Acute ibuprofen ingestion does not attenuate fatigue during maximal intermittent knee extensor or all-out cycling exercise

Original investigation

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Running title: Influence of ibuprofen on skeletal muscle fatigue

Abstract word count: 250 words

Text-only word count: 5031 words

Disclosure of funding: This research was not supported by any funding body external to University of Exeter

ABSTRACT

Purpose: Recent research suggests that acute consumption of pharmacological analgesics can improve exercise performance, but the ergogenic potential of ibuprofen (IBP) administration is poorly understood. This study tested the hypothesis that IBP administration would enhance maximal exercise performance. **Methods**: In one study, 13 physically active males completed 60 × 3-s maximum voluntary contractions (MVC) of the knee extensors interspersed with a 2-s passive recovery period, on two occasions, with the critical torque (CT) estimated as the mean torque over the last 12 contractions (part A). In another study, 16 active males completed two 3-min all-out tests against a fixed resistance on an electrically-braked cycle ergometer with the critical power (CP) estimated from the mean power output over the final 30-s of the test (part B). All tests were completed 60 min after ingesting maltodextrin (placebo, PL) or 400 mg of IBP. Peripheral nerve stimulation was administered at regular intervals and electromyography was measured throughout. **Results**: For part A, mean torque (IBP: 60±12 vs. PL: 58±14% of pre-exercise MVC) and CT (IBP: 40±15 vs. PL: 41±16% of pre-exercise MVC) were not different between conditions (P>0.05). For part B, end-test power output (IBP: 292±28 W vs PL: 288±31 W) and work done (IBP: 65.9±5.9kJ vs PL: 65.4±6.4kJ) during the 3-min all-out cycling tests were not different between conditions (all P>0.05). For both studies, neuromuscular fatigue declined at a similar rate in both conditions (P>0.05). **Conclusion**: Acute ingestion of 400 mg IBP does not improve single-leg or maximal cycling performance in healthy humans.

Key words: Electromyography; neuromuscular fatigue; non-steroidal anti-inflammatory drugs; single leg exercise; whole-body cycling exercise

INTRODUCTION

Ibuprofen (IBP), a non-steroidal anti-inflammatory drug (NSAID) predominantly used to treat pain and reduce inflammation and fever, is considered safe for oral ingestion within healthy populations at the standard therapeutic dose (Albert & Gernaat, 1984; García-Martín et al. 2004). Consequently, utilisation of analgesic (i.e., pain relieving) and anti-inflammatory medication, such as IBP, has emerged as a popular pre-competition strategy in elite athletes attempting to enhance athletic performance (Alaranta et al. 2008; Corrigan & Kazlauskas, 2003; Da Silva et al. 2015; Gorski et al. 2011; Huang et al. 2006). It is believed that NSAIDs act centrally and peripherally to reduce the perception of pain and tissue inflammation, respectively (Friden & Lieber, 1992). The therapeutic effect of NSAIDs in treating inflammation and pain has largely been ascribed to inhibited synthesis of prostaglandins (i.e. PGE_2, Friden & Lieber, 1992). Specifically, IBP limits the metabolism of arachidonic acid, a precursor for the synthesis of prostaglandins, by inhibiting the enzyme, cyclooxygenase (Albert & Gernaat, 1984).

Following the onset of muscle contractions, changes in contraction-induced mechanical stimuli and noxious chemicals (including an increased PGE_2 release) activate and/or sensitise molecular receptors located on the terminal end of group III and IV nerve fibers, contributing to an increased sensation of muscle pain during exercise (O'Connor & Cook, 1999; McCord & Kaufmann, 2010; Pollak et al. 2014). The activation of these receptors appears to play a role in neuromuscular fatigue development through modulating both central and peripheral fatigue. Indeed, when the ascending projection of group III and IV muscle afferents is attenuated via intrathecal fentanyl administration, central motor drive is increased (as inferred via electromyography, EMG) and peripheral fatigue development is expedited (Amann et al. 2009, 2011; Blain et al. 2016). Therefore, it is possible that an intervention that is able to

reduce the magnitude of afferent feedback, such as NSAID administration, may attenuate the decline in skeletal muscle activation during intense exercise and thus improve exercise performance (Amann & Calbet, 2008; Morgan et al. 2018a; Morgan et al. 2018b). Indeed, elevating the magnitude of muscle afferent feedback is known to impair endurance exercise capacity (i.e. Amann et al. 2013).

