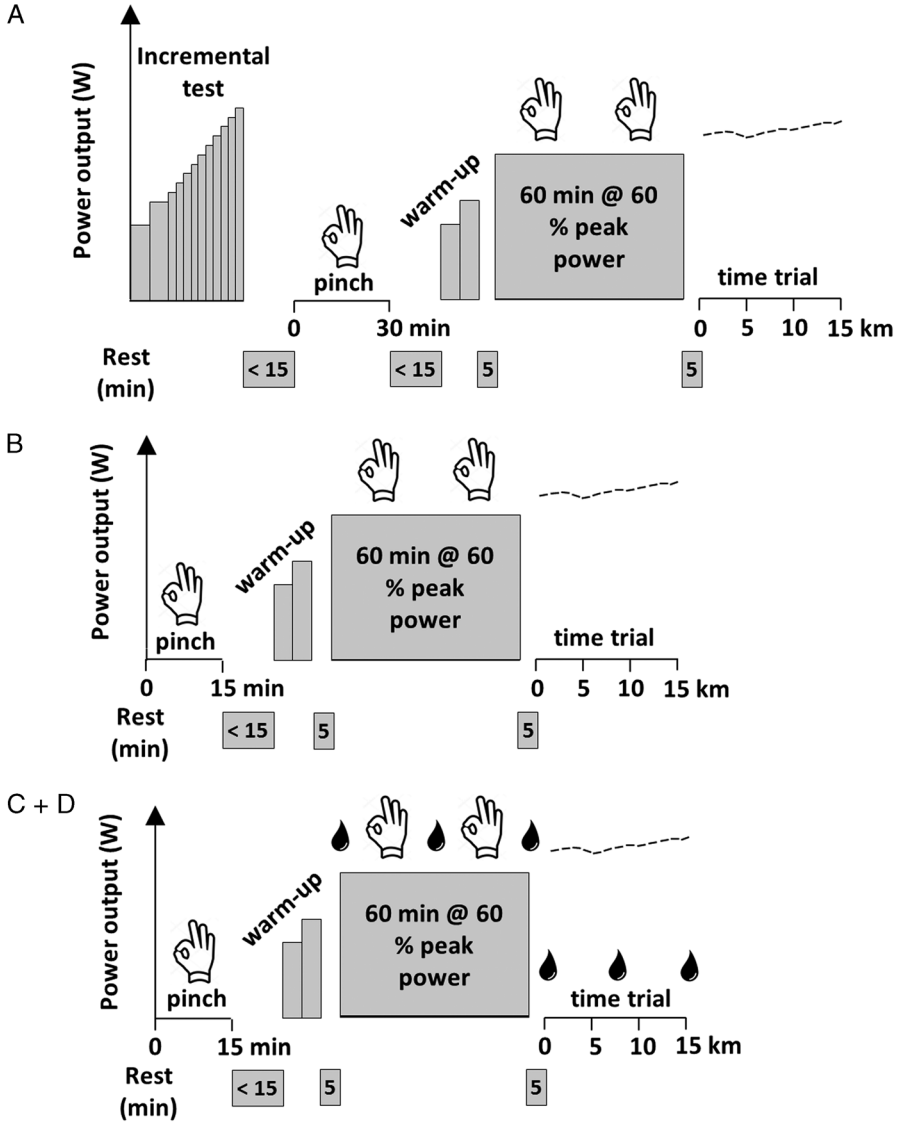

FIGURE 1—Illustration of the testing procedures at days A, B, C, and D. The *y*-axis represents power output and the *x*-axis the timeline. The hand indicates performance of the motor-cognitive tasks, and the blood drop indicates blood sample collection.

Standard stock solutions containing Tramadol (Fluka Chemie GmbH, Switzerland) or d_6-Tramadol were prepared in methanol, and intermediate Tramadol solutions were made by spiking blank urine with the stock solution. Calibrators (n = 6, from 5 to 2500 ng·mL^{-1}) and quality control samples were prepared by spiking blank urine with intermediate Tramadol solutions.

