Effects of acetaminophen and ibuprofen on renal function in anesthetized normal and sodium-depleted dogs

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Colletti, Adria E., Helen W. Vogl, Therese Rahe, and Edward J. Zambraski. Effects of acetaminophen and ibuprofen on renal function in anesthetized normal and sodium-depleted dogs. J. Appl. Physiol. 86(2): 592–597, 1999.—In certain conditions, renal prostaglandins (PGs) are important determinants of kidney function. Under these “renal PG-dependent states,” pharmacological inhibition of vasodilatory PG may result in excessive renal vasoconstriction and adversely affect kidney function. The purposes of this study were to determine whether acetaminophen (Acet), a weak PG-synthesis inhibitor, influences kidney function in the renal PG-dependent state of anesthesia and sodium depletion. Comparisons were made with ibuprofen (Ibu). Measurements of PGE₂ excretion were used to assess renal PG synthesis. Acet (15 mg/kg) and Ibu (10 mg/kg) both decreased renal blood flow and glomerular filtration rate by ~20–30% in normal, anesthetized, sodium-replete dogs. Although Acet produced similar changes in renal blood flow and glomerular filtration rate in the low-sodium dogs, Ibu caused a significantly greater renal vasoconstriction (64 ± 10%) in these animals. Both Acet and Ibu inhibited urinary PGE₂ excretion in sodium-replete and low-sodium dogs. Ibu tended to have a greater and more prolonged effect than did Acet. These results suggest that Acet alters PGE₂ excretion and kidney function under renal PG-dependent conditions; the effects, however, are less severe than those seen with Ibu.

prostaglandins; glomerular filtration rate; renal blood flow; sodium depletion

RENA L PROSTAGLANDINS (PGs) are vasodilators that play an important role in the preservation of kidney function when activity of the renin-angiotensin system or the renal sympathetic nerves are elevated. They act to maintain glomerular filtration rate (GFR) and renal blood flow (RBF) by modulating the effects of vasoconstrictors such as ANG II or norepinephrine on the renal vasculature (9). Such conditions would exist during hypotension, dehydration, or sodium depletion (13), as well as in disease states such as cirrhosis (32), lupus (20), and chronic renal failure (8). These are often referred to as “renal PG-dependent” states.

Aspirin and nonsteroidal anti-inflammatory drugs, such as ibuprofen (Ibu) and indomethacin, have been shown to significantly reduce PGE₂ synthesis and consequently adversely alter kidney function (i.e., renal vasoconstriction, sodium retention) in both humans (2, 14, 17, 32) and animals (28–30) in renal PG-dependent states. Acetaminophen (Acet) is an analgesic drug that is believed to be a very weak inhibitor of PG synthesis (27). Thus Acet, in contrast to Ibu, would not be predicted to have a deleterious effect on the kidney in a renal PG-dependent state. Acet has no effect on GFR in normal subjects (2). Acet is also the recommended analgesic for subjects with renal dysfunction (11).

There are, however, isolated medical case reports of renal vasoconstriction and acute renal failure resulting from therapeutic Acet use (3, 6, 12). There are also reports suggesting that Acet may reduce PGE₂ excretion, especially in patients with chronic renal insufficiency (1). We have been unable to find reports that have evaluated the effects of Acet on kidney function in a renal PG-dependent state, nor, under these conditions, the effects of Acet on renal PG synthesis been quantified.

The purpose of this study was to determine whether Acet altered renal function in a renal PG-dependent state. A combination of the stress of anesthesia and the low-dietary-sodium dog model described by Blasingham and Nasljeiti (4) was used as a model of a renal PG-dependent state. Changes in renal function, as well as changes in PGE₂ synthesis with Acet administration, were evaluated. Comparisons were made with the known PGE₂-synthesis inhibitor Ibu.

METHODS

Animals. All animal procedures were approved by the Rutgers Institutional Animal Care and Use Committee. Thirty-two adult beagles (10.8 ± 1.6 kg) were used for these studies. Twenty animals were fed a daily ration of 450 g of Purina dog chow containing 4 g sodium/kg. Twelve dogs were fed 400 g of a low-sodium diet (0.3 g sodium/kg; Research Diets, New Brunswick, N J ) for 7 days before surgery. In addition, on the first day of the low-sodium diet, animals on this diet received an intramuscular injection of Lasix (100 mg furosemide; Hoechst Roussel Agri-Vet, Somerville, N J ). This procedure was used originally to develop one of the first models of a renal PG-dependent state (4). Water was provided ad libitum. The animals were fasted for 20–24 h before surgery.