Acute consumption of analgesics (e.g. acetaminophen, ACT) has been shown to improve exercise performance (Foster et al. 2014; Mauger et al. 2010; Morgan et al 2018a; Morgan et al. 2018b). Mauger et al. (2010) administered an acute dose of 1.5 g ACT to trained cyclists and reported a 2% improvement in 16.1-km time-trial (TT) performance. Moreover, an acute dose of ACT has been shown to improve exercise tolerance in the heat (Mauger et al. 2014), repeated sprint performance (Foster et al. 2014), repeated maximal voluntary contraction (MVC) performance of the knee extensors (Morgan et al. 2018a) and maximal cycling performance (Morgan et al. 2018b). However, while these studies suggest that oral administration of a commercially-available pharmaceutical analgesic can delay fatigue development and improve exercise performance (Foster et al. 2014; Mauger et al. 2010; Morgan et al 2018a, b), the ergogenic effects of IBP are unclear despite widespread use of IBP as a putative performance aid (Cleak, & Eston. 1992; Nosaka & Clarkson, 1996).

In contrast to the effects of ACT consumption on exercise performance, there is currently very limited published research on NSAID and NSAID-like compounds during exercise when muscle damage is not present. Despite the prevalence of its use amongst athletic populations, it is unclear whether IBP will provide an ergogenic benefit to performance in a ‘fresh’ state. Other NSAID-like compounds have elicited no ergogenic effect on endurance performance (e.g., aspirin, Cook et al. 1997; ginger, Black & O’Connor, 2008). In contrast,

enhanced aerobic exercise performance following caffeine ingestion has been related, at least in part, to altered pain perception and enhanced endurance performance (e.g., Gonclach et al. 2016). In addition, whilst exercise has been shown to increase PGE_2 release (Trappe et al. 2001; Novak & Wennmalm, 1979; Wilson & Kapoor, 1993; Vinikka et al. 1984), the extent to which it plays an important role, especially following interventions aimed at reducing PGE_2 synthesis, during endurance exercise in the absence of muscle damage is unclear.

The purpose of this study was to test the hypotheses that, compared to a placebo, acute consumption of 400 mg IBP would increase total work done, and reduce the rate of fatigue development by enabling a better maintenance of muscle activation during exercise. Two studies are presented using two different types of exercise: a 5-min single-leg intermittent MVC test and a 3-min maximal whole body cycling test to provide a more comprehensive understanding of the ergogenic potential of IBP.

MATERIALS AND METHODS

Participants

Two independent groups of thirteen recreationally-active males (mean ± SD: age 31 ± 7 years, height 1.76 ± 0.08 m, body mass 75 ± 11 kg), and sixteen recreationally-active males (mean ± SD: age 29 ± 9 years, height 1.79 ± 0.07 m, body mass 77 ± 8 kg, $\dot{V}O_{2peak}$ 60.8 ± 7.8 $ml \cdot kg^{-1} \cdot min^{-1}$), volunteered for the first (A) and second (B) part of this study, respectively. All participants provided written, informed consent to participate in this study, which was approved by the Sport and Health Sciences Ethics Committee at the University of Exeter. After being informed of the experimental procedures and associated risks, all participants completed a medical health questionnaire to ensure it was safe for them to consume IBP prior to performing exhaustive exercise, due to the potential contraindications associated with IBP

ingestion. Participants were not consumers of any 'pain relief' or anti-inflammatory medication (prescription or non-prescription) over the course of the study. None of the participants had a history of motor or neurological disorders. Participants were instructed to arrive at the laboratory in a rested and fully hydrated state, at least 3 h post-prandial, and to avoid strenuous exercise and refrain from consuming caffeine and alcohol in the 24 h preceding each testing session. Participants were also instructed to consume their habitual diet and continue normal training activities for the experimental period. For part A and B, participants recorded their diet and physical activity for 7 d prior to the first experimental visit and then replicated this for all remaining experimental visits.

Experimental Design

Both protocols (part A and B) followed identical experimental designs to previous research conducted within our laboratory (Morgan et al. 2018a, 2018b). For part A (Morgan et al. 2018a), participants visited the laboratory on three occasions over a 3-4 week period with tests being conducted on an isokinetic dynamometer (Biodex System 3, Shirley, NY, USA). For part B (Morgan et al. 2018b), participants visited the laboratory on five occasions over a 5-6 week period and tests were conducted on an electronically braked cycle ergometer (Lode Excalibur Sport, Groningen, the Netherlands). Experimental tests were separated by at least 7, but no more than 9, days (part A) and for at least 72 h (part B), and were completed at a similar time of day (± 90 mins). The first laboratory visits for each study were used to familiarise participants to the measurements and experimental protocols described below. Subsequently, participants performed the fatiguing protocol (s) under two conditions *(see 'Experimental Protocol')*: placebo (PL) and IBP.

