Pseudoephedrine and its Effect on Performance

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Scott Sheng-Yi Betteridge

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Abstract

Pseudoephedrine is a mild stimulant which partially mimics the action of noradrenaline and adrenaline. Recently, pseudoephedrine has been removed from the World Anti Doping Agency (WADA) prohibited substances list. This occurred despite limited research in regards to its effects on sporting performance, and no studies on prolonged exercise performance (>2hrs). There is some evidence to suggest pseudoephedrine may have an ergogenic effect at dosages exceeding therapeutic levels, possibly by masking fatigue. This study investigated the possible ergogenic effects of pseudoephedrine on endurance cycling performance.

Using a double blind, randomised cross over design, eight well-trained cyclists (VO_{2max} 69 ± 2 ml·kg^{-1}) performed two self- paced performance time trials at least 6 days apart. Ninety minutes prior to the trial, subjects consumed either placebo or pseudoephedrine (2.5 mg·kg-^{1}) capsules. Diet and exercise were controlled for 48 hrs prior to each trial. The time trial required completion of a set amount of work, equivalent to riding at two and half hours at a power output calculated to elicit 70% VO_2 max. Power output was measured using a Powertap system (Cycle Ops Power, Saris Cycling Group, USA). Venous blood samples were collected prior to capsule ingestion, just before starting the trial, and at every 20% increment in completed work until completion and were analysed for glucose and lactate. Heart rate was recorded throughout the trial.

There was no significant effect of pseudoephedrine on average performance (*p=0.235*). Heart rate was significantly higher with pseudoephedrine consumption compared to placebo ($p<0.05$), but there was no significant difference in glucose or lactate between trials.

Pseudoephedrine does not significantly improve self-paced endurance cycling performance, though the individual response was variable. However, exercising heart rate was significantly higher during exercise after ingestion of the stimulant.

Acknowledgements

There are many people I would like to mention who have been a part of this study and have helped make it possible for me to carry out.

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The Central Regional Health and Disability Ethics Committee (CEN/07/05/032) approved testing procedures and written consent was obtained from all participants prior to commencing the study.

Table of Contents

Table of Figures and Tables

1. Introduction

Pseudoephedrine is a mild stimulant that partially mimics the actions of noradrenaline and adrenaline. It is commonly used therapeutically to relieve nasal and sinus congestion. Anecdotally, athletes are using pseudoephedrine in the belief that it improves their performance.

Recently pseudoephedrine has been controversially removed from the World Anti Doping Agency (WADA) list of prohibited substances. This replaced the International Olympic Committee (IOC) list of prohibited substances, as at 1st January 2004. The removal from this list occurred despite there being little research regarding its effect on sporting performance, and no research investigating the ergogenic effects on endurance performance (>2hrs).

This report will firstly define endurance performance and review the literature on the methodology of measuring endurance cycling performance. Secondly, the physiological limitations to endurance performance will be reviewed. Finally, the pharmacology of pseudoephedrine will be discussed and studies investigating the effects of pseudoephedrine on sporting performance will be reviewed.

2. Literature review

2.1. Endurance Cycling

The discipline of competitive road cycling involves racing over distances from 40 to 300 km. A professional road cyclist may compete over 90-100 days per year, ranging from single day events to tours of up to 3-weeks in duration (Lucia et al. 2001). Within each competition, cyclists may perform a number disciplines, including, long flat stages, uphill ascents, and individual and team time trials. The duration of a professional cycle event ranges from one to five hours, and a typical sub-elite road race is about two and half hours or about 100km.

A successful cyclist needs to be able to maintain a high power output for a prolonged length of time; this being achieved by possessing a great ability to resist fatigue (Abbiss and Laursen 2005). A number of factors have been proposed to induce fatigue in road cycling and there is controversy over which ones are the main limitations to performance. These limitations include, maximum oxygen utilisation (VO_{2max}), and other peripheral and central limitations.

2.2. Measuring endurance cycling performance in the laboratory

Studies investigating endurance performance have commonly adopted an open ended exercise protocol. Performance is measured by time to exhaustion at a fixed sub-maximal workload (Schabort et al. 1998). However, such protocols have not proven to be reliable, shown by a high coefficient of variation (CV) (Krebs and Powers 1989; McLellan et al. 1995; Jeukendrup et al. 1996). Alternatively closed end exercise protocol requiring a set amount of work or distance to be completed as quickly as possible has been shown to be more reliable and also more closely mimics the variability in intensity exhibited in field competition (Hickey et al. 1992; Jeukendrup et al. 1996; Schabort et al. 1998).

Jeukendrup et al. (1996) tested the reliability of three different exercise protocols. A) cycling to exhaustion at 75% of maximal power output (W_{max}), B) riding at 70%

W_{max} followed by a 15 min time trial where subjects had to complete as much work as possible, and C) completing a set amount of work (equilavent to riding at 75% W_{max} for an 1hr) as fast as possible. Thirty well-trained subjects who were matched on age, weight and W_{max} were divided between the three protocols and repeated the protocol six times. Individual CV for protocol A) ranged from 17.4 - 39.5% and the overall CV was 26%. In contrast to the variability shown with protocol A) (cycling to exhaustion) individual CV ranged from 1.7-5.8% and 0.8-5.8% with an overall CV of 3.5% and 3.4% for protocol B and C respectively. The findings of this study demonstrate the unreliability of an exercise protocol that is terminated upon exhaustion. This study also showed there to be no test order effect suggesting that there is no learning or training effect across the trials with well trained cyclists. The high reliability of an exercise protocol with a set end point was confirmed in a study by Schabort et al. (1998), but where a longer exercise protocol was used. A 100 km time trial interspersed with four 1 km and 4 km sprints was performed three times by each participant. The between test correlation for the time trial was 0.93 (0.79-0.98, 95 % C.I.) and the CV was 1.7 % (1.1-2.5 %, 95% C.I.), consistent with the studies using a shorter closed ended exercise protocol. The large CV with open ended trials has been suggested by Jeukendrup et al. (1996) to be a result of psychological factors such as motivation and boredom to be more pronounced compared to exercise protocols with a defined end point.

Little research could be found comparing laboratory performance to performance on the road, and those that were found looked at short term cycling performance. Palmer et al. (1996) investigated the correlation between a 40-km laboratory time trial and a 40-km time trial on the road. Eight participant performed three laboratory time trials and two time trials on the road. There was found to be a strong relationship between laboratory and road times for the time trial ($r = 0.98$, $p < 0.001$).

In summary the use of a closed end exercise protocol has been shown to be a reliable laboratory exercise test for endurance performance. It is therefore suited to evaluate the effects of training programmes or interventions such as nutrition or ergogenic aids.

2.3. Limitations to endurance performance

2.3.1. Maximum oxygen utilisation

One of the major factors proposed to limit endurance performance is the ability of the cardiovascular system to deliver oxygen to the muscle. An athlete's maximum ability to utilise oxygen is reflected by their maximal oxygen uptake (VO_2 max) and is a measure of cardiorespiratory fitness (Bassett and Howley 2000). .
However, although a high VO_2 max is required for success in most endurance-based sports, it is believed that for most well-motivated endurance athletes, peripheral (skeletal muscle related) limitations are usually the most important over competition distances. However, the role of the central nervous system (CNS) in fatigue during prolonged exercise is gaining more attention. Indeed, there may be some important interactions between peripheral fatigue factors and CNS drive (Noakes 2000).

2.3.2. Peripheral

A major factor in the limitation of endurance performance is the inability to supply ATP at the required rate to the working muscles. Arguably, the most important fuel source during competition intensity is carbohydrate. This is firstly because the body is unable to store these in large quantities, and secondly high intensities depended on the larger glycolytic motor units where substrate level phosphorylation (within glycolysis) becomes a very important means of regenerating ATP.

The importance of carbohydrates as a fuel during strenuous exercise was established by (Christensen and Hansen 1939). They showed that time to exhaustion at a fixed intensity (176 W) was significantly longer with the consumption of a high carbohydrate diet (83% CHO and 3% fat) during the three days leading up to the trial compared to consuming a high fat diet (94% fat and 4% CHO).
With the introduction of needle muscle biopsy technique for skeletal muscle physiological research in the 1960's an association between low levels of muscle glycogen and the onset of fatigue during endurance exercise was demonstrated.

Bergstrom et al. (1967) showed that time to exhaustion was greater with a larger initial glycogen store at a workload set at about 75% of the participants VO_2 max. This and more recent studies showing an association between initial muscle glycogen content and performance has lead to the common practice of ingesting a very high carbohydrate diet (7-12 g/kg body mass a day) leading up to a race. This practice is often referred to as glycogen or carbohydrate loading and maximises or super compensates muscle and liver glycogen stores to optimise performance, (Costill et al. 1981).

The ingestion of carbohydrates during prolonged exercise has also been shown to improve performance, (Coyle et al. 1983; Coyle et al. 1986) in many situations. For example Coyle et al. (1983) investigated the effects of ingesting carbohydrates in the form of a glucose polymer drink on cycling to exhaustion at 71% of VO_2 max in 10 well trained cyclists. The time to fatigue with and without carbohydrate supplementation was 157 ± 6 min and 134 ± 5 min respectively. The findings from this study show a delay in fatigue with carbohydrate ingestion during exercise. A later study by Coyle et al. (1986) developed these findings further using the same exercise protocol with the addition of muscle biopsies taken from the vastus laterialis. Muscle glycogen utilisation during exercise was not affected by carbohydrate ingestion. Therefore the ingestion of carbohydrates during endurance exercise has been suggested to delay the onset of fatigue by maintaining euglycaemia (normal blood glucose concentrations) and sustaining the high rates of blood glucose oxidation later in exercise, rather than reducing the rate of muscle glycogen utilisation (Coggan and Coyle 1991). The ingestion of carbohydrate during exercise has also been shown to spare liver glycogen, (McConnell et al. 1994; Jeukendrup et al. 1999). Liver glycogen is the primary source of blood glucose at rest and while exercising. Metabolic demand is greater with increased exercise. The increased glucose demand is meet by increased glycogenolysis and gluconeogenesis, (Evans and Hughes 1985). Carbohydrate ingestion during exercise is thought to spare liver glycogen, through the decreased need for glycogenolysis.

The importance of ensuring adequate carbohydrate intake during prolonged exercise is so well established that the American College of Sports Medicine (ACSM) has developed a ‘Position Stance” on the topic. They recommend consuming

carbohydrates at a rate of 30-60 g/hr when exercising for longer than 90 minutes. This recommendation is based on carbohydrate oxidation of 1.0 to 1.1 $g \cdot min^{-1}$ (Jeukendrup and Jentjens 2000) .

In summary, maximising muscle and liver glycogen stores with the ingestion of plenty of carbohydrates in the days leading up to a race as well as the ingestion of carbohydrates throughout a race is of great importance in delaying the onset of fatigue and as a result enhancing performance in prolonged exercise. However, it is notable that the vast majority of studies investigating the importance of muscle glycogen on endurance performance have employed an open-ended exercise protocol.

2.3.3. Central

Peripheral limitations to fatigue can be overcome and in some studies they do not appear to be a limiting factor in endurance performance. For example muscle glycogen has shown to remain after prolonged exhaustive exercise, (Krssak et al. 1999)**.** Consequently, there is assumed to be a loss in central drive attributed to a disturbance in the synthesis and metabolism of central monoamines. In particular, disturbances in central nervous system levels of serotonin, dopamine, noradrenaline and adenosine result in a reduction in motor unit recruitment (Meeusen et al. 2006).

The neurotransmittors dopamine and noradrenaline may have a possible role in central fatigue during prolonged exercise. They have a known role on motivation and motor behaviour and altered levels could play a part in reduced central drive (Meeusen and De Meirleir 1995). Dopamine activity in the caudate and accumbens nuclei has been suggested to be involved in the control of voluntary movement and locomotion (Freed and Yamamoto 1985). It was one of the first neurotransmitters to be associated with central fatigue as a result of studies investigating the effects of amphetamine use (Borg et al. 1972; Davis and Bailey 1997). Studies involving the use of animals have shown there to be an increase in brain dopamine activity during prolonged exercise, which has been suggested to be important to exercise performance (Gerald 1978; Chaouloff et al. 1987; Bailey et al. 1993).

Other neurotransmittors proposed to have a possible role in the development of central fatigue include γ-amino butyric acid (GABA), glutamate, and acetylcholine. After administering a GABAergic agonist (Baclofen) in rats, Abdelmalki et al. (1997) showed there to be an increase in run-time to exhaustion. A study by Guezennec et al. (1998) had consistent findings with a reduction in brain glutamate (precursor to GABA) levels during prolonged exercise. Conlay et al. (1992) demonstrated a decrease in plasma choline concentration by approximately 40% after trained athletes had run 26 km. As choline is a constituent of acetyl-choline it was suggested that a reduction in plasma choline may reduce acetylcholine, leading to a decrease in performance.
The significance of GABA, glutamate, and acetylcholine in regards to central fatigue is not fully understood due to a lack of published data concerning them.

Other substances which may possibly contribute to central fatigue are ammonia (Banister and Cameron 1990), and cytokines that have been proposed as a factor in the aetiology of over training syndrome (Smith 2000).

