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

Original investigation

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1 **ABSTRACT**

2 **Purpose:** Recent research suggests that acute consumption of pharmacological analgesics can
3 improve exercise performance, but the ergogenic potential of ibuprofen (IBP) administration
4 is poorly understood. This study tested the hypothesis that IBP administration would enhance
5 maximal exercise performance. **Methods:** In one study, 13 physically active males completed
6 60×3 -s maximum voluntary contractions (MVC) of the knee extensors interspersed with a
7 2-s passive recovery period, on two occasions, with the critical torque (CT) estimated as the
8 mean torque over the last 12 contractions (part A). In another study, 16 active males
9 completed two 3-min all-out tests against a fixed resistance on an electrically-braked cycle
10 ergometer with the critical power (CP) estimated from the mean power output over the final
11 30-s of the test (part B). All tests were completed 60 min after ingesting maltodextrin
12 (placebo, PL) or 400 mg of IBP. Peripheral nerve stimulation was administered at regular
13 intervals and electromyography was measured throughout. **Results:** For part A, mean torque
14 (IBP: 60 ± 12 vs. PL: $58 \pm 14\%$ of pre-exercise MVC) and CT (IBP: 40 ± 15 vs. PL: $41 \pm 16\%$ of
15 pre-exercise MVC) were not different between conditions ($P > 0.05$). For part B, end-test
16 power output (IBP: 292 ± 28 W vs PL: 288 ± 31 W) and work done (IBP: 65.9 ± 5.9 kJ vs PL:
17 65.4 ± 6.4 kJ) during the 3-min all-out cycling tests were not different between conditions (all
18 $P > 0.05$). For both studies, neuromuscular fatigue declined at a similar rate in both conditions
19 ($P > 0.05$). **Conclusion:** Acute ingestion of 400 mg IBP does not improve single-leg or
20 maximal cycling performance in healthy humans.

21

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

24 **INTRODUCTION**

25 Ibuprofen (IBP), a non-steroidal anti-inflammatory drug (NSAID) predominantly used to
26 treat pain and reduce inflammation and fever, is considered safe for oral ingestion within
27 healthy populations at the standard therapeutic dose (Albert & Gernaat, 1984; García-Martín
28 et al. 2004). Consequently, utilisation of analgesic (i.e., pain relieving) and anti-inflammatory
29 medication, such as IBP, has emerged as a popular pre-competition strategy in elite athletes
30 attempting to enhance athletic performance (Alaranta et al. 2008; Corrigan & Kazlauskas,
31 2003; Da Silva et al. 2015; Gorski et al. 2011; Huang et al. 2006). It is believed that NSAIDs
32 act centrally and peripherally to reduce the perception of pain and tissue inflammation,
33 respectively (Friden & Lieber, 1992). The therapeutic effect of NSAIDs in treating
34 inflammation and pain has largely been ascribed to inhibited synthesis of prostaglandins (i.e.
35 PGE₂, Friden & Lieber, 1992). Specifically, IBP limits the metabolism of arachidonic acid, a
36 precursor for the synthesis of prostaglandins, by inhibiting the enzyme, cyclooxygenase
37 (Albert & Gernaat, 1984).

38

39 Following the onset of muscle contractions, changes in contraction-induced mechanical
40 stimuli and noxious chemicals (**including an increased PGE₂ release**) activate and/or sensitise
41 molecular receptors located on the terminal end of group III and IV nerve fibers, contributing
42 to an increased sensation of muscle pain during exercise (O'Connor & Cook, 1999; McCord
43 & Kaufmann, 2010; Pollak et al. 2014). The activation of these receptors appears to play a
44 role in neuromuscular fatigue development through modulating both central and peripheral
45 fatigue. Indeed, when the ascending projection of group III and IV muscle afferents is
46 attenuated via intrathecal fentanyl administration, central motor drive is increased (as inferred
47 via electromyography, EMG) and peripheral fatigue development is expedited (Amann et al.
48 2009, 2011; Blain et al. 2016). Therefore, it is possible that an intervention that is able to

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

54

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

67

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

74 enhanced aerobic exercise performance following caffeine ingestion has been related, at least
75 in part, to altered pain perception and enhanced endurance performance (e.g., Gonclach et al.
76 2016). In addition, whilst exercise has been shown to increase PGE₂ release (Trappe et al.
77 2001; Novak & Wennmalm, 1979; Wilson & Kapoor, 1993; Vinikka et al. 1984), the extent
78 to which it plays an important role, especially following interventions aimed at reducing
79 PGE₂ synthesis, during endurance exercise in the absence of muscle damage is unclear.