Experimental Protocol A (60 MVC protocol)

124 The isokinetic dynamometer was initially adjusted so that the axis of rotation of the lever arm
125 was in line with the lateral epicondyle of the right femur. Participants were seated with the
126 hip and knee joints at relative angles of 155° and 90°, respectively. The remainder of the
127 chair settings were recorded (during familiarisation) and replicated in all subsequent tests to
128 ensure identical body position throughout the experimental trials. Inelastic padded Velcro
129 straps were fastened at the ankle, quadriceps, hip and shoulders to maintain a stable body
130 position.
131
132 Following the familiarisation trial, visits 2 and 3 were completed in a double-blind,
133 randomised fashion using a cross-over experimental design. 1000 mg of maltodextrin
134 (placebo) or 400 mg IBP (combined with 600 mg maltodextrin) was ingested orally, 60
135 minutes prior to the exercise bout such that the start of the exercise trial was expected to
136 coincide with peak plasma [ibuprofen] concentration (Janssen & Venema, 1985). For IBU, 2
137 identical capsules containing 200 mg ibuprofen and 300 mg maltodextrin each were ingested.
138 The placebo was made from dextrose powder inserted into 2 gelatine capsules (500 mg in
139 each capsule) designed to have a similar appearance and the weight to IBU capsules. The
140 trials started with a standardised isometric warm-up routine (10 isometric contractions for 3 s
141 at 50% of pre-exercise MVC as measured during familiarisation testing) and testing of the
142 optimal EMG electrode, anode, and cathode placement and stimulation intensity for
143 peripheral nerve stimulation. The experimental protocol consisted of 60 brief MVCs (3 s
144 contraction, 2 s rest), in response to a visual prompt to ‘go’ and ‘relax’, accompanied by the
145 same verbal instructions from the experimenter. Every 6th contraction was accompanied by
146 peripheral nerve stimulation during and 1 s post MVC (as described for pre-trial
147 measurements below). Participants were not made aware of the time or the number of MVCs

148 that had elapsed during the protocol and were instructed to continue to perform maximal
149 contractions throughout.
150
151 *Experimental protocol B (3-min cycling test)*
152 For the 3-min cycling protocol, participants initially completed an incremental ramp test to
153 exhaustion for the determination of gas exchange threshold (GET), linear factor, peak aerobic
154 power output and peak oxygen uptake $\dot{V}O_{2peak}$ as previously described (Black et al. 2014;
155 Morgan et al. 2018b). The fixed resistance for the 3-min cycling protocol was set using the
156 linear mode (i.e. linear factor) of the ergometer such that on reaching their preferred cadence,
157 the participants would achieve a power output equivalent to 50% of the difference between
158 GET and $\dot{V}O_{2peak}$ (linear factor = 50%Δ peak aerobic power output/preferred cadence^2).
159 During this visit, the seat and handlebar positions were adjusted for comfort and replicated
160 for all tests. During the second and third laboratory visits, participants completed a 3-min all-
161 out test with these serving as familiarization trials to the experimental protocol as described
162 below and to ensure the coefficient of variation for work done and critical power (CP)
163 between visits was <1%. Participants then performed the 3-min all-out cycling test under two
164 conditions: placebo (PL) and IBP.
165
166 The experimental protocol consisted of a 3-min period of unloaded pedalling at each
167 participant's preferred cadence (85-100 rpm), followed by a 3-min all-out sprint, 60 min
168 following ingestion of either placebo (1000 mg maltodextrin) or 400 mg of IBP. The order of
169 trials on visits 4 and 5 were administered in a double-blind, randomised fashion using a cross-
170 over experimental design. The 3-min all-out cycling protocol used in this study replicated the
171 procedures described previously by Vanhatalo et al. (2007, 2008).
172

Neuromuscular function (Parts A and B)

For part A and B, neuromuscular function was assessed pre-, during- and post-trial (< 10 s). Single peripheral nerve stimulation pulses were manually triggered at rest to determine pre-exercise neuromuscular function, namely the characteristics of the M-wave response (M-wave amplitude; M_{max}) to supra-maximal nerve stimulation, voluntary activation (for part A only) and potentiated twitch torque (pTw, for part A only). During MVCs, peripheral nerve stimulation pulses were triggered to occur as soon as a peak torque was achieved (typically 1.5 s into a 3 s contraction) and were each separated by a 45 s rest period. The stimuli were also delivered 1-s after the cessation of the contraction to provide a resting pTw. Identical measurements were repeated as soon as possible (< 10s) after the fatiguing exercise to determine post-exercise neuromuscular function (see figure 1).

Torque (Part A)

For part A, knee-extensor torque from the Biodex isokinetic dynamometer was sampled at 1000 Hz and low-pass filtered at 40 Hz, before being displayed on a wide screen monitor using Spike2 (CED, Cambridge, UK). Torque was expressed throughout as a percentage (%) of initial pre-exercise MVC.

