

Pseudoephedrine is without ergogenic effects during prolonged exercise

HUNTER GILLIES, WAYNE E. DERMAN, TIMOTHY D. NOAKES,
PETER SMITH, ALICIA EVANS, AND GARY GABRIELS

Liberty Life Chair of Exercise and Sports Science, Medical Research Council/University of Cape Town Bioenergetics of Exercise Research Unit, and Departments of Physiology and Pharmacology, University of Cape Town Medical School, Observatory 7925, South Africa

Gillies, Hunter, Wayne E. Derman, Timothy D. Noakes, Peter Smith, Alicia Evans, and Gary Gabriels.

Pseudoephedrine is without ergogenic effects during prolonged exercise. *J. Appl. Physiol.* 81(6): 2611–2617, 1996.— This study was designed to measure whether a single dose of 120 mg pseudoephedrine ingested 120 min before exercise influences performance during 1 h of high-intensity exercise. The effects of exercise on urinary excretion of the drug were also studied. Ten healthy male cyclists were tested on two occasions, separated by at least 7 days, by using a randomly assigned, double-blind, placebo-controlled, crossover design. Exercise performance was tested during a 40-km trial on a laboratory cycle ergometer, and skeletal muscle function was measured during isometric contractions. On a third occasion, subjects ingested 120 mg pseudoephedrine but did not exercise [control (C)]. Pseudoephedrine did not influence either time trial performance [drug (D) vs. placebo: 58.1 ± 1.4 (SE) vs. 58.7 ± 1.5 min] or isometric muscle function. Urinary pseudoephedrine concentrations were significantly increased 1 h after exercise (D vs. C: 114.3 ± 27.2 vs. 35.4 ± 13.1 $\mu\text{g/ml}$; $P < 0.05$). Peak plasma pseudoephedrine concentrations ($P < 0.05$) but not time taken to reach peak plasma concentrations or the area under the plasma pseudoephedrine concentration vs. time curve was significantly increased in the total group with exercise (D vs. C). In three subjects, plasma pseudoephedrine concentrations were not influenced by exercise. Only these subjects showed increased urinary pseudoephedrine excretion during exercise. We conclude that a single therapeutic dose of pseudoephedrine did not have a measurable ergogenic effect during high-intensity exercise of 1-h duration, but plasma drug concentrations and urinary excretion were altered by exercise. These findings have practical relevance to doping control regulations in international sporting competitions.

ephedrine; performance; pharmacokinetics

APPROXIMATELY 50% of all positive doping tests in South African sports are for the use of stimulants, most commonly the sympathomimetic amines, including pseudoephedrine, phenylpropanolamine, and ephedrine (17). Because pseudoephedrine has central nervous system-stimulating properties, it could theoretically decrease the central component of fatigue and therefore be ergogenic in nature (14, 20).

These drugs are constituents of many proprietary preparations frequently used by athletes for legitimate medical reasons, including the treatment of minor intercurrent illnesses. Current doping control measures in international sport do not make allowance for the use of any of these agents for medical reasons immediately before competition. Hence it is probable that some of the positive tests for stimulant use in

competitive sport may have falsely criminalized athletes who unwisely or unwittingly used proprietary medications for legitimate medical reasons in the hours or days before competition.

The scientific method to resolve this dilemma would be to determine whether these agents are truly ergogenic. If they are not, then there may be no justification for restricting their use for legitimate medical reasons by competitive athletes. Surprisingly, few studies have evaluated the ergogenic effects of the stimulants commonly present in proprietary medicines (13, 14). Furthermore, no study has shown these agents to be ergogenic, at least at therapeutic doses.

In addition, to our knowledge, there are few studies of the effects of exercise on the excretion rates of these agents. In particular, the duration for which the urine continues to contain measurable amounts after the cessation of stimulant use may not yet have been established. This information is essential if athletes are to be advised appropriately about the use of these agents for legitimate medical reasons in the hours or days before sporting competitions.

Accordingly, the dual aims of this study were to determine 1) whether a single high dose (120 mg) of pseudoephedrine, equivalent to 48 mg ephedrine (3, 10), has a measurable ergogenic effect during high-intensity exercise of ~1-h duration and 2) whether this type of exercise influences urinary excretion of the drug, in particular whether it increases urinary drug concentrations, thereby increasing the probability of detection.

