# Pseudoephedrine Enhances Performance in 1500-m Runners

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**ABSTRACT**

HODGES, K., S. HANCOCK, K. CURRELL, B. HAMILTON, and A. E. JEUKENDRUP. Pseudoephedrine Enhances Performance in 1500-m Runners. *Med. Sci. Sports Exerc.*, Vol. 38, No. 2, pp. 329–333, 2006. **Abstract:** Pseudoephedrine is an over-the-counter drug to relieve nasal and sinus congestion. Although it has been suggested that pseudoephedrine could be a stimulant and ergogenic aid, pseudoephedrine was recently removed from the banned substance list by the International Olympic Committee and placed on the monitoring program (from January 2004). It was felt that evidence was lacking for an ergogenic effect, although few studies have investigated the effects of pseudoephedrine on exercise performance. This study, therefore, aimed to investigate the effects of pseudoephedrine on 1500-m running performance. **Methods:** In a double-blind, randomized crossover design, seven male athletes completed two 1500-m running trials on an outdoor track after having completed a familiarization trial. All trials were 7 d apart. After a 12-h overnight fast, subjects reported to the laboratory and received a standardized breakfast (energy $\approx$ 500 kcal 50% CHO). Subjects were given either 2.5 mg·kg$^{-1}$ bw pseudoephedrine or 2.5 mg·kg$^{-1}$ bw maltodextrins (placebo) in gelatin capsules 70 min before the start of the warm-up, which started 20 min before they ran 1500 m all-out. Pre- and postexercise blood samples were collected and analyzed for lactate and glucose concentrations, partial pressure of oxygen ($PO_2$) and carbon dioxide ($PCO_2$), and percent oxygen saturation. **Results:** Pseudoephedrine significantly decreased time to completion of 1500-m time trials in the present study by 2.1% (from 279.65 ± 4.36 s with placebo to 273.86 ± 4.36 s with pseudoephedrine) with no reported side effects. No changes in the measured blood parameters were found, suggesting a central effect of pseudoephedrine rather than a metabolic effect. **Conclusion:** The finding was that 2.5 mg·kg$^{-1}$ bw pseudoephedrine ingested 90 min preexercise improves 1500-m running performance. **Key Words:** SYMPATHOMIMETRIC DRUGS, DOPING, RUNNING, RELIABILITY

Pseudoephedrine is a sympathomimetic amine with a structure very similar to ephedrine and amphetamines (11). Sympathomimetics are drugs known for their stimulant properties that partially or completely mimic the actions of noradrenaline (NE) and adrenaline. Pseudoephedrine is primarily an $\alpha$-adrenergic agonist that is available over the counter for therapeutic use to relieve nasal and sinus congestion associated with the common cold, sinusitis, and allergic rhinitis. Nonprescription products containing pseudoephedrine include Sudafed (30 mg) tablets and Sudafed (120 mg) sustained-release capsules (3). When used in these recommended doses, side effects of pseudoephedrine are minor and uncommon. Occasional central nervous system (CNS) excitation is noticed and insomnia can occur. A slight risk exists of nervousness, irritability, or light-headedness, with elevated heart rate (HR) and blood pressure (BP). No adverse side effects were noted of 180 mg given to subjects who undertook a number of anaerobic tests including a 30-s "all-out" cycle sprint test (9). Pseudoephedrine has been removed from the banned substance list by the World Anti Doping Agency and placed on the monitoring program from January 2004. It is felt that research and evidence for an ergogenic effect were lacking.

Some have argued, however, that pseudoephedrine could have ergogenic effects because of its similarities in structure with the sympathomimetic group of drugs (ephedrine, pseudoephedrine, and amphetamines). Physiologic effects include an increase in systolic and diastolic BP, HR, peripheral vascular tone, respiratory stimulation, bronchiole tube dilation, and relaxation of gastrointestinal smooth muscles (9). Sympathomimetics also cause vasoconstriction of cutaneous blood vessels, vasodilation in skeletal muscle, and help in the redistribution of blood flow from skin and the splanchnic bed to skeletal muscles. By increasing HR, myocardial contractility, and greater venous return, cardiac output may increase to provide more blood supply to working muscle. Despite its potential

