Effects of acetaminophen and ibuprofen on renal function in the stressed kidney

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Farquhar, W. B., A. L. Morgan, E. J. Zambraski and W. L. Kenney. Effects of acetaminophen and ibuprofen on renal function in the stressed kidney. J. Appl. Physiol. 86(2): 598–604, 1999.—Exercise, salt restriction, and/or dehydration causes transient reductions in renal function that may be buffered by vasodilatory prostaglandins (PGs). Over-the-counter (OTC) analgesics have the potential to alter renal hemodynamics by inhibiting renal PGs. Therefore, we tested the renal effects of the maximal recommended dose of acetaminophen (Acet, 4 g/day) and ibuprofen (Ibu, 1.2 g/day) vs. a placebo (Pl) in humans subjected to progressive renal stresses. After baseline measurements, 12 fit young (25 ± 1 yr) men and women underwent 3 days of a low (10 mice/day)-sodium diet while taking one of the drugs or Pl (crossover design). Day 4 involved dehydration (3.6% body wt) followed by 45 min of treadmill exercise (65% maximal O2 uptake) in the heat (36°C). These combined stressors caused dramatic decreases in effective renal plasma flow, glomerular filtration rate (GFR), and sodium excretion. Baseline GFR (range: 118–123 ml/min) decreased to 78 ± 4, 73 ± 5, and 82 ± 5 ml/min postexercise in the Acet, Ibu, and Pl trials, respectively, with a significantly greater decrease in GFR in the Ibu trial (P < 0.05 vs. Pl). OTC Ibu has small but statistically significant effects on GFR during exercise in a sodium- and volume-depleted state; OTC Acet was associated with no such effects.

RENAL PROSTAGLANDINS (PGs) are important determinants of renal function when renal sympathetic outflow is enhanced and when there is an increase in plasma renin-ANG II. These conditions are referred to as "renal PG-dependent" states (18, 29). PGs, such as PGE2 and PGI2, are vasodilators that help to counteract the neural and hormonal vasoconstrictor stimuli. Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen (Ibu) have been shown to inhibit PGE2 and therefore depress renal function [glomerular filtration rate (GFR) and effective renal plasma flow (ERPF)] when the kidney is in a PG-dependent state (19, 32). Examples of renal PG-dependent states include sodium depletion, hypovolemia, and pathological conditions such as chronic heart failure, hepatic cirrhosis, and chronic renal failure. In all of these conditions, predictable decrements in renal function follow the administration of NSAIDs (9, 14, 24, 32).

Dynamic exercise would be predicted to cause a renal PG-dependent state because of associated increases in sympathetic outflow, circulating catecholamine concentrations, and renin-ANG II (20, 21), but the experimental data do not support this. For example, Zambraski et al. (30) found no difference in creatinine clearance with aspirin treatment compared with placebo (PI) when subjects exercised at 70% maximal O2 consumption (Vo2max) for 30 min. Similarly, Walker et al. (25) found no significant differences in GFR (inulin clearance) after indomethacin treatment compared with Pl when subjects exercised at 80% Vo2max for 30 min. There was, however, a suggestion of renal PG-dependency because ERPF was significantly lower in the indomethacin trial. One limitation of these studies is that the kidney may have only been moderately stressed by the exercise bouts chosen. To date, no one has examined the effects of NSAIDs on renal function when exercise is combined with other factors such as thermal stress and dehydration. These combined physiological perturbations would be predicted to stress the kidney to a greater extent and render it PG dependent. There are anecdotal case reports (17, 23) of renal dysfunction associated with aspirin or NSAID use in athletes competing in marathons and ultramarathons, situations that often present the combined stresses of dehydration, heat stress, and exercise. Therefore, this investigation attempted to reconcile the earlier experimental studies with the anecdotal case reports of NSAID-induced renal dysfunction during exercise.