MATERIALS AND METHODS

Ten healthy male cyclists with no history of renal or other diseases volunteered to participate in the study, which was approved by the Research and Ethics Committee of the Faculty of Medicine of the University of Cape Town. Each gave his written informed consent.

A randomly assigned, double-blind, placebo-controlled crossover design was used. Before starting the trial, each subject came to the laboratory on two occasions to determine subject characteristics, including, on the first visit, peak power output during a maximal exercise test according to the method of Keen et al. (6). On the second visit, subjects completed a 40-km familiarization time trial on the test ergometer. The study then commenced and consisted of three separate trials, each separated by a minimum of 7 days to allow for physical recovery and adequate drug wash out between trials. The subjects maintained their normal training schedules for the full duration of the trial and reported to the laboratory on each occasion adequately rested and prepared as if they were to perform a 40-km cycling time trial.

Subjects were not permitted to ingest caffeine or chocolate on the morning of the trial.

On arrival at the laboratory at 0745, subjects emptied their bladders into a volumetric flask. An aliquot of ~50 ml urine was stored at -20°C for later analysis of pseudoephedrine concentration and pH. An intravenous cannula (Jelco, Halfway House, South Africa) was then inserted into a forearm vein. Thereafter, on the first two occasions, 120 mg of either pseudoephedrine or placebo (Wellcome) were ingested with water at 0800, and a 10-ml blood sample was drawn shortly thereafter and stored at -20°C for later analysis of resting plasma pseudoephedrine concentrations. The testing procedures were identical for the two exercise trials. On the third visit, subjects ingested the same dose of pseudoephedrine but did not exercise so that drug pharmacokinetics could be studied under resting conditions. On subsequent questioning, subjects were unable to identify whether they had ingested the placebo or the active agent before either exercise bout.

At 0930, that is, 90 min after drug ingestion, the maximal voluntary isometric torque produced by the right quadriceps muscle was measured on a custom-made leg-stabilizing chair according to methods previously described (2). Each subject first performed four to five maximum isometric contractions for measurement of the maximum voluntary contraction (MVC). After a recovery period, the subject then performed repetitive MVCs for 6 s followed by a 4-s rest period. Maximum contractions were repeated until the subject was unable to maintain a torque $\geq 70\%$ of the initial MVC for at least 3 s of the 6-s contraction. The duration of activity to this point was recorded as the time to fatigue. This value is considered to be a measure of the resistance of the skeletal muscle to fatigue (2).

After a 20-min rest period, subjects began a 40-km cycling time trial on the Kingcycle ergometer (ver. 4.1, 1991, EDS Portaprompt, High Wycombe, Buckinghamshire, UK) at 1000, that is, 120 min after drug ingestion. This system allows subjects to be studied while riding their own racing bicycles, thus closely simulating time trial conditions in the field. This system has a test-retest correlation of 0.98 for measurement of the maximal aerobic power of cyclists (6) and a coefficient of variation of $1.0 \pm 0.5\%$ (SD) for 40-km time trial performance (12).

The Kingcycle was calibrated before each test by using a run-down calibration in which the cyclist first accelerated to a predetermined power and then stopped cycling while maintaining his position on the cycle. The computer compares the power decay curve so produced with a previously determined reference curve. Calibration is achieved by adjusting the bottom bracket supporting the cyclist's rear wheel to produce a rolling resistance equivalent to that of a 65-kg rider.

During the trial, the cyclist's power output and cadence were recorded by a computer, and the distance traveled was displayed on a video display unit in front of the cyclist. Cyclists did not receive information about the duration of cycling because this was the tested variable. The time taken to complete the 40-km time trial was recorded. Each subject drank a minimum of 500 ml of water during the time trial; the amount for each individual was kept constant for the second trial and ranged from 500 to 1,000 ml. Twenty minutes after the time trial, subjects repeated the tests of isometric skeletal muscle function.

Urine samples were collected immediately after completion of the 40-km time trial and 1 h later and were analyzed for pH within 4 h of collection. The pH was determined by using a model PHM 80 portable pH meter (Radiometer, Copenhagen, Denmark). A further 3 ml of urine were frozen and stored

overnight for analysis of urinary pseudoephedrine concentrations the next day.