Surgical procedures. The dogs were anesthetized with pentobarbital sodium (30 mg/kg iv). The trachea was intubated, and the animal was ventilated with room air. Polyethylene canulas were inserted into both jugular veins and into the abdominal aorta inferior to the origin of the renal arteries. One jugular catheter was used to administer a priming dose of inulin and p-aminohippuric acid (PAH) in 0.9% NaCl; sustaining solutions of inulin and PAH in saline were infused at a rate of 1 ml/min. The second jugular catheter was used to administer Acet or Ibu solutions. The arterial catheter was connected to a Statham pressure transducer to monitor mean arterial pressure (MAP). Heart rate (HR) was determined from pulsatile blood pressure (BP). The
bladder was approached through a midline ventral incision, and both ureters were catheterized. After surgery, the animals were allowed an equilibration period of at least 30 min before the start of data collection.

Monitoring and analytic procedures. BP was monitored continuously on a Grass recorder; BP was electronically meaned to determine MAP. HR was derived from pulsatile BP by using a Grass electrophysiograph tachograph. Data from the Grass recorder were digitized (MacLab ADInstruments, Milford, MA) and stored on computer disk for analysis. Hematocrit was determined by using a microhematocrit centrifuge. Plasma and urine samples were assayed for PAH and inulin concentration. Renal plasma flow and GFR were estimated by PAH and inulin clearances, respectively. RBF was calculated from renal plasma flow and hematocrit; renal vascular resistance (RVR) was calculated as the quotient of MAP and RBF. Serum and urine samples were analyzed for sodium and potassium by flame photometry. Plasma renin activity (PRA) and urine PGE2 concentration were determined by radioimmunoassay (DuPont-NEN, Boston, MA). Urine was assayed directly, in triplicate, for PGE2 (28). All renal data are for the left kidney only.

Experimental protocols. Five experimental protocols in total were performed, and they were designated as groups 1–5. For all groups, the protocol began with a 40-min control period to establish baseline values. After baseline, a saline vehicle, Acet (15 mg/kg iv), or Ibu (10 mg/kg iv) was infused in 10 ml of saline over 10 min; a sustaining dose of Acet (5 mg·kg⁻¹·h⁻¹) was also administered. Administration of the drug or vehicle was followed immediately by two consecutive 40-min experimental periods (Exp 1 and Exp 2, respectively). Blood samples were collected from the arterial catheter at the midpoint of each period; urine was collected over each of the periods.

Group 1 (n = 5) served as a control group, having received a normal-sodium diet and a saline vehicle. Groups 2 (n = 9) and 3 (n = 6) consisted of normal-sodium animals, administered Acet and Ibu, respectively. Groups 4 (n = 7) and 5 (n = 5) were low-sodium dogs, receiving Acet and Ibu, respectively.

Statistical analysis. Repeated-measures ANOVA was used to determine significant differences between the control and experimental periods within each group. The Fisher least significant difference was used as a post hoc test. Comparisons were made across groups (i.e., normal vs. low sodium or Acet vs. Ibu) by using an unpaired t-test. A difference was considered significant if P < 0.05. Data are expressed as means ± SE.

RESULTS

Effects of a low-sodium diet. Across all groups, comparisons were made between normal and low-sodium animals. Control values for hemodynamic and renal function parameters are shown in Table 1. The two groups matched closely with similar values for renal hemodynamics and urine flow rate. MAP was higher in the low-sodium animals (P < 0.05). Mean baseline sodium excretion was 44% lower in the low-sodium animals (P > 0.05). A trend toward greater urinary potassium excretion was observed in the low-sodium dogs. As expected, PRA in the low-sodium dogs was significantly elevated, being four times greater than that seen in the normal animals. The PRA measurements for the three sodium-replete groups (groups 1, 2, and 4) were 3.57 ± 0.46, 3.41 ± 0.60, and 3.16 ± 1.46, respectively. For the two sodium-depleted groups (groups 3 and 5), they were 12.48 ± 3.63 and 13.77 ± 2.87, respectively. Renal PGE2 excretion was also significantly elevated in the low-sodium dogs, being approximately doubled (Table 1).

