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The influence of allopurinol on urinary purine loss after repeated sprint exercise in man

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Abstract

The influence of allopurinol on urinary purine loss was examined in 7 active male subjects (age 24.9 ± 3.0 years, weight 82.8 ± 8.3 kg, $\dot{V}O_2$peak 48.1 ± 6.9 mL · kg^{-1} · min^{-1}). These subjects performed, in random order, a trial with 5 days of prior ingestion of a placebo or allopurinol. Each trial consisted of eight 10-second sprints on an air-braked cycle ergometer and was separated by at least a week. A rest period of 50 seconds separated each repeated sprint. Forearm venous plasma inosine, hypoxanthine (Hx) and uric acid concentrations were measured at rest and during 120 minutes of recovery from exercise. Urinary inosine, Hx, xanthine, and uric acid excretion were also measured before and for 24 hours after exercise. During the first 120 minutes of recovery, plasma Hx concentrations, as well as the urinary Hx and xanthine excretion rates, were higher ($P < .05$) with allopurinol compared with the placebo trial. In contrast, plasma uric acid concentration and urinary uric acid excretion rates were lower ($P < .05$) with allopurinol. The total urinary excretion of purines (inosine + Hx + xanthine + uric acid) above basal levels was higher in the allopurinol trial compared with placebo. These results indicate that the total urinary purine excretion after intermittent sprint exercise was enhanced with allopurinol treatment. Furthermore, the composition of urinary purines was markedly affected by this drug.

1. Introduction

The metabolic demand of intense sprint exercise produces a large efflux of purine bases from the muscle into the blood during recovery after exercise [1-3]. The inability of adenosine triphosphate (ATP) resynthesis to match the rate of ATP hydrolysis and the subsequent action of myokinase and adenosine monophosphate deaminase results in a degradation of the skeletal muscle ATP content [2,4,5] and a stoichiometric increase in inosine monophosphate (IMP) [2,5]. The accumulated IMP can undergo further degradation to produce inosine, which is converted to hypoxanthine (Hx) [6]. Both inosine and Hx can be resynthesised to IMP via the purine salvage pathway [7,8] or leave the muscle and accumulate in the plasma [1,3,9,10]. Once in the plasma, Hx can no longer be a precursor for purine salvage by the muscle as no Hx uptake has been measured in muscle after intense exercise [11]. The extent of the purine base efflux from the muscle after intense exercise has been reported to be equivalent to 9% of the resting preexercise ATP content [12] and represents a large increase in purine load in the plasma. Once in the plasma, Hx can be converted to xanthine and uric acid in the liver [1,13] as a result of the action of xanthine dehydrogenase/oxidase [14]. Uric acid is the end point metabolite of purine metabolism, and it accumulates in the plasma after intense exercise [2,15]. The major mechanism responsible for the removal of inosine, Hx, xanthine, and uric acid from the plasma is renal excretion [3,16-18]. Uric acid can also efflux via the gut [18], and to a lesser extent, when plasma uric acid levels are high [11], circulating uric acid may also be taken up by the recovering muscle where it is used as an oxygen free radical scavenger [19]. Hx loss via the gut is small [20] suggesting that the major mechanism for removal of plasma purine bases (Hx and xanthine) is via the kidney.

The renal transport mechanism of uric acid involves glomerular filtration, near-complete presecretory reabsorption, tubular secretion, and postsecretory reabsorption [21,22]. Manipulation with uricosuric and antiuricosuric

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agents demonstrates differences in renal transport mechanisms of Hx, xanthine, and uric acid by the kidney [21-25]. Considering that intense exercise results in the accumulation of these metabolites in the plasma [2,3,17], any manipulation of the purine composition delivered to the kidney could be expected to influence the urinary excretion pattern and the magnitude of total urinary purine excretion.