Blood samples were drawn just before the time trial was started, at the 20-km mark, and at the finish for subsequent measurement of blood lactate concentrations by conventional techniques using an enzymatic kit method (Lactate PAP, Bio Merieux, Lyon, France).

Blood samples were also collected in heparinized tubes for measurement of plasma pseudoephedrine concentrations at 0, 30, 60, 90, 120, 150, 180, 210, 240, 300, 360, 420, 480, 720, and 1,440 min after ingestion of pseudoephedrine. These samples were centrifuged at 3,000 revolutions/min, and the serum was stored at -20°C for analysis the next day.

Plasma and urinary pseudoephedrine concentrations were measured with high-performance liquid chromatography (HPLC) according to the method of Brendel et al. (1). One-half milliliter of each sample was diluted with 0.5 ml of water, and to this 15 μl of 25% ammonia were added. The sample was thoroughly mixed and applied to a Bond Elut solid-phase extraction column (Analytichem International, Harbor City, CA), which had been preconditioned by successive washing with 5 ml of methanol, 0.3 M methanolic HCl, and water. Unbound material was washed from the column with 2 ml of a 50:40 mixture of 0.03 M HCl (pH 3.0) and acetonitrile. Pseudoephedrine was eluted from the column with 300 μl of 0.1 M methanolic HCl.

Extracted samples were analyzed on an HPLC system (model LC-10A, Shimadzu, Kyoto, Japan) fitted with a C_{18} reversed-phase column (150 \times 3.9 mm, 10 μm) (Phenomenex, Torrance, CA). The flow rate was 2 ml/min. The mobile phase contained 0.03 M sodium heptane sulfonate (pH 3.0)-acetonitrile (74:26 vol/vol). The wavelength was set at 205 nm.

Statistical analyses were performed by using a repeated-measures one-way analysis of variance, and subsequent paired Student's *t*-tests used *P* values corrected for multiple comparisons by using Bonferroni's test. Significance was determined at the 0.05 and 0.01 levels. All values are expressed as means \pm SE.

In a subsequent analysis, data from plasma and urine involving two groups ($n = 3$ and $n = 7$) were initially scanned with Levene's test of homogeneity to show unequal variances. Thereafter, a Mann-Whitney *U*-test was used if the statistics were found to be nonparametric.

RESULTS

The characteristics of the 10 subjects were the following: age, 22.3 ± 0.9 (SE) yr (range 19–27 yr); height, 180 ± 2 cm; mass, 74.7 ± 2.6 kg; peak power achieved during maximal exercise, 402 ± 15 W; and serum urea and creatinine concentrations, 4.9 ± 0.3 mmol/l and 86.8 ± 3.7 $\mu\text{mol/l}$, respectively.

All subjects successfully completed both 40-km time trials. Times ranged from 53.8 to 69.7 min after drug ingestion and from 53.1 to 65.9 min after placebo ingestion. Time trial times after the drug (58.7 ± 1.5 min) or placebo (58.1 ± 1.4 min) ingestion were not different. Equal (5) numbers of cyclists performed either better or worse when ingesting the drug. Nor were times different when analyzed for a trial effect, because times for the first (58.6 ± 1.3 min) and the second (58.3 ± 1.6 min) trials were not different. Slightly more (6) subjects performed better on the second than on the first test.

Blood lactate concentrations at the start (drug vs. placebo: 2.2 ± 0.7 vs. 2.8 ± 1.2 mmol/l), midpoint (6.4 ± 3.1 vs. 6.3 ± 3.3 mmol/l), and completion (10.0 ± 3.7 vs. 9.6 ± 2.6 mmol/l) of the time trials were also not significantly different.

Table 1 lists the results of the isometric muscle function testing. Neither MVC nor time to fatigue was different between drug and placebo trials, either before or after exercise. However, both MVC and time to fatigue fell significantly ($P < 0.05$) after exercise in both groups.

The mean volumes of urine passed in the first 3 h of the experiment (0–180 min), comprising the 2 h before exercise and the hour of exercise, and in the following hour after exercise (180–240 min) were significantly lower than the corresponding volumes passed under resting conditions ($P < 0.001$; Fig. 1). As a result, the total urine volume passed during the exercise trial was significantly lower than the volume passed at rest ($P < 0.001$; Fig. 1). Urine pH was significantly lower in the second urine sample in the exercise trial (180–240 min; $P = 0.04$), but mean urine pH was not different for the total trial (0–240 min) between exercise and control conditions.