Concentrations of Tramadol were analyzed by gas chromatography-tandem mass spectrometry (GC-MS/MS). The GC-MS/MS quantification was performed using the 7890A GC coupled to the G7000 B mass detector (Agilent Technologies, Santa Clara, CA). The separation was carried out on a BPX5 column (0.25 mm × 15 m, 0.25 µm) (SGE Analytical Science, Melbourne, Australia), with helium as carrier gas. A volume of 1 µL of derivatized sample was injected using pulsed split less mode at 280°C. The column temperature program was increased from 160°C to 200°C at 8°C·min^{-1}, then at 30°C·min^{-1} to 310°C, and held for 3 min. The mass spectrometer was operated in multiple reaction monitoring. Monitored precursor/product ion pairs were m/z 335.2 > 58.0 (CE15), 335.2 > 84.0 (CE25), and 335.2 > 210.1 (CE5) for Tramadol, and m/z 341.2 > 64.0 (CE15) and 341.2 > 90.0 (CE25) for d6-Tramadol.

Tracking protocol. The 10 subjects providing urine samples also completed a motor-cognitive test protocol that was adapted from a previously developed method and has been

TABLE 2. Timing and laboratory conditions.

	Tramadol	Placebo
Time of day for ingestion (hh:mm)	11:12 ± 02:33	12:07 ± 02:53
Time from ingestion to preload (min)	96 ± 10	94 ± 6
Time from ingestion to time trial (min)	162 ± 9	159 ± 6
Laboratory temperature (°C)	23.0 ± 0.9	23.1 ± 1.2
Laboratory humidity (%)	39 ± 15	37 ± 14

Timing of Tramadol and placebo ingestion and the duration from ingestion to testing as well as laboratory conditions. Values are means ± SD for n = 16.

described in detail elsewhere (18). In brief, four tasks performed on a computer monitor constituted the protocol. Task 1: the subject applied a pinch force to a strain gauge transducer with the thumb and index finger, thereby adjusting the vertical position of a cursor moving with constant horizontal speed across the monitor to hit and stay within five target boxes. Tasks 2 and 3: four random numbers (from 1 to 25) appear in each corner of the monitor and the subject calculated the sum of the numbers and typed the result (task 2) or pinched/adjusted the force (task 3). Task 4: a random target force was displayed and the subject attempted to pinch the target force with aid of visual feedback. Each task lasted for 12 s and a performance score appeared following each task. A 3-s break separated each task.

A sequence consisted of task 1 followed by task 2 or task 3 and finished with task 4. In total, 160 sequences were completed during familiarization with 80 being during the preload. At the experimental days subjects completed 20 warm-up sequences before the cycling protocol and 20 sequences from min 10 to 25 and min 35 to 50 during the preload. The average score of the two preload pinch periods for each task was used as outcome. During the preload the subjects were able to reach the transducer with the thumb and index finger and a numpad while resting on the handlebar. The front fork of the bike was mounted on a stabilizing construction to eliminate the normal rocking of the handlebars during cycling. The subject sat on a chair for sequences not performed during the preload.

Statistics. Analyses were performed by a linear mixed model approach (19). Fixed factors were "treatment," "period," and "treatment–period" for variables with no temporal measurements, whereas "time" and "time–treatment" were added as fixed factors for variables with temporal measurements. Subject identified repeated measures and defined a random factor. Significant main effects were further analyzed by a *post hoc* analysis with Sidak adjusted pairwise comparison. The level of significance was set at $P > 0.05$ and analyses completed in SPSS (IBM SPSS Statistics, v. 25). The results are presented as means ± SD.

The coefficient of variance of the time trial test was calculated by dividing the SD of the differences between results of the second familiarization day and the placebo treatment day.

RESULTS

No significant effect of period (day C vs day D) was observed. The Bang Blinding Index was 0.50 (95% CI, 0.08–0.92) and 0.88 (95% CI, 0.64–1.11) for the Tramadol and placebo treatment arm, respectively, demonstrating an unsuccessful blinding.

1-h submaximal effort. Preload mean power output and heart rate was similar in the Tramadol (245 ± 26 W, 148 ± 10 bpm) and the placebo (244 ± 27 W, 147 ± 10 bpm) trials. Likewise, no significant time–treatment interaction existed for blood and pulmonary variables (Table 3) or RPE and pain assessment (Fig. 2) during the preload.