Allopurinol, a structural analogue of Hx, and its major metabolic product oxypurinol are both potent inhibitors of xanthine oxidase [26]. The inhibition of xanthine oxidase reduces the oxidation of Hx to uric acid, and it is for this reason allopurinol is commonly used in the treatment of hyperuricemia and gout [27]. Given the prevalence of allopurinol usage, it is perhaps surprising that only 2 studies have examined the influence of allopurinol on purine metabolism after high-intensity exercise in human beings [17,28]. Unfortunately, these studies have several limitations. For example, Sutton et al [17] reported that allopurinol had no effect on the exercise-induced uric acid excretion. However, this finding must be treated cautiously because blood sampling only occurred for 30 minutes after exercise, whereas urine sampling was only taken up to 15 minutes after exercise. This is probably insufficient to observe peak changes in uric acid concentration in these fluids [3,15]. Sutton et al [17] also reported that allopurinol resulted in an increase in plasma oxypurine (Hx and inosine) concentration after exercise; however, no statistical comparison was made with the control condition. Interestingly, these authors also reported that urinary oxypurine excretion increased significantly after 15 minutes of recovery in the control but was unchanged in the allopurinol condition. This finding was attributed to a decrease in renal clearance of the oxypurines in the allopurinol trial. The results from the Hadano et al [28] study are difficult to interpret because they compared plasma purine concentrations and urinary purine excretion rates in subjects ingesting allopurinol in the resting condition with those recovering from intense cycling exercise. Such an experimental design without the comparison with control conditions does not provide information on the influence of allopurinol ingestion on urinary purine loss after high-intensity exercise.

The present study investigated the effects of an increased plasma purine load after intense exercise, combined with the effects of allopurinol to examine the purine handling functions of the kidneys and whole body purine excretion.

2. Methods

2.1. Subjects

Seven active nonspecifically trained men (age 24.9 ± 3.0 years, weight 82.8 ± 8.3 kg, $\dot{V}O_2$peak 48.1 ± 6.9 mL · kg^{-1} · min^{-1}) volunteered for the study, which was approved by the Victoria University Human Research Ethics Committee. All subjects were fully informed of the experimental procedures and voluntarily consented to take part in the study.

2.2. Exercise protocols

Peak oxygen consumption of each subject was determined approximately 1 week before beginning the experimental trials. The exercise protocol involved riding on a cycle ergometer (Lode, Groningen, the Netherlands) for 3 minutes at 3 submaximal work rates, after which the work rate was increased every minute thereafter until volitional exhaustion. Expired air was directed, by a Hans Rudolph valve, through a ventilometer (Pneumoscan S30, California, USA) into a mixing chamber and analyzed for oxygen and carbon dioxide content by gas analyzers (Applied Electrochemistry S-3A O_2 and CD-3A CO_2, Ametek, Pennsylvania, USA). These analyzers were calibrated before each test using commercially prepared gas mixtures. Oxygen consumption was calculated by a microprocessor using standard equations.

Subjects were asked to perform 2 exercise trials separated by at least 1 week. The trials were allocated using a double-blind, random, crossover design. The exercise protocol in each of these trials consisted of eight 10-second "all-out" sprint bouts on an air-braked cycle ergometer (series A, Repco, Melbourne, Australia) modified to enable computerized determination of peak and mean power. The power output of the air-braked cycle ergometer is approximately proportional to the cube of the wheel velocity, which was measured using a tachometer (Hall-effect device and a cog at the wheel hub). The subjects were instructed to remain seated and pedal as fast as possible for the 10-second exercise periods. Sprints were separated by 50 seconds of passive rest. Subjects were familiarized with the intermittent sprint task at least 1 week before the trials. In the placebo and experimental trials, the subjects ingested a tablet of calcium carbonate or a 300-mg dose of allopurinol, respectively, once a day for the 5 days preceding each trial. Pilot testing indicated that exercise performance, plasma purine concentrations, and total urinary purine excretion after intermittent exercise were similar when the placebo treatment was compared with no treatment (data not shown). These data indicate that calcium carbonate was an appropriate placebo for this study. The subjects were also instructed to refrain from strenuous exercise, caffeine, and alcohol consumption 24 hours before the experimental trials. In addition, subjects recorded their diet for the 24 hours before the first experimental trial and were asked to consume similar foods before subsequent trials. All experimental trials were conducted in the morning after an overnight fast. During the first 15 minutes of recovery from each intermittent exercise session, the subjects ingested 500 mL of water. Subjects were also provided with food (snack bar, fruit juice, and salad sandwich) after 2 hours of recovery in each trial and were restricted from any other food intake until after the 8-hour urine sample was obtained.