Pseudoephedrine was detected in 8 of 10 urine samples taken immediately after exercise (0–180 min). The concentrations ranged from 4 to 117 $\mu\text{g/ml}$; the mean value was 45 ± 14 $\mu\text{g/ml}$ (Fig. 1). Pseudoephedrine was detected in all 10 urine samples taken 1 h after exercise (180–240 min). Concentrations ranged from 7 to 261 $\mu\text{g/ml}$ with a mean of 114 ± 27 $\mu\text{g/ml}$ (Fig. 1, 3rd panel). This value was significantly higher ($P < 0.05$) than the value measured during the resting trial. As a result, average urine pseudoephedrine concentration during the complete trial (0–240 min) was significantly higher ($P < 0.05$) in the exercise than in the resting study (Fig. 1, 3rd panel).

There were no significant differences in the total amount of pseudoephedrine excreted during any measured period in the two trials (urine pseudoephedrine content; Fig. 1, 4th panel). But there was considerable intraindividual variability in drug excretion patterns under either condition (see below).

Mean plasma pseudoephedrine concentrations under rest and exercise conditions are shown in Fig. 2. Peak plasma concentrations (exercise vs. control: 0.5 ± 0.2 vs. 0.24 ± 0.2 $\mu\text{g/ml}$), time to reach peak plasma concentration (exercise vs. control: 123 ± 19 vs. $171 \pm$

Table 1. Isometric muscle function test results before and after 40-km cycling time trial preceded by ingestion of 120 mg pseudoephedrine or placebo

	Pseudoephedrine	Placebo
Before exercise		
Maximum voluntary contraction, N·m	247 ± 18	251 ± 21
Time to fatigue, s	91 ± 9	82 ± 14
After exercise		
Maximum voluntary contraction, N·m	$238 \pm 21^*$	$232 \pm 16^*$
Time to fatigue, s	$65 \pm 8^*$	$67 \pm 13^*$

Values are means \pm SE for 10 cyclists. *Before vs. after exercise, $P < 0.05$.

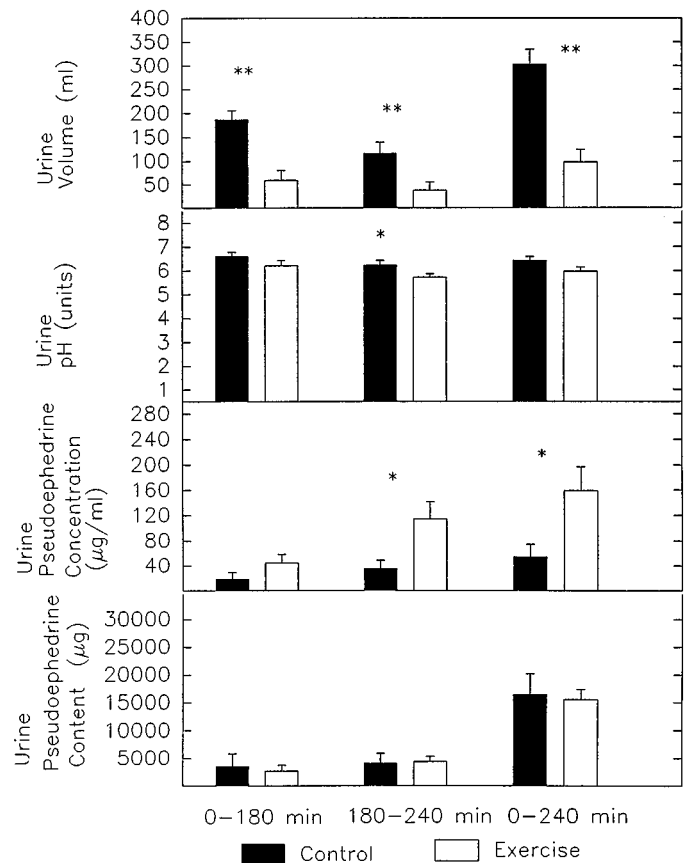


Fig. 1. Urine volume, pH, urine pseudoephedrine concentration, and urine pseudoephedrine content for samples corresponding to periods 0–180, 180–240, and 0–240 min. Values are given for 10 subjects. Drug was ingested at time 0; exercise began at 120 min and lasted for ~1 h. *Exercise vs. control, $P < 0.05$. **Exercise vs. control, $P < 0.001$.