Acetaminophen (Acet) is a widely used analgesic that is thought to be a very weak peripheral inhibitor of PG synthesis (12). Therefore, Acet would not be predicted to adversely affect renal function in a renal PG-dependent state. In this regard, Acet might be considered the analgesic of choice for subjects who are in a PG-dependent state. In fact, Acet is the recommended analgesic for patients with renal dysfunction (12). However, there are some reports of Acet causing renal failure (1, 2). On the basis of these case reports and because of the lack of prior experimental data, a renal PG-dependent animal model (using a low-sodium diet; see Ref. 5a) was used to assess the effects of Acet on PG synthesis and renal function. The animal study demonstrated that Acet inhibited renal PGs and produced similar decreases in GFR and renal blood flow in normal (sodium-replete) and sodium-depleted animals. However, Ibu caused more-pronounced declines in renal function in the PG-dependent animals. Consequently, we thought it would be beneficial to also test Acet during exercise conditions in humans.
Accordingly, in the present study, we attempted to simulate the combined conditions of sodium and/or water deficit along with exercise under heat stress conditions to evoke a potentially PG-dependent state and determine the renal effects of over-the-counter (OTC) doses of Acet and Ibu on renal function.

METHODS

Subjects. Twelve fit healthy men \( (n = 6) \) and women \( (n = 6) \) gave their oral and written consent to participate in this institutionally approved study. Subject screening consisted of a physical exam by a physician, a resting electrocardiogram, body composition estimate from skinfold measurement (13), and a maximal graded exercise test on a motor-driven treadmill to measure \( \dot{V}O_{2\max} \). The treadmill protocol consisted of a 4-min warm-up followed by 2-min stages in which speed was held constant and grade was increased by 2%/stage until the subject was unable to continue. To determine the individual treadmill workloads that elicited 65% \( \dot{V}O_{2\max} \) (used for the subsequent exercise trials), subjects returned on a separate day and ran at various speeds while oxygen consumption was measured. Subjects' characteristics are presented in Table 1.

A Chem-24 was also performed (American Medical Laboratories) while the subjects were in a fasted state to ensure normal baseline venous electrolyte concentrations and to rule out any evidence of kidney or liver dysfunction.

Protocol. Each subject completed three, single-blind, randomized 5-day trials (crossover design; see Fig. 1) that were identical in all respects except for the type of analgesic (or Pl) ingested. Day 1 began (6:30 AM) with indwelling venous catheter placement (1 catheter was placed in each arm; 1 for infusing, 1 for sampling). Subjects then drank 5 ml/kg of water. Baseline plasma volume and renal function measurements (described below) were performed with subjects seated. Subjects then began a very-low-sodium diet (10 meg/day), where water intake was ad libitum (with encouragement to drink) for 3 full days. All meals were prepared and served in the General Clinical Research Center metabolic kitchen at Pennsylvania State University (Noll Laboratory). Total caloric intake was estimated by using the Harris-Benedict equation with an activity factor of two, and a Centrum multivitamin (Advanced Formula Centrum, Lederle Laboratories, Pearl River, NY) was given daily. Maximal OTC doses of the drug (Acet was given 4 times/day for a total of 4 g/day, and Ibu was given 3 times/day for a total of 1.2 g/day) were started after baseline measurements and continued into the morning of day 4. Daily exercise was limited to 30 min during this 3-day period. Daily weights were recorded (scale accuracy \( \pm 50 \) g) throughout the protocol, and 24-h urine samples were collected for subsequent analysis of sodium, potassium, and PGE\(_2\) concentrations. All subjects lived in the laboratory and were under observation the day before and the day after the exercise bout in the heat.

Table 1. Subject characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>25 ( \pm 1 )</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>65 ( \pm 5 )</td>
</tr>
<tr>
<td>Height, cm</td>
<td>173 ( \pm 3 )</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>13 ( \pm 2 )</td>
</tr>
<tr>
<td>Body surface area, m(^2)</td>
<td>1.8 ( \pm 0.1 )</td>
</tr>
<tr>
<td>( \dot{V}O_{2\max} ), ml·kg(^{-1})·min(^{-1})</td>
<td>54 ( \pm 1 )</td>
</tr>
<tr>
<td>Plasma volume, ml/kg</td>
<td>49 ( \pm 1 )</td>
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</table>

Data are means \( \pm SE; n = 12, 6 \) men and 6 women. \( \dot{V}O_{2\max} \), maximal \( O_2 \) consumption.

Day 4 began with a low-sodium breakfast (consisting of 25% of the day's calories), 5 ml/kg of water, and catheter placement, followed by repeat measurements of renal function and sodium and potassium excretion. The last dose of the drug (or Pl) was given at 7 AM for the women and 11 AM for the men. A 60- to 75-min period of light exercise (starting at 9:30 AM) on a cycle ergometer (60-90 W) in a hot environmental chamber (40°C) was used to dehydrate the subjects.

