Effects of Acute High Intensity Intermittent Exercise on Gut Permeability Following Ibuprofen or Placebo Ingestion.

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Introduction

Nonsteroidal anti-inflammatory drugs (NASIDs) are widely available over the counter agents used in the acute and chronic treatment of soft-tissue injuries as well as for analgesic purposes (Tscholl et al., 2016). Due to NSAIDs analgesic, anti-inflammatory, and antipyretic effects, they have become one of the most commonly used drug groups by recreational and high level athletes to ameliorate a plethora of musculoskeletal pathologies including post exercise muscle soreness (Da Silva et al., 2015; Holgado et al., 2017; Vaso et al., 2015). In particular prevalence data on the use of NSAIDs indicates team sports participants express high consumption rates of both officially prescribed and unofficially consumed NSAIDs (Holgado et al., 2017; Tscholl et al., 2012; 2015). The high prevalence rates of NSAID consumption for prophylactic purposes are often accompanied by limited awareness of the side effects of their use and more appropriately overuse particularly on a chronic basis (Didier et al., 2017; Gorski et al., 2009).

Clinically, NSAIDs induce GI mucosal damage in the form of mucosal erosion and ulceration, they increase GI permeability and GI inflammation all off which are well described adverse effect of their normal clinical usage (Marlicz et al., 2014; Blackler et al., 2014; Sostres et al., 2017). Significantly, NSAIDs such as Ibuprofen have previously been reported to increase gastrointestinal GI permeability and inflammation following prolonged, sub-maximal endurance exercise such as marathon and triathlons. No data exists on the effects expressed during other forms of exercise in particular during intermittent and supramaximal high intensity activity exist where NSAID use in conjunction with exercise is widespread (Jeukendrup et al., 2000; Küster et al., 2013; McAnulty et al., 2007; Nieman et al., 2006; Smetanka et al., 1999; Whatmough et al., 2017). Since the use of NSAIDs in a variety of sports and individual events is widespread, it is important to characterise the effect they have on the GI barrier function especially when they are ingested

prior to exercise performance; a common occurrence many sports (Tscholl et al., 2012). As such athletes may be particularly vulnerable to adverse GI symptoms and damage due to the effects of NSAIDs and exercise interacting to damage the GI system.

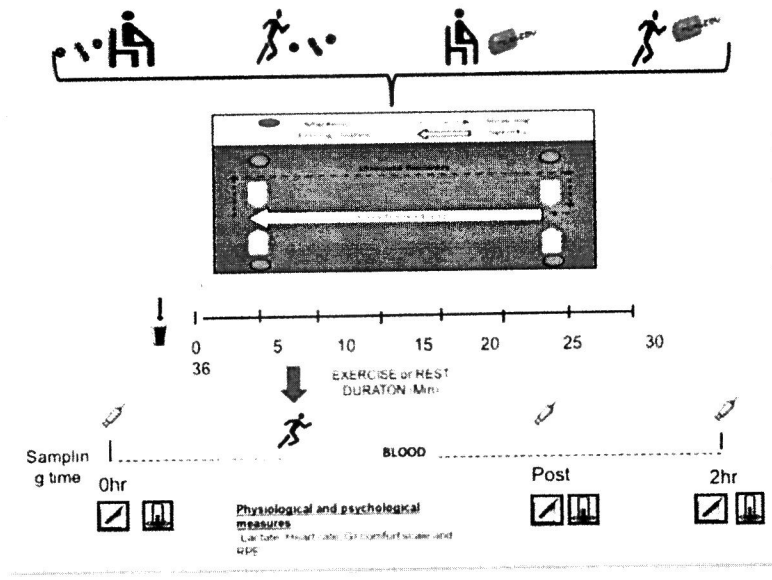
Several animal models have indicated a synergistic effect when both exercise and NSAIDS are combined leading to increased GI permeability and mucosal damage (Bradford et al., 2007; Lambert et al., 2007; Lambert et al., 2012). Empirical data on the effects of NSAIDs ingestion on GI permeability and damage in athletes is limited; having been described in endurance activity alone the effects following intermittent and high intensity intermittent exercise (HIIT) are undetermined (van Wijck et al., 2012). Given NSAIDs widespread use amongst invasion field sports (Tscholl et al., 2015) were exercise activity requires high intensity repeated bouts of activity, data on the interaction between exercise and NSAIDs would provide insight into potential effects on GI function.

The aims of the current study are therefore twofold; **1.** to assess the effects of repeated high intensity interval sprint exercise on gut permeability and symptomology relative to rest and **2.** Assess the effect of the co-administration of the NSAID [Ibuprofen] and exercise and compare to corresponding rest conditions. It is hypothesised that GI permeability will increase following HIIT exercise relative to rest, when combined exercise and ibuprofen will act synergistically further accentuating the exercise mediated increase in permeability. GI permeability is hypothesised to increase following ibuprofen ingestion at rest when compared to a placebo in the same condition.