Central nervous stimulants such as amphetamines, ephedrine, pseudoephedrine, caffeine and nicotine have been either shown or suggested to improve endurance performance, (Borg et al. 1972; Graham and Spriet 1991; Greer et al. 2000; Hodges et al. 2006; Mundel and Jones 2006). These stimulants have two actions. The first, a peripheral effect as a sympathomimetic, mimicking the role of catecholamines, thereby increasing heart rate, increasing blood pressure, peripheral vasoconstriction and muscle vasodilation (George 2005). However the sympathetic output is already high when a moderate intensity is sustained and the peripheral effect of these stimulants is inconsequential. The second action, a direct effect on neurotransmission and catecholamine release, influencing motor control and motivation is the assumed mechanism by which these stimulants reduce central fatigue and exhibit an ergogenic effect (Borg et al. 1972; Graham and Spriet 1991; Greer et al. 2000; Hodges et al. 2006; Mundel and Jones 2006).

Amphetamines indirectly activate adrenoreceptors and dopamine receptors by assisting the action of dopamine and noradrenaline. This occurs by inhibiting reuptake, facilitating release into the synaptic cleft, and inhibiting the catabolic

activity of monoamine oxidase, (Sulzer et al. 2005). Through these actions central fatigue is reduced and as performance enhanced.

A reduction in endurance performance in hot conditions has been shown in many studies (Galloway and Maughan 1997; Parkin et al. 1999). This reduction in performance has been attributed to central fatigue, as a result of an increase in core body temperature (Nybo and Nielsen 2001; Low et al. 2005). Low et al. (2005) demonstrated an increase in circulating prolactin, in response to both active and passive heating to the same core body temperature. Prolactin is an indirect marker of central seronergic and dopaminergic activity and used as a measure of central fatigue (Bridge et al. 2003). A significantly lower blood pressure was present with passive heating compared to active heating. Low et al. (2005) suggested that core body temperature, rather than alterations in peripheral blood flow and pressure was the main stimulus for prolactin release. In the hyperthermic state, central fatigue can be said to be affected by the increase in body temperature rather than the change in peripheral blood flow. Thus, during exercise when metabolic heat production is high, a critical core temperature may be reached which initiates a central fatigue effecting process which, in turn, reduces exercising intensity and thus heat production.

In summary central fatigue is a form of fatigue where the central nervous system functioning is altered, influencing mood, sensation of fatigue, motivation, the ability to tolerate pain and discomfort, and is consequentially detrimental to exercise performance. Therefore the nutritional or pharmacological intervention targeting central fatigue has the potential to significantly enhance performance. Central fatigue is integrated with peripheral factors with both having at least some influence over the other, making it difficult to separate and quantify the importance of either (Meeusen et al. 2006).

2.4. Pseudoephedrine

2.4.1. Pharmacology

Pseudoephedrine is a sympathomimetic amine and a less potent diastereomer of ephedrine. The chemical structure of both compounds is shown below in figure 1.

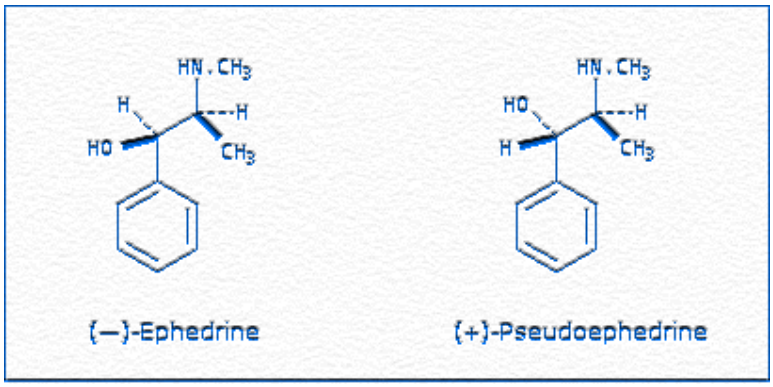

Fig. 1 – The Chemical Structure of Ephedrine and Pseudoephedrine

The majority (70-90%) of pseudoephedrine is excreted in the urine unchanged with only a small percentage being metabolised to norpseudoephedrine through N-demethylation, (Benezra and McRae 1979). The amount metabolised depends on the pH of the urine. Alkaline urine results in pseudoephedrine being retained in the body for longer, allowing more extensive metabolism to occur (Wilkinson and Beckett 1968). The half-life of pseudoephedrine is 9-16 hours, (Meyers et al. 1968).

Pseudoephedrine exerts its effects by indirectly acting upon the neurones of the sympathetic and central nervous system. It's main action is via the displacement of noradrenaline from neuronal storage sites, and it also has a weak agonistic effect on the α and β adrenergic receptors (Rang et al. 2003; George 2005). The central nervous effects of pseudoephedrine, exhibited by locomotor behaviour are similar to those seen with amphetamines (Christie and Crow 1971). Christie and Crow (1971) used a method by Andren et al. (1966), and observed turning behaviour in rats with a unilateral lesion of the nigro-neostriatal pathway after ingestion of central nervous stimulants. Turning behaviour in this instance is an index of the action of methylamphetamine, amphetamines and the ephedrine isomers, (ephedrine,

norpseudoephedrine and pseudoephedrine) on central-dopamine-containing neurones. The stimulants tested increased the rate of turning behaviour in relation to the potency. Peudoephedrine had similar effects to amphetamines on central-dopamine-containing neurones but was shown to be not as potent. Norpseudoephedrine, the metabolic by-product of pseudoephedrine was the most potent of the ephedrine isomers. This effect of pseudoephedrine on the central dopamine mechanism is further supported by a imminocytochemical study by Kumarnsit et al. (1999). A pseudoephedrine induced activity observed in the rat nucleus accumbens and striatum was completely and partially blocked respectively with the pre-injection of a D_1 dopamine receptor antagonist. Consequently, it was suggested that the action of pseudoephedrine is mediated via dopamine release and it's activation of D_1 dopamine receptors.

The systemic physiological effects of pseudoephedrine include increased heart rate and force of myocardial contraction, raised arterial pressure, bronchodilation, inhibition of gut motility and peripheral vasoconstriction (Rang et al. 2003). Therapeutically pseudoephedrine is used as a decongestant causing vasoconstriction of the blood vessels of the nose, throat and sinus linings decreasing inflammation of nasal membranes and mucus production (Taverner et al. 1999). Its cardiovascular effects at therapeutic dosages are small but significant as shown in a meta-analysis review by Salerno et al. (2005). An elevation in systolic blood pressure of 0.08 to 1.90 mmHg and heart rate increase of 2 to 3.6 bpm was seen in the reviewed studies.

2.4.2. Pseudoephedrine and performance

Anecdotally pseudoephedrine is taken by athletes as a means of improving performance. Between 1995 and 2000 showed that 22% of the stimulants detected by a UK sports testing programme were identified as pseudoephedrine (George 2005).

In 2004 pseudoephedrine, along with caffeine (another central nervous stimulant) was controversially removed from the WADA ban list. Current research at the time was not believed to support a performance enhancing effect of pseudoephedrine. Prior to 2004 pseudoephedrine was restricted to 25µg ml^{-1} of urine and caffeine restricted to 12µg ml^{-1} (Weatherby and Rogerson 2001). Pseudoephedrine has been suggested to have a possible performance enhancing effect due it similarities in structure to amphetamines. The suggested mechanism by which pseudoephedrine may improve performance is the reduction of an individuals perceived exertion, occuring in response to an increase in dopamine (Hodges et al. 2006). As discussed earlier dopamine is one of the main neurotransmitters suggested to be involved in central fatigue.

The studies by Christie and Crow (1971) and Kumarnsit (1999) injected high doses (50 - 60 $mg \cdot kg^{-1}$ cf 2.5 $mg \cdot kg^{-1}$, the maximum used in human studies to date) directly into the brain to observe maximum effects on central-dopamine-containing neurones. There were no studies found looking at dopamine effects using lower doses. An oral dose, closer to that taken therapeutically in humans (~0.8 $mg \cdot kg^{-1}$) could be expected to have a similar effect on dopamine, but to a lesser degree. The metabolic by-product norpseudoephedrine would be expected to contribute to the ergogenic effect of pseudoephedrine ingestion, despite the small percentage of pseudoephedrine metabolised to norpseudoepherine.

There has been little research investigating the effects of pseudoephedrine on performance. In particular, dosages above therapeutic levels and the effects of pseudoephedrine on prolonged performance (>2hr) have not been investigated. The majority of the studies investigating the effects of pseudoephedrine have found no significant difference in either aerobic and anaerobic performance (Clemons and

Crosby 1993; Gillies et al. 1996; Swain et al. 1997; Chu et al. 2002; Chester et al. 2003; Hodges et al. 2003). At higher dose rates there is some evidence suggesting a possible performance enhancing effect of pseudoephedrine (Gill et al. 2000; Hodges et al. 2006). These studies are summarised in table 1 below.

Hodges et al. (2006) administered pseudoephedrine at 2.5mg·kg^{-1}, almost 3 times the therapeutic dose. A double blind randomised cross over design was used to investigate the effects of pseudoephedrine on 1500-m running performance using seven male athletes. Pseudoephedrine or the placebo was given 90-min prior to running 1500-m on an athletic track as fast as possible. Pseudoephedrine significantly ($p=0.001$) improved performance by 2.1% (279.65 ± 4.36 s with placebo to 273.86 ± 4.36 s). No significant difference was shown in the blood parameters (glucose and lactate concentrations, PO_2, PCO_2 and oxygen saturation) before, during and after the trial. This finding excludes the ergogenic action of pseudoephedrine via a metabolic mechanism. Hodges et al. (2006) suggest that a more plausible explanation for this ergogenic effect may be an increase in central nervous stimulation resulting in a reduction in perceived effort by the subject as described earlier. Gill et al. (2000) also showed an increase in performance, after twenty-two male athletes were given 180 mg of pseudoephedrine 45-min prior to a short-term maximal bout of exercise.

In summary despite the majority of studies finding no significant increase in performance, the two studies by Hodges et al. (2006) and Gill et al. (2000) which used a dose exceeding therapeutic levels suggest that at such dosages there may be an ergogenic effect. This higher dosage may be what is required to elicit a useful response on the central-dopamine-containing neurones.

Study	Subjects	Pseudoephedrine dose	Exercise Protocol	Performance
(Chu et al. 2002)	10 Males 10 Females	120 mg	- Maximal voluntary contraction strength and fatigability for handgrip and ankle dorsi-flexion. - 30-sec maximal cycle test	Not significant
(Hodges et al. 2003)	11 Males	60 mg	- 30-sec maximal cycle test - Cycling efficiency test	Not significant
(Gillies et al. 1996)	10 males	120 mg	40 km cycle time trial	Not significant
(Swain et al. 1997)	20 make	1 and 2 mg/kg	- VO_2 max test - Time to exhaustion on an ergometer test	Not significant
(Clemons and Crosby 1993)	10 Females	60 mg	Graded treadmill exercise test (Bruce Protocol)	Not significant
(Chester et al. 2003)	8 males	60 mg and 25 mg of phenylpropanolamine every 4 hrs 36 hrs prior to trial	5000-m time trial on the treadmill	Not significant
(Hodges et al. 2006)	7 males	2.5 mg/kg	1500-m run on the track	Increase
(Gill et al. 2000)	22 males	180 mg	- Max isometric knee extension torque - Bench press - 30-sec maximal cycle test	Increase Not significant Increase

Table 1 – Summary of Studies Investigating Pseudoephedrine and Performance

3. Objective

This study was designed primarily to determine if pseudoephedrine at dosages approximately 3 times the therapeutic level improves endurance cycling performance.

Secondary objectives were to determine the effects, if any of pseudoephedrine on exercising heart rate and the metabolic substrates lactate and glucose.

Our null hypothesis is that pseudoephedrine will have no effect on performance, heart rate, lactate, or glucose.

4. Method

4.1. Subjects

Eight endurance-trained cyclists (age 29 ± 2 years, body mass 75 ± 2 kg, VO_{2max} 69 ± 2 $ml \cdot kg^{-1} \cdot min^{-1}$) volunteered to participate in this study. An endurance-trained cyclist was defined as "cycling more than 200 km a week and competing on a regular basis". Participants were informed of the study protocol and risks before providing their written consent. The Central Regional Health and Disability Ethics Committee (CEN/07/05/032) approved this study.

4.2. Preliminary testing

At least one week prior to the first performance trial, each participant completed a submaximal and maximal maximum oxygen uptake (VO_{2max}) test on an electronically braked cycle ergometer (Lode, Groningen, The Netherlands). They were required to perform four consecutive submaximal steady-state power outputs of 100, 150, 200, and 250 Watts for 6 minutes each. After completing the submaximal workloads, the participants had a warm-down period at a self selected intensity followed by a five minute rest. An incremental (40 W min^{-1}) ramp test was then performed beginning at 100 watts until volitional exhaustion.

During these tests a nose clip and two way rebreathing mouthpiece (Hans-Rudolph, USA) was fitted to enable the collection of expired respiratory gas. Gas was collected into a Douglas bag during the last minute of each sub-maximal workload. During the ramp test, a Douglas bag was collected approximately every 30 seconds once the subject had exceeded the respiratory compensation point. Douglas bags were analysed for gas concentrations and volume after each test had been completed. The fractions of O_2 and CO_2 were analysed using Ametek gas analysers (Pittsburgh, PA). Both analysers were calibrated immediately prior to testing using gases of known composition (0.157 O_2 and 0.05 CO_2).

The volume of air was measured by evacuating the Douglas bag using a vacuum measuring device. Standard temperature, pressure, dry (STPD) values for VO_2, VCO_2, and respiratory exchange ratio, were calculated adjusting for ambient barometric pressure and temperature. External power output and VO_2 during the final min of each sub-maximal workload was used to formulate a linear regression equation to describe the relationship between both variables as shown in Figure 2. Using this equation together with the maximum VO_2 (obtained from the ramp test) power output at 70% of $VO_{2\ max}$ was determined. The work required to be completed in the performance time trial was calculated to be equivalent to riding at 70% of $VO_{2\ max}$ for two and half- hours. This exercise protocol was adapted from the study by Johnson et al. (2006).