After the dehydration period, subjects rested in a thermoneutral environment for 2 h to allow core temperature to return to normal. During this time, infusions were again started for the subsequent analysis of renal function during exercise. Exercise consisted of treadmill running for 45 min (or to a core temperature of 39.3°C) at 65% \( \dot{V}O_{2\max} \) in the heat (dry bulb temperature = 36°C, wet bulb temperature = 24°C). Subjects who reached a core temperature of 39.3°C continued to exercise at a reduced intensity to complete the 45 min. Exercise intensity was verified by collecting 4-min samples of expired air into two Douglas bags (15 min into exercise) for subsequent \( O_2 \) and \( CO_2 \) concentration and volume analysis. A 90-min recovery period in the heat followed, during which 60% of the body fluid lost was replaced with water.

Procedures. All blood samples were collected into EDTA- and heparin-containing Vacutainers (Becton-Dickinson, Franklin Lakes, NJ) and immediately placed on ice. Hemoglobin concentration and hematocrit were determined by using a Coulter hematology analyzer (Coulter Microdiff 16; Coulter, Miami, FL). All samples were subsequently centrifuged, and the plasma was frozen. Urine volume was measured by using a graduated cylinder, and one aliquot was frozen in 15 ml propylene Falcon tubes (Becton-Dickinson) with toluene (Fisher Scientific, Fair Lawn, NJ) added as a preservative.

Rectal temperature (\( T_r \)) was used as an index of core temperature. A rectal thermistor (YSI series 400) was inserted 10 cm past the anal sphincter. A temperature-controlled water bath (verified with a mercury thermometer) was used to calibrate the thermistor. \( T_r \) was recorded before, every 5 min during, and every 10 min after exercise.

Baseline plasma volume was determined by using a single bolus injection (3.0-3.5 ml) of Evans blue dye (New World Trading, Debar, FL). The absorbance of the plasma samples was read at 620 nm 10, 20, and 30 min after the injection by using a spectrophotometer (Spectronic 21D-Milton Roy, Rochester, NY). Reported values (Table 1) are based on the peak
absorbance reading, which occurred at 10 min for all subjects. Subsequent changes in plasma volume (from baseline) were calculated (7) from changes in the hemoglobin concentration and hematocrit.

ERPF and GFR were determined by using p-aminohippurate sodium (PAH; Merck, West Point, PA) and inulin (Cypros Pharmaceutical, Carlsbad, CA), respectively. A bolus priming injection (5.6 mg/kg of PAH and 45 mg/kg of inulin) was followed by a constant infusion (Harvard Apparatus 22; South Natick, MA) of the substances mixed in 5% dextrose (Abbott Laboratories, North Chicago, IL). The infusion rates for PAH and inulin were 13 and 39 mg/min, respectively. Forty-five to 60 min elapsed before venous blood sampling to allow the plasma concentrations of PAH and inulin to reach steady state. Blood samples were subsequently collected at 90 and 120 min after the start of the infusion for the pre- and postdiet renal function measurements and during and after exercise. ERPF and GFR were calculated by using the following formulas

\[
ERPF = (\frac{[I]_{PAH} \cdot R}{[P]_{PAH}}) - 1
\]

\[
GFR = (\frac{[I]_{inulin} \cdot R}{[P]_{inulin}}) - 1
\]

where \([I]_{PAH}\) and \([I]_{inulin}\) are concentrations of the infusate (mg/ml), \(R\) is the infusion rate (ml/min), and \([P]_{PAH}\) and \([P]_{inulin}\) are the plasma concentrations of PAH and inulin, respectively (mg/ml). Although there may be some inherent error in measuring absolute ERPF (and GFR) this way because of extrarenal clearance of PAH, this technique has proved to be accurate and reliable in determining relative changes in flow from baseline within a given individual (5, 11, 15, 22). Plasma concentrations of PAH and inulin were assayed by using spectrophotometric techniques (3, 4, 26). A continuous-flow autoanalyzer (Technicon Instruments, Tarry-town, NY) and a spectrophotometer (Spectronic 21D-Milton Roy) were utilized for the PAH and inulin assays.