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ergogenic effects, very few studies have actually investigated the effects of pseudoephedrine on exercise performance, with most of the findings showing little or no effect. A dose of 60 mg of pseudoephedrine did not produce a measurable ergogenic effect during high-intensity exercise (4,8,11). The ingestion of 120 mg of pseudoephedrine had no effect on anaerobic performance (7) or on high-intensity exercise of approximately 1-h duration (10). A dose of 2 $mg \cdot kg^{-1}$ bw had no ergogenic effect on measures such as $\dot{V}O_{2max}$ and time to exhaustion on an ergometer test (19). Furthermore, maximal multiple therapeutic doses of pseudoephedrine (4 × 60 mg over a 36-h period) did not have a beneficial effect on endurance running (5). A 180-mg dose, however, did enhance maximal torque in isometric knee extension and peak power in the all-out Wingate cycle test (9). Walton et al. (20) found 120 mg of pseudoephedrine tended to improve anaerobic performance, including increased maximal voluntary contraction (MVC) of quadriceps muscle and greater absolute and relative mean power output in the Wingate test.

Overall, these results seem to show little or no effect of pseudoephedrine on anaerobic and aerobic performance, although at doses higher than therapeutic doses, some evidence suggests increased anaerobic performance and, possibly, aerobic performance. Currently, no research has been done into the effects of pseudoephedrine on 1500-m track running performance, and therefore in this study we investigated the effect of 2.5 $mg \cdot kg^{-1}$ bw pseudoephedrine (equating to 180 mg for a reference average weight of 70 kg) on 1500-m track running performance.

The second aim of this study was to determine the reliability of 1500-m running performance on the track. Reliability of a performance test is critical when concluding on the usefulness of a test because it has an impact on the power of the test to find changes in performance as a direct result of a treatment (17).

## METHOD

### General Design

**Study 1.** Eight male athletes from the University of Birmingham Athletics Club volunteered to complete a familiarization trial, followed by two trials to measure the reproducibility of 1500-m running.

**Study 2.** Seven male athletes completed two trials to study the effects of pseudoephedrine on 1500-m running. Both studies were approved by the Birmingham University School of Sport and Exercise Sciences ethics committee. The sample was limited to male subjects to avoid for possible confounding factors of hormonal fluctuations during the menstrual cycle. All subjects provided informed consent, passed medical screening, and completed a general medical questionnaire.

Subject characteristics can be seen in Table 1.

Before the experimental protocol, the subjects completed a graded exercise test to exhaustion on a treadmill (Woodway, Birmingham, UK). On arrival, nude body mass was measured (Seca Alpha, Hamburg, Germany) after voiding. Treadmill speed remained constant and the gradient increased by 1% at the end of each minute. Breath-by-breath measurements were obtained throughout exercise using an online automated gas analysis system (Oxycon Pro, Jaeger, Wuerzberg, Germany). The volume sensor was calibrated using a 3-L calibration syringe and the gas analyzers were calibrated using a 5.03% $CO_2$/94.97% $N_2$ gas mixture. Maximal oxygen consumption was taken to be peak $\dot{V}O_2$.

All subjects first completed a familiarization trial where the protocol was performed with no blood samples or intervention given. A further four experimental trials were completed at the same time of day and separated by at least 3 d. The first two trials were used to calculate reproducibility of 1500-m time trial performance. A double-blind, counterbalanced crossover design was then used in which subjects completed two trials, one with consumption of pseudoephedrine and one with placebo. All subjects were told to abstain from alcohol and caffeine-containing foods and beverages at least 24 h before testing. Food intake and training activity was recorded 24 h before each test. Subjects were asked to keep diet and training activity the same between tests.