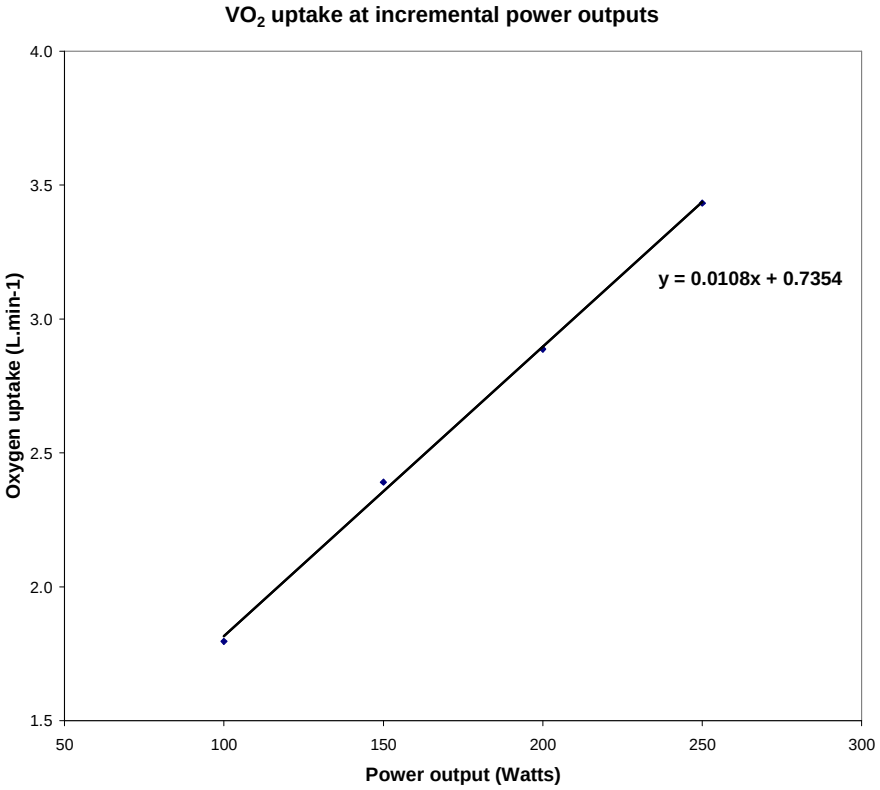

Fig. 2 – Example from Subject showing the Linear Relationship between the Four Submaximal Workloads and Corresponding Oxygen Uptake to form a Linear Regression Equation.

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4.3. Experimental protocol

Participants were asked to avoid any exercise for the 48 hrs prior to each performance trial, except the day before when participants performed a laboratory-based one-hour training ride at 65% VO_2 max on an electronically braked cycle ergometer (Lode, Groningen, The Netherlands). The two performance time trials were carried out at the same time of day for each participant and were performed under standard laboratory conditions (20°C, 50% relative humidity). A standard meal consisting of a "One Square meal " (Cookie Time Limited, NZ) bar, "Up and Go" liquid meal (Sanitarium Health Food Company, Australia) and a banana totalling approximately 4596 Kj (60% carbohydrate) was consumed 4 hours prior to arriving at the laboratory for the initial blood test.

Upon arriving at the laboratory participants rested for about 5 minutes prior to a venous blood sample being taken via needle and syringe. Immediately after the blood sample had been taken, the capsules containing either placebo or pseudoephedrine were ingested along with a muesli bar (Tasti Products Limited, NZ) 769 Kj (34% carbohydrate).

After 80 minutes of rest, participants were fitted with a heart monitor (Polar Sport, Kempele, Finland) and a venous cannula was inserted into a forearm vein. This remained there for the duration of the trial, as shown in Figure 3. A resting blood sample was taken just prior to beginning the performance trial, 86 minutes after ingesting the capsules. Prior to and following each blood sample, and periodically between the samples, the cannula was flushed with saline to maintain patency.

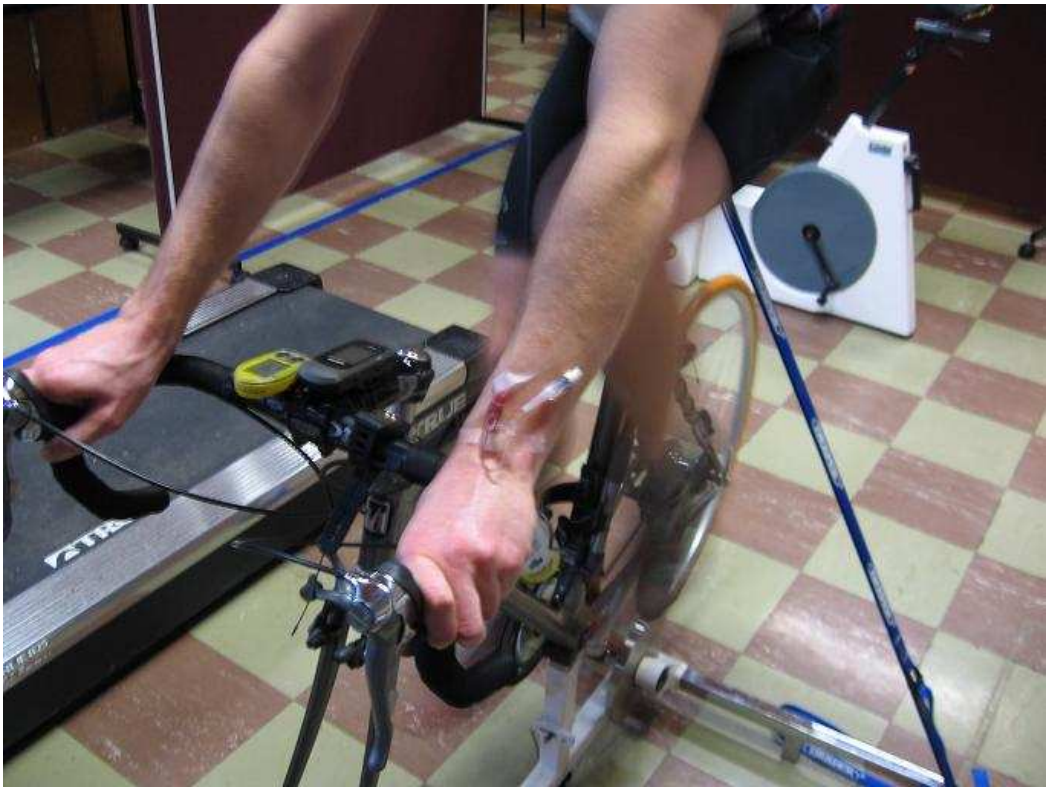

Fig. 3 - Showing the Cannula Inserted into the Participant's Forearm

4.4. Cycling endurance time trial

The time trial was carried out on the participant's own bike which was fitted on a Kingcycle cycling ergometer (High Wycombe, UK) to provide resistance only. A wheel built around a PowerTap system (Cycle Ops Power, Saris Cycling Group, USA) fitted with the subjects own cogs was used to measure external power output from the hub. This is considered to be a suitable device for power output measurements during sub-maximal laboratory testing (Bertucci et al. 2005)**.**
In both experimental trials individuals were prescribed a set amount of work described previously, which they had to complete as quickly as possible.
During the trials, participants ingested an 8% glucose polymer solution at a rate of 400 ml every 20% of the workload completed to reduce the risk of dehydration and hypoglycaemia (Burke et al. 2000).

Participants received feedback on power output and the percentage of the time trial that they had completed during each trial. They were verbally encouraged to perform to the best of their ability during both experimental trials.
During each time trial, venous blood samples were taken at each 20% of the workload completed, and upon completion. Time to complete each 20% increment in workload and the total time to completion was also recorded. Heart rate was continually recorded every second throughout the trial on the heart rate monitor and downloaded after the trial. The experimental protocol is illustrated in figure 4.

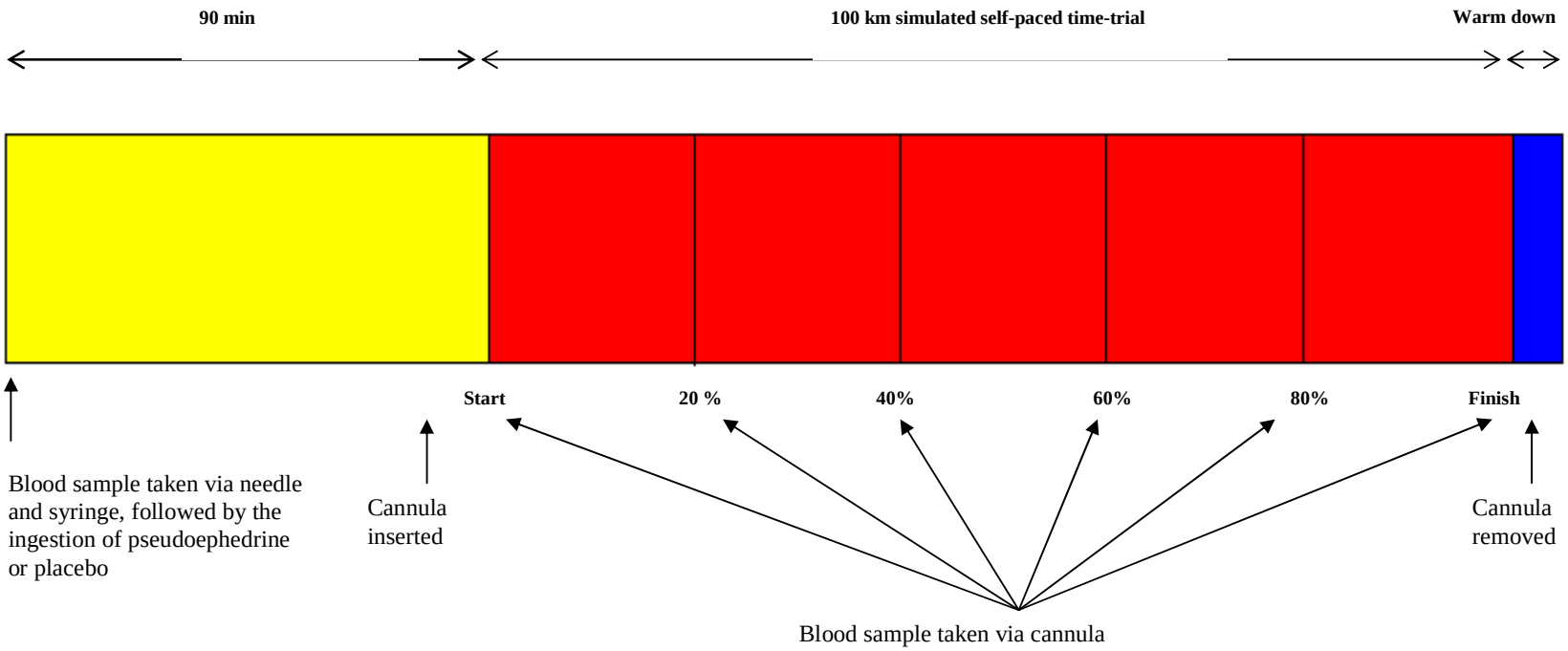

Fig. 4 – Timeline of Experimental Protocol

4.5. Pseudoephedrine

Prior to each experimental trial, participants ingested either a placebo capsule containing galactose or a treatment capsule containing pseudoephedrine (Sudomyl™) at a dose rate of 2.5 $mg \cdot kg^{-1}$. Half the participants received the placebo in the first trial, and the other half received the treatment first, reducing the possibility of a training effect. This was managed by a third party not involved in the study to ensure the trials were double blind.

4.6. Analytical procedures and calculations

Blood samples were drawn into a syringe for the immediate analyses of lactate (YSI 1500, Ohio, USA) and glucose (HemoCue Glucose 201+, Sweden).

The YSI 1500 analyses whole lactate using an electrode which contains a thin film of lactate enzyme immobilised within a membrane. Hydrogen peroxide is produced as the lactate diffuses through the membrane, which is then measured at the platinum electrode. The resulting current is proportional to the hydrogen peroxide, which is in turn proportional to the lactate in the blood sample (manufacturer's website, www.ysilifesciences.com). The YSI was pre-calibrated prior to each trial using a 5 $mmol \cdot L^{-1}$ standard. The accuracy stated by the manufacturer is ± 2% or 0.01 $mmol \cdot L^{-1}$.

The HemoCue Glucose analyser uses disposable microcuvettes, which are filled with blood by capillary action. Within the microcuvettes are dried reagents that initiate a glucose dehydrogenase-based reaction producing a coloured formazan which is quantified photometrically with a two wave length (660 and 840 nm) method (Banauch et al. 1975). The Hemocue is pre-calibrated by the manufacturer using a wet chemical glucose dehydrogenase method (hemolysation and deproteinisation) and the accuracy has a standard deviation of 0.3 $mmol \cdot L^{-1}$ (manufacturer's web site, www.hemocue.com).

4.7. Statistical Analyses

Time to complete the set workload, overall mean power output, and split mean power output were recorded. Plasma glucose and lactate for each sample time was determined. All data was initially tabulated in Excel (Microsoft, USA) before being copied to SPSS (Illinois, USA) to perform statistical calculations. All factors were compared using a two-way repeated measure ANOVA for treatment and time (treatment × time) interactions. Interaction between trial order was also assessed by a two-way repeated measure ANOVA. A post hoc student *t* test was used to confirm significance at each level. Statistical significance was accepted at $P < 0.05$. All values were expressed as means ± SE.