Breath-by-breath pulmonary gas exchange (Part B)

For the 3-min maximal cycling protocol, participants wore a face mask connected to an impeller turbine transducer assembly (Cortex Metalyzer, Cortex, Leipzig, Germany). Inspired and expired gas volume and concentration signals were continuously sampled at 100 Hz. The analyser was calibrated before each test with gases of known concentration, and a calibration syringe of known volume (3-L; Hans Rudolph, KS).

198 *Electromyography (Parts A and B)*

199 For parts A and B, surface EMG activity was recorded from *m.*vastus lateralis, *m.*vastus
200 medialis and *m.*rectus femoris of the quadriceps and *m.*biceps femoris of the hamstring of the
201 right leg using active bipolar bar electrodes in a single differential configuration (DE2.1,
202 DelSys Inc, Boston, MA, USA). The electrodes were placed over the respective muscle
203 bellies (SENIAM guidelines). Double-sided adhesive tape and a hypoallergenic medical tape
204 were used to ensure the EMG sensor stability. The skin area underneath each EMG electrode
205 was shaved, then exfoliated and cleaned with alcohol to minimise the skin impedance. The
206 EMG and torque signals were pre-amplified (1,000 x), band-pass filtered (20–450 Hz,
207 Bagnoli-8, DelSys Inc, Boston, MA, USA), and then transferred to a computer with a
208 sampling frequency of 2 kHz and high-pass filtered at 10 Hz. EMG and torque data were
209 recorded continuously and digitised synchronously with 16 bit resolution via an A/D
210 converter (±5 V range, CED 1401 power, Cambridge, UK). EMG was average rectified using
211 the root mean square method (EMG_{RMS}). EMG_{RMS} was then normalised to the pre-exercise
212 maximum (or maximal EMG signal) and the local M-wave amplitude (closest time point
213 measure of the M-wave) in order to exclude any changes to the EMG trace to changes in
214 local excitability. The ground electrode was placed over the patella of the right leg.

215

216 *Peripheral Nerve Stimulation (Parts A and B)*

217 Electrical stimulation was applied with a constant current stimulator (Digitimer Stimulator
218 DS7A, Digitimer, UK) for the assessment of M-waves (parts A and B) and potentiated twitch
219 force (part B). M-waves were elicited by supramaximal percutaneous electrical stimulation of
220 the femoral nerve (200 μs duration). The cathode was placed over the femoral nerve in the
221 inguinal fossa, approximately 3–5 cm below the inguinal ligament in the femoral triangle.
222 The cathode was systematically moved vertically and horizontally and the amplitude of the

muscle action potential (i.e. M-wave) was monitored to identify the optimal position of the cathode for attaining maximal peak-to-peak M-wave amplitude. Once the M-wave was elicited, the maximum amplitude (peak-to-peak) of the M-wave was determined (M_{max}) for the vastus lateralis and vastus medialis. To determine the stimulation intensity, single stimuli were delivered in 20 mA step-wise increments from 100 mA until a plateau in quadriceps pTw (part A only) and M-wave were observed. To ensure a supramaximal response, the current was increased by an additional 30% (mean ± SD current = 214 ± 66 mA; 251 ± 46 mA, part A and B, respectively). The average M_{max} was obtained from 3 stimuli, with ~8-10 s separating each pulse at rest. For the 3-min maximal cycling protocol, single peripheral nerve stimulation pulses were manually triggered at 'rest' (defined as 80 rpm at 20 W) to determine pre-exercise neuromuscular function. Initially, the crank angle at which peripheral nerve stimulation was to be delivered during the trials was determined for each subject as described by Black et al. (2014) and as performed by Sidhu et al. (2012). Peripheral nerve stimulation pulses were triggered to coincide with maximal muscle activation around the crank cycle (typically around 50-60º from top-dead centre) 3 times, randomly, during a 10 s period using a custom written sequencer script. Identical measurements were repeated every 30 s in the all-out sprint.

Data Analyses

Data were analysed using a custom written script developed in Spike2 software (CED, Cambridge, UK). For part A, mean torque for each 3 s contraction during the 60 MVC protocol was determined as the mean value over a 1-s period which approximated the plateau level of the highest torque (i.e. 500 ms before and after the peak torque). The pTw was calculated as the peak torque achieved following the single pulse delivered 1-s post-MVC. The twitch torque superimposed onto the peak force production of the MVC (sTw) was