### Experimental Protocol

**Study 1. Reproducibility of the 1500-m time trial.** Subjects reported to the laboratory in the morning having fasted for the previous 12 h. Subjects were at rest for 70 min and were given a 7 $mL \cdot kg^{-1}$ bw Nutrament (Mead Johnson Nutritionals Hounslow, England) high-energy milkshake for breakfast with an average energy intake of 1986.0 ± 130.7 kJ (68.5 ± 4.5 g CHO, 21.1 ± 1.4 g protein, and 13.1 ± 0.9 g fat). Water was available *ad libitum*. After 70 min of rest, subjects reported to the 400-m Birmingham University athletics track to perform a standardized warm-up lasting 20 min, which consisted of a 2000-m self-paced jog followed by an individual static stretching program and ending with 3 × 80-m strides. Then, 90 min after the ingestion of the breakfast, the 1500 m was run individually. No encouragement was given and watches were removed. Split times at 300, 700, 1100, and 1500 m were given to simulate competition. The 1500-m trial was timed using electronic timing lights (Eleiko, Sport, Sweden). Time to completion was not given to the subjects until after the completion of the study. Weather measurements for wind speed (05103 Wind monitor, Campbell Scientific Ltd, Loughborough, UK), dry and wet-bulb temperature, and relative humidity (Temperature and Relative Humidity Probe MP100A,

TABLE 1. Subject characteristics (means ± SD).

| Characteristic | Study 1 Reproducibility | Study 2 Pseudoephedrine |
|---|---|---|
| Age (yr) | 20.4 ± 1.6 | 20.1 ± 1.2 |
| Body mass (kg) | 67.1 ± 4.5 | 67.9 ± 4.9 |
| $\dot{V}O_{2max}$ ($mL \cdot kg^{-1} \cdot min^{-1}$) | 68.4 ± 8.9 | 68.7 ± 9.2 |

Pseudoephedrine: $N = 7$; reproducibility: $N = 8$.



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Campbell Scientific Ltd, Loughborough, UK) were recorded for the first minute of each trial.

**Study 2. Investigating the effects of pseudoephedrine.** Following the familiarization, the subjects had an initial screening and medical history by a physician. The valve function and consequent rhythm of each subject's heart was examined aurally. If it was not deemed safe for them to participate because of illness or elevated blood pressure that would increase the risk of possible side effects from pseudoephedrine, they were excluded from the study. The protocol for study 2 was identical to that of the first, except for the following highlighted differences. A resting blood sample of 7 mL was taken from the antecubital vein of the arm by venopuncture. The sample was stored in a vacutainer on ice. Along with the standardized breakfast containing an average intake of 2009.9 ± 143.6 kJ (69.4 ± 5.0 g CHO, 21.4 ± 1.5 g protein, and 13.3 ± 1.0 g fat), subjects were given either 2.5 $mg \cdot kg^{-1}$ bw pseudoephedrine (Sigma–Aldrich) or 2.5 $mg \cdot kg^{-1}$ bw maltodextrins (placebo). To mask the trials, the drugs were placed in standard gelatin capsules of equal number in each condition. Heart rate was measured during the trial using the Polar Team System (Kempele, Finland). A preexercise blood sample and postexercise sample within 2 min of completing the trial were taken. No split times were given during the 1500 m. On completion, a short questionnaire was administered to find out what condition the subjects thought they were running under and to highlight any side effects both immediately after and up to 24 h after the trial.

**Blood analyses.** Immediately postexercise, the blood samples were stored in three 7-mL heparinized vacutainers on ice for later analysis. A minimum of 200 mL of whole blood was placed in a 1.5-mL Eppendorf tube and analyzed using a blood gas analyzer at 37°C within 4 h of trial completion (Nova biomedical stat profile phox plus L). The samples were analyzed for lactate and glucose concentrations, partial pressure of oxygen ($PO_2$), and carbon dioxide ($PCO_2$) and percent oxygen saturation.

**Cardiovascular measures.** Heart rate was measured throughout and downloaded using Polar Precision SW 3.0. Average HR over 5 min before the warm-up was calculated as resting HR. Heart rates were recorded at start of exercise and at 300, 700, 1100, and 1500 m.