5. Results

Mean work required to be completed for the performance trial was 2474 ± 113 kJ (33 ± 1 kj·kg^{-1}) and the average amount of pseudoephedrine consumed was 186 ± 5 mg. All participants completed both trials.

One participant suffered significant discomfort during the treatment trial. Choosing to complete the trial, he experienced muscle cramps mid-way through, followed by increasing nausea. He vomited on completion, and also commented that he felt unusually hot. Slight nausea was also experienced in two of other participants during the pseudoephedrine trial, but their performance was not impaired. One other participant also commented that he felt noticeably "hotter" during the treatment trial. This participant performed faster on the placebo compared to pseudoephedrine. These are known possible side effects of pseudoephedrine (Rossi 2006).

Five out of the eight participants correctly guessed what they were on for each trial, four of which performed better with the pseudoephedrine. One participant was unsure which trial was the placebo or pseudoephedrine.

5.1. Performance

5.1.1. Time to completion of time trial

Overall mean times between placebo and pseudoephedrine were 186.1 ± 6.4 and 182.3 ± 8.5 min respectively. Time to completion was not significantly different between treatments (p = 0.234) (see Figure 5).

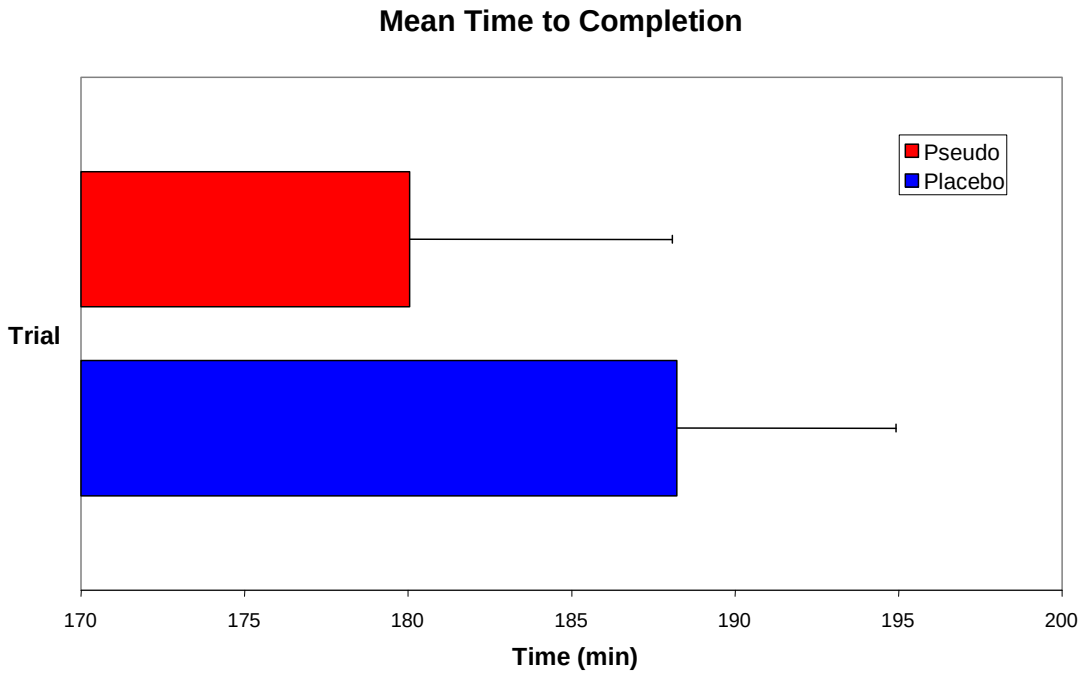

Fig. 5 - Time to Complete Set Work (Mean ± SE)

5.1.2. Power

Mean power output during each 20% work intervals for both treatments is presented in Figure 6. There was no significant interaction in power output between treatment and time ($p = 0.084$).

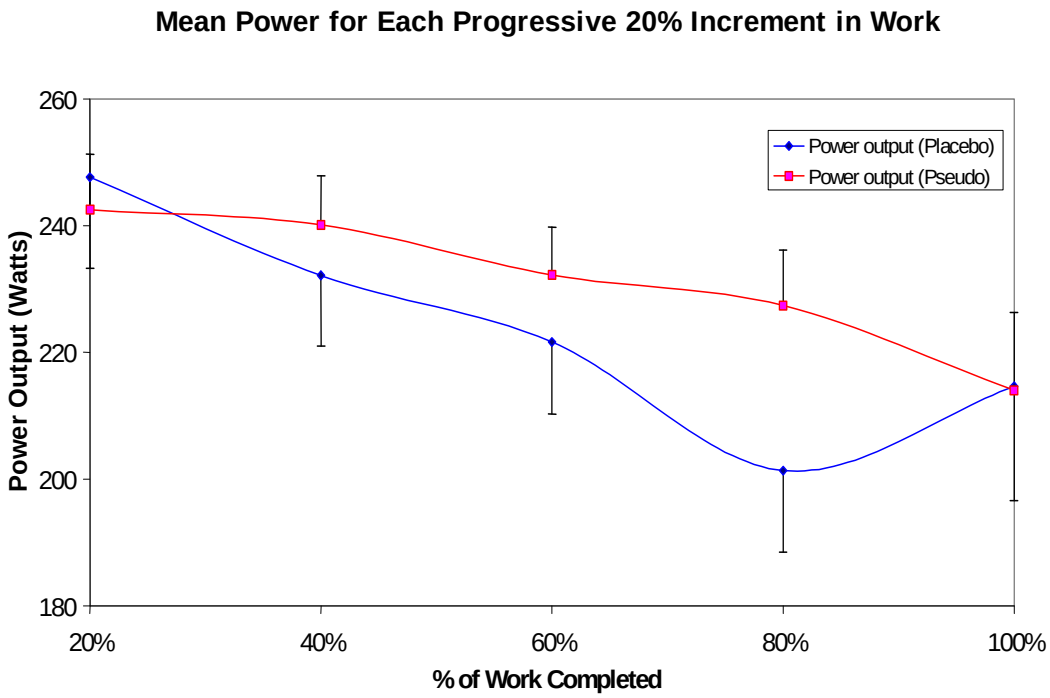

Fig. 6 – Power for Each Progressive 20% Increment in Work Completed (Mean ± SE)

5.2. Heart rate

Mean heart rate during each 20% work period is presented in Figure 7. There was a significant interaction in heart rate between treatment and time.

Post hoc t-tests between treatments at individual work intervals indicated a difference in heart rate response over time (time x treatment interaction) ($p < 0.001$). Overall mean heart rate for the placebo and pseudoephedrine trial was 152 ± 2 and 162 ± 2 bpm respectively ($p=0.001$) as shown in Figure 8.

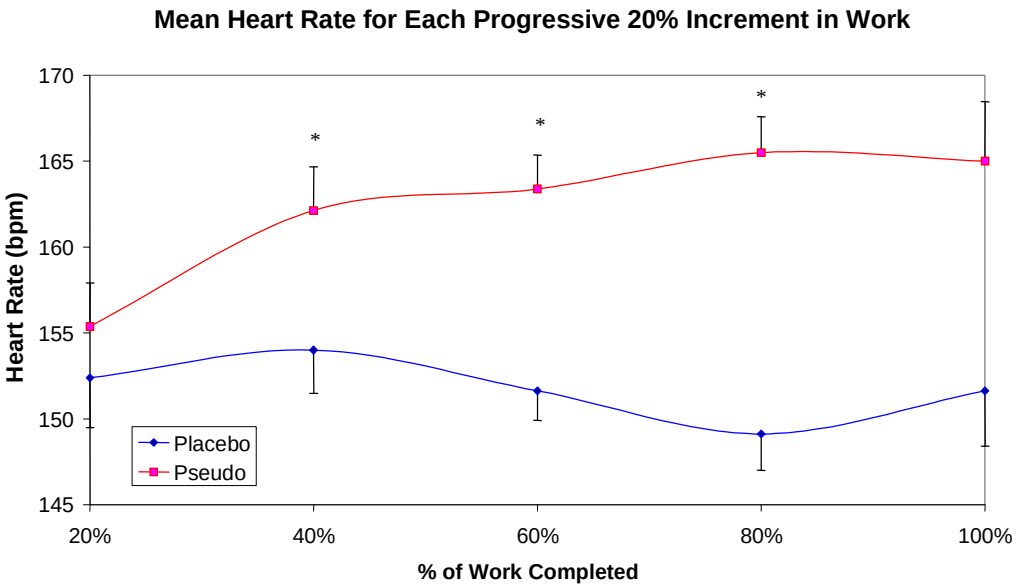

Fig. 7 – Heart Rate for each Progressive 20% Increment in Workload (Mean ± SE) (Significant, p≤0.01)*

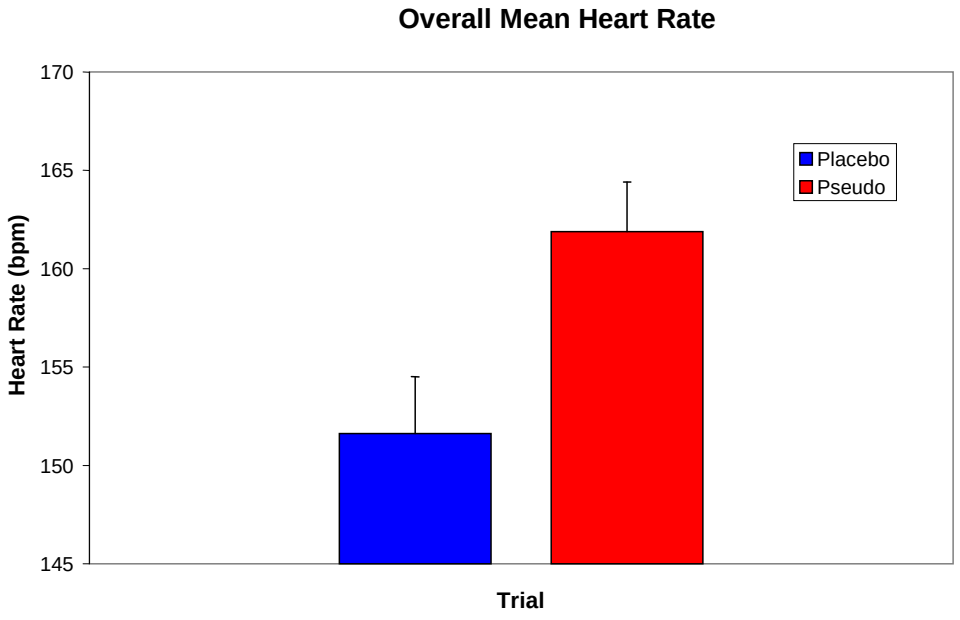

Fig. 8 - Overall Mean Heart Rate (Mean ± SE)

5.3. Metabolic factors

5.3.1. Glucose

There was no significant interaction between whole blood glucose concentration and time. ($p = 0.169$). The whole blood glucose response during testing did not differ between treatments ($p = 0.438$), (Figure 9)

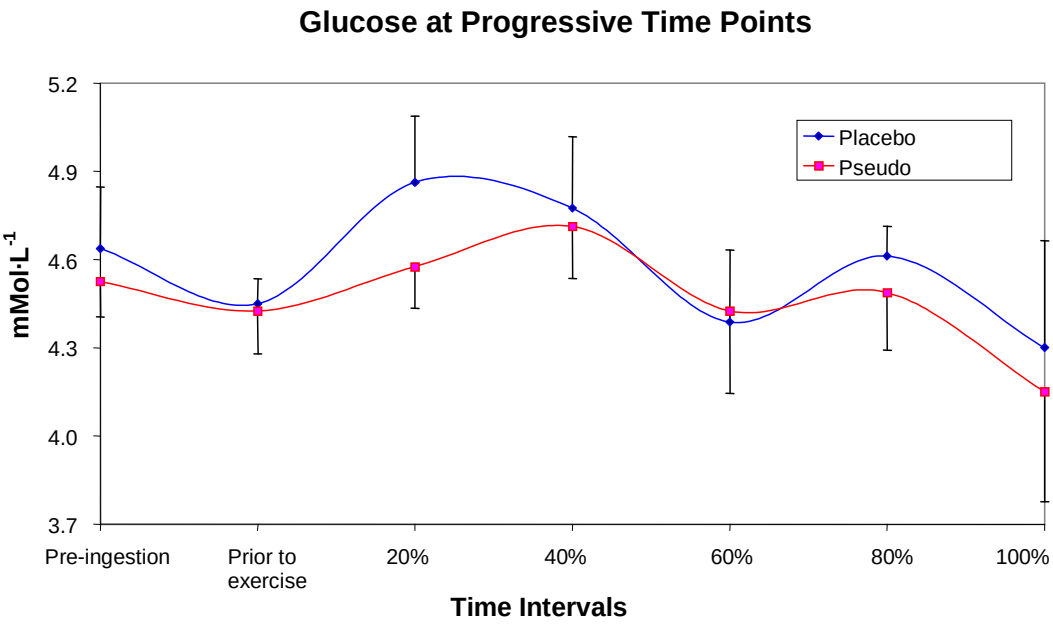

Fig. 9 – Blood Glucose Concentrations at each Time Point throughout Trial (Mean ± SE)

5.3.2. Lactate

The whole blood lactate response during testing also did not differ between treatments (p = 0.390), (see Figure 10 below).