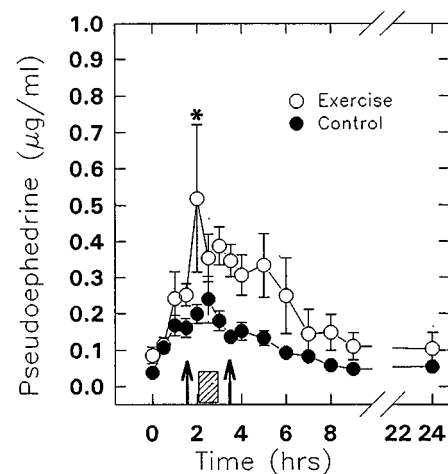
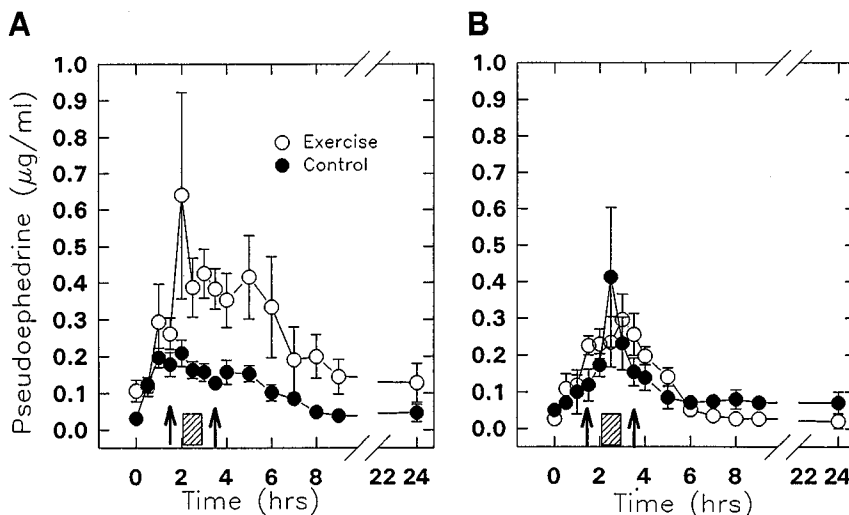


Fig. 2. Plasma pseudoephedrine concentrations for 24 h after ingestion of 120 mg pseudoephedrine at time 0 for exercise and control conditions. Values are given for 10 subjects. Arrows, isometric muscle function tests; hatched bar, 40-km time trial in which subjects performed a simulated 40-km cycle race in the laboratory in the shortest possible time. *Exercise vs. control, $P < 0.05$.

Fig. 3. Plasma pseudoephedrine concentrations for 24 h after ingestion of 120 mg pseudoephedrine at time 0 for exercise and control conditions in 2 groups of subjects showing different responses. In 7 subjects in group A (A), plasma pseudoephedrine concentrations were higher during exercise than at rest, whereas in 3 subjects in group B (B), no such difference was present. Arrows, isometric muscle function tests; hatched bar, 40-km time trial.



30 min), and the area under the plasma concentration vs. time curve (exercise vs. control: 224 ± 63 vs. $108 \pm 14 \mu\text{g}\cdot\text{ml}^{-1}\cdot\text{min}^{-1}$) for the group were all altered by exercise, but only the effect on peak plasma pseudoephedrine concentration was statistically significant ($P < 0.05$).

However, there appeared to be two distinct patterns for plasma drug kinetics under exercise and rest conditions. Group A subjects ($n = 7$) showed an increased

area under the plasma concentration vs. time curve after exercise (Fig. 3A), whereas in the remainder of the subjects (group B; $n = 3$) the area under the curve was the same under exercise and control conditions (Fig. 3B).