Changes in renal hemodynamics. In the vehicle-treated normal animals (group 1), over the duration of the entire protocol MAP decreased from 108 ± 3 to 100 ± 5 mmHg (P < 0.05). This time-dependent decrease was seen in most of the other groups. There were no other significant changes in MAP with either of the drug treatments for any of the groups (data not shown).

The effects of the vehicle, Acet, and Ibu on renal hemodynamics in the normal and low-sodium dogs are displayed in Table 2. In the normal animals treated with the vehicle, RBF and GFR decreased with time. These changes appeared to be due to the decrease in MAP because RVR did not change in these animals. In groups 2 and 3, both Acet and Ibu significantly decreased RBF by ~30% (Table 2, Fig. 1). This change was seen during Exp 1. This renal vasoconstriction appeared to be transient with Acet, whereas with Ibu the changes persisted through Exp 2 (Table 2). In group 4 (low-sodium animals), the decrease in RBF with Acet was similar to that seen in the group 1 normal animals (39 ± 3%). Ibu, however, had a much more dramatic effect in the low-sodium animals (group 5), decreasing RBF by 64 ± 10%.

As shown in Table 2, RVR was increased significantly in normal and low-sodium dogs with either Acet or Ibu. In both normal (group 2) and low-sodium (group 4) dogs, Acet resulted in a 50–60% increase in RVR. Ibu, however, produced a dramatically greater increase in RVR in the low-sodium dogs (group 5; 270 ± 92%) compared with that seen in the normal animals (group 3; 52 ± 18%). Thus, although Acet and Ibu treatment caused similar increases in RVR in normal animals, Ibu had a significantly greater effect than Acet on RVR in the low-sodium condition.

Changes in GFR tended to parallel the responses noted for RBF (Table 2). GFR was not changed by the vehicle in normal animals (group 1). In the normal animals, both Acet and Ibu decreased GFR by ~20-

### Table 1. Baseline hemodynamic and renal function values in normal and low-sodium dogs

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal (n = 20)</th>
<th>Low Sodium (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP, mmHg</td>
<td>111 ± 3</td>
<td>120 ± 3*</td>
</tr>
<tr>
<td>GFR, ml/min</td>
<td>20.7 ± 1.5</td>
<td>18.9 ± 2.1</td>
</tr>
<tr>
<td>RBF, ml/min</td>
<td>85.3 ± 6.3</td>
<td>87.7 ± 9.1</td>
</tr>
<tr>
<td>RVR, mmHg·ml⁻¹·min</td>
<td>1.44 ± 0.11</td>
<td>1.61 ± 0.20</td>
</tr>
<tr>
<td>UV, ml/min</td>
<td>0.05 ± 0.01</td>
<td>0.05 ± 0.01</td>
</tr>
<tr>
<td>U₅₆⁻V, µeq/min</td>
<td>12.2 ± 2.8</td>
<td>6.78 ± 2.22</td>
</tr>
<tr>
<td>U₅⁻V, µeq/min</td>
<td>8.5 ± 1.1</td>
<td>11.8 ± 1.2</td>
</tr>
<tr>
<td>PGE₂, pg/min</td>
<td>247 ± 32</td>
<td>484 ± 85*</td>
</tr>
<tr>
<td>PRA, ngANGI·l·ml⁻¹·h⁻¹</td>
<td>3.41 ± 0.60</td>
<td>13.77 ± 2.87*</td>
</tr>
</tbody>
</table>

Values are means ± SE. n, No. of animals; MAP, mean arterial pressure; GFR, glomerular filtration rate; RBF, renal blood flow; RVR, renal vascular resistance; UV, urine flow; U₅₆⁻V, urinary sodium excretion; U₅⁻V, urinary potassium excretion; PRA, plasma renin activity. *P < 0.05 vs. normal.
excretion. In contrast, in the low-sodium animals

tent effects on urine volume, sodium, or potassium

the vehicle, Acet, nor Ibu had any significant or consis-
table 3, in the three groups of normal animals, neither

cause an exaggerated response, with GFR decreasing

decrease sodium and potassium excretion, an effect

Changes in renal excretory function. As shown in

Values are means ± SEM. n, No. of animals; Acet, acetaminophen; Ibu, ibuprofen; Exp 1 and Exp 2, 1st and 2nd experimental periods,

30% (Fig. 2, groups 2 and 3) (P < 0.05). In the

low-sodium dogs (group 4), the decrease in GFR with

Acet was the same as that seen in normal animals

(26 ± 5%). In the low-sodium animals (group 5), Ibu

caused an exaggerated response, with GFR decreasing

by 58 ± 11% (P < 0.05) in Exp 1.