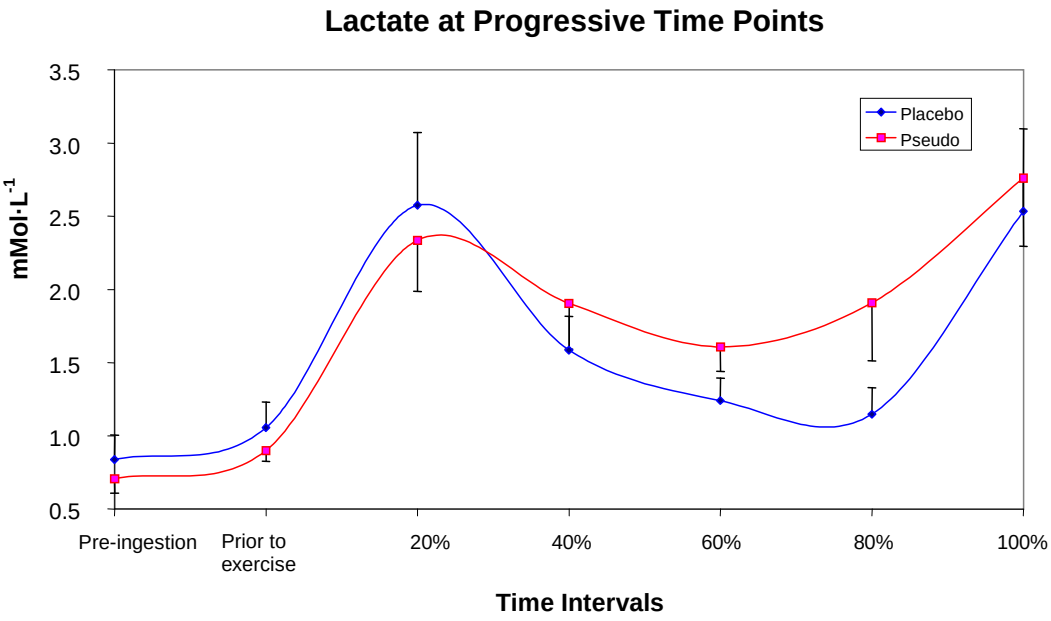

Fig. 10 – Blood Lactate Concentrations at each Time Point from Prior to Ingestion of Pills to Completion of Trial (Mean ± SE)

6. Discussion

It was interesting to note that none of the participants experienced sympathetic nervous effects at rest that would indicate the prior ingestion of pseudoephedrine (e.g. restlessness, tachycardia, decreased ability to concentrate). This indicates that a dosage exceeding commonly prescribed therapeutic levels is well tolerated in physically active males, at least for the first 90 min after ingestion. However, the small amount of food concurrently ingested may have slightly delayed pseudoephedrine ingestion and thus also delayed the onset of any side effects.

6.1. Performance

The ingestion of pseudoephedrine at a dose of approximately three times that given therapeutically improved performance in five out of the eight participants. These participants commented that they felt "good" or "strong" during the time trial, supporting a possible ergogenic effect of pseudoephedrine in some individuals.

However, because of the variation in individual response, overall mean performance was not significantly improved with pseudoephedrine ingestion. This large variability is shown in figure 11. Performance increased 10-15% with ingestion of pseudoephedrine for four of the participants. On the contrary, two participants had a decrease in performance of similar proportion. One of these participants experienced adverse effects during the trial as described in the results. These symptoms can be assumed to be main reason for poor performance during the pseudoephedrine trial. The large variability is unlikely to be explained by day to day variation in performance. Schabort et al. (1998) found a low coefficient of variation within cyclist, (1.7 %) using a closed end exercise protocol of a similar duration. The close control on diet and prior exercise in the present study suggests that the varied performance response is more likely to be a result of the differing responses of individuals to pseudoephedrine. Pseudoephedrine may improve performance for some individuals, where as for others it has little or even impairs endurance performance. The differing responses are likely to be due to varying sensitivities to the drug, as noted by the adverse effects on some of the participants and beneficial effects on others (e.g. feeling "stronger" and performing better). All participants

ingested pseudoephedrine at the same dose rate; therefore a reduced dose may have a more beneficial effect on individuals with greater sensitivity.

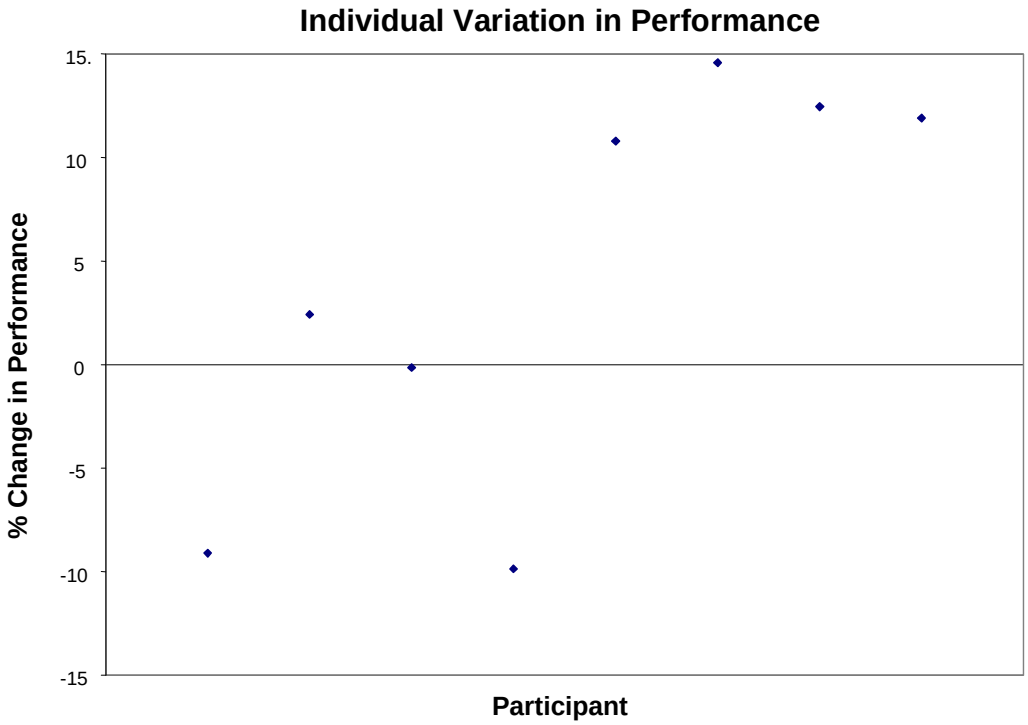

Fig. 11 – The Percentage Change in Performance with Pseudoephedrine compared to Placebo

6.2. Temperature

Pseudoephedrine may have an effect on core temperature. This could be a result of the vasoconstrictive effect of pseudoephedrine (Rang et al. 2003), thereby decreasing the ability to lose heat. An effect on temperature has not been noted in previous studies. The anecdotal increase in this study may be due to the more prolonged exercise protocol employed than in previous studies.

A reduction in exercise performance with a significantly elevated core temperature has been well documented (Gonzalez-Alonso et al. 1999) (Nielsen et al. 2001; Nybo and Nielsen 2001; Nybo et al. 2002). This impairment in performance with hyperthermia is associated with two major sets of homeostatic disturbances. Firstly, an elevation in body (especially brain) temperature may reduce central arousal, increasing perception of fatigue (Nielsen et al. 2001) as well as causing an impairment in central neuromuscular activation (Nybo and Nielsen 2001). Secondly, hyperthermia results in a greater cardiovascular strain and reduced blood flow to the brain and viscera. An increase in cerebral metabolic activity occurs concurrently with the reduction in blood flow resulting in glycogen deprivation, in turn impairing cerebral function (Nybo et al. 2002). A significant reduction in visceral blood flow results in the integrity of the intestinal walls being compromised which can lead to endotoxemia (Sakuranda and Hales 1998). Both these effects result in the onset of fatigue being more rapid (Gonzalez-Alonso et al. 1999; Nybo et al. 2002; Cheung and Sleivert 2004)**.**

The reduction in performance observed in two participants in this study, may be due to hyperthermia. Temperature was not recorded, but two of the participants commented that they felt "hotter" than normal. They may have a greater response to the vasoconstrictive properties of psuedoephedrine resulting in a higher core temperature, and negating possible ergogenic effects of the drug.

It was noted that there was a significant ($p=0.034$) negative linear correlation ($R^2 = 0.55$) between VO_{2max} and the effect of pseudoephedrine on performance as shown in fig 12. It appears from the graph that with an increased VO_{2max} pseudoephedrine had a reduced ergogenic or even ergolytic effect. Since a higher VO_{2max} is an indicator of

an ability to work at a greater metabolic rate, these participants may have an increased risk of reaching a critical body temperature. However, without measurement of body temperature during exercise such a theory remains purely speculative.

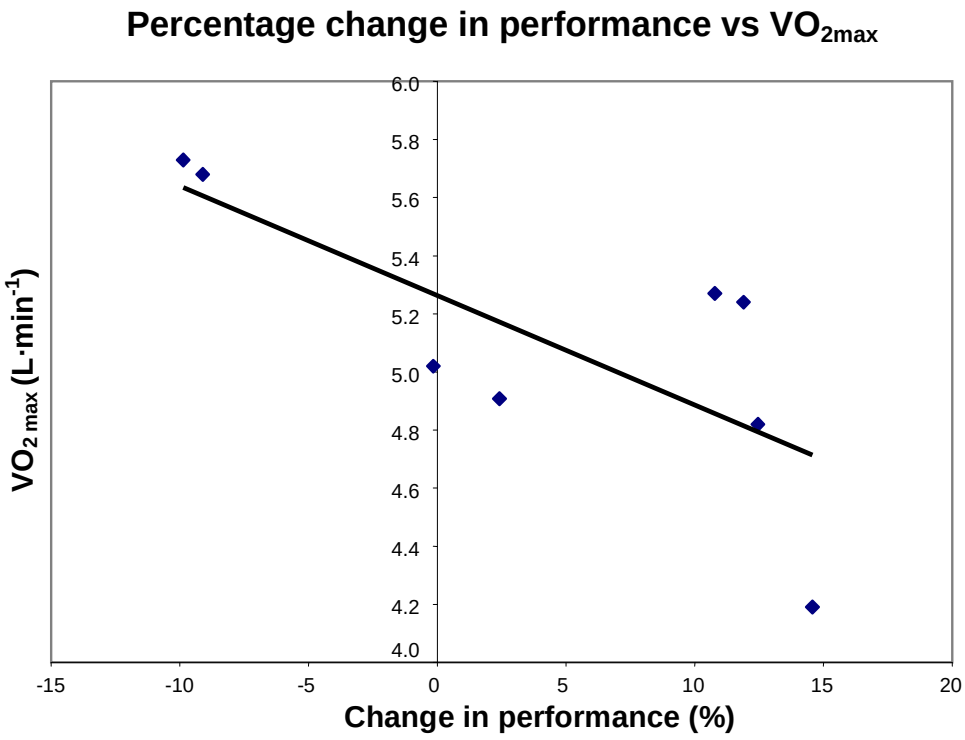

Fig. 12 – The Percentage Change in Performance with Pseudoephedrine compared to Placebo

6.3. Heart rate

Pseudoephedrine was found to significantly increase heart rate consistent with findings by Clemons and Crosby (1993) and Gill et al. (2000). No effect on heart rate was seen in studies by Swain et al. (1997), Chester et al. (2003), Hodges et al. (2003; 2006) and Hodges et al. (Hodges et al. 2006). Gill et al.(2000) used a similar dose to that used in our study (180 mg cf 186 ± 5 mg), whilst Clemons and Crosby (1993) observed a significant increase in heart rate in response to a therapeutic dose (60 mg).

The elevation in heart rate observed is likely to be due to the stimulation by pseudoephedrine on the sympathetic nervous system thereby increasing the rate of contraction of the cardiac muscle, (Empey et al. 1980). The possible elevation in core body temperature may also contribute to the elevation in heart rate. There is an increase in heart rate as core temperature increases, in attempt to maintain cardiac output as stroke volume decreases (Rowell et al. 1966; Gonzalez-Alonso et al. 1999).

6.4. Metabolic factors

Pseudoephedrine did not have a significant effect on the metabolic factors measured (glucose and lactate), consistent with findings from studies by Gill et al. (2000), Chester et al. (2003), and Hodges et al. This (especially lactate) is also consistent with the lack of difference in power output.

Chester et al (2003) also measured non-esterified fatty acids (NEFA) and found that pseudoephedrine did not affect the NEFA levels compared to the placebo. These consistent findings suggest that pseudoephedrine exhibits its effects through central mechanisms rather than metabolic factors.

6.5. Safety and sensitivities

The adverse effects experienced by some in this study also brings into question the safety of consuming pseudoephedrine at such high dosages. With no restrictions to the use of pseudoephedrine, athletes may freely use the drug at increasing dosages with the belief that "more is better". This could lead to serious side effects and the risk of possibly fatal cardiovascular complication (Cantu et al. 2003; Rossi 2006).

6.6. Future Research

More research is required to determine the effects of pseudoephedrine on endurance and sporting performance, especially the use of doses exceeding therapeutic levels. Rate of perceived exertion (RPE) at set points throughout the trial would have been useful and is recommended in further studies to determine more quantifiably the effect of pseudoephedrine on a participant's perception of fatigue.

A greater number of participants and/or more trials per participant would distinguish more definitively if the variation observed in this study was due to variation in individual response to pseudoephedrine.

The measurement of core temperature is recommended for future studies to determine if pseudoephedrine has a significant effect on thermo-regulation. This would assist in determining if temperature influences the performance effect of pseudoephedrine. Other suggestions for future research would be to reduce the feedback given to participants during the trial and to vary dose rates. The varying effects of pseudoephedrine observed in this study may be a result of different individual sensitivity. It would be interesting in a future study to vary dose rates and determine if lower doses in more sensitive individuals would avoid adverse effects and result in a possible performance enhancement, as observed in some of the participants in this study.