Figure 4 compares urine measures in the seven group A subjects, whose plasma pseudoephedrine concentrations were higher during exercise than under

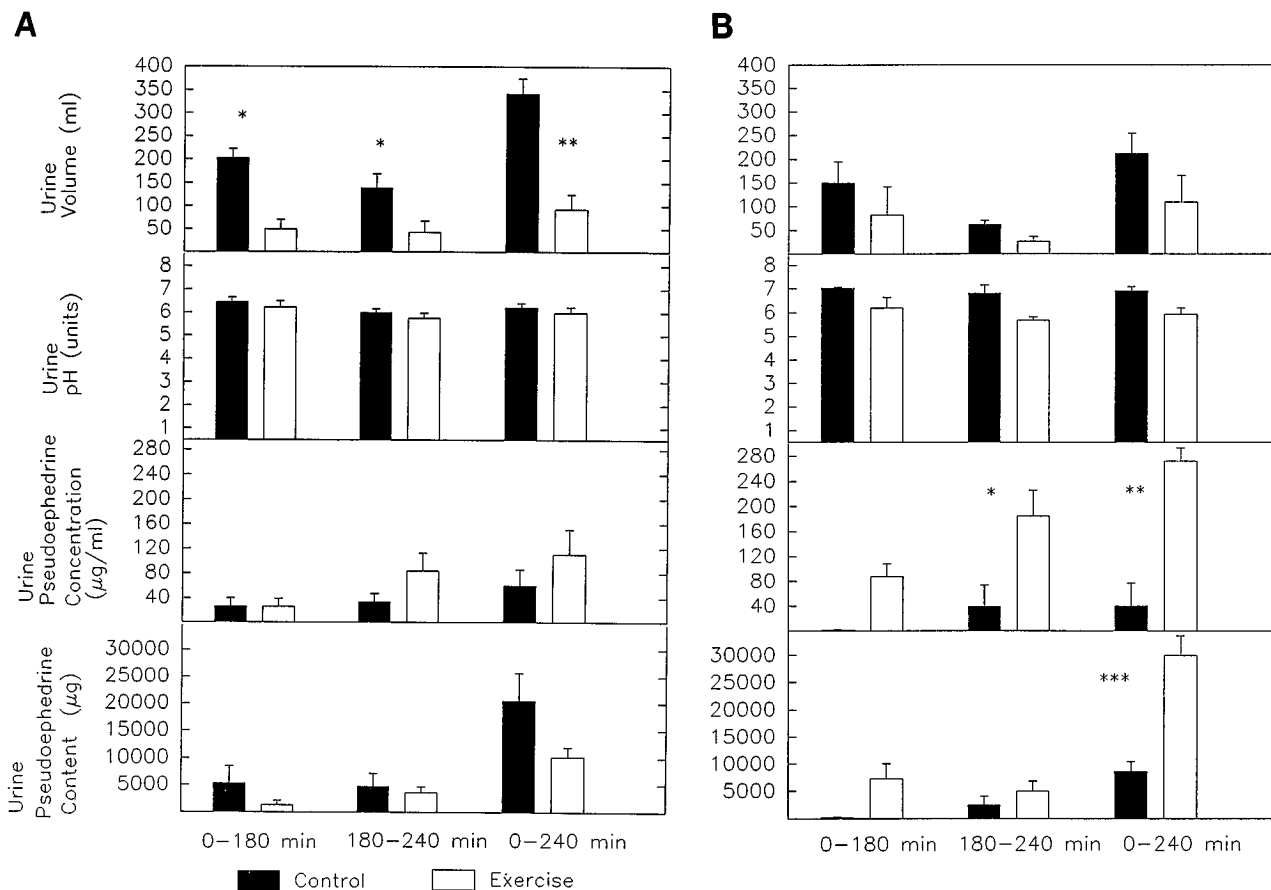


Fig. 4. Urine volume, pH, urine pseudoephedrine concentrations, and urine pseudoephedrine content for exercise and control conditions in 7 group A subjects (A) and in 3 group B subjects (B). *Exercise vs. control, $P < 0.05$. **Exercise vs. control, $P < 0.001$. ***Exercise vs. control, $P < 0.0001$.

control conditions (A), with values for the three *group B* subjects, whose plasma concentrations were essentially unaffected by exercise (B).

Urine volume was significantly lower with exercise in the seven *Group A* subjects ($P < 0.007$ to $P < 0.0006$), whereas urine pH was unchanged and urine pseudoephedrine concentration and content were not significantly altered.

In contrast, urine volume (Fig. 4B) was not decreased as a result of exercise in the three *Group B* subjects who maintained similar plasma pseudoephedrine concentrations under rest and exercise conditions. Urinary pseudoephedrine concentration and content were significantly increased ($P < 0.001$) after exercise in these subjects.