Changes in renal excretory function. As shown in

Table 3, in the three groups of normal animals, neither

the vehicle, Acet, nor Ibu had any significant or consist-
tent effects on urine volume, sodium, or potassium

excretion. In contrast, in the low-sodium animals

(groups 4 and 5), both Acet and Ibu significantly
decreased urine flow rate. Both of these changes were

transient, with the values returning to baseline during

Exp 2. In the low-sodium animals, both drugs tended to
decrease sodium and potassium excretion, an effect

that was not seen by Exp 2.

Changes in PG2 excretion. In the vehicle-treated

normal animals (group 1), baseline PG2 excretion was

221 ± 27 pg/min (Table 4). This value was not signifi-
cantly different from the baseline PG2 measurements

for the normal dogs in the Acet and Ibu groups (groups

2 and 3, respectively). In the normal dogs the vehicle
did not alter PG2 excretion, whereas both Acet and

Ibu reduced PG2 excretion by ~45% (P < 0.05). In the

normal dogs (group 3), Ibu had a greater and more

pronounced effect on PG2 excretion than did Acet

(group 2). During Exp 2, PG2 excretion after Ibu was

approximately one-third of that seen in the Acet group.

The low-sodium animals (groups 4 and 5) had

elevated baseline PG2 excretion rates that were appro-

imately double that seen in the normal animals (Table 1

and 4). In the low-sodium animals both drugs signifi-
cantly decreased PG2 excretion to levels that were

comparable to that seen in the drug-treated normal
dogs. During Exp 2, mean PG2 excretion in the Ibu
group (group 5) was 39% lower than that seen with

Acet (group 4) (P > 0.05).

DISCUSSION

Under certain normal and pathophysiological condi-
tions, when there is an elevation of peripheral and/or

renal sympathetic nerve activity or enhanced levels of

ANG II, vasodilatory renal PGs are important determi-
nants of renal function (9). In these renal PG-depend-
ent conditions, drugs that inhibit renal PG synthesis,
such as nonsteroidal anti-inflammatory drugs, may

cause severe renal vasoconstriction and salt and water

retention (25).

Acet is a widely used mild analgesic that has long

been available as an over-the-counter product. Because

its inhibitory effects on peripheral PG synthesis are

thought to be minimal, Acet is considered less likely to

have adverse effects on kidney function in renal PG-

dependent states (27). The data on the effects of Acet on

renal PG synthesis and renal function, however, are

limited. Although Fitzpatrick and Wynalda (10) re-

ported that Acet does not affect renal PG2 synthesis in

animals in vivo, other investigators have shown that

Acet inhibits renal PG synthesis both in vitro (16) and

in vivo (31). However, in these studies, renal PG2

synthesis is reduced to a lesser degree by Acet than by

other analgesics and/or anti-inflammatory drugs. In

Table 2. Effects of Acet or Ibu on renal hemodynamic function in normal and low-sodium dogs