7. Conclusion

In summary this study suggests that pseudoephedrine may have an ergogenic effect on individual endurance performance despite there being a lack of overall significance between the placebo and pseudoephedrine trials. The possibility of the drug enhancing performance can not be eliminated based on this current study and the studies by Gill et al. (2000) and Hodges et al. (2006). Therefore its complete removal from the WADA list of banned substance can not be justified at this present time. Pseudoephedrine significantly elevated heart rate during exercise while having no effect on the metabolic factors, glucose and lactate.

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9. Appendix 1: ANOVA tables

Time

Descriptive Statistics

	Mean	Std. Deviation	N
Timeplacebo20	2016.1250	182.38142	8
Timepseudo20	2038.3750	144.06540	8
Timeplacebo40	4152.6250	364.95203	8
Timepseudo40	4097.2500	308.68511	8
Timeplacebo60	6399.7500	571.22944	8
Timepseudo60	6231.6250	526.86348	8
Timeplacebo80	8925.8750	891.99094	8
Timepseudo80	8440.8750	787.17822	8
Timeplacebo100	11293.3750	1137.39865	8
Timepseudo100	10803.3750	1360.85960	8

Mauchly's Test of Sphericity(b)

Within Subjects Effect	Mauchly's W	Approx. Chi-Square	df	Sig.	Epsilon(a)		
					Greenhouse-Geisser	Huynh-Feldt	Lower-bound
Time	.000	54.172	9	.000	.278	.292	.250
Trial	1.000	.000	0	.	1.000	1.000	1.000
Time * trial	.001	40.213	9	.000	.319	.358	.250

Tests of Within-Subjects Effects

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
Time	Sphericity Assumed	817874912.675	4	204468728.169	523.975	.000
	Greenhouse-Geisser	817874912.675	1.111	736320166.316	523.975	.000
	Huynh-Feldt	817874912.675	1.169	699478121.993	523.975	.000
	Lower-bound	817874912.675	1.000	817874912.675	523.975	.000
Error(time)	Sphericity Assumed	10926322.925	28	390225.819		
	Greenhouse-Geisser	10926322.925	7.775	1405257.138		
	Huynh-Feldt	10926322.925	8.185	1334944.592		
	Lower-bound	10926322.925	7.000	1560903.275		
Trial	Sphericity Assumed	1106851.250	1	1106851.250	1.694	.234
	Greenhouse-Geisser	1106851.250	1.000	1106851.250	1.694	.234
	Huynh-Feldt	1106851.250	1.000	1106851.250	1.694	.234
	Lower-bound	1106851.250	1.000	1106851.250	1.694	.234
Error(trial)	Sphericity Assumed	4574969.750	7	653567.107		
	Greenhouse-Geisser	4574969.750	7.000	653567.107		
	Huynh-Feldt	4574969.750	7.000	653567.107		
	Lower-bound	4574969.750	7.000	653567.107		
Time * trial	Sphericity Assumed	921758.625	4	230439.656	2.587	.058
	Greenhouse-Geisser	921758.625	1.275	722805.648	2.587	.140
	Huynh-Feldt	921758.625	1.433	643359.135	2.587	.133
	Lower-bound	921758.625	1.000	921758.625	2.587	.152
Error(time*trial)	Sphericity Assumed	2493661.375	28	89059.335		
	Greenhouse-Geisser	2493661.375	8.927	279346.842		
	Huynh-Feldt	2493661.375	10.029	248642.693		
	Lower-bound	2493661.375	7.000	356237.339		

Time (trial effect)

Descriptive Statistics

	Mean	Std. Deviation	N
Timetrial120	33.3125	2.98445	8
Timetrial220	34.3000	2.34886	8
Timetrial140	68.5000	6.49879	8
Timetrial240	69.0000	4.67394	8
Timetrial160	105.2625	10.66006	8
Timetrial260	105.3000	7.65898	8
Timetrial180	144.9125	17.83083	8
Timetrial280	144.5500	10.58436	8
Timetrial1100	182.2500	23.94488	8
Timetrial2100	186.0500	18.21436	8

Mauchly's Test of Sphericity(b)

Within Subjects Effect	Mauchly's W	Approx. Chi-Square	df	Sig.	Epsilon(a)		
					Greenhouse-Geisser	Huynh-Feldt	Lower-bound
Time	.000	54.496	9	.000	.278	.292	.250
Trial	1.000	.000	0	.	1.000	1.000	1.000
*Time * trial*	*.000*	*44.680*	*9*	*.000*	*.318*	*.357*	*.250*

Tests of Within-Subjects Effects

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
Time	Sphericity Assumed	227176.329	4	56794.082	523.015	.000
	Greenhouse-Geisser	227176.329	1.111	204523.943	523.015	.000
	Huynh-Feldt	227176.329	1.169	194290.787	523.015	.000
	Lower-bound	227176.329	1.000	227176.329	523.015	.000
Error(time)	Sphericity Assumed	3040.515	28	108.590		
	Greenhouse-Geisser	3040.515	7.775	391.048		
	Huynh-Feldt	3040.515	8.185	371.482		
	Lower-bound	3040.515	7.000	434.359		
Trial	Sphericity Assumed	19.701	1	19.701	.088	.775
	Greenhouse-Geisser	19.701	1.000	19.701	.088	.775
	Huynh-Feldt	19.701	1.000	19.701	.088	.775
	Lower-bound	19.701	1.000	19.701	.088	.775
Error(trial)	Sphericity Assumed	1559.160	7	222.737		
	Greenhouse-Geisser	1559.160	7.000	222.737		
	Huynh-Feldt	1559.160	7.000	222.737		
	Lower-bound	1559.160	7.000	222.737		
Time * trial	Sphericity Assumed	43.491	4	10.873	.335	.852
	Greenhouse-Geisser	43.491	1.272	34.195	.335	.629
	Huynh-Feldt	43.491	1.427	30.474	.335	.653
	Lower-bound	43.491	1.000	43.491	.335	.581
Error(time*trial)	Sphericity Assumed	909.373	28	32.478		
	Greenhouse-Geisser	909.373	8.903	102.142		
	Huynh-Feldt	909.373	9.990	91.029		
	Lower-bound	909.373	7.000	129.910		

Power

Descriptive Statistics

	Mean	Std. Deviation	N
Powerplacebo20	247.7500	40.60172	8
Powerpseudo20	242.5000	24.95138	8
Powerplacebo40	232.1250	31.51615	8
Powerpseudo40	240.2500	21.95287	8
Powerplacebo60	221.5000	32.25789	8
Powerpseudo60	232.1250	21.26995	8
Powerplacebo80	201.5000	36.40644	8
powerpseudo80	227.3750	24.85350	8
powerplacebo100	214.7500	50.73672	8
powerpseudo100	214.0000	34.73162	8

Mauchly's Test of Sphericity(b)

Within Subjects Effect	Mauchly's W	Approx. Chi-Square	df	Sig.	Epsilon(a)		
					Greenhouse-Geisser	Huynh-Feldt	Lower-bound
Time	.018	21.831	9	.013	.385	.473	.250
Trial	1.000	.000	0	.	1.000	1.000	1.000
time * trial	.004	29.683	9	.001	.391	.483	.250

Tests of Within-Subjects Effects

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
Time	Sphericity Assumed	11670.675	4	2917.669	4.536	.006
	Greenhouse-Geisser	11670.675	1.542	7569.150	4.536	.045
	Huynh-Feldt	11670.675	1.894	6163.528	4.536	.033
	Lower-bound	11670.675	1.000	11670.675	4.536	.071
Error(time)	Sphericity Assumed	18011.525	28	643.269		
	Greenhouse-Geisser	18011.525	10.793	1668.797		
	Huynh-Feldt	18011.525	13.255	1358.895		
	Lower-bound	18011.525	7.000	2573.075		
Trial	Sphericity Assumed	1193.512	1	1193.512	.987	.354
	Greenhouse-Geisser	1193.512	1.000	1193.512	.987	.354
	Huynh-Feldt	1193.512	1.000	1193.512	.987	.354
	Lower-bound	1193.512	1.000	1193.512	.987	.354
Error(trial)	Sphericity Assumed	8462.588	7	1208.941		
	Greenhouse-Geisser	8462.588	7.000	1208.941		
	Huynh-Feldt	8462.588	7.000	1208.941		
	Lower-bound	8462.588	7.000	1208.941		
Time * trial	Sphericity Assumed	2312.675	4	578.169	2.293	.084
	Greenhouse-Geisser	2312.675	1.562	1480.258	2.293	.153
	Huynh-Feldt	2312.675	1.931	1197.810	2.293	.140
	Lower-bound	2312.675	1.000	2312.675	2.293	.174
Error(time* trial)	Sphericity Assumed	7058.725	28	252.097		
	Greenhouse-Geisser	7058.725	10.936	645.433		
	Huynh-Feldt	7058.725	13.515	522.278		
	Lower-bound	7058.725	7.000	1008.389		

Heart rate

Descriptive Statistics

	Mean	Std. Deviation	N
HRplacebo20	152.3750	8.15804	8
HRpseudo20	155.3750	7.15017	8
HRplacebo40	154.0000	7.13142	8
HRpseudo40	162.1250	7.19995	8
HRplacebo60	151.6250	4.83846	8
HRpseudo60	163.3750	5.57898	8
HRplacebo80	149.1250	5.98659	8
HRpseudo80	165.5000	5.90399	8
HRplacebo100	151.6250	9.11729	8
HRpseudo100	165.0000	9.79796	8

Mauchly's Test of Sphericity(b)

Within Subjects Effect	Mauchly's W	Approx. Chi-Square	df	Sig.	Epsilon(a)		
					Greenhouse-Geisser	Huynh-Feldt	Lower-bound
Time	.042	17.109	9	.056	.415	.527	.250
Trial	1.000	.000	0	.	1.000	1.000	1.000
time * trial	.069	14.472	9	.121	.410	.519	.250

Tests of Within-Subjects Effects

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
Time	Sphericity Assumed	207.425	4	51.856	1.127	.364
	Greenhouse-Geisser	207.425	1.658	125.077	1.127	.346
	Huynh-Feldt	207.425	2.109	98.339	1.127	.353
	Lower-bound	207.425	1.000	207.425	1.127	.324
Error(time)	Sphericity Assumed	1288.175	28	46.006		
	Greenhouse-Geisser	1288.175	11.609	110.967		
	Huynh-Feldt	1288.175	14.765	87.245		
	Lower-bound	1288.175	7.000	184.025		
Trial	Sphericity Assumed	2215.512	1	2215.512	27.814	.001
	Greenhouse-Geisser	2215.512	1.000	2215.512	27.814	.001
	Huynh-Feldt	2215.512	1.000	2215.512	27.814	.001
	Lower-bound	2215.512	1.000	2215.512	27.814	.001
Error(trial)	Sphericity Assumed	557.587	7	79.655		
	Greenhouse-Geisser	557.587	7.000	79.655		
	Huynh-Feldt	557.587	7.000	79.655		
	Lower-bound	557.587	7.000	79.655		
Time * trial	Sphericity Assumed	424.925	4	106.231	7.880	.000
	Greenhouse-Geisser	424.925	1.641	258.953	7.880	.009
	Huynh-Feldt	424.925	2.076	204.647	7.880	.005
	Lower-bound	424.925	1.000	424.925	7.880	.026
Error(time*trial)	Sphericity Assumed	377.475	28	13.481		
	Greenhouse-Geisser	377.475	11.487	32.862		
	Huynh-Feldt	377.475	14.535	25.971		
	Lower-bound	377.475	7.000	53.925		

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	HRplacebo20	152.3750	8	8.15804	2.88430
	HRpseudo20	155.3750	8	7.15017	2.52797
Pair 2	HRplacebo40	154.0000	8	7.13142	2.52134
	HRpseudo40	162.1250	8	7.19995	2.54557
Pair 3	HRplacebo60	151.6250	8	4.83846	1.71065
	HRpseudo60	163.3750	8	5.57898	1.97247
Pair 4	HRplacebo80	149.1250	8	5.98659	2.11658
	HRpseudo80	165.5000	8	5.90399	2.08738
Pair 5	HRplacebo100	151.6250	8	9.11729	3.22345
	HRpseudo100	165.0000	8	9.79796	3.46410

Paired Samples Correlations

		N	Correlation	Sig.
Pair 1	HRplacebo20 & HRpseudo20	8	.747	.033
Pair 2	HRplacebo40 & HRpseudo40	8	.573	.138
Pair 3	HRplacebo60 & HRpseudo60	8	.609	.109
Pair 4	HRplacebo80 & HRpseudo80	8	.305	.462
Pair 5	HRplacebo100 & HRpseudo100	8	.320	.440

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	Hrplacebo20 – Hrpseudo20	-3.00000	5.52914	1.95485	-7.62248	1.62248	-1.535	7	.169
Pair 2	Hrplacebo40 – Hrpseudo40	-8.12500	6.62112	2.34092	-13.66040	-2.58960	-3.471	7	.010
Pair 3	Hrplacebo60 – Hrpseudo60	-11.75000	4.65219	1.64480	-15.63933	-7.86067	-7.144	7	.000
Pair 4	Hrplacebo80 – Hrpseudo80	-16.37500	7.00892	2.47803	-22.23461	-10.51539	-6.608	7	.000
Pair 5	Hrplacebo100 – Hrpseudo100	-13.37500	11.04455	3.90484	-22.60848	-4.14152	-3.425	7	.011