In *Group B*, urine pH did not change under control conditions but was lower and fell markedly, albeit not significantly, in response to exercise.

Figure 5A shows that there was a significantly negative correlation ($r = 0.76$; $P < 0.05$) between average urine pH and average urine pseudoephedrine concentration for samples taken during the exercise trial, and, although not significant, there was also a trend for the same relationship at rest ($P = 0.15$). There was no significant difference between the gradients of the two slopes. In contrast, in *group B*, the relationship between exercise and rest conditions was different, so that the relationship was negative at rest ($r = -1.0$) but positive ($r = 1.0$) during exercise (Fig. 5B).

DISCUSSION

The aim of doping control in international competition should be the elimination from competition of athletes who willfully use drugs with a known ergogenic effect to enhance their performances. Yet the list of drugs currently banned by the International Olympic Committee and other agencies has been compiled in the absence of firm scientific evidence of the real ergogenic properties of most of the illegal substances. Hence, a wide range of agents, especially the stimulants, are banned without their true ergogenic nature having been established.

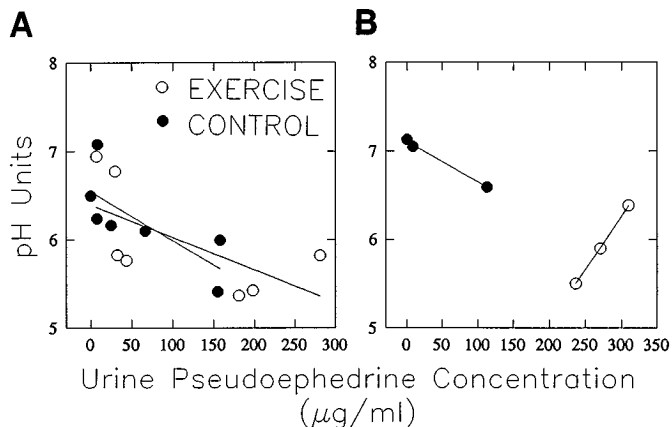


Fig. 5. Correlations between average urine pH and average urine pseudoephedrine concentrations for exercise and rest conditions in 7 *group A* (A) and 3 *group B* (B) subjects.

Thus the first important finding of this study was that a single therapeutic dose of 120 mg pseudoephedrine, sufficient to cause large increases in urine (Fig. 1) and plasma (Fig. 2) pseudoephedrine concentrations, did not influence 40-km time trial performance in well-trained cyclists. Nor did it influence isometric skeletal muscle function measured as either MVC or time to fatigue (Table 1).

We took special care to ensure that the prolonged endurance test, which requires a high degree of motivation on the part of the athlete, would provide valid results. Subjects first performed a full familiarization test; they then completed the drug and placebo trials in random order. The test-retest validity of this system has already been established (6, 12). Not only did pseudoephedrine fail to influence cycling performance, with equal numbers of cyclists performing either better or worse after drug ingestion, but also their performance in the first and second trials was also not different, indicating the absence of a learning effect.

Thus we conclude that when used in the dose tested in this study, pseudoephedrine is without ergogenic effect in endurance exercise at intensities similar to those investigated in this study. Nor does this agent influence skeletal muscle function assessed during maximal exercise of short duration. Nor did pseudoephedrine reduce the degree of skeletal muscle fatigue measured isometrically after the 40-km time trial.

These findings are similar to those of Sidney and Lefcoe (13), who compared the effects of a therapeutic dose (24 mg) of ephedrine and placebo in a double-blind, crossover trial. They concluded that, at this dose, ephedrine did not influence muscle strength, endurance, power, reaction time, or hand-eye coordination.

The second relevant finding was that exercise influenced urine and plasma drug concentrations. Thus urinary drug concentrations were increased with exercise (Fig. 1), although the total amount of drug excreted was unchanged (Fig. 1). This effect was therefore due largely to the reduction in urine volume after the 40-km time trial.

In addition, plasma drug concentrations reached higher peak concentrations and the area under the plasma concentration vs. time curve was greater under exercise conditions for the total group (Fig. 2). A probable explanation for this finding is that plasma volume may decrease by up to 10% during prolonged cycling (18). It is also possible that pseudoephedrine might be cleared by presynaptic uptake and then released as a false neurotransmitter during exercise. These factors may account for the higher plasma pseudoephedrine concentrations during exercise.