<table>
<thead>
<tr>
<th>Period</th>
<th>RBF, ml/min</th>
<th>GFR, ml/min</th>
<th>RVR, mmHg·ml⁻¹·min⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1, normal, vehicle (n = 5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>87.95 ± 15.30</td>
<td>23.12 ± 2.81</td>
<td>1.37 ± 0.20</td>
</tr>
<tr>
<td>Exp 1</td>
<td>81.93 ± 14.07</td>
<td>21.26 ± 2.78</td>
<td>1.39 ± 0.23</td>
</tr>
<tr>
<td>Exp 2</td>
<td>72.32 ± 10.85*+</td>
<td>17.76 ± 1.55*+</td>
<td>1.52 ± 0.23</td>
</tr>
<tr>
<td>Group 2, normal, Acet (n = 9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>82.66 ± 10.97</td>
<td>18.07 ± 2.06</td>
<td>1.62 ± 0.20</td>
</tr>
<tr>
<td>Exp 1</td>
<td>49.35 ± 5.00*</td>
<td>11.07 ± 0.97x</td>
<td>2.43 ± 0.25*</td>
</tr>
<tr>
<td>Exp 2</td>
<td>60.03 ± 6.06**</td>
<td>16.73 ± 2.67†</td>
<td>1.91 ± 0.17</td>
</tr>
<tr>
<td>Group 3, normal, Ibu (n = 6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>87.04 ± 7.33</td>
<td>22.69 ± 2.97</td>
<td>1.24 ± 0.09</td>
</tr>
<tr>
<td>Exp 1</td>
<td>59.97 ± 7.39*</td>
<td>16.83 ± 1.70x</td>
<td>1.83 ± 0.18*</td>
</tr>
<tr>
<td>Exp 2</td>
<td>60.68 ± 12.68*</td>
<td>15.95 ± 1.75x</td>
<td>1.90 ± 0.23*</td>
</tr>
<tr>
<td>Group 4, low sodium, Acet (n = 9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>103.64 ± 12.03</td>
<td>22.74 ± 2.93</td>
<td>1.29 ± 0.19</td>
</tr>
<tr>
<td>Exp 1</td>
<td>64.40 ± 9.39*</td>
<td>17.62 ± 3.14*</td>
<td>2.16 ± 0.43*</td>
</tr>
<tr>
<td>Exp 2</td>
<td>70.90 ± 10.63*</td>
<td>18.47 ± 2.85*</td>
<td>1.87 ± 0.30*</td>
</tr>
<tr>
<td>Group 5, low sodium, Ibu (n = 5)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>65.44 ± 11.00</td>
<td>13.43 ± 1.66</td>
<td>2.07 ± 0.36</td>
</tr>
<tr>
<td>Exp 1</td>
<td>25.28 ± 8.53*</td>
<td>6.18 ± 2.11*</td>
<td>8.40 ± 3.18*</td>
</tr>
<tr>
<td>Exp 2</td>
<td>47.66 ± 11.79†</td>
<td>10.38 ± 1.92†</td>
<td>3.30 ± 1.04</td>
</tr>
</tbody>
</table>

Values are means ± SE. n, No. of animals; Acet, acetaminophen; Ibu, ibuprofen; Exp 1 and Exp 2, 1st and 2nd experimental periods, respectively. *P < 0.05 vs. baseline. †P < 0.05 vs. Exp 1.
Effects of Acet or Ibu on renal excretory function in normal and low-sodium dogs

Table 4. Effects of Acet or Ibu on renal PGE₂ excretion in normal and low-sodium dogs

<table>
<thead>
<tr>
<th>Period</th>
<th>Group 1, normal, vehicle (n = 5)</th>
<th>Group 2, normal, Acet (n = 9)</th>
<th>Group 3, normal, Ibu (n = 6)</th>
<th>Group 4, low sodium, Acet (n = 9)</th>
<th>Group 5, low sodium, Ibu (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UV, µeq/min</td>
<td>Uᵥ-V, µeq/min</td>
<td>Uᵥ-V, µeq/min</td>
<td>Uᵥ-V, µeq/min</td>
<td>Uᵥ-V, µeq/min</td>
<td>Uᵥ-V, µeq/min</td>
</tr>
<tr>
<td>Baseline</td>
<td>0.08 ± 0.02</td>
<td>23.61 ± 8.20</td>
<td>9.78 ± 2.27</td>
<td>0.05 ± 0.01</td>
<td>7.12 ± 2.87</td>
</tr>
<tr>
<td>Exp 1</td>
<td>0.08 ± 0.02</td>
<td>20.66 ± 9.24</td>
<td>10.54 ± 0.99</td>
<td>0.04 ± 0.01</td>
<td>8.09 ± 4.19</td>
</tr>
<tr>
<td>Exp 2</td>
<td>0.08 ± 0.01</td>
<td>18.65 ± 0.67</td>
<td>9.99 ± 1.19</td>
<td>0.05 ± 0.01</td>
<td>9.94 ± 4.50</td>
</tr>
<tr>
<td>Baseline</td>
<td>0.04 ± 0.01</td>
<td>9.45 ± 1.55</td>
<td>5.14 ± 0.63</td>
<td>0.04 ± 0.02</td>
<td>13.93 ± 4.89</td>
</tr>
<tr>
<td>Exp 1</td>
<td>0.04 ± 0.01</td>
<td>16.03 ± 3.22</td>
<td>7.64 ± 0.95*</td>
<td>0.04 ± 0.01</td>
<td>16.03 ± 3.22</td>
</tr>
<tr>
<td>Exp 2</td>
<td>0.06 ± 0.01</td>
<td>10.72 ± 3.44</td>
<td>12.47 ± 1.85</td>
<td>0.06 ± 0.01</td>
<td>12.14 ± 3.06†</td>
</tr>
<tr>
<td>Baseline</td>
<td>0.04 ± 0.01</td>
<td>1.25 ± 0.38</td>
<td>10.04 ± 1.72</td>
<td>0.04 ± 0.01</td>
<td>1.25 ± 0.38</td>
</tr>
<tr>
<td>Exp 1</td>
<td>0.01 ± 0.00*</td>
<td>0.50 ± 0.05</td>
<td>4.48 ± 1.32*</td>
<td>0.03 ± 0.01†</td>
<td>2.25 ± 0.98†</td>
</tr>
<tr>
<td>Exp 2</td>
<td>0.06 ± 0.01</td>
<td>12.14 ± 3.06†</td>
<td>14.09 ± 1.80†</td>
<td>0.04 ± 0.01</td>
<td>12.14 ± 3.06†</td>
</tr>
</tbody>
</table>