2.3. Blood and urine sampling, treatment, and analysis

Blood was sampled from an antecubital vein, via an indwelling catheter, at rest and after 0, 10, 15, 20, 30, 60,

and 120 minutes of passive recovery after the final sprint bout. The blood was immediately placed into lithium heparin tubes and spun in a centrifuge. Subsequently, 100 μL of plasma was added to 200 μL of ice-cold 3 mol/L perchloric acid and spun, and the supernatant was stored at −80°C before analysis for lactate. The remaining plasma was stored in liquid nitrogen for analysis of inosine, Hx, and uric acid. The plasma stored for these metabolites was deproteinized with 1.5 mol/L perchloric acid and subsequently neutralized with 2.1 mol/L potassium hydrogen carbonate immediately before analysis. Plasma lactate was determined in duplicate, using an enzymatic spectrophotometric technique [29]. Plasma Hx, inosine, and uric acid were determined on neutralized perchloric acid extracts, using a modification of the reverse-phase high-performance liquid chromatography technique described by Wynants and Van Belle [30]. Urine was collected for 12 hours before the first exercise bout and for the first 2 and the subsequent 6- and 16-hour periods after the completion of the last sprint bout. Urine volume was determined, and then the samples were stored at −80°C before analysis. Samples were deproteinized, neutralized, and analyzed for inosine, Hx, and xanthine using the same sample treatment and high-performance liquid chromatography procedures as described for plasma. Urinary uric acid concentration was determined by an enzymatic colorimetric method using a Beckman Synchron CX system (Beckman Coulter, Brea, Calif).

2.4. Statistical analysis

Where appropriate, the metabolite and performance data were analyzed using analysis of variance with repeated-measures (BMDP Statistical Software, Cork, Ireland). Simple main effects analyses and Newman-Kuels post hoc tests were used to locate differences when analysis of variance revealed a significant interaction. Comparison of urinary purine loss during 8 hours of recovery was analyzed using paired-sample t tests. The level of probability to reject the null hypothesis was set at $P < .05$. All values are reported as means ± SE.

3. Results

3.1. Exercise performance

There were no differences in peak or mean power between the trials. Both peak (1074 ± 50 vs 1072 ± 46 W; allopurinol vs placebo) and mean power (866 ± 36 vs 848 ± 35.3) were highest in the first sprint and decreased significantly ($P < .05$) by the third sprint with a further significant reduction during sprint 5. No further decreases in performance were observed during the final 3 sprints.

3.2. Plasma metabolites

Plasma inosine concentration increased ($P < .05$) above resting levels in both trials and peaked around 20 to 30 minutes into recovery, before returning to preexercise levels by 120 minutes (Fig. 1A). There was no difference in plasma inosine concentration between trials. Plasma Hx concentrations were similar at rest and increased ($P < .05$) immediately after exercise in both trials (Fig. 1B). They remained above basal levels even after 120 minutes of recovery. The Hx concentrations were higher with allopurinol treatment compared with placebo from 10 minutes until at least 120 minutes of recovery ($P < .05$). Peak Hx levels in the allopurinol trial were almost twice that of the placebo trial. Exercise elevated the uric acid concentrations above resting concentrations at 15 and 30 minutes in the placebo and allopurinol trials, respectively (Fig. 1C), and did not return to basal concentrations in both trials by 120 minutes. Plasma uric acid was lower in the allopurinol trial at rest ($P < .05$) and remained markedly lower throughout recovery compared with the placebo trial. Plasma lactate concentrations were 0.84 ± 0.1 and 1.0 ± 0.1 mmol/L (allopurinol