80

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

87

88 **MATERIALS AND METHODS**

89 *Participants*

90 **Two independent groups** of thirteen **recreationally-active** males (mean \pm SD: age 31 ± 7
91 years, height 1.76 ± 0.08 m, body mass 75 ± 11 kg), and sixteen **recreationally-active** males
92 (mean \pm SD: age 29 ± 9 years, height 1.79 ± 0.07 m, body mass 77 ± 8 kg, $\dot{V}O_{2peak}$ 60.8 ± 7.8
93 $ml \cdot kg^{-1} \cdot min^{-1}$), volunteered for the first (A) and second (B) part of this study, respectively.
94 All participants provided written, informed consent to participate in this study, which was
95 approved by the Sport and Health Sciences Ethics Committee at the University of Exeter.
96 After being informed of the experimental procedures and associated risks, all participants
97 completed a medical health questionnaire to ensure it was safe for them to consume IBP prior
98 to performing exhaustive exercise, **due to the potential contraindications associated with IBP**

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

108

109 *Experimental Design*

110 Both protocols (part A and B) followed identical experimental designs to previous research
111 conducted within our laboratory (Morgan et al. 2018a, 2018b). For part A (Morgan et al.
112 2018a), participants visited the laboratory on three occasions over a 3-4 week period with
113 tests being conducted on an isokinetic dynamometer (Biodex System 3, Shirley, NY, USA).
114 For part B (Morgan et al. 2018b), participants visited the laboratory on five occasions over a
115 5-6 week period and tests were conducted on an electronically braked cycle ergometer (Lode
116 Excalibur Sport, Groningen, the Netherlands). **Experimental tests were separated by at least**
117 **7, but no more than 9, days (part A) and for at least 72 h (part B),** and were completed at a
118 similar time of day (\pm 90 mins). The first laboratory visits for each study were used to
119 familiarise participants to the measurements and experimental protocols described below.
120 Subsequently, participants performed the fatiguing protocol (s) under two conditions (*see*
121 *‘Experimental Protocol’*): placebo (PL) and IBP.

122

123 *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 $\dot{V}O_{2\text{peak}}$ 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 $\dot{V}O_{2\text{peak}}$ (linear factor = $50\% \Delta$ peak aerobic power output/preferred cadence²).
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

173 *Neuromuscular function (Parts A and B)*

174 For part A and B, neuromuscular function was assessed pre-, during- and post-trial (< 10 s).
175 Single peripheral nerve stimulation pulses were manually triggered at rest to determine pre-
176 exercise neuromuscular function, namely the characteristics of the M-wave response (M-
177 wave amplitude; M_{\max}) to supra-maximal nerve stimulation, voluntary activation (for part A
178 only) and potentiated twitch torque (pTw, for part A only). During MVCs, peripheral nerve
179 stimulation pulses were triggered to occur as soon as a peak torque was achieved (typically
180 1.5 s into a 3 s contraction) and were each separated by a 45 s rest period. The stimuli were
181 also delivered 1-s after the cessation of the contraction to provide a resting pTw. Identical
182 measurements were repeated as soon as possible (< 10s) after the fatiguing exercise to
183 determine post-exercise neuromuscular function (see figure 1).

184

185 *Torque (Part A)*

186 For part A, knee-extensor torque from the Biodex isokinetic dynamometer was sampled at
187 1000 Hz and low-pass filtered at 40 Hz, before being displayed on a wide screen monitor
188 using Spike2 (CED, Cambridge, UK). Torque was expressed throughout as a percentage (%)
189 of initial pre-exercise MVC.