An unchanged total urinary pseudoephedrine excretion (Fig. 1) would not explain why plasma pseudoephedrine concentrations rose in response to exercise (Fig. 2). A reduced volume of distribution due to changes in renal blood flow and glomerular filtration rate (4, 5, 11) in blood flow distribution, in plasma protein and tissue binding, or as a result of temperature or pH changes (10, 16, 17) might explain this finding.

Renal clearance is the principal method by which pseudoephedrine is eliminated (3), so a fall in the glomerular filtration rate would decrease pseudoephedrine clearance. But this mechanism alone seems unlikely because total urinary excretion was unaffected by exercise (Fig. 1).

Alternatively, the reduction in urine pH after exercise (Fig. 1) would have favored urinary excretion of pseudoephedrine because the sympathomimetic drugs are weak bases with values of the negative logarithm of the acidic dissociation constant in the range of 9.4–9.6. Hence excretion is increased at low urinary pH (3, 7, 19). Thus a reduction in urinary pH might offset any effects of a fall in glomerular filtration rate on drug elimination.

The third relevant finding was the identification of two apparently different responses in urine and plasma drug concentration. In the majority of subjects (*group A*), exercise increased the plasma pseudoephedrine concentrations substantially (Fig. 3A). In this group, urinary pseudoephedrine content was high at rest and lower, albeit not significantly, during exercise (Fig. 4A).

In contrast, in the group who maintained unchanged plasma pseudoephedrine concentrations after exercise, urinary excretion of the drug was low under resting conditions but increased substantially during and after exercise (Fig. 4B) so that significantly higher urinary pseudoephedrine concentrations and contents were achieved with exercise. Urine pH fell more in this group of subjects with exercise (Figs. 4 and 5) and could, perhaps, explain why they were better able to excrete pseudoephedrine under exercise than rest conditions.

In the group of seven subjects, there was a significant negative correlation between urine pH and urine pseudoephedrine concentration (Fig. 5A), as would be expected (3, 7, 19). This inverse relationship was the same under resting and exercising conditions. In contrast, the three subjects showed the same inverse relationship at rest, but the relationship became positive with exercise.

Lefebvre et al. (8) showed that there is considerable interindividual variability in urinary concentrations of ephedrine after a single dose and that both urine concentration and content were increased 1 h after exercise.

The important practical relevance of this study is to indicate that, because of individual variations in urinary excretion patterns for pseudoephedrine after exercise, it is unlikely that the amount of drug ingested before exercise can be reliably predicted from a single urine sample taken sometime after exercise. As a result, the use of urine drug concentrations in an attempt to distinguish whether preexercise drug use has been for therapeutic or malicious reasons is unlikely to find scientific support.

Most particularly, the data of this study indicate that very high urine drug concentrations can be achieved from therapeutic doses of these agents. Furthermore, the drug is still detectable in blood 24 h after exercise (Fig. 2) and might therefore still be detectable in urine, particularly if the athlete were to perform vigorous exercise, causing the excretion of a concentrated urine.

In summary, this study extends previous work for therapeutic doses of ephedrine by establishing that a single dose of 120 mg, twice the therapeutic dose, taken 2 h before exercise is without ergogenic effect during prolonged exercise lasting for ~1 h. This dose also fails to influence isometric skeletal muscle function. Hence this study provides no evidence to support the current listing of pseudoephedrine, taken at therapeutic doses, as a banned ergogenic agent by the International Olympic Committee, at least for those sporting activities similar to the one studied here.

Furthermore, in view of the high proportion of positive tests for this agent, usually in subjects who have used proprietary medications for the treatment of intercurrent illnesses, the status of this specific group of agents on the banned list should be reviewed, at least when the drugs are used in therapeutic doses and without concurrent use of other drugs that might act synergistically to produce an ergogenic effect.

Finally, as a result of individual variations in urinary excretion patterns in response to exercise, it is unlikely that urinary drug concentrations can be used as a reliable predictor of the amount of drug ingested before exercise and thus the likely intent for which the drug had been ingested.

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Address for reprint requests: T. D. Noakes, MRC/UCT Bioenergetics of Exercise Research Unit, Dept. of Physiology, Sports Science Institute of South Africa, Boundary Rd., Newlands 7700, South Africa.

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