248 calculated as the increment in torque immediately following the pulse during MVCs. The
249 end-test torque (i.e. critical torque, CT) during the 60 MVC test was defined as the mean of
250 the last 12 contractions (i.e., the last 60 s; Burnley, 2009; Morgan et al. 2018a). The torque-
251 impulse was calculated as the area under the torque-time curve by accumulating the time
252 integral of each MVC (3 s).
253
254 Voluntary activation (VA, %) was calculated using the interpolated twitch method from
255 peripheral nerve stimulation (Merton, 1954; Goodall et al. 2010). Specifically, the increment
256 in torque evoked during the MVCs was expressed as a fraction of the amplitude of the
257 potentiated twitch produced with the same stimulus in the relaxed muscle post-MVC. The
258 level of voluntary drive was then quantified as a percentage: [1 – evoked torque
259 (superimposed on voluntary torque, sTw)/ (mean control evoked response, pTw) × 100] (i.e.,
260 Allen at al. 1998). The changes in voluntary torque and pTw, were used to assess global
261 fatigue and peripheral fatigue, respectively with VA, M_{Max} and EMG_{RMS} used to assess
262 central fatigue. The maximal EMG was taken from the first MVC during the 60 MVC task
263 and compared to the last MVC at task end. The neuromuscular parameters extracted from the
264 three sets of maximal contractions completed post-exercise were tested for statistical
265 differences between sets of contractions and then compared to the first set of MVCs
266 completed pre-exercise (Froyd et al. 2013; Pageaux et al. 2015; Doyle-Baker et al. 2017).
267 Neuromuscular function was also measured for each of the stimulated contractions during the
268 exercise and normalised to the corresponding pre-exercise values at 100% MVC.
269
270 For the 3-min cycling protocol (part B), the end-test power (i.e. CP) during the 3-min test was
271 defined as the mean of the last 30 s (Vanhatalo et al. 2007; 2008). The W' was calculated as
272 the area above the CP from the power-time curve. Power output was recorded second-by-

second, and the peak power was determined as the highest 1-s value. The changes in power output, M_{Max} and EMG_{RMS}, were used to quantify neuromuscular fatigue development and changes in muscle activation. Peak $\dot{V}O_2$ was determined as the highest value recorded in a 15-s interval. The achievement of $\dot{V}O_{2peak}$ was an essential criterion for a valid 3-min test. All neuromuscular parameters and torque were averaged across the protocol using 30-s bin averages.

Statistics

Paired-samples *t*-tests were used to compare the mean torque, total work done, CT, W′ and pTw between IBP and PL in part A. In addition, paired-samples *t*-tests were used to compare the total work done, CP, W′ and cardiorespiratory responses between IBP and PL obtained from the 3-minute maximal cycling test. For the 60 MVC test, the profiles of VA and M-wave amplitude were analysed using two-way ANOVAs with repeated measures (using 12 contraction averages; i.e. 6 time points). In addition, a two-way ANOVA with repeated measures (condition × work rate) was used to assess differences in end exercise $\dot{V}O_2$ and the profiles of EMG and M-wave amplitude. Normalised EMG_{RMS} were analysed using two-way ANOVAs with repeated measures using 30-s means (i.e. 10 time points). Where sphericity was violated, Greenhouse-Geisser correction factor was used. For all tests, results were considered statistically significant when $P<0.05$. Data are presented as means ± SD unless otherwise indicated. All statistical analyses were conducted using IBM SPSS Statistics version 23.

RESULTS

Part A (60 MVC test)

297 The mean MVC torque achieved prior to the 60 MVC protocol was 232 ± 47 and 230 ±
298 55 N.m for PL and IBU, respectively. VA of the knee extensors achieved during the
299 preliminary MVCs was 88 ± 7 and 89 ± 6% for PL and IBU, respectively. Baseline MVC and
300 VA were not different between conditions (P>0.05). The profile for mean torque during each
301 contraction across all participants for the 60 MVC protocol is illustrated in figure 2a. During
302 the PL trial, torque declined from a peak of 99 ± 3% MVC (relative to pre-exercise MVC)
303 during the first contraction to 40 ± 15% MVC during the last 12 contractions (*P*<0.01, Table
304 1, figure 2a). During the IBP trial torque declined from a peak of 99 ± 3% to 41 ± 16% MVC.
305 The mean torque (relative to pre-exercise MVC) achieved across the 60 MVCs not different
306 with IBP (60 ± 13%, 87.1 ± 22.2 N.m,) compared to PL (58 ± 14%, 83.8 ± 22.7 N.m,
307 *P*=0.39). There was no difference in CT (PL: 40 ± 15% vs. IBP: 41 ± 16%. *P*=0.74), W′ (PL:
308 6.97 ± 2.43 vs. IBP: 7.23 ± 3.57 N.m.s; *P*=0.69) or total impulse, the surrogate measure of
309 total work done (PL: 22,055 ± 3,885 vs. IBP: 22,919 ± 3,394 N.m.s; *P*=0.26) between the PL
310 and IBP conditions.
311
312 *Part A (Neuromuscular Function)*
313 Alongside the decline in voluntary force (figure 2a), pTw (figure 3a), VA (figure 3b),
314 EMG_{RMS} (figure 3c) and M_{Max} (figure 3d) were also reduced as protocol A progressed (main
315 effect of time, all *P*<0.01). There were no differences between PL and IBP in pTw, VA,
316 EMG amplitude or M-wave amplitude at any time point (all *P*>0.05). pTw declined from 63
317 ± 14 to 30 ± 21 N·m and from 68 ± 17 to 31 ± 23 N·m, VA declined from 89 ± 8 to 59 ± 19%
318 and from 88 ± 7 to 60 ± 18%, EMG declined from 99 ± 4 to 59 ± 17% and 100 ± 2 to 64 ±
319 20% (from first 6 to last 6 contractions) and M-wave amplitude declined from 100 ± 1 to 96 ±
320 14% and 100 ± 1 to 95 ± 12% in the PL and IBP conditions, respectively (*P*<0.05), with no
321 differences between PL and IPB for any of these variables (*P*>0.05).