## Data Analysis

Data for subject characteristics are presented as mean ± SD. All other data are presented as mean ± SEM unless otherwise stated. A paired samples *t*-test was used to detect any significant difference between pseudoephedrine and placebo trials. A two-way ANOVA with repeated measures was used to determine any differences between HR, blood lactate, and glucose concentrations, $PCO_2$, and $PO_2$ and percent oxygen saturation. Paired samples *t*-tests were used to determine any differences in the weather variables recorded and diet components. Reproducibility data were analyzed for reliability using coefficient of variation (CV), typical error (TE), intraclass correlation coefficient (ICC), and limits of agreement (LOA). CV for individual subjects were calculated as each athlete's SD divided by mean value. CV = (SD (of values)/mean of values)*100. The mean CV was calculated from individual CV. TE was calculated as the SD (difference scores)/$\sqrt{2}$). Paired sample *t*-tests were used to detect any significant systematic errors in time to completion data. The data were analyzed for heteroscedasticity using Pearsons r. Statistical significance was set at $P < 0.05$.

## RESULTS

**Study 1. Reproducibility of 1500-m time trial.** Individual subject data for time to completion during two outdoor 1500-m time trials are presented in Table 2. Mean time to completion for trial 2 was 273.13 ± 4.61 s and for trial 3 was 272.73 ± 5.17 s. The mean CV for time to completion of the time trial was 0.82% (95% CI = 0.16–1.47%), the TE was 3.08 s, and the ICC was 0.953 (95% CI 0.779–0.991). No significant difference was seen for time to completion between trials 2 and 3 ($t = 0.26$, $P = 0.802$). No heteroscedasticity was observed (r = 0.369, $P = 0.369$). No significant difference was found between trials for the variables of wind speed ($P = 0.667$), dry-bulb temperature ($P = 0.125$), wet-bulb temperature ($P = 0.152$), or relative humidity ($P = 0.488$). The diet consumed by each subject in the 24 h previous to each trial did not differ significantly for mean %CHO ($P = 0.811$), %protein ($P = 0.520$), %fat ($P = 0.151$), and mean energy intake ($P = 0.241$). No difference in training activity occurred in the previous 24 h before trials.

**Study 2. Investigating the effect of pseudoephedrine.** All subjects successfully completed both 1500-m time trials. The mean time to completion for pseudoephedrine trial (273.86 ± 4.36 s) was significantly shorter than that for placebo (279.65 ± 4.36 s) ($P = 0.001$). Time to completion for pseudoephedrine trials ranged from 255.90 to 295.46 s and from 261.80 to 300.10 s for placebo trials. Individual subject data for time to completion are presented in Table 3. Blood lactate concentration at rest (pseudoephedrine vs placebo ($mmol \cdot L^{-1}$): 1.08 ± 0.09 vs

TABLE 2. Time to completion (s) achieved by each subject in two 1500-m time trials.

| Subject | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | Mean ± SD |
|---|---|---|---|---|---|---|---|---|---|
| Trial 2 | 276.05 | 258.95 | 275.93 | 271.17 | 251.83 | 279.17 | 294.56 | 277.40 | 273.13 ± 13.03 |
| Trial 3 | 269.42 | 254.42 | 283.42 | 268.11 | 252.2 | 280.42 | 295.01 | 278.86 | 272.73 ± 14.62 |
| Mean | 272.74 | 256.69 | 279.68 | 269.64 | 252.02 | 279.80 | 294.79 | 278.13 | 272.93 |
| SD | 4.69 | 3.20 | 5.30 | 2.12 | 0.26 | 0.88 | 0.32 | 1.03 | |
| CV (%) | 1.72 | 1.23 | 1.89 | 0.80 | 0.10 | 0.32 | 0.11 | 0.38 | 0.82 |

CV, coefficient of variation.



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TABLE 3. Time to completion (s) for pseudoephedrine and placebo 1500-m time trials.

| Subject | 1 | 2 | 3 | 4 | 5 | 6 | 7 | Mean ± SEM |
|---|---|---|---|---|---|---|---|---|
| Pseudoephedrine | 269.71 | 265.94 | 255.90 | 272.30 | 281.30 | 295.46 | 276.40 | 273.86 ± 4.36 |
| Placebo | 280.40 | 269.71 | 261.80 | 274.81 | 287.16 | 300.10 | 283.60 | 279.65 ± 4.36 |
| Improvement (s) | 10.69 | 3.77 | 5.90 | 2.51 | 5.86 | 4.64 | 7.2 | 5.80 ± 4.36 |