Method

Participants. All participants were recruited from a physically fit, healthy male population of intermittent games players from the Liverpool John Moores University who were experienced in completing high intensity training. Initially 17 male participant's were recruited to participate, due to drop out for logistical, illness and failure to comply with inclusion criteria instructions in the final analysis, twelve male participants (age: 19.6 ± 2.3 years; height 1.78 ± 0.06m); body mass 75.1 ± 5.9 kg) participated. None of the participants had any previous history of GI related diseases or other gastric problems and were not regularly consuming non-steroidal anti-inflammatory drugs (NSAIDs). Participants were asked to abstain from exercise and alcohol at least 24 h prior to experimental assessment and refrain from using NSAID during the study apart from that dispensed under the experimental allocation. Participant's confirmed verbally compliance with these requirements prior to experimental data collection. All experimental procedures and potential risks/discomforts were explained in detail and written informed consent was obtained prior to testing. The study was approved by the Liverpool John Moore's University Ethics Committee. Sample size estimates were determined a priori based upon data of Pals et al. (1997). Assuming

a type I error of .05, a type II error rate (i.e. power of 80%) with an exercise to rest GI permeability ratio difference of 0.05 arbitrary units and an anticipated SD of 0.02. A total of 12 participants were estimated as required for this study.



Experimental design

Participants' completed a double blind placebo controlled counterbalanced repeated measure design separated by several days. Participants were required to complete four experimental trials at LJMU physiology Laboratory; **1)** ingestion of Ibuprofen prior to resting protocol, **2)** placebo ingestion prior to resting protocol, **3)** ingestion of Ibuprofen prior to repeated sprint protocol and **4)** placebo ingestion prior to repeated sprint protocol. All participants were asked to avoid strenuous exercise 24 h prior to both trials and were asked to consume either 800 mg of Ibuprofen or Placebo (400 mg the evening before and 400 mg on the morning of experiment) as detailed.

GI Permeability: Lactulose/L-Rhamnose.

Lactulose-/L-Rhamnose: There was no significant main effect on drug or placebo treatment ($F_{1,10} = .465$, $P > 0.05$) on GI permeability ratio. There was no significant main effect of activity ($F_{1,10} = 2.24$, $P > 0.05$). There were no significant interaction effects ($F_{1,10} = .465$, $P > 0.05$).

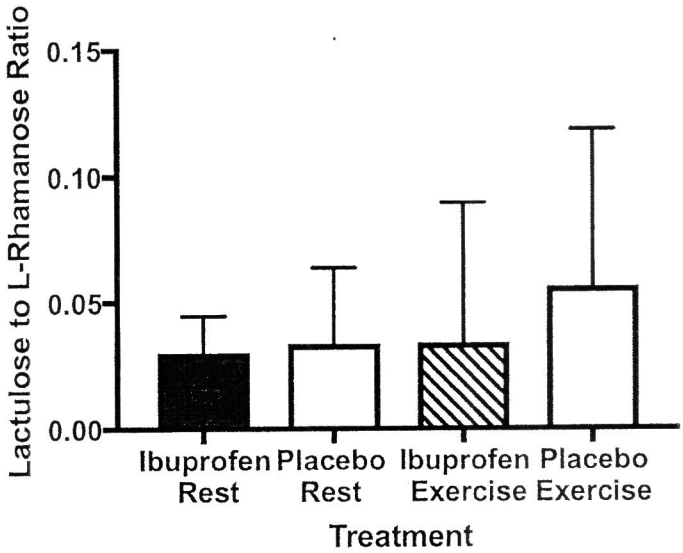


Figure 6.3 Lactulose/L-Rhamnose ratio (%) in the four exercise conditions; placebo rest, placebo exercise, ibuprofen rest and exercise.

Plasma Metabolite Responses to Exercise;

Lactate: *There was no significant main effect for condition (placebo and ibuprofen) ($F_{1, 10} = 0.02$, $P = 0.88$). There was a significant main effect for activity rest vs sprints with significant increases in lactate concentrations from pre to post for both conditions ($F_{1, 10} = 801.2$, $P < 0.001$) (Figure 6.4). There was no significant interaction between activity and drug ($F_{1.19, 8.94} = 0.01$, $P = 0.92$).*