Sodium and potassium concentrations were measured by using an automatic flame photometer (IL943TM; Instrumentation Laboratories, Lexington, MA). PGE\(_2\) concentration in the urine (28) in women was measured by using a radioimmunoassay [\(125I\)] kit (DuPont Medical Products, Boston, MA). In men, urinary PGE\(_2\) excretion does not reflect renal PGE\(_2\) production as it does in women because men also produce PGs from nonrenal sources such as the seminal vesicles (27). All excretion rates were calculated by using the following formula: volume (L)·time (min)\(^{-1}\)·concentration (meq/L). Plasma renin activity (PRA) was measured by using a Rianen Assay system ANG I [\(125I\)] radioimmunoassay kit (DuPont Medical Products).

Statistical analysis. All data are reported as means ± SE. The three trials were compared by using a repeated-measures ANOVA. A \(P\) value of 0.05 was considered significant. The Scheffé method of multiple comparisons was used for the post hoc analysis when the ANOVA determined that there was a difference in one of the trials. Two-tailed dependent t-tests were used to compare the post-low-sodium-diet, exercise, and recovery data to baseline values within each trial.

RESULTS

Baseline. Subject characteristics are reported in Table 1. Baseline (before drug administration) GFR was 119 ± 6, 123 ± 6, and 118 ± 6 ml/min and baseline ERPF was 745 ± 46, 767 ± 50, and 798 ± 59 ml/min in the Acet, Ibu, and Pl trials, respectively (no difference among trials; see Figs. 2 and 3). Urinary sodium excretion (\(U_{Na}\)·V), urinary potassium excretion (\(U_{K}\)·V), urine production (Table 2), PRA (Table 3), and 24-h urinary PGE\(_2\) excretion (measured in the women only; Table 4) were also similar among drug trials at baseline. Body weights were 65.9 ± 3.3, 65.5 ± 3.4, and 65.7 ± 3.3 kg in the Acet, Ibu, and Pl trials, respectively.

Low-sodium diet. In response to the low-sodium diet, \(U_{Na}\)·V decreased (P < 0.001) and urine production
Plasma volume decreased 17% respectively, as a consequence of the low-sodium diet.

Values are means ± SE; n = 12 subjects. Baseline measurements (before placebo or drug administration) and effects of acetaminophen (Acet), ibuprofen (Ibu), and a placebo (Pl) on renal excretory function after a low-sodium diet, immediately after 45 min of exercise, and 90 min into recovery from exercise are shown. UNaV, urinary sodium excretion; UK, urinary potassium excretion. *P ≤ 0.05 vs. baseline.

### Table 2. Renal excretory function

<table>
<thead>
<tr>
<th>Function</th>
<th>Baseline</th>
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<tbody>
<tr>
<td>UNaV, µeq/min</td>
<td>147 ± 23</td>
</tr>
<tr>
<td>UKV, µeq/min</td>
<td>63 ± 9</td>
</tr>
<tr>
<td>Urine production, ml/min</td>
<td>1.39 ± 0.30</td>
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### Table 4. PGE2 Excretion

<table>
<thead>
<tr>
<th>PGE2 Excretion</th>
<th>Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>UNaV, µeq/min</td>
<td>26 ± 8*</td>
</tr>
<tr>
<td>UKV, µeq/min</td>
<td>74 ± 17</td>
</tr>
<tr>
<td>Urine production, ml/min</td>
<td>2.56 ± 0.50*</td>
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</tbody>
</table>

Plasma renin activity increased (P < 0.01) similarly in all three trials (Table 2). Body weight decreased 1.1–1.7% (P < 0.05 vs. baseline). UNaV, GFR, and ERPF (Figs. 2 and 3) were unchanged in all groups. Twenty-four-hour PGE2 excretion increased in each trial (P < 0.05 vs. baseline; no drug effect). PRA (see Table 3) was significantly increased (from baseline) in the Acet and Pl trials (P < 0.01) but less so in the Ibu trial (P = 0.05). Plasma volume decreased 17 ± 1, 17 ± 1, and 16 ± 1% from baseline (P < 0.05) in the Acet, Ibu, and Pl trials, respectively, as a consequence of the low-sodium diet.