1.08 ± 0.07) immediately before (2.87 ± 0.58 vs 2.68 ± 0.34) and immediately after (9.45 ± 1.04 vs 10.86 ± 0.53) the tests were not significantly different ($P$ = 0.42). No significant main effect was seen of trial on blood glucose concentration ($P$ = 0.515). No significant difference was seen between conditions at rest, immediately before exercise, or after exercise of $PCO_2$ ($P$ = 0.801), $PO_2$ ($P$ = 0.433), or $\%O_2$ saturation ($P$ = 0.335). No main effect was found of trial on subjects HR ($P$ = 0.234). Mean blood variables and mean HR for pseudoephedrine and placebo are shown in Table 4.

No significant difference was found between trials for the variables of wind speed ($P$ = 0.088), dry-bulb temperature ($P$ = 0.883), wet-bulb temperature ($P$ = 0.072), or relative humidity ($P$ = 0.371). The diet consumed by each subject in the 24 h previous to each trial did not differ significantly for mean %CHO ($P$ = 0.44), %protein ($P$ = 0.72), %fat ($P$ = 0.85), and mean energy intake ($P$ = 0.94). No difference in training activity occurred in the previous 24 h before trials. Results of the questionnaire showed subjects either immediately or up to 24 h following each trial reported no side effects and, indeed, were blind to their particular condition.

## DISCUSSION

The most important finding of this study was that oral ingestion of 2.5 $mg \cdot kg^{-1}$ bw pseudoephedrine, equating to three times the therapeutic dose, significantly reduced time to completion of 1500-m running performance by a mean of 5.8 s. The results of this study oppose findings of most of the previous studies into the effects of pseudoephedrine, but they are consistent with the previous positive findings by Gill et al. (9) and Walton et al. (20). A possible explanation for the differing results across the studies into pseudoephedrine is likely results from the dosage of pseudoephedrine used. In both this study and the study by Gill et al. (9), a dose equivalent to 180 mg was used. Furthermore, the time delay between dosing and testing is important and varies greatly between studies. It has been suggested that pseudoephedrine exerts its effects approximately 1 h after ingestion (8), and 180 mg has been shown to reach peak concentration in the plasma at approximately 2 h (2). It was for this reason pseudoephedrine was ingested 90 min before exercise in this study.

Pseudoephedrine is a sympathomimetic amine that acts directly by stimulating tissues (e.g., the heart) and indirectly by causing the release of NE from its storage sites, therefore activating $\alpha$- and, to a somewhat lesser extent, $\beta$-adrenergic receptors (8). A proposed mechanism of pseudoephedrine's action is through the drug's inotropic and chronotropic effect on the heart. Mixed findings are seen of pseudoephedrine's effect on the heart. Pseudoephedrine ingestion in this study did not significantly affect HR at rest, although a trend was noted for higher HR during exercise with the drug. Blood lactate and glucose concentrations, $PO_2$, $PCO_2$, and oxygen saturation were not significantly affected by pseudoephedrine ingestion. This excludes a purely metabolic mechanism for action. A more plausible explanation for pseudoephedrine's ergogenic effect may be by an increase in CNS stimulation, thereby reducing the subject's perceived effort. Previous studies have shown no significant difference between pseudoephedrine and placebo in Borg's rating of perceived exertion (RPE) (5,8). It is possible that such effects were not shown because of the relatively low dosage used. Ephedrine, which is similar in structure to pseudoephedrine, has been shown to significantly reduce subject RPE during cycling ergometry at the same exercise intensity when combined with caffeine (1).