Time trial. The coefficient of variance was 2.5% for 15-km time trial mean power. Mean power output (298 ± 42 W vs 294 ± 44) and performance (1474 ± 77 s vs 1483 ± 85 s) was similar ($P = 0.19$ and $P = 0.22$, respectively) with Tramadol and placebo treatment, respectively. However, mean heart rate after Tramadol treatment was higher ($P < 0.001$) than during placebo (171 ± 8 bpm vs 167 ± 9 bpm, respectively). No significant time–treatment interactions were apparent for blood variables (Table 3), ratings of perceived exertion and pain assessment (Fig. 2), or mean power per kilometer during the 15-km time trial (Fig. 3). There was a tendency ($P = 0.094$) that existed for a time–treatment effect for venous blood lactate, where pairwise analysis demonstrated a difference ($P < 0.01$) at 7.5 km (9.1 mM vs 7.0 mM) and 15 km (11.3 mM vs 9.8 mM) between Tramadol and placebo, respectively.

Motor-cognitive tasks. The average score for task 1 (62% ± 8% vs 60% ± 7%) and task 4 (95% ± 1% vs 94% ± 1%) was higher ($P < 0.05$) with Tramadol than placebo treatment,

TABLE 3. Pulmonary and venous blood values.

Preload		$\dot{V}O_2$ (mL·min^{-1})	RER	VE (L·min^{-1})			
Start of preload	Tramadol	3.34 ± 0.36	0.92 ± 0.03	78.20 ± 9.91			
	Placebo	3.37 ± 0.40	0.93 ± 0.03	83.09 ± 9.53			
End of preload	Tramadol	3.58 ± 0.37	0.90 ± 0.03	84.20 ± 11.10			
	Placebo	3.54 ± 0.44	0.90 ± 0.04	87.67 ± 11.31			
Preload		**pH**	**Lactate (mmol·L^{-1})**	**HCO_3^- (mmol·L^{-1})**	**Glucose (mmol·L^{-1})**	**K^+ (mmol·L^{-1})**	**Na^+ (mmol·L^{-1})**
Pre	Tramadol	7.363 ± 0.024	1.2 ± 0.6	27.2 ± 2.0	4.7 ± 0.8	4.2 ± 0.2	140 ± 2
	Placebo	7.359 ± 0.026	1.2 ± 0.6	27.4 ± 1.6	4.6 ± 0.7	4.2 ± 0.4	141 ± 2
30 min	Tramadol	7.376 ± 0.022	3.0 ± 1.5	24.0 ± 1.9	5.2 ± 0.8	4.9 ± 0.7	142 ± 2
	Placebo	7.386 ± 0.017	2.5 ± 1.2	24.2 ± 1.5	5.2 ± 0.6	4.8 ± 0.3	143 ± 2
60 min	Tramadol	7.352 ± 0.061	2.7 ± 1.7	24.5 ± 1.9	5.1 ± 0.6	5.1 ± 0.7	143 ± 3
	Placebo	7.384 ± 0.026	2.4 ± 1.3	24.2 ± 2.1	5.1 ± 0.7	4.8 ± 0.6	143 ± 2
Time Trial		**pH**	**Lactate (mmol·L^{-1})**	**HCO_3^- (mmol·L^{-1})**	**Glucose (mmol·L^{-1})**	**K^+ (mmol·L^{-1})**	**Na^+ (mmol·L^{-1})**
Pre	Tramadol	7.335 ± 0.026	2.1 ± 1.3	25.1 ± 2.7	5.8 ± 0.7	4.2 ± 0.3	141 ± 3
	Placebo	7.374 ± 0.031	1.9 ± 0.9	25.5 ± 2.1	5.8 ± 0.7	4.3 ± 0.3	141 ± 3
7.5 km	Tramadol	7.319 ± 0.072	9.1 ± 3.1	17.5 ± 3.3	4.7 ± 0.8	5.3 ± 0.3	144 ± 2
	Placebo	7.364 ± 0.047	7.0 ± 3.5	19.2 ± 3.9	4.3 ± 0.8	5.1 ± 0.4	145 ± 3
15 km	Tramadol	7.269 ± 0.090	11.3 ± 3.5	17.2 ± 3.3	4.9 ± 1.1	5.5 ± 0.4	145 ± 3
	Placebo	7.302 ± 0.077	9.8 ± 3.5	18.1 ± 4.1	4.7 ± 1.0	5.4 ± 0.4	146 ± 3

Pulmonary and venous blood values collected during the preload and the time trial following Tramadol and placebo treatment. Values are means ± SD for $n = 16$.