### Table 3. Plasma renin activity

<table>
<thead>
<tr>
<th>PRA</th>
<th>Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0 ± 0.4</td>
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Dehydration and exercise. The dehydration period caused an additional decrease of 1.6 ± 0.1% in body weight from that after the low-sodium diet. Forty-five minutes of subsequent exercise in the heat caused dramatic decreases in urine production (P < 0.02; no drug effect) and in GFR (P < 0.001) in all three trials, with the greatest GFR decrease occurring in the Ibu trial (P < 0.05 vs. Pl; Fig. 2). GFR decreased (from baseline) by 34 ± 3, 41 ± 2, and 31 ± 3% in the Acet, Ibu, and Pl trials, respectively. ERPF decreased to a similar extent in all three trials (P < 0.001), and PRA increased in all three trials (P < 0.05 vs. baseline). UNaV and UKV were both depressed during exercise (P < 0.05 vs. baseline), but there was no drug effect. PGE2 excretion (Table 4) was not different among drug trials, even when normalized for GFR (data not shown). Exercise O2 consumption was 36.6 ± 1.0, 36.1 ± 1.1, and 36.5 ± 1.3 ml·kg⁻¹·min⁻¹ in the Acet, Ibu and Pl trials, respectively (no drug effect). Preexercise TRe was 37.3 ± 0.1, 37.2 ± 0.1, and 37.3 ± 0.1°C and at 45 min of exercise averaged 38.9 ± 0.1, 39.2 ± 0.1, and 38.9 ± 0.1°C in the Acet, Ibu, and Pl trials, respectively (no drug effect). Also, although the timing of the last dose of the drug (or Pl) was different for the men and women, this did not have an effect on any of the measured or calculated variables.

Recovery. Ninety minutes after exercise, urine production remained below baseline (P < 0.03) with no drug effect noted (Table 2), whereas GFR and ERPF returned to near-baseline values (Fig. 2). PRA remained elevated in all three trials, but the PRA in the Ibu trial was lower than in the Acet and Pl trials (P < 0.05). UNaV remained depressed, whereas UKV returned to baseline with no difference among trials. PGE2 excretion was not different among trials. TRe remained elevated (compared with preexercise values) 90 min after exercise (P < 0.05) without, again, no drug effect.

**DISCUSSION**

This study was the first to assess renal excretory and hemodynamic function during exercise in a sodium- and volume-depleted state along with the administra-
In the kidney, NSAIDs typically inhibit PG synthesis catalyzes the formation of PGs from arachidonic acid. Cyclooxygenase is a heme-containing enzyme that causes beneficial therapeutic effects during exercise along with the administration of aspirin and indomethacin, respectively. We hypothesized that, if the addition of dehydration and heat stress to exercise increases the kidney's reliance on PGs, PG inhibition with Ibu would cause further decrements in renal function. A major finding of this study is the lack of dramatic effect of Ibu despite the care taken to stress the kidney with a low-sodium diet, dehydration, and exercise in the heat. On the other hand, under these conditions, 4 days of an OTC dose of Ibu did significantly depress GFR; the mean GFR was 9 ml lower in the Ibu trial compared with the Pl trial (an 11% greater decrease). Consistent with this lower GFR, the mean values for ERPF, $U_{Na} \cdot V$, $U_{K} \cdot V$, and urine production were all lower during the Ibu trial ($P > 0.05$). It is important to emphasize that we purposely chose the OTC dose of Ibu and not the higher anti-inflammatory dose often prescribed by physicians.

The most plausible mechanism responsible for the lower GFR in the Ibu trial is renal PG inhibition. NSAIDs such as Ibu have been shown to inhibit cyclooxygenase, which causes beneficial therapeutic effects but potentially adverse effects as well (18). Cyclooxygenase is a heme-containing enzyme that catalyzes the formation of PGs from arachidonic acid. In the kidney, NSAIDs typically inhibit PG synthesis by 50–60% (29). This impacts on renal hemodynamics because the vasodilatory PGs, such as PGE$_2$ and PGJ$_2$, are thought to alter efferent, and to a greater extent, afferent arteriolar diameter. Therefore, PG-mediated vasodilation enhances filtration. The companion study by Colletti et al. (5a) demonstrates how PG inhibition with Ibu can cause decrements in renal hemodynamic function in an animal model. Conversely, in the present human study, we were unable to demonstrate any significant drug differences in PGE$_2$ excretion (used as an index of PG production; 28) in the 24-h, exercise, and recovery urine samples in the female subjects. However, with the present study design, it is not possible to determine the effects of Ibu (or Acet) alone, that is, independent of sodium depletion or exercise. Sodium depletion is a known stimulus for PG synthesis (19), and PGE$_2$ excretion increased from baseline in all trials after the low-sodium diet. During exercise, PGE$_2$ excretion decreased in all trials. Normally, during exercise in the absence of dramatic changes in urine flow rate and GFR, PGE$_2$ excretion increases (27). The decreases (seen here) may have been due to the dramatic reduction in urine production during exercise because PGE$_2$ excretion (pg/min) is calculated as the product of PGE$_2$ concentration (pg/ml) and urine production (ml/min). There were also significant decreases in GFR. An important point is that the decrease in PGE$_2$ excretion was the same for all treatments.