190

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

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

197

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 μ s 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

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

240

241 *Data Analyses*

242 Data were analysed using a custom written script developed in Spike2 software (CED,
243 Cambridge, UK). For part A, mean torque for each 3 s contraction during the 60 MVC
244 protocol was determined as the mean value over a 1-s period which approximated the plateau
245 level of the highest torque (i.e. 500 ms before and after the peak torque). The pTw was
246 calculated as the peak torque achieved following the single pulse delivered 1-s post-MVC.
247 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: $[1 - \text{evoked torque}$
259 $(\text{superimposed on voluntary torque, sTw}) / (\text{mean control evoked response, pTw}) \times 100]$ (i.e.,
260 Allen et 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-

273 second, and the peak power was determined as the highest 1-s value. The changes in power
274 output, M_{Max} and EMG_{RMS} , were used to quantify neuromuscular fatigue development and
275 changes in muscle activation. Peak $\dot{V}\text{O}_2$ was determined as the highest value recorded in a
276 15-s interval. **The achievement of $\dot{V}\text{O}_{2\text{peak}}$ was an essential criterion for a valid 3-min test.** All
277 neuromuscular parameters and torque were averaged across the protocol using 30-s bin
278 averages.

279

280 *Statistics*

281 Paired-samples *t*-tests were used to compare the mean torque, total work done, CT, W' and
282 $p\text{Tw}$ between IBP and PL in part A. In addition, paired-samples *t*-tests were used to compare
283 the total work done, CP, W' and cardiorespiratory responses between IBP and PL obtained
284 from the 3-minute maximal cycling test. For the 60 MVC test, the profiles of VA and M-
285 wave amplitude were analysed using two-way ANOVAs with repeated measures (using 12
286 contraction averages; i.e. 6 time points). In addition, a two-way ANOVA with repeated
287 measures (condition \times work rate) was used to assess differences in end exercise $\dot{V}\text{O}_2$ and the
288 profiles of EMG and M-wave amplitude. Normalised EMG_{RMS} were analysed using two-way
289 ANOVAs with repeated measures using 30-s means (i.e. 10 time points). Where sphericity
290 was violated, Greenhouse-Geisser correction factor was used. For all tests, results were
291 considered statistically significant when $P < 0.05$. Data are presented as means \pm SD unless
292 otherwise indicated. All statistical analyses were conducted using IBM SPSS Statistics
293 version 23.

294

295 **RESULTS**

296 *Part A (60 MVC test)*

297 The mean MVC torque achieved prior to the 60 MVC protocol was 232 ± 47 and $230 \pm$
298 55 N.m for PL and IBU, respectively. VA of the knee extensors achieved during the
299 preliminary MVCs was 88 ± 7 and $89 \pm 6\%$ 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 $99 \pm 3\%$ MVC (relative to pre-exercise MVC)
303 during the first contraction to $40 \pm 15\%$ MVC during the last 12 contractions ($P<0.01$, Table
304 1, figure 2a). During the IBP trial torque declined from a peak of $99 \pm 3\%$ to $41 \pm 16\%$ MVC.
305 The mean torque (relative to pre-exercise MVC) achieved across the 60 MVCs not different
306 with IBP ($60 \pm 13\%$, 87.1 ± 22.2 N.m,) compared to PL ($58 \pm 14\%$, 83.8 ± 22.7 N.m,
307 $P=0.39$). There was no difference in CT (PL: $40 \pm 15\%$ vs. IBP: $41 \pm 16\%$. $P=0.74$), 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: $22,055 \pm 3,885$ vs. IBP: $22,919 \pm 3,394$ 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 $59 \pm 19\%$
318 and from 88 ± 7 to $60 \pm 18\%$, EMG declined from 99 ± 4 to $59 \pm 17\%$ and 100 ± 2 to $64 \pm$
319 20% (from first 6 to last 6 contractions) and M-wave amplitude declined from 100 ± 1 to $96 \pm$
320 14% and 100 ± 1 to $95 \pm 12\%$ in the PL and IBP conditions, respectively ($P<0.05$), with no
321 differences between PL and IPB for any of these variables ($P>0.05$).