Glucose

Descriptive Statistics

	Mean	Std. Deviation	N
glucose1placebo	4.6375	.59266	8
glucose1pseudo	4.5250	.34122	8
glucose2placebo	4.4500	.23905	8
glucose2pseudo	4.4250	.41318	8
glucose3placebo	4.8625	.63906	8
glucose3pseudo	4.5750	.39911	8
glucose4placebo	4.7750	.68817	8
glucose4pseudo	4.7125	.49982	8
glucose5placebo	4.3875	.69372	8
glucose5pseudo	4.4250	.79237	8
glucose6placebo	4.6125	.28504	8
glucose6pseudo	4.4875	.55404	8
glucose7placebo	4.3000	1.02956	8
glucose7pseudo	4.1500	1.05695	8

Mauchly's Test of Sphericity(b)

Within Subjects Effect	Mauchly's W	Approx. Chi-Square	df	Sig.	Epsilon(a)		
					Greenhouse-Geisser	Huynh-Feldt	Lower-bound
Time	.033	16.243	20	.782	.511	.955	.167
Trial	1.000	.000	0	.	1.000	1.000	1.000
time * trial	.000	39.222	20	.015	.352	.509	.167

Tests of Within-Subjects Effects

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
Time	Sphericity Assumed	3.215	6	.536	1.606	.169
	Greenhouse-Geisser	3.215	3.067	1.048	1.606	.217
	Huynh-Feldt	3.215	5.732	.561	1.606	.173
	Lower-bound	3.215	1.000	3.215	1.606	.246
Error(time)	Sphericity Assumed	14.008	42	.334		
	Greenhouse-Geisser	14.008	21.472	.652		
	Huynh-Feldt	14.008	40.121	.349		
	Lower-bound	14.008	7.000	2.001		
Trial	Sphericity Assumed	.300	1	.300	.677	.438
	Greenhouse-Geisser	.300	1.000	.300	.677	.438
	Huynh-Feldt	.300	1.000	.300	.677	.438
	Lower-bound	.300	1.000	.300	.677	.438
Error(trial)	Sphericity Assumed	3.105	7	.444		
	Greenhouse-Geisser	3.105	7.000	.444		
	Huynh-Feldt	3.105	7.000	.444		
	Lower-bound	3.105	7.000	.444		
Time * trial	Sphericity Assumed	.257	6	.043	.172	.983
	Greenhouse-Geisser	.257	2.115	.122	.172	.855
	Huynh-Feldt	.257	3.054	.084	.172	.917
	Lower-bound	.257	1.000	.257	.172	.691
Error(time*trial)	Sphericity Assumed	10.477	42	.249		
	Greenhouse-Geisser	10.477	14.805	.708		
	Huynh-Feldt	10.477	21.380	.490		
	Lower-bound	10.477	7.000	1.497		

Lactate

Descriptive Statistics

	Mean	Std. Deviation	N
lactateplacebo1	.8375	.47767	8
lactatepseudo1	.7075	.27850	8
lactateplacebo2	1.0563	.49182	8
lactatepseudo2	.9000	.20723	8
lactateplacebo3	2.5750	1.40698	8
lacatepseudo3	2.3363	.99041	8
lactateplacebo4	1.5863	.64942	8
lactatepseduo4	1.9050	.88345	8
lactateplacebo5	1.2400	.43889	8
lactatepseudo5	1.6075	.47052	8
lactateplacebo6	1.1475	.51439	8
lactatepseudo6	1.9088	1.12105	8
lactateplacebo7	2.5325	1.59995	8
lactatepseudo7	2.7612	1.32215	8

Mauchly's Test of Sphericity(b)

Within Subjects Effect	Mauchly's W	Approx. Chi-Square	df	Sig.	Epsilon(a)		
					Greenhouse-Geisser	Huynh-Feldt	Lower-bound
Time	.000	49.216	20	.001	.277	.352	.167
Trial	1.000	.000	0	.	1.000	1.000	1.000
time * trial	.019	18.989	20	.626	.505	.933	.167

Tests of Within-Subjects Effects

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
Time	Sphericity Assumed	47.030	6	7.838	7.633	.000
	Greenhouse-Geisser	47.030	1.659	28.344	7.633	.010
	Huynh-Feldt	47.030	2.111	22.279	7.633	.005
	Lower-bound	47.030	1.000	47.030	7.633	.028
Error(time)	Sphericity Assumed	43.133	42	1.027		
	Greenhouse-Geisser	43.133	11.615	3.714		
	Huynh-Feldt	43.133	14.777	2.919		
	Lower-bound	43.133	7.000	6.162		
Trial	Sphericity Assumed	.757	1	.757	.838	.390
	Greenhouse-Geisser	.757	1.000	.757	.838	.390
	Huynh-Feldt	.757	1.000	.757	.838	.390
	Lower-bound	.757	1.000	.757	.838	.390
Error(trial)	Sphericity Assumed	6.328	7	.904		
	Greenhouse-Geisser	6.328	7.000	.904		
	Huynh-Feldt	6.328	7.000	.904		
	Lower-bound	6.328	7.000	.904		
Time * trial	Sphericity Assumed	3.110	6	.518	1.668	.153
	Greenhouse-Geisser	3.110	3.028	1.027	1.668	.204
	Huynh-Feldt	3.110	5.596	.556	1.668	.159
	Lower-bound	3.110	1.000	3.110	1.668	.238
Error(time* trial)	Sphericity Assumed	13.055	42	.311		
	Greenhouse-Geisser	13.055	21.197	.616		
	Huynh-Feldt	13.055	39.171	.333		
	Lower-bound	13.055	7.000	1.865		

10. Appendix 2: Characteristic data

Participant	Age	Weight (kg)	VO2 max		Work to complete	
			Absolute (L/min)	Relative (ml/kg)	Total (kj)	Relative (kj/kg)
A.M.	32	86.7	5.68	65.52	2997	34.6
S.B.	23	76	4.91	64.58	2435	32.0
S.C	22	76.9	5.02	65.3	2403	31.2
S.S	39	74.9	5.73	76.53	2741	36.6
J. G	27	71.3	5.27	73.88	2645	37.1
J.M.	24	72.8	4.19	57.59	2385	32.8
M.W	34	68.6	4.82	70.26	2232	32.5
S.H.	27	69.2	5.24	75.3	1953	28.2

11. Appendix 3: Raw data

Placebo										
	Time									
Participant	20%	20% (min)	40%	40% (min)	60%	60% (min)	80%	80% (min)	Overall Time (Sec)	Minutes
A.M.	1968	32.8	4210	70.2	6701	111.7	10054	167.6	12262	204.4
S.B.	1855	30.9	3895	64.9	6210	103.5	8820	147.0	11790	196.5
S.C	2049	34.2	4201	70.0	6303	105.1	8398	140.0	10267	171.1
S.S	1781	29.7	3703	61.7	5611	93.5	7596	126.6	9702	161.7
J. G	2269	37.8	4757	79.3	7453	124.2	10285	171.4	13227	220.5
J.M.	1857	31.0	3776	62.9	5876	97.9	8345	139.1	11183	186.4
M.W	2240	37.3	4541	75.7	6759	112.7	9116	151.9	11351	189.2
S.H.	2110	35.2	4138	69.0	6285	104.8	8793	146.6	10565	176.1

Pseudoephedrine										
	Time									
Participant	20%	20% (min)	40%	40% (min)	60%	60% (min)	80%	80% (min)	Overall Time (Sec)	Minutes
A.M.	2112	35.2	4350	72.5	6924	115.4	9812	163.5	13380	223.0
S.B.	2064	34.4	4185	69.8	6360	106.0	8665	144.4	11505	191.8
S.C	2031	33.9	4202	70.0	6345	105.8	8358	139.3	10283	171.4
S.S	1978	33.0	4010	66.8	6033	100.6	8241	137.4	10660	177.7
J. G	2333	38.9	4637	77.3	7017	117.0	9311	155.2	11800	196.7
J.M.	1841	30.7	3696	61.6	5661	94.4	7647	127.5	9554	159.2
M.W.	1947	32.5	3824	63.7	5734	95.6	7813	130.2	9937	165.6
S.H.	2001	33.4	3874	64.6	5779	96.3	7680	128.0	9308	155.1

Placebo												
	Power output						**Heart Rate**					
Participant	20%	40%	60%	80%	100%	Overall	20%	40%	60%	80%	100%	Overall
A.M.	304	268	240	179	271	244	158	162	157	156	158	158
S.B.	263	239	210	187	164	207	158	158	153	151	147	153
S.C	238	220	229	229	257	234	156	156	157	157	167	158
S.S	308	285	288	276	261	283	148	145	144	144	140	144
J. G	233	213	196	187	180	200	159	157	150	151	154	153
J.M.	211	203	186	158	138	175	156	157	155	139	140	149
M.W	199	194	201	190	200	197	135	141	146	147	153	145
S.H.	226	235	222	206	247	226	149	156	151	148	154	153

Pseudoephedrine												
	Power output						**Heart Rate**					
Participant	20%	40%	60%	80%	100%	Overall	20%	40%	60%	80%	100%	Overall
A.M.	284	268	233	208	168	224	161	172	172	168	151	163
S.B.	236	230	224	211	171	212	159	162	164	170	166	164
S.C	237	221	224	238	250	234	160	159	163	164	173	163
S.S	277	270	271	248	227	257	149	153	155	153	151	152
J. G	227	230	222	231	213	224	151	154	156	164	162	158
J.M.	212	210	199	196	205	204	161	170	165	164	167	165
M.W	229	238	234	215	210	225	142	159	165	169	174	162
S.H.	238	255	250	272	268	256	160	168	167	172	176	168

Placebo														
	Glucose							**Lactate**						
Participant	1	2	3	4	5	6	7	1	2	3	4	5	6	7
A.M.	5.5	4.4	4.3	4.7	4.3	4.4	4.2	1.37	0.94	4.4	2.04	1.33	1.19	2.07
S.B.	4.4	4.4	4.2	4.4	4.0	4.9	3.8	0.65	1.57	3.50	1.19	1.56	1.25	2.05
S.C	5.6	4.4	5.9	6.3	5.7	4.7	6.3	1.79	2.02	1.36	1.31	1.42	2.04	6.09
S.S	4.0	4.7	5.2	4.7	4.3	4.5	3.5	0.58	0.86	4.04	2.73	2.03	1.68	2.20
J. G	4.6	4.1	5.3	4.8	4.9	4.6	3.4	0.56	0.57	1.79	1.01	0.85	1.05	1.43
J.M.	4.3	4.8	5.2	4.2	4.4	4.1	3.6	0.72	0.81	3.42	2.12	1.12	0.79	0.89
M.W	4.5	4.2	4.1	4.1	3.3	5	5.4	0.46	1.01	0.91	1.46	0.94	0.61	3.35
S.H.	4.2	4.6	4.7	5	4.2	4.7	4.2	0.57	0.67	1.18	0.83	0.67	0.57	2.18

Pseudoephedrine														
	Glucose							**Lactate**						
Participant	1	2	3	4	5	6	7	1	2	3	4	5	6	7
A.M.	4.9	4.2	4.7	3.7	4.5	4.5	4.8	1.02	1.00	3.98	3.54	1.49	1.5	3.06
S.B.	3.9	4.9	3.9	5.3	3.7	4.4	2.5	0.5	0.83	2.04	1.33	1.53	1.37	1.28
S.C	4.8	4.8	5.1	5.0	5.8	4.4	5.2	1.07	1.08	2.04	2.11	1.41	2.68	4.76
S.S	4.9	4.5	5.0	5.0	4.4	4.8	4.2	0.58	0.75	2.8	2.59	2.59	1.39	1.62
J. G	4.5	3.6	4.4	4.9	4.7	4.7	3.7	0.34	1.22	1.62	0.98	1.92	1.38	2.02
J.M.	4.4	4.7	4.4	4.9	4.8	5.5	5.7	0.64	0.58	3.43	2.21	1.52	1.44	3.14
M.W.	4.5	4.3	4.3	4.5	3.1	3.7	3.2	0.99	0.98	1.02	1.00	0.99	1.09	1.74
S.H.	4.3	4.4	4.8	4.4	4.4	3.9	3.9	0.52	0.76	1.76	1.48	1.41	4.42	4.47

12. Appendix 4: Information sheet, health screening questionnaire and consent form

Participant Information Sheet

Project Title : The effects of Pseudoephedrine on endurance cycling performance

"This project has been reviewed and approved by the Central Ethics Committee Application CEN/07/05/032. If you have any questions or concerns about your rights as a participant in this research study you can contact an independent health and disability advocate. This is a free service provided under the Health and Disability Commissioner Act. Telephone: (NZ wide) 0800 555 050 Free Fax (NZ wide): 0800 2787 7678 (0800 2 SUPPORT) Email (NZ wide): advocacy@hdc.org.nz"

The chief investigator of this project is:

Scott Betteridge MSc student, Institute of Food, Nutrition and Human Health.
Ph 354 6809
S.Betteridge@massey.ac.nz

The supervisors of this project are:

Dr. Steve Stannard Senior Lecturer, Institute of Food, Nutrition and Human Health
Ph 350 5799 Ext 7465
S.Stannard@masssey.ac.nz

Dr. Toby Mundel Lecturer, Institute of Food, Nutrition and Human Health
Ph 350 5799 Ext 7763
T.Mundel@massey.ac.nz

This research will form part of a thesis required for the completion of a Masters of Science degree for Scott Betteridge.