We also included an Acet trial to assess its effects on the kidney during exercise. The animal data (5a) demonstrated that Acet can inhibit renal PGs and cause decrements in RBF and GFR, with Ibu causing greater decreases in renal function in the PG-dependent state. On the basis of this animal data, we would have expected the greatest decreases in renal function to occur in the Ibu trial (as we did with the exercise GFR), and the smallest decreases to occur in the Pl trial. Although this trend appeared to be evident for some of the measured or calculated variables (GFR, $U_{K} \cdot V$, and urine production), none of these values reached significance. Therefore, within the constraints of this study, Acet had no significant effects on renal function.

The low-sodium diet decreased plasma volume in all of the trials, which, due to the consequent increase in PRA and ANG II, served as an effective renal stressor (6). However, PRA increased to a lesser extent ($P = 0.05$) in the Ibu compared with the Acet and Pl trials. PRA is released from the juxtaglomerular cells in response to a decrease in renal perfusion pressure and to a decrease in sodium delivery to the macula densa. PGs have been reported (8, 31) to be involved in mediating this increase in PRA. For example, Francisco et al. (10) found that, in rats, the increase in PRA in response to a low-sodium diet was abolished with indomethacin treatment, concluding that the increase in PRA was a PG-dependent mechanism. Our data are consistent with these observations because the increase in PRA (in response to the low-sodium diet) was blunted in the Ibu trial.

In contrast to a low-sodium diet, acute exercise may cause a PG-independent increase in PRA. Renal perfusion pressure is usually elevated during exercise; therefore, the mechanism responsible for the increase in PRA during exercise is separate from the aforementioned mechanisms. Zambraski et al. (31) found that the elevation of PRA during exercise in dogs is mediated by increased sympathetic nerve activity involving $\beta_1$-receptors that does not require enhanced PG synthesis. These data are likewise consistent with our exercise results because PRA increased similarly (no significant drug effect) in all of the trials. It is noteworthy that there appeared to be a trend for a lower PRA during exercise in the Acet and Ibu trials (compared with Pl). This slightly lower PRA is probably associated with a lower production of ANG II. Therefore, both Ibu and Acet may have been decreasing the renal vasoconstrictor activity (ANG II) as well as the renal vasodilator activity. This could explain the lack of profound changes in renal function with Acet and Ibu.

Our data show that the combination of a low-sodium diet along with Ibu or Acet administration does not alter GFR or ERPF. This is in contrast to the study done by Muther et al. (19), who found that GFR was depressed when aspirin was combined with a sodium-
Research in dehydrating effects than did Ibu in the PG-dependent animal model. PG inhibition could potentially have adverse renal effects during acute perturbations such as exercise. Therefore, older kidney relies to a greater extent on renal PGs decreased in the older adult, due to a progressive loss of reserve. This study has not addressed the question of possible Ibu-mediated reductions in renal function in the older adult engaging in exercise. Because renal reserve is lost in the older adult, due to a progressive loss of functioning nephrons, it might be predicted that the older kidney relies to a greater extent on renal PGs during acute perturbations such as exercise. Therefore, PG inhibition could potentially have adverse renal effects.

In conclusion, because Acet had less severe renal effects than did Ibu in the PG-dependent animal model and no significant effects in the human data, Acet would appear to be a safer analgesic (in terms of the kidney) for athletes who plan to engage in dehydrating exercise.

The authors thank all of the subjects for participating in the study as well as Omar Bashir, Stacey Wladkowski, Christopher Minson, and Esther Brooks-Asplund for data-collection assistance. We also acknowledge the expert biochemical assistance of Marlin Druckenmiller and Adria Colletti. The nursing care provided by the staff of the Penn State General Clinical Research Center at the Noll Physiological Research Center is appreciated.

This work was supported, in part, by a gift from McNeil Consumer Products Co. and by Division of Research Resources Grant M01-RR-10732. PAH was generously donated by Merck.

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Received 19 March 1998; accepted in final form 7 October 1998.

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