Part B (3-min cycling test)

The mean power output profile for all participants during the 3-min all-out cycling test is shown in figure 2b for the PL and IBP conditions. During the PL trial, power output declined from 820 ± 139 W to 288 ± 31 W during the last 30 s of the 3-min test (P<0.01; table 1, figure 2b). During the IBP trial, power output declined from 816 ± 131 W to 292 ± 28 W during the last 30 s of the 3-min test. There were no differences in CP (PL: 288 ± 31 vs. IBP: 292 ± 28 W, P=0.11), total work done (PL: 65.4 ± 6.4 vs. IBP: 65.9 ± 5.9 kJ, P=0.11) or W′ (PL: 13.6 ± 2.4 vs. IBP: 13.7 ± 2.8 kJ, P=0.84) between conditions.

Part B (Neuromuscular Function)

Similar to the 60 MVC protocol, alongside the decline in power output, there was a progressive decline in M-wave (P<0.01, figure 4b) and EMG amplitudes (P<0.01, figure 4a). The profiles of the M-wave and EMG amplitudes were not altered following IBP ingestion at any time point (both P>0.05). Using 30 s mean values, EMG decreased from 94 ± 4 to 54 ± 17% and from 96 ± 6 to 57 ± 14% (figure 4b) in PL and IBP, respectively.

DISCUSSION

Contrary to our experimental hypotheses, the principal findings of this study were that acute ingestion of 400 mg of IBP in a ‘fresh’ state had no effect on fatigue development or neuromuscular function during either a 5-min single-leg intermittent MVC test or a 3-min maximal cycling test. Across both protocols, power output and torque declined, and neuromuscular fatigue was evident in both the IBP and PL conditions. However, there were no differences in CT or CP, total work done or neuromuscular fatigue markers between the

IBP and PL conditions. These findings do not support the acute ingestion of IBP as a strategy to blunt fatigue development during exercise in healthy, recreationally active adults.

Effects of acute IBP ingestion on exercise performance

In contrast with our previous findings of improved CT and CP following the acute ingestion of ACT (Morgan et al. 2018a; Morgan et al. 2018b), these variables were not improved in the current study following the acute ingestion of IBP. However, our findings in the current study are in line with some previous observations that IBP ingestion does not improve performance during whole body exercise in humans (e.g., Cleak, & Eston. 1992; Da Silva et al. 2015; Nosaka & Clarkson, 1996; Tokmakdis et al. 2003). Previous studies that have reported improved exercise performance following IBP administration have typically assessed exercise performance following muscle damage. Nonetheless, while there is some evidence to suggest that the increases in muscle soreness, pain, damage and contractile dysfunction after contraction-induced muscle damage can be attenuated following NSAID administration (Ebbeling & Clarkson, 1989; Hasson et al. 1993; Pizza et al. 1999; Tokmakdis et al. 2003), there is also evidence that NSAID administration does not impact these variables after muscle damage is induced (Da Silva et al. 2015; Tokmakdis et al. 2003). Taken together, these observations suggest that the ergogenic potential of administering IBP, a purported analgesic and anti-inflammatory agent (Friden & Lieber, 1992), is limited without prior induction of muscle damage, and even when muscle damage is induced, and inflammation and pain sensation are correspondingly increased, the effect of IBP ingestion on exercise performance is equivocal.