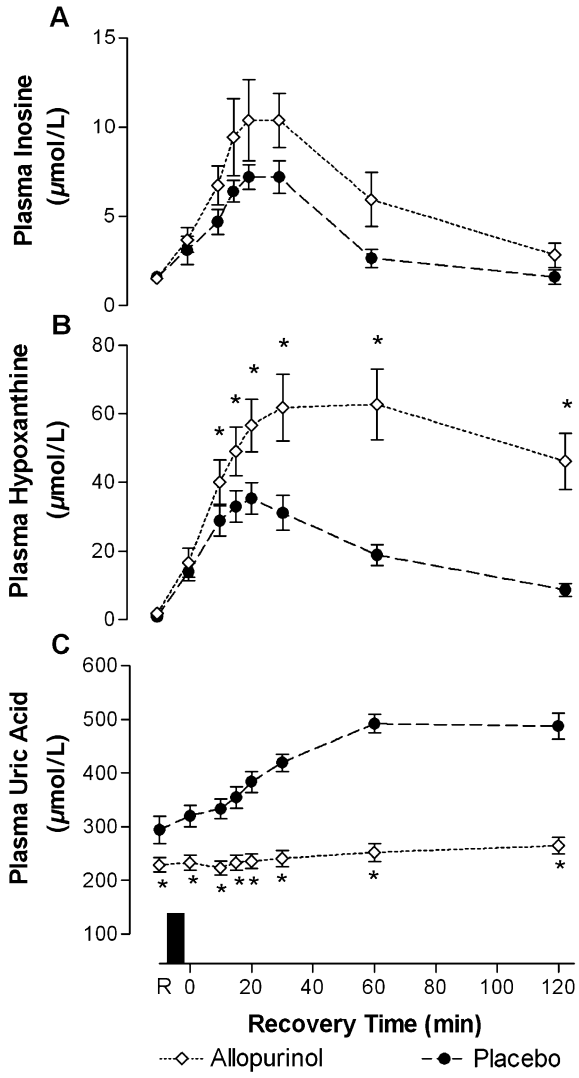

Fig. 1. Forearm venous plasma inosine (A), Hx (B), and uric acid (C) concentrations at rest (R) and during recovery from eight 10-second intermittent sprint bouts with allopurinol or placebo ingestion. Values are means ± SE, n = 7, *Different from placebo; $P < .05$ (note difference in scale).

vs control) at rest and increased markedly after the sprint bouts in both trials peaking at 5 minutes after the last exercise bout (17.8 ± 1.3 vs 17.1 ± 1.0 mmol/L; allopurinol vs placebo) with no differences in concentrations observed between treatments at any time point during the 2-hour recovery period (data not shown).

3.3. Urinary metabolites

Allopurinol had no effect on basal urinary excretion of inosine Hx or uric acid (Fig. 2A, B, and D). In contrast, basal urinary excretion of xanthine was greater ($P < .05$) in the allopurinol compared with placebo (Fig. 2C). The excretion rate of all measured urinary metabolites in both trials increased ($P < .05$) in the 2-hour period after sprinting, with the notable exception of uric acid in the allopurinol trial which remained similar to basal levels. The Hx and xanthine excretion rates in this period were greater ($P < .05$) in the allopurinol trial compared with placebo and remained higher during the 2- to 8-hour period after sprint exercise. Although a similar pattern was observed, urinary inosine excretion was not different in the first 2 hours ($P = .06$) or the 2- to 8-hour period of recovery from exercise. In contrast, the excretion rate of uric acid in the placebo trial was markedly elevated in the 0- to 2-hour and 2- to 8-hour periods after exercise ($P < .05$) in comparison with the allopurinol trial. In the 8- to 24-hour period of recovery, the excretion rates of inosine, Hx, xanthine, and uric acid were similar between trials and had returned to basal values. A significant interaction ($P < .05$) for total purine excretion was observed (Fig. 2E); however, post hoc analysis only revealed a tendency ($P = .08$) for an elevated excretion in the allopurinol trial in the 0- to 2-hour and 2- to 8-hour recovery periods.

Because urinary excretion of all purines had returned to basal levels by the end of the first 8 hours of recovery, the exercise-induced urinary purine loss was calculated using the first 8 hours of urinary data. Total urinary inosine, Hx, and xanthine loss during this period were ~2-, 4.5-, and 10-fold greater ($P < .05$) in the allopurinol trial (Table 1). In contrast, the amount of uric acid excreted above basal levels was 3-fold lower ($P < .05$) in the allopurinol trial compared with placebo (Table 1). The total urinary