Introduction

Pseudoephedrine is a mild stimulant that partially mimics the actions of noradrenaline and adrenaline, and is found in over the counter drugs to relieve nasal and sinus congestion. Pseudoephedrine was removed from the banned substance list by the World Anti Doping Agency (WADA) from January 2004 as it was felt there was little evidence for an performance enhancing effect despite there being little research investigating its effect on sporting performance, and no research on endurance performance (>2hr). Pseudoephedrine may have a performance enhancing effect due to its stimulatory effect on the central nervous system, and as a result possibly masking an individual's perception of fatigue thus increasing performance. Therefore the aim of this study is to investigate if pseudoephedrine does have an effect on endurance performance.

Participation

We are recruiting fit and healthy male cyclists 18-40 years of age, who train on average more than 200 km a week and regularly competes at club level, to participate in this study. All participation is voluntary and you may withdraw from participating in the study at any time. If you agree to participate, you will be asked to participate in 3 trials during which time you will be exercising on a cycle ergometer for 2 trials and your blood will be sampled. You will also be asked to adhere to certain dietary and exercise controls in the 24 hours preceding the trials.

These sessions will take place under supervision in the Human Performance Laboratory (HPL), the Institute of Food, Nutrition and Human Health (IFNHH) at Massey University.

The names and contact details of the researchers undertaking this project are given above. Please do not hesitate to contact any one of them if you have any questions about this project at any time.

Testing

Prior to the first pseudoephedrine performance trial a number of baseline and calibratory measurements will be made including resting measurements. You will also be required to perform a 10km self-paced time trial on a cycle ergometer. The performance of this time-trial will not be recorded and is only performed in order that you become familiar with the equipment to be used in the subsequent performance trials.

Thereafter, on two separate occasions at least 6-days apart, you will be asked again to attend the laboratory. Upon arriving at the laboratory, you will be weighed, and then be asked to lie down while a small (5ml) blood sample is taken from a vein on the front of your forearm. You will then be given either pseudoephedrine at a dose equating to 2.5mg per kg of body weight or a placebo containing glucose to be ingested. Seventy five minutes after ingestion you will again be asked to lie down whilst a cannula is inserted into a vein on the back of your forearm opposite to which your first blood sample was taken from. The place where the cannula is inserted will be in the opposite arm each trial. A 10-minutes warm up will be performed just prior to beginning the exercise trial. Exactly 90 minutes after the ingestion of the placebo or pseudoephedrine you will begin the 100-km self-paced time-trial, which you will be asked to perform as quickly as possible.

A small (5ml) blood sample will be collected from the cannula just prior to commencing the time-trial, then at 20, 40, 60, 80km into the time trial and upon completing the time trial. Between blood samples the cannula will be regularly flushed with saline. Power output will measured and displayed using the Powertap® throughout the trial. Heart rate is measured electronically using the commonly available Polar® chest band and wristwatch combination. You will be provided with a commercially available sports drink at regular intervals throughout the trial. Once the time trial is complete, the cannula will be removed form your hand and you will be able to warm down.

To ensure that everyone performs each test with a similar metabolic profile, your food intake and physical activity will be controlled for the 24 hours prior to testing. This will involve provision of a meal, which will be required to be consumed 4 hours prior to the test.

In summary, you will be required to come to the laboratory to perform the following:

1) A 10-km familiarisation self-paced time-trial
2) Trial 1 - Ingestion of pseudoephedrine or placebo (glucose) 90 minutes prior to performing 100-km self-paced time-trial
3) Trial 2 - Ingestion of pseudoephedrine or placebo (glucose) 90 minutes prior to performing 100-km self-paced time-trial

Potential risks and discomforts

The procedures involved in participating in this study are of low risk. Nevertheless, as in any invasive and exercise procedures, there are small risks and some discomfort may be experienced:

Venous cannula

Needle insertion into a vein is required for collecting the initial blood sample via syringe as well as for the placement of the cannula, and you will feel minor to moderate discomfort as a result. However with the placement of the cannula, the needle is quickly removed and only a flexible plastic tube remains in your vein for the duration of blood sampling (approximately 2 ½ hours). In order to reduce the risks of infection, we made need to clip any body hair from a small area on your arm, surgical gloves will be worn and the area will be cleaned with an isopropyl alcohol wipe before we insert the needle. When the cannula is removed, direct pressure will be applied to the area to reduce the changes of bruising. Cannulas are routinely placed into veins of participants in clinical research studies and in hospital patients. The risks of IV cannulation are low, but occasionally significant bruising or infection can occur. Both Dr. Stannard and Dr. Mundel are qualified and experienced in venous cannula placement and the use of aseptic techniques. Blood samples are disposed of in their vacutainers or storage tubes into biohazard bags, which are autoclaved at 121°C and disposed of by Nuplex medical waste. Alternatively, you can request to have any/all portions of your samples returned to you.

Exercise

You are likely to experience the fatigue associated with strenuous exercise, particularly during the time trial. Nevertheless, as in any physical activity, there is a very small possibility of injuries that include, but are not restricted to, muscle, ligament or tendon damage, breathing irregularities and dizziness. However, all protocols are commonly performed in exercise physiology laboratories and potential risks to participants have been minimised.

Pseudoephedrine

There are possible side effects associated with the ingestion of pseudoephedrine. The most common side effects are nervousness, restlessness, and trouble sleeping. Other less common side effects include difficult or painful urination, dizziness or lightheadedness, headache, nausea, rapid or pounding heartbeat, trembling, weakness and drowsiness. Very rare and more severe side effects include hallucinations, irregular or slow heartbeat, seizures and trouble breathing.

In the unlikely event of a physical injury as a result of your participation in this study, you may be covered by ACC under the Injury Prevention, Rehabilitation and Compensation Act. ACC cover is not automatic and your case will need to be assessed by ACC according to the provisions of the 2002 Injury Prevention Rehabilitation and Compensation Act. If your claim is accepted by ACC, you still might not get any compensation. This depends on a number of factors such as whether you are an earner or non-earner. ACC usually provides only partial reimbursement of costs and expenses and there may be no lump sum compensation payable. There is no cover for mental injury unless it is a result of physical injury. If you have ACC cover, generally this will affect your right to sue the investigators.

If you have any questions about ACC, contact your nearest ACC office the chief investigator or supervisors of the study.

Participants' rights

No material which could personally identify you will be used in any reports on this study. You can ask questions on any aspect of the project at any time, and we will do our best to answer them to your satisfaction. As a participant in the study you will provide information on the understanding that your name will not be used unless you give permission to the researcher. You have the right to view your own data at any stage and have it explained to you. Individual results will remain confidential. You have the right to have any blood samples returned to you after they have been analysed. You will also be given access to a summary of the project findings when it is concluded. You can withdraw from the project at any time, without giving any reason and without penalty.

Exclusion Criteria

If any of the following apply:

- ***You have a history of gastrointestinal discomfort after the ingestion pseudoephedrine***
- ***You have any known heart or cardiovascular condition or if a member of your family died below the age of fifty (50) as a result of a heart condition.***
- ***You have asthma or any respiratory disease.***
- ***In the last six months you have suffered from any painful injury or condition that lasted more than one week.***
- ***You have ever had an injury or any medical condition that you think may affect your ability to sense pain or discomfort.***
- ***You have ever had persistent or regular lower back pain.***
- ***You are taking prescribed medication.***
- ***You have cultural or religious sensitivities about human body measurements.***
- ***You have any other reason to consider that you are not in good health and of average, or better than average, fitness.***
- ***You commonly have trouble sleeping***

…you should <u>NOT</u> participate in this project.

Thank you for your time and cooperation.

Pre-Exercise Health Screening Questionnaire

Name:_____

Address: _____

Phone: _____

Age: _____

Please read the following questions carefully. If you have any difficulty, please advise the medical practitioner, nurse or exercise specialist who is conducting the exercise test.

Please answer all of the following questions by ticking only <u>one</u> box for each question:

This questionnaire has been designed to identify the small number of persons (15-69 years of age) for whom physical activity might be inappropriate. The questions are based upon the Physical Activity Readiness Questionnaire (PAR-Q), originally devised by the British Columbia Dept of Health (Canada), as revised by [1]Thomas *et al.* (1992) and [2]Cardinal *et al.* (1996), and with added requirements of the Massey University Human Ethics Committee. The information provided by you on this form will be treated with the strictest confidentiality.

Qu 1. Has your doctor ever said that you have a heart condition and that you should only do physical activity recommended by a doctor?

Yes ☐ No ☐

Qu 2. Do you feel a pain in your chest when you do physical activity?

Yes ☐ No ☐

Qu 3. In the past month have you had chest pain when you were not doing physical activity?

Yes ☐ No ☐

Qu 4. Do you lose your balance because of dizziness or do you ever lose consciousness?

Yes ☐ No ☐

Qu 5. Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition?

Yes ☐ No ☐

Qu 6. Do you have a bone or joint problem that could be made worse by vigorous exercise?

Yes ☐ No ☐

Qu 7. Do you know of any other reason why you should not do physical activity?

Yes ☐ No ☐

Qu 8. Has a member of your immediate family, below the age of 50 died as a result of a heart condition?

Yes ☐ No ☐

Qu 9. Have you been hospitalised recently?

Yes ☐ No ☐

Qu 10. Do you have any infectious disease that may be transmitted in blood?

Yes ☐ No ☐

Qu 11. This test includes the taking of blood. Do you have any objection to this?

Yes ☐ No ☐

You should be aware that even amongst healthy persons who undertake regular physical activity there is a risk of sudden death during exercise. Though extremely rare, such cases can occur in people with an undiagnosed heart condition. If you have any reason to suspect that you may have a heart condition that will put you at risk during exercise, you should seek advice from a medical practitioner before undertaking an exercise test.

I have read, understood and completed this questionnaire.

Signature: _____ Date: _____

References

1. Thomas S, Reading J and Shephard RJ. Revision of the Physical Activity Readiness Questionnaire (PAR-Q). *Can J Sport Sci* 17(4): 338-345.
2. Cardinal BJ, Esters J and Cardinal MK. Evaluation of the revised physical activity readiness questionnaire in older adults. *Med Sci Sports Exerc* 28(4): 468-472

CONSENT FORM

Experiment Title: *The effects of Pseudoephedrine on endurance cycling performance*

I have read the Participant Information Sheet for the above experiment and had the procedures and potential risks explained to me by the researchers. I am satisfied that my concerns and questions have been addressed fully.

Yes ☐ No ☐

I understand that I have the right to withdraw my consent for being a participant at any time without giving reasons and without penalty.

Yes ☐ No ☐

I have read the information sheet describing this project and I have no known medical or other condition which would exclude me from being a participant in this experiment.

Yes ☐ No ☐

I would like my blood samples returned to me after analysis

Yes ☐ No ☐

I have been given one week to consider my involvement in the project.

Yes ☐ No ☐

I agree to participate as an experimental subject

Yes ☐ No ☐

I understand that thereafter I can withdraw at any time without reason and without penalty.

Yes ☐ No ☐

Signed: …….

Name: …….

Date: …….

13. Appendix 5 – Letter notifying ethics approval

Health and Disability Ethics Committees

Central Regional Ethics Committee
Ministry of Health
Level 2, 1–3 The Terrace
PO Box 5013
Wellington
Phone (04) 496 2405
Fax (04) 496 2191

14 June 2007

Mr Scott Betteridge
21 College Street
Palmerston North

Dear Scott

CEN/07/05/032 - The effects of pseudoephedrine ingestion on endurance cycling performance
Mr Scott Betteridge
Massey University

The above study has been given ethical approval by the **Central Regional** Ethics Committee.

Approved Documents
Information sheet and consent form version 1, dated 2007

Certification
The Committee is satisfied that this study is not being conducted principally for the benefit of the manufacturer or distributor of the medicine or item in respect of which the trial is being carried out.

Accreditation
The Committee involved in the approval of this study is accredited by the Health Research Council and is constituted and operates in accordance with the Operational Standard for Ethics Committees, April 2006.

Final Report
The study is approved until **June 2008**. A final report is required at the end of the study. The report form is available on http://www.newhealth.govt.nz/ethicscommittees and should be forwarded along with a summary of the results. If the study will not be completed as advised, please forward a progress report and an application for extension of ethical approval one month before the above date.

Requirements for SAE Reporting
The Principal Investigator will inform the Committee as soon as possible of the following:

- Any related study in another country that has stopped due to serious or unexpected adverse events
- withdrawal from the market for any reason
- all serious adverse events occurring during the study in New Zealand which result in the investigator or sponsor breaking the blinding code at the time of the SAE or which result in hospitalisation or death.
- all serious adverse events occurring during the study worldwide which are considered related to the study medicine. Where there is a data safety monitoring board in place, serious adverse events occurring outside New Zealand may be reported quarterly.

All SAE reports must be signed by the Principal Investigator and include a comment on whether he/she considers there are any ethical issues relating to this study continuing due to this adverse event. If the adverse event is local and does not have the sponsor's report attached, an opinion on whether the event is thought to be related to the study should be given along with any other pertinent information. It is assumed by signing the report, the Principal Investigator has undertaken to ensure that all New Zealand investigators are made aware of the event.

Amendments
All amendments to the study must be advised to the Committee prior to their implementation, except in the case where immediate implementation is required for reasons of safety. In such cases the Committee must be notified as soon as possible of the change.

Please quote the above ethics committee reference number in all correspondence.

The Principal Investigator is responsible for advising any other study sites of approvals and all other correspondence with the Ethics Committee.

It should be noted that Ethics Committee approval does not imply any resource commitment or administrative facilitation by any healthcare provider within whose facility the research is to be carried out. Where applicable, authority for this must be obtained separately from the appropriate manager within the organisation.

Yours sincerely

Claire Yendoll
Central Ethics Committee Administrator
Email: claire_yendoll@moh.govt.nz