One explanation for the lack of performance improvement following IBP ingestion in our study may be the reduced ability to regulate the distribution of effort (i.e., pacing strategy) in

371 the maximal protocols employed in response to a potential modulation of pain. For example,
372 Mauger et al. (2010) reported that pain` sensation was reduced (i.e., a greater power output
373 was possible for the same pain sensation) and cycling time trial performance was enhanced
374 following ingestion of ACT. Similarly, Gonglach et al. (2016) reported that manipulating
375 pain perception via caffeine ingestion lead to higher power outputs when participants were
376 asked to pace their effort based upon pain perception. Therefore, we cannot exclude the
377 possibility that IBP consumption could be ergogenic in situations wherein pacing strategy is
378 self-selected such as during longer duration endurance exercise.
379
380 Another possible explanation for the absence of an ergogenic effect of IBP in our study is that
381 inhibiting cyclooxygenase may induce secondary effects that may limit the cardiopulmonary
382 response to exercise (Takayama et al. 2002) including a reduction in exercise-induced
383 hyperaemia (Bradford et al. 2007; Scharage et al. 2004). If skeletal muscle perfusion was
384 impaired following IBP ingestion as a function of cyclooxygenase inhibition (Albert &
385 Gernaat, 1984), this could have negated any potential ergogenic effects following IBP
386 ingestion. However, given that performance was not enhanced during either smaller (single-
387 leg exercise) or larger (double leg cycling) muscle mass exercise following acute IBP
388 ingestion in the current study, and that skeletal muscle perfusion is less likely to be a limiting
389 factor for performance in a single leg model (Joyner & Casey, 2015), this seems unlikely.
390
391 ***Effects of acute IBP ingestion on neuromuscular function***
392 The ingestion of 400 mg of IBP was not associated with attenuation of neuromuscular fatigue
393 development as estimated with peripheral muscle excitability (part A and B), voluntary
394 activation (part A), potentiated twitch (part A) or EMG amplitude (part A and B), consistent
395 with the lack of change in exercise performance. We previously investigated the influence of

acute ingestion of 1 g of ACT on neuromuscular function during exercise and reported that, whilst EMG declined across the 3-min cycling protocol in both conditions, EMG declined to a lesser extent in the ACT (~72 %) compared to the PL (~54 %) condition (Morgan et al. 2018b). The magnitude of this effect was remarkably similar to the results we obtained during a 60 MVC protocol completed in a single leg exercise model (ACT: 87% vs. PL: 59 %, Morgan et al. 2018a). This observation suggests that improved maintenance of muscle activation contributed to the ergogenic effect of ACT (Morgan et al. 2018a). It is of interest, therefore, that similar effects were not evident following IBP ingestion. We are not aware of any research to suggest that ACT acts as a more potent stimulus to reduce pain sensation or alter muscle activation. However, it is possible that a combination of the higher ACT dose administered (1000 mg vs 400 mg for IBU), ACT's potential as an antipyretic (Foster et al. 2014) and differences in pharmacokinetics (Anderson, 2008; Albert & Gernaat, 1984) may have contributed to the disparate effects of IBP in our current study and ACT in our previous studies (Morgan et al. 2018a; Morgan et al. 2018b) on exercise performance and neuromuscular fatigue development. It is also pertinent to note that ACT ingestion has been reported to increase corticospinal excitability at rest, a factor which may contribute to its ergogenic potential (Mauger & Hopker, 2013).

Experimental considerations

Whilst our study contributes to a further understanding of the effect of IBP on exercise-induced fatigue and some of its underlying mechanisms, there are some limitations that require consideration. Firstly, it is acknowledged that we did not measure pain sensation or biomarkers of inflammation. Pain was not assessed due to the protocols requiring the completion of maximal exercise. Asking participants to rate pain sensation may have compromised their ability to focus on the exercise task and to provide a true maximal effort.

The effect of IBP on exercise performance when pacing is permitted, and the individual can adjust their pacing strategy in response to potential differences in pain sensation, warrants further investigation. In addition, the extent to which prostaglandin synthesis during endurance exercise plays a role in pain perception in the absence of muscle damage requires further consideration. It is also important to point out that individuals intending to ingest IBP need to consider its potential side effects and be aware that it could impair the adaptive response to exercise (Schoenfield, 2012) and aspects of the beneficial remodelling of skeletal muscle to exercise training (Mikkelsen, 2009). Therefore, individuals wishing to explore the use of pain relievers to enhance exercise performance should do so infrequently, with caution, and at the recommended therapeutic doses.

Conclusion

Acute ingestion of IBP did not attenuate the decline in neuromuscular function or improve CT or CP during a 60 MVC protocol of the knee extensors or a 3-min maximal cycling test. Therefore, our results indicate that IBP ingestion does not attenuate neuromuscular fatigue development, during either single-limb or whole-body cycling exercise, and do not support IBP ingestion as an ergogenic aid.