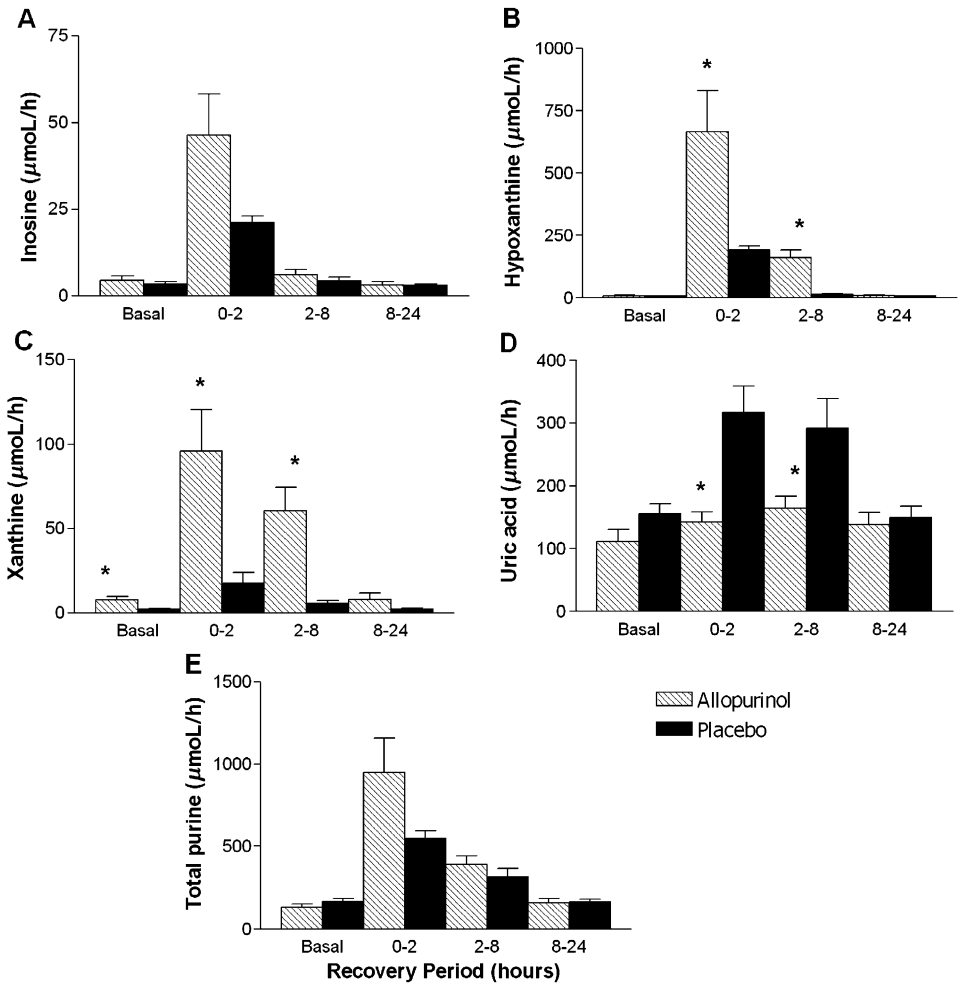

Fig. 2. Urinary inosine (A), Hx (B), xanthine (C), uric acid (D), and total purine (E) excretion rate at rest (basal) and during the first 2 hours and the subsequent 6 and 16 hours of recovery after eight 10-second intermittent sprint bouts with allopurinol or placebo ingestion. Values are means ± SE, n = 7. *Different from placebo, $P < .05$ (note difference in scale).

Table 1
Urinary purine loss above basal levels during the first 8 hours of recovery from eight 10-second sprints after 5 days of prior ingestion of allopurinol or a placebo

	Placebo (μmol)	Allopurinol (μmol)
Inosine lost to urine	41 ± 7	94 ± 25[a]
Hx lost to urine	421 ± 43	2232 ± 419[a]
Xanthine lost to urine	52 ± 23	493 ± 111[a]
Uric acid lost to urine	1137 ± 360	380 ± 222[a]
Total urinary purine loss	1651 ± 410	3198 ± 639[a]

Values are means ± SE, n = 7.
[a] Different from placebo ($P < .05$).

excretion of purines (inosine + Hx + xanthine + uric acid) was 2-fold higher ($P < .05$) in the allopurinol trial compared with placebo (Table 1).

4. Discussion

This study is the first to demonstrate a substantially greater loss of total urinary purines after intermittent sprint exercise with allopurinol treatment. Consistent with the characteristic pharmacological effects of allopurinol, we report markedly attenuated urinary uric acid excretion (33%) and enhanced urinary Hx (530%) and xanthine (950%) excretion during recovery from sprint exercise (Table 1). Exercise performance was not different between the trials, and plasma lactate concentrations were unaffected by the treatment, demonstrating that 5 days of allopurinol ingestion does not influence intermittent sprint performance. This is supported by the work of others [17] and indicates that the metabolic stress and subsequent purine base production within the contracting musculature were likely to be similar between trials.