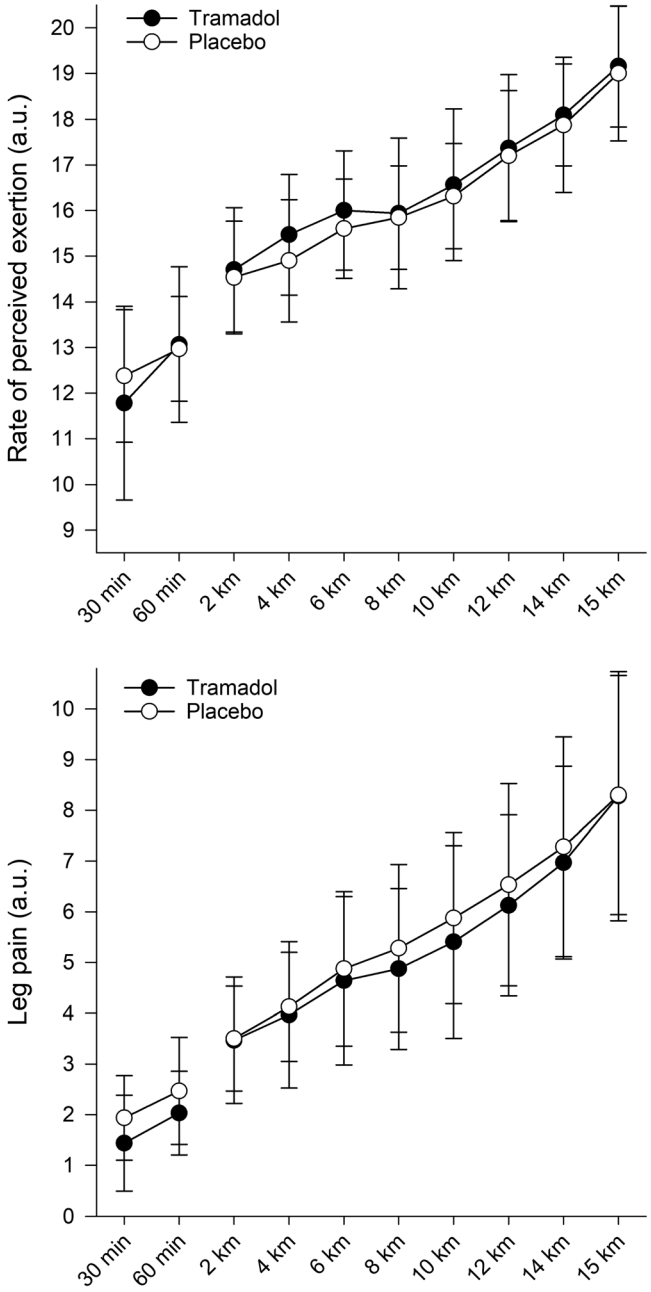

FIGURE 2—Rate of perceived exertion (A) and leg pain (B) measured 30 and 60 min into the preload as well as every second kilometer and at the end of the time trial during Tramadol and placebo treatment. Values are means and error bars indicate one SD.

respectively, while the scores for task 2 (98% ± 2% vs 98% ± 3%) and task 3 (92% ± 6% vs 91% ± 7%) were similar following the two treatments.

Tramadol concentration. The average urine concentration of Tramadol was below limit of quantification prior to administration, but Tramadol was detectable in all subjects immediately, 6 and 24 h after administration with average concentrations of 22,238 ± 14,424 ng·mL^{-1}, 28,700 ± 16,929 ng·mL^{-1}, and 1946 ± 1794 ng·mL^{-1}, respectively. All urine samples collected during the placebo trial had a concentration of Tramadol below the limit of quantification.