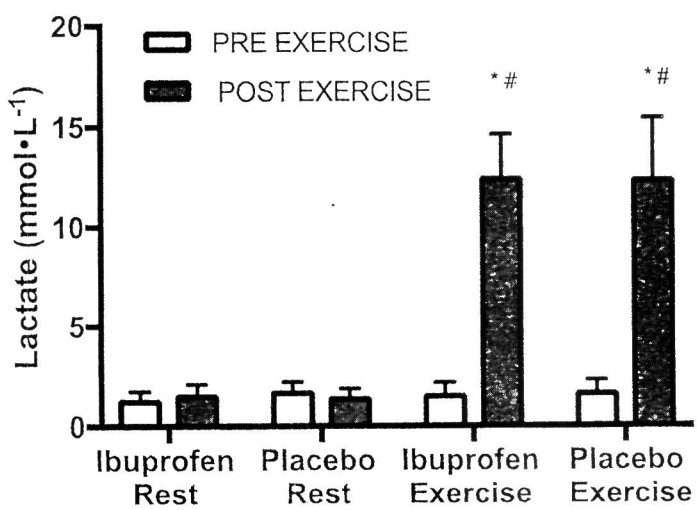


Figure 6.4 Lactate concentrations (mmol·L^{-1}) pre-to post exercise across trials after rest and exercise (4 x [6 x 35 m]) maximal intermittent sprints in the all four experimental conditions; * significantly different pre to post and # compared to passive experimental trials ($P<0.001$).

Discussion.

Given the prevalence of NSAIDs usage in sport and their known GI toxicity profile it was hypothesised that when the NSAID (Ibuprofen) were co-administered prior to exercise and passive rest there would be a synergistic effect increasing GI permeability above that noted with placebo; present data indicate that this outcome was not observed. These findings are contrary to previous studies that have examined the issue of NSIAD ingestion following exercise over a range of dosing regimen, NSIAD agents Cox 1-[aspirin] and COX 2 [ibuprofen], exercise duration and type (s) (Audet et al., 2016; Lambert et al., 2001; Lambert et al., 2007a; Lambert et al., 2012; McAnulty et al., 2007; Smetanka et al., 1999; van Wijck, et al., 2012). These differences are not unsurprising given the contrasting exercise protocols applied; repeated sprint interval relative to continuous endurance activity.

The present HIIT sprinting protocol with ibuprofen co-administered demonstrated no difference in permeability relative to the same exercise activity without ibuprofen ingestion. Indeed at rest no increase in permeability was apparent which is contrary other reports on ibuprofen effects after passive ingestion (van Wijck et al., 2012). Mechanistically, studies have reported that after the consumption of NSAIDs and via the inhibition of cyclooxygenase (COX) isotypes 1 and/or 2 a reduction in nitric oxide production occurs. Physiological and tissue effects include reduced GI tissue perfusion, as well as mucosal cytoskeleton integrity impairment leading to elevated permeability and inflammation causing GI enterocyte damage and necrosis (Holgado et al., 2017; Iwamoto, 2013; Tscholl et al., 2016). Ibuprofen is a specific COX-2 inhibitor and is categorized as a weak acid although it is undetermined the exposure dose and frequency required to elicit these responses. These findings contribute to the idea that ibuprofen ingestion with a very short duration exercise protocols and adequate rest periods may not increase permeability when a normal conservative dosing regimen(s) on a single use basis are followed. It should be considered that the participants in this study were well trained intermittent games players thus one may assume some degree of training related adaption to HIIT type activity as well as possible GI training related adaption as well due to prior exposure to NSAIDs in the past (Costa et al., 2017; Miall et al., 2017). These considerations may limit the generalisability of the data beyond these strict delimitations. It is known that conservative dosing/usage of NSAIDs by recreational and elite athletes may not be adhered too (Gorski et al., 2011a; Tscholl & Dvorak, 2012; Vaso et al., 2015). Further work should consider longer duration dosing regimen and approximate the usage patterns reported in athletes more closely to determine if the present data can be replicated.

Conclusions

In conclusion, the current study is the first to assess the effects of HIIT intermittent maximal sprints on GI permeability and symptom expression. It was initially hypothesized that both exercise and ibuprofen would act synergistically accentuating their known individual adverse Gastrointestinal profile to increase GI permeability and elevate GI symptom expression. No increase in GI permeability or symptomology was present under both conditions (ibuprofen or placebo) either at rest or following exercise. The implications of the current findings, suggest that immediately preceding supramaximal HIIT exercise activity with the use of ibuprofen (400mg) will not adversely affect the GI permeability in participants who express no previous contraindications to their use. An important caveat, is that we must limit our findings to the ingestion of Ibuprofen in line with recommended UK prescribing guidelines. We also suggest that unlike longer duration steady state exercise, supramaximal HIIT does not seem to increase permeability or

symptoms of GI distress. Given the popularity of HIIT exercise this may add a further advantage to its efficacy profile.

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