As previously reported, allopurinol induced resting hypouricemia but had no effect on plasma inosine or Hx concentrations (Fig. 2) [17,31]. Sprint exercise increased ($P < .05$) plasma inosine, Hx, and uric acid concentrations during recovery in both trials (Fig. 1). This is likely caused by an increase in circulating purines as a result of the production and subsequent efflux of purines from the muscle after intense exercise, rather than a decrease in plasma purine removal rates [1,9,11]. As mentioned above, the metabolic stress is likely to be similar in both trials, and hence, the magnitude of purine base efflux across the sarcolemma is probably the same after exercise. However, consistent with the inhibitory effect of allopurinol [31], the inhibition of xanthine oxidase influenced the mix of the circulating purines and resulted in greater rises in plasma inosine (Fig. 1A) and Hx (Fig. 1B) and blunted the rise in uric acid concentrations (Fig. 1C) during recovery from sprint exercise. The increase in plasma metabolite concentrations in the placebo trials has been observed previously during similar experimental conditions [3], but there are no comparable studies with the allopurinol intervention trial.

The exercise-induced rise of plasma Hx and inosine and the augmentation of this rise with allopurinol ingestion have been previously reported [17]. However, the uric acid results of the present study are in conflict with those of Sutton et al [17] who reported no increase in plasma uric acid in either trial after exercise. It is unclear why no increase was observed in the placebo trial because the exercise was intense enough to produce a 30% fall in the contracting muscle total adenine nucleotide pool (ATP + adenosine diphosphate + adenosine monophosphate) after exercise and a 250% increase in plasma oxypurine concentration during recovery [17]. A likely explanation is that they did not measure the plasma metabolites 30 minutes after exercise where changes in uric acid levels above rest are more likely to occur [15].

The small (15%) increase in plasma uric acid concentration after 2-hour recovery (Fig. 1C) and the elevated urinary xanthine excretion during the first 8 hours of recovery in the allopurinol trial (Fig. 2C) indicate that the inhibition of xanthine oxidase was incomplete. Furthermore, basal level urinary uric acid excretion was maintained during the 24-hour recovery period in the allopurinol trial, suggesting that there was some production of uric acid despite the presence of the drug. It should be noted that dietary sources of purine possibly help maintain basal levels of plasma uric acid with allopurinol administration [32]. The small increase in plasma uric acid during recovery in the allopurinol trial may also be caused by a decreased removal rate. In support of this possibility, a decreased urinary excretion of uric acid has been demonstrated during the first 45 minutes of recovery from intense exercise [33].

Allopurinol had no effect on urinary basal excretion rates of inosine, Hx, or uric acid excretion rates; however, xanthine excretion was increased by the drug (Fig. 2). Our inability to measure a decrease in basal urinary uric acid excretion with allopurinol is in contrast to previous research [31]. The increase in basal xanthine excretion confirms the data of Klinenberg et al [34] who reported that approximately half of the increase in basal oxypurine excretion after allopurinol treatment was attributed to xanthine.

Consistent with previous research [3,10,17], sprint exercise increased the excretion rates of purines (Fig. 2). The rates of urinary loss, especially inosine and Hx, are higher than we have previously observed after a similar exercise protocol [3]. However, allopurinol further enhanced total urinary purine loss after intermittent sprint exercise (Table 1) as a result of differences in the excretion of the individual purine bases. The differences in the excretion rates of Hx, xanthine, and uric acid (Table 1) in the first 8 hours of recovery from exercise after taking allopurinol reflect the altered plasma purine concentrations and the subsequent change in purine mix delivered to the kidney. Although not measured in this study, previous research on horses has demonstrated that plasma xanthine is elevated after exercise with allopurinol [35]. Furthermore, there was a tendency ($P = .06$) for an elevated excretion of inosine with allopurinol, and like Hx and xanthine, it is probably a reflection of the concentration changes in the plasma. Although the difference in the plasma was not significant

(P = .13), Sutton et al [17] have demonstrated a higher plasma inosine concentration with allopurinol treatment after exercise.