DISCUSSION

The major finding of the present study was that ingestion of 100 mg Tramadol does not increase mean power of highly trained cyclists in a 15-km cycling time trial after a 1-h submaximal effort in a randomized, double-blind, placebo-controlled, counterbalanced cross-over design. Furthermore, ingestion of 100 mg Tramadol does not impair the ability to complete certain cognitive and fine motor task performance during submaximal exercise. Finally, ingestion of 100 mg Tramadol is detectable in urine for 24 h in highly trained men.

Time trial performance. Our results demonstrate that mean power output during a 15-km cycling time trial after a 1-h submaximal effort is similar following ingestion of 100 mg Tramadol compared with placebo. In contrast, the only other study to investigate Tramadol's effect on time trial performance in healthy subjects demonstrated a 5% increase in mean power output during 20 min of maximal cycling (5). A major difference is the approximately 15-mL $O_2 \cdot min^{-1} \cdot kg^{-1}$ higher $\dot{V}O_{2peak}$ in the present study. The difference provides a possible explanation for the discrepancy, as athletes in general possess a higher pain tolerance than normally active controls (8) and chronic exercise can decrease the sensitivity of μ-opioid receptors (10) and morphine's analgesic properties (11). It should be noted that 9 out of 28 subjects were females in the study by Holgado et al., which to some extent may explain the lower average $\dot{V}O_{2peak}$ compared with the present study. Additionally, the females ingested an approximately 30% larger dose Tramadol (mg·kg^{-1}), but as no differences between genders was observed (5) it appears that the larger dose cannot explain the discrepancy. Also, the present study applied a 50-min longer preload compared with Holgado et al. (5). Indeed, prolonged preloaded time trials are highly reproducible (20) and resembles the metabolic demand during competition (21). Thus, the applied protocol in the present study must be considered to more closely reflect the physical and psychological demands of competition than a protocol with only a

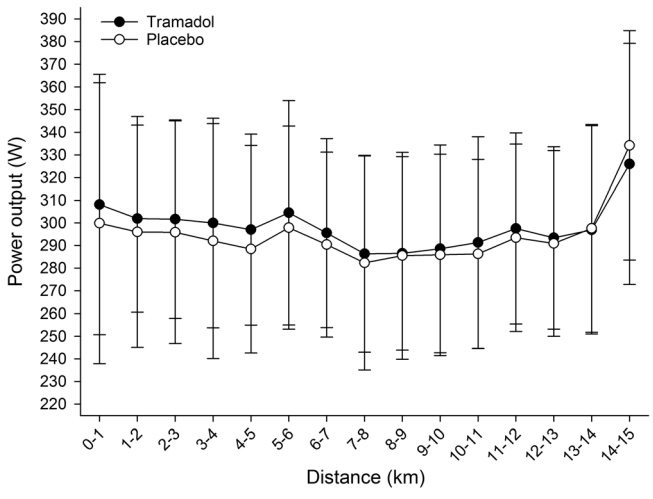

FIGURE 3—Mean power output per km of the 15-km time trial during Tramadol and placebo treatment. Values are means and error bars indicate one SD.

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brief warm-up. However, the impact of the different preloads on the treatment effect remains speculative. Other studies investigating analgesics observe a similar pain perception during exercise despite a higher power output (22,23), indicating an efficient treatment. However, pain perception was similar between treatments in the present study during the preload and time trial despite a similar power output, supporting the hypothesis that the Tramadol treatment was inefficient. Finally, it should be noted that Holgado and colleagues did not include a familiarization test (5), which complicate the interpretation. The present study applied $CaCO_3$ as placebo treatment, which may act as a buffer. However, venous pH, lactate and bicarbonate was similar between treatments preexercise (Table 3), demonstrating that the applied amount does not provide an effective buffering.

The conclusion that 100 mg Tramadol does not improve time trial performance in highly trained cyclists is also supported by the similar blood pH, lactate and HCO_3^- concentration (Table 3) and pacing strategy (Fig. 3) between treatments. In contrast, the heart rate was 4 bpm higher during the Tramadol time trial, which combined with a tendency for augmented blood lactate concentration following Tramadol treatment indicate a shift in metabolism possibly related to a small and undetected increase of exercise intensity at some point during the Tramadol time trial. The CV for time trial mean power output was 2.5%, corresponding to approximately 7 W. However, assuming that Tramadol and placebo has similar effects based on our results, the calculated CV between days C and D was 1.8% or approximately 5 W. The lower CV between days C and D is likely a result of additional familiarization from day B to C. This demonstrate that if we by chance identified a false-negative result, the undetected positive effect of Tramadol would be less than 5 W. If a postexperiment power analysis is calculated using the SD of the differences obtained from the second familiarization and placebo trial, inclusion of 16 subjects allow a detection of a 7.6-W change with alpha = 0.05 and power > 0.8 and a change of 5.7 W is detectable using SD of the differences obtained from the placebo and tramadol trial. Notably, the previously demonstrated increase of 5% or 11 W with Tramadol treatment (5) is well above the present detection limit. Importantly, the unsuccessful blinding did not compromise the findings as there was no treatment effect of Tramadol.