Conflict of interest

The author declares that there is no conflict of interest regarding the publication of this article.

Author contribution

P.T. Morgan, A. Vanhatalo, A.M. Jones and S.J. Bailey conceived and designed the research. P.T. Morgan conducted all experiments. J.L. Bowtell provided assistance with pilot testing prior to experimental data collection as well supporting data analysis. P.T. Morgan wrote the manuscript. J.L. Bowtell, A. Vanhatalo, A.M. Jones and S.J. Bailey helped supervise the project throughout. All authors contributed to the interpretation of results and read, edited and approved the manuscript.

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668 **Tables**

Table 1: Performance and neuromuscular function parameters of the 60 MVC (protocol A) and 3-min all-out cycling (protocol B) tests following placebo and ibuprofen ingestion.

	Placebo (PL)	**Ibuprofen (IBU)**
Protocol A		
Performance		
Peak MVC (N.m)	232 ± 47	230 ± 55
Mean torque (% MVC)	58 ± 14	60 ± 13
Total Impulse (N.m.s)	22055 ± 3885	22919 ± 3394
Critical torque, CT (% MVC)	40 ± 15	41 ± 16
W' (N.m.s^{-1})	6971 ± 2432	7231 ± 3570
Neuromuscular function		
Change in pTw (N.m)	44 ± 27	43 ± 25
End-exercise pTw (N.m)	30 ± 21	31 ± 23
End-exercise VA (%)	59 ± 19	60 ± 18
End-exercise M-wave amplitude (%)	96 ± 14	95 ± 12
End-exercise EMG amplitude (%)	59 ± 17	64 ± 20
Protocol B		
Performance		
Peak power output (W)	820 ± 139	816 ± 131
Total Work Done (kJ)	65.4 ± 6.4	65.9 ± 5.9
Critical power, CP (W)	288 ± 31	292 ± 28
W' (kJ)	13.6 ± 2.4	13.7 ± 2.8
Neuromuscular function		
End-exercise M-wave amplitude (%)	84 ± 21	83 ± 18
End-exercise EMG amplitude (%)	54 ± 17	57 ± 14

MVC, maximal voluntary contraction; CT, critical torque measured in the last 6 contractions; CP, critical power measured in the last 30 s of the 3-minute maximal cycling test; pTw, potentiated twitch force; VA, voluntary activation measured using the interpolated twitch method technique; EMG, electromyography; N.m, newton metres; N.m.s-1, newton metres per second; ms, milliseconds.

669 **Figure captions**

670 *Figure 1*

671 Schematic of the procedures used prior to (panel a), during (panel b) and within 10 s
672 following (panel c) the 60 maximal isometric voluntary contraction (MVC) protocol. 10 s
673 separated each single pulse stimulation administered at rest (small dashed arrows). A, C 45 s
674 rest period separated maximal efforts (MVCs). Single pulse stimuli were administered during
675 peak force production of MVCs (large solid arrow) and immediately (<1-s) post MVCs
676 (small grey arrows). B: 60 MVC protocol of the knee extensors. The figure presents a period
677 of 30 s which is repeated sequentially for 5 min. Each MVC was held for 3 s and interspersed
678 by a 2 s passive recovery period. Every 6^{th} MVC was accompanied by single pulse stimuli
679 administered during peak force production (large solid arrow) and immediately following (>1
680 s) post MVCs (small grey arrows). This cycle was repeated 10 times such that the protocol
681 spanned 5 minutes requiring the completion of 60 MVCs. Surface electromyography (EMG)
682 was measured throughout.

683

684 *Figure 2*

685 The torque profile during the 60 maximal contractions for placebo (PL, clear circles) and
686 ibuprofen (IBU, filled circles) trials in protocol (a) is demonstrated in panel A. The torque
687 during all contractions was normalized to a control maximal voluntary contraction (MVC)
688 performed before the test commenced. Note that torque falls over the first ~150 s before
689 reaching stable values between 240 and 300 s (the end-test torque; last 12 MVCs). Panel B
690 illustrates the mean ± SE power output profile during the 3-min maximal cycling protocol for
691 placebo (clear circles) and ibuprofen (filled circles) trials. Note that power output falls over
692 the first ~120-150 s before reaching stable values (the end-test power output; i.e. CP).

693

Figure 3

Mean ± SE potentiated twitch (A), voluntary activation (B), and EMG amplitude (C) and M-wave amplitude (D) responses during the 60 MVC test for placebo (clear circles) and ibuprofen (filled circles) trials for protocol a.

Figure 4

Mean ± SE M-wave amplitude (A) and EMG amplitude (B) responses during the 3-minute maximal cycling exercise for placebo (clear circles) and ibuprofen (filled circles) trials for protocol b.