322

323 *Part B (3-min cycling test)*

324 The mean power output profile for all participants during the 3-min all-out cycling test is
325 shown in figure 2b for the PL and IBP conditions. During the PL trial, power output declined
326 from 820 ± 139 W to 288 ± 31 W during the last 30 s of the 3-min test ($P < 0.01$; table 1,
327 figure 2b). During the IBP trial, power output declined from 816 ± 131 W to 292 ± 28 W
328 during the last 30 s of the 3-min test. There were no differences in CP (PL: 288 ± 31 vs. IBP:
329 292 ± 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'
330 (PL: 13.6 ± 2.4 vs. IBP: 13.7 ± 2.8 kJ, $P = 0.84$) between conditions.

331

332 *Part B (Neuromuscular Function)*

333 Similar to the 60 MVC protocol, alongside the decline in power output, there was a
334 progressive decline in M-wave ($P < 0.01$, figure 4b) and EMG amplitudes ($P < 0.01$, figure 4a).
335 The profiles of the M-wave and EMG amplitudes were not altered following IBP ingestion at
336 any time point (both $P > 0.05$). Using 30 s mean values, EMG decreased from 94 ± 4 to $54 \pm$
337 17% and from 96 ± 6 to $57 \pm 14\%$ (figure 4b) in PL and IBP, respectively.

338

339 **DISCUSSION**

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

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

348

349 *Effects of acute IBP ingestion on exercise performance*

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

368

369 One explanation for the lack of performance improvement following IBP ingestion in our
370 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

396 acute ingestion of 1 g of ACT on neuromuscular function during exercise and reported that,
397 whilst EMG declined across the 3-min cycling protocol in both conditions, EMG declined to
398 a lesser extent in the ACT (~72 %) compared to the PL (~54 %) condition (Morgan et al.
399 2018b). The magnitude of this effect was remarkably similar to the results we obtained
400 during a 60 MVC protocol completed in a single leg exercise model (ACT: 87% vs. PL: 59
401 %, Morgan et al. 2018a). This observation suggests that improved maintenance of muscle
402 activation contributed to the ergogenic effect of ACT (Morgan et al. 2018a). It is of interest,
403 therefore, that similar effects were not evident following IBP ingestion. We are not aware of
404 any research to suggest that ACT acts as a more potent stimulus to reduce pain sensation or
405 alter muscle activation. However, it is possible that a combination of the higher ACT dose
406 administered (1000 mg vs 400 mg for IBU), ACT's potential as an antipyretic (Foster et al.
407 2014) and differences in pharmacokinetics (Anderson, 2008; Albert & Gernaat, 1984) may
408 have contributed to the disparate effects of IBP in our current study and ACT in our previous
409 studies (Morgan et al. 2018a; Morgan et al. 2018b) on exercise performance and
410 neuromuscular fatigue development. **It is also pertinent to note that ACT ingestion has been**
411 **reported to increase corticospinal excitability at rest, a factor which may contribute to its**
412 **ergogenic potential (Mauger & Hopker, 2013).**

413

414 *Experimental considerations*

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

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

431

432 **Conclusion**

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

438 **Conflict of interest**

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

441

442 **Author contribution**

443 P.T. Morgan, A. Vanhatalo, A.M. Jones and S.J. Bailey conceived and designed the research.

444 P.T. Morgan conducted all experiments. J.L. Bowtell provided assistance with pilot testing
445 prior to experimental data collection as well supporting data analysis. P.T. Morgan wrote the

446 manuscript. J.L. Bowtell, A. Vanhatalo, A.M. Jones and S.J. Bailey helped supervise the

447 project throughout. All authors contributed to the interpretation of results and read, edited and

448 approved the manuscript.

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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)
<i>Protocol A</i>		
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
<i>Protocol B</i>		
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 6th 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 \pm 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

694 *Figure 3*

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

698

699 *Figure 4*

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