Figure 3 indicates numerical differences between placebo and tramadol mean power output in the beginning and at the end of the time-trial but no significant time–treatment interaction for mean power existed. Nevertheless, an exploratory analyses based on paired t-testing for each time-point indicated that mean power output was higher in the last kilometer in the placebo trial (see Table, Supplemental Digital Content 1, mean power output for each kilometer segment of the time trial in the tramadol and placebo trial, http://links.lww.com/MSS/B840). Thus, a small undetected effect on pacing strategy may have existed. However, the conclusion is unaffected since the possible undetected difference is small and in favor of placebo treatment for performance.

Treatment side effects. All subjects were able to complete all trials, but three subjects reported nausea during the time trial and vomited immediately upon completion in the Tramadol trial. Exclusion of those subjects result in significant ($P < 0.05$) treatment effect with the *post hoc* analysis revealing a higher ($P < 0.05$) mean power (297 ± 43 W vs 290 ± 44 W) following Tramadol compared with placebo treatment, respectively. This indicate that highly trained cyclists ingesting 100 mg Tramadol can improve time trial performance if side effects are absent. Despite the increased mean power, exclusion of the subjects did not result in a significant time–treatment effect for blood lactate ($P = 0.07$), RPE ($P = 0.99$) or pain ($P = 0.77$) levels, with the last two being in accordance to previous studies demonstrating an improved exercise performance following acetaminophen treatment (5,22).

One subject experiencing negative side-effects during the time trial also completed motor-cognitive testing. However, the subject did not report negative side-effects during the motor-cognitive testing, indicating that the results are unaffected by the side-effects. Additionally, it was not possible to identify a variable with a unique level, for example, treatment dose relative to body mass or $\dot{V}O_{2peak}$, indicating why the three subjects experienced negative side-effects.

Motor-cognitive performance. Complex and simple visuomotor performance (tasks 1 and 4, respectively) improved during exercise at a submaximal intensity after Tramadol compared with placebo treatment, but no difference was observed during math solving tasks (tasks 2 and 3). The latter is in accordance with a recent study finding a similar cognitive performance following Tramadol and placebo treatment during a cycling time trial (5), although electroencephalography measures indicated that more attentional resources were allocated to achieve a similar cognitive performance with Tramadol treatment (5). However, limited evidence exist regarding the motor-cognitive performance effects of Tramadol in healthy humans. The conclusion that a therapeutic oral dose of Tramadol does not impair motor-cognitive performance is supported by studies on recreational drugs users (24) and opioid-dependent volunteers (25,26) demonstrating that ingestion of 50 to 100 mg and 50 to 400 mg Tramadol, respectively, does not impair psychomotor performance.

Detection of tramadol in urine. The present study demonstrates that ingestion of 100 mg Tramadol is detectable in urine for at least 24 h in highly trained subjects following exercise with a detection rate and specificity of 100%. Similarly, ingestion of 50 to 100 mg Tramadol is detectable in plasma for 24 to 48 h (13,14). Thus, the detection window for Tramadol appear sufficient for antidoping purposes, as the analgesic effect is expected to be negligible 24 h after ingestion.

CONCLUSIONS

Ingestion of 100 mg Tramadol as compared with placebo does not improve mean power output in a 15-km time trial performance after a 1-h submaximal effort in highly trained male cyclists. Further, the ability to complete certain cognitive and fine motor performance tasks is not impaired by ingestion of

100 mg Tramadol. Future research should clarify whether minimizing side-effects associated with Tramadol intake may result in improved performance.

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Competing interests: None declared.

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