The fact that the reduction in urinary uric acid excretion was not balanced proportionally to the increase in the aggregate of urinary purine bases suggests that other factors are influenced by allopurinol. The processes that may be influenced by allopurinol are the renal handling mechanism(s) of purine excretion, hemodynamic factors, and the loss of purine bases via the gut. Although this study cannot provide any evidence on the precise mechanism(s), hemodynamic factors are not likely to play a role, as previous studies show no effect of allopurinol [36] or oxypurinol [37] on the blood pressure or renal blood flow in rats. Perhaps the best explanation for the increased excretion of purines in the drug trial is the influence of the different renal handling mechanisms by which the kidney excretes these metabolites [23-25,38,39]. Renal uric acid excretion involves filtration at the glomerulus, near-complete reabsorption at the proximal tubule, secretion into the proximal tubule, and further reabsorption [40]. At present, the evidence indicates that renal excretion of Hx is mainly dependent upon glomerular filtration [38,39], whereas xanthine excretion is dependent upon glomerular filtration and tubular secretion [23]. The fractional clearance of uric acid is one seventh of Hx [41] and is not altered by allopurinol [42]. Thus, the increased urinary excretion of purines after allopurinol ingestion and intense exercise could simply be caused by an altered mix of plasma purines being presented to the kidney. Furthermore, Yamamoto et al [25] have also demonstrated that hyperlactatemia inhibited urinary excretion of uric acid but does not influence that of Hx or xanthine. This would further exacerbate the potential for increased loss of purines in the allopurinol trial via the kidneys. Plasma lactate concentration increased after both trials, and the recovery profile was not different between trials during the 2 hours after exercise. From this, it is assumed that the inhibition of uric acid excretion by lactate will be similar in both trials.

Assuming the total purine production and efflux from the muscle was the same between the trials and that the action of xanthine oxidase effectively produces a 1:1 stoichiometric replacement of uric acid with Hx, then the 2-fold greater total urinary purine excretion after 8 hours' recovery in the allopurinol trial needs to be accounted for. The fate of these unaccounted purines in the placebo trial is not clear, but there are several possibilities. The difference in uric acid and Hx exchange across the gut may provide an explanation for this difference. One third of the resting circulating uric acid is excreted via the gut compared with two thirds excreted in the urine [18], whereas the efflux of Hx into the gut has been measured at 3% [20]. Hence, a change in composition of plasma purines with allopurinol will favor a reduced uric acid loss in the gut effectively shunting the purines to the kidney for excretion. If the ratios of excretion across the gut stay the same under all plasma concentrations, the uric acid excretion via the gut in the 8 hours after exercise reduces from 568-190 μmol, and this only accounts for approximately one third of the difference in total purine loss observed between trials. Uric acid excretion is an exponential function of the plasma concentration [43], and the results in this study are consistent with this except that there is no difference in basal excretion in the allopurinol trial when the plasma concentration is significantly lower. Thus, the relationship between plasma concentration and excretion rates of uric acid is not a factor in the large unaccounted purine excretion. A further possibility lies in the potential pool of uric acid in the plasma still to be excreted at 8 hours' recovery in the placebo trial. This is difficult for us to ascertain in this study because we did not measure the plasma concentrations at 8 hours, and the excretion data taken between 8 and 24 hours are not different between the trials. Hence, we cannot confirm this as a potential source for the greater urinary purine base excretion with allopurinol.

A 2-fold increase in exercise-induced urinary purine excretion after allopurinol (Table 1) raises an interesting question if a shift from fecal to urinary excretion pathways is not a factor. On the premise that total urinary purine loss after exercise equates to endogenously produced purines, intramuscular purine concentrations may be depleted as a consequence of allopurinol ingestion combined with intense repeated exercise. However, the widespread therapeutic use of allopurinol without incident over several decades suggests that there are likely to be adaptations that attenuate the loss or maintain the content of muscle purines with chronic intense exercise training and allopurinol ingestion. In addition, intense repeated exercise during sprint training has produced reductions in muscle nucleotides at rest [2], and further investigation with allopurinol and chronic exercise is needed.

In conclusion, the present study demonstrated that allopurinol augments the exercise-induced rise in plasma Hx concentration but markedly attenuated the increase in plasma uric acid levels. These changes were reflected in higher Hx and xanthine and lower urinary uric acid excretion rates after exercise with allopurinol administration. The increase in urinary Hx and xanthine excretion markedly exceeded the fall in urinary uric acid loss, and as a consequence, total urinary purine loss was 2-fold greater after intense exercise with allopurinol treatment. These results suggest that altering the mix of plasma purines filtered by the kidney combined with a higher fractional clearance of Hx will change the magnitude of total urinary purine loss. This is likely related to the different renal transport mechanisms that have been previously described for each of the purine molecules. In addition, the changes in plasma purine composition may reduce intestinal purine loss because efflux mechanisms appear to differ from one purine to another at the gut. If this occurred, the elevated total urinary purine excretion with allopurinol treatment after exercise may also be explained, at least in part, by a greater delivery of purines to the kidney.

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