Values are means ± SE. n, No. of animals. *P < 0.05 vs. baseline. †P < 0.05 vs. Exp 1.

isolated case reports of acute nephrotoxicity resulting from therapeutic Acet use in healthy subjects (3) and in patients with cardiac and renal insufficiency (6, 16a) or alcoholic cirrhosis (12), although these cases are complicated by many factors.

Surprisingly, we were unable to identify any studies that have examined the effects of Acet on kidney function and PG synthesis in an animal model of a renal PG-dependent state. Consequently, the purpose of this study was to evaluate the effects of Acet under these conditions.

In this study, we used the anesthetized, sodium-deficient dog as a model of a renal PG-dependent state. Although anesthesia alone does render the kidney's PG dependent, sodium depletion heightens the effect by elevating both PRA and renal sympathetic nerve activity (19). Also, increased basal urinary PGE₂ excretion is seen with the low-sodium diet (4). In this model, it has been repeatedly shown that drugs that inhibit renal PG synthesis, such as indomethacin (19) and medlofenamate (4), adversely affect kidney function. As expected, a significantly greater baseline PRA was observed in the low-sodium dogs; however, on the basis of a mean PRA of ~14 ng ANG I·ml⁻¹·h⁻¹, these animals were clearly only moderately stressed in this regard. In addition, basal PGE₂ excretion was more than doubled in the low-sodium animals. With increased PGE₂ synthesis, it would be expected that blockade of PG synthesis would have greater effects on RBF and GFR in the low-sodium animals compared with the normal animals.

The variability across the groups in their baseline sodium excretion (Table 3) was unexpected. The reason for these differences, especially among the replete groups, is unknown. What is important, in terms of being able to make fair comparisons of the drugs tested across the groups, is whether the renin-angiotensin systems were similar or differentially activated in the normal or depleted groups. This parameter is probably more important than basal sodium excretion because PRA values are directly linked to, and are predictive of, the amount of renal vasoconstriction seen with PG inhibition (5). As indicated in RESULTS, PRA values were similar for the three groups of normal, sodium-replete dogs, ranging from 3.16 to 3.57 ng ANG I·ml⁻¹·h⁻¹, whereas in the two groups of depleted animals the PRA values were 12.48 and 13.77 ng ANG I·ml⁻¹·h⁻¹. These data are important because they demonstrate that the

normal healthy humans, Acet has been reported to decrease (15, 23) or to have no effect on urinary PGE₂ excretion (2). Acet has no significant effect on RBF or filtration rate in normal or low-sodium dogs. Values shown represent %change from baseline compared with Exp 1 for each of the 5 groups. Bars and symbols are defined as in Fig. 1.

Table 3. Effects of Acet or Ibu on renal excretory function in normal and low-sodium dogs

<table>
<thead>
<tr>
<th>Period</th>
<th>UV, µeq/min</th>
<th>Uᵥ-V, µeq/min</th>
<th>Uᵥ-V, µeq/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1, normal, vehicle (n = 5)</td>
<td>0.08 ± 0.02</td>
<td>23.61 ± 8.20</td>
<td>9.78 ± 2.27</td>
</tr>
<tr>
<td>Baseline</td>
<td>Exp 1</td>
<td>0.08 ± 0.02</td>
<td>20.66 ± 9.24</td>
</tr>
<tr>
<td>Exp 2</td>
<td>0.08 ± 0.01</td>
<td>18.65 ± 0.67</td>
<td>9.99 ± 1.19</td>
</tr>
<tr>
<td>Group 2, normal, Acet (n = 9)</td>
<td>0.05 ± 0.01</td>
<td>7.12 ± 2.87</td>