The actions of pseudoephedrine on the CNS, as shown by its effects on locomotor activity and feeding behavior, are similar to those of amphetamine (16). Christie and Crow (6) found ephedrine initiates turning behavior in rats and concluded ephedrine resembles amphetamine in its action on central dopamine mechanisms. Dopamine is an important neurotransmitter in the CNS, especially in the hypothalamus, which is important for body arousal and it may reduce fatigue. Dopamine is particularly important in the regulation of movement. In a study investigating the central stimulation of rats caused by a number of sympathomimetic amines, it was concluded that ephedrine was most potent in producing central stimulation with pseudoephedrine having a lesser effect than both ephedrine and amphetamine (18). It has been claimed that pseudoephedrine can be used to obtain an amphetaminelike euphoria that could suppress the central component of fatigue (9). Gillies et al. (10) suggest that pseudoephedrine, through its CNS-stimulating properties, theoretically could

TABLE 4. Blood variables and heart rate (HR) for pseudoephedrine and placebo at three time points. (Mean ± SEM); $N$ = 7.

| | | Pseudoephedrine | Placebo |
|---|---|---|---|
| Glucose ($mmol \cdot L^{-1}$) | −90 | 5.3 ± 0.1 | 5.4 ± 0.1 |
| | 0 | 4.5 ± 0.3 | 4.5 ± 0.3 |
| | Post | 6.2 ± 0.8 | 7.3 ± 0.3 |
| $PO_2$ (mm Hg) | −90 | 43.0 ± 2.7 | 41.6 ± 5.3 |
| | 0 | 35.8 ± 2.1 | 36.8 ± 3.0 |
| | Post | 47.8 ± 3.3 | 46.0 ± 3.3 |
| $PCO_2$(mm Hg) | −90 | 49.0 ± 5.0 | 50.5 ± 2.2 |
| | 0 | 49.2 ± 4.7 | 59.5 ± 1.9 |
| | Post | 45.9 ± 8.9 | 52.5 ± 5.0 |
| $\%O_2$ saturation | −90 | 67.4 ± 9.9 | 67.5 ± 3.9 |
| | 0 | 59.8 ± 5.5 | 51.8 ± 4.0 |
| | Post | 65.3 ± 9.2 | 67.0 ± 5.6 |
| HR (bpm) | Rest | 65 ± 5 | 64 ± 5 |
| | Start | 125 ± 11 | 125 ± 12 |
| | 300 m | 173 ± 7 | 176 ± 3 |
| | 700 m | 185 ± 2 | 181 ± 2 |
| | 1100 m | 187 ± 2 | 180 ± 6 |
| | 1500 m | 190 ± 3 | 185 ± 3 |



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decrease fatigue and thereby be ergogenic. It is likely, therefore, that the observed improvement with pseudoephedrine is caused by CNS stimulation in similar manner than amphetamine, possibly through increased dopamine, ultimately masking of fatigue.

To know what magnitude of changes can be detected with a certain test, the reliability of that test should be known. Another purpose of this study, therefore, was to measure the reliability of 1500-m running performance. The reproducibility of 1500-m time trial on an outdoor track for time to completion gave a mean CV of 0.82% (95% CI = 0.22–1.42%) with a TE of 3.08 s. This day-to-day variability is small compared with most available performance tests (13). Hopkins et al. (15) reported that the CV between the first two cycling time trials is approximately 1.3 times the CV between subsequent trials. This study found that the CV for familiarization and trial 2 was 1.08%, which is approximately 1.3 times that of CV for trials 2 and 3, supporting the findings of Hopkins et al. (15).

Variability in athlete's performance from competition to competition is important when analyzing possible chances of winning (12). The smallest enhancement of performance that has a substantial effect on an athlete's chance of winning is approximately 0.3 of the typical variation in competitive performances (14). The typical variation in competitive performance of adult male distance runners in short endurance events (2500–12,000 m) has been calculated as approximately 1.5% (14). The smallest worthwhile change in performance, therefore, is approximately 0.5%. Performance tests suitable for tracking this smallest change need to have a CV similar to or less than the CV of the event they simulate (13). The CV of 0.82% found in this study is indeed less than the approximately 1.5% found in competition of shorter endurance events.

In conclusion, reliability of 1500-m track running performance is high. A dose of approximately 180 mg of pseudoephedrine (three times the therapeutic dose) significantly decreased time to completion of 1500-m time trials in the present study by 2.1%, with no detected side effects.

Scientific research is clearly needed to investigate the effects of ingestion of different doses of pseudoephedrine and different exercise intensities and duration and possible mechanisms for its ergogenic effect. A dose of 2.5 $mg \cdot kg^{-1}$ bw pseudoephedrine significantly improved 1500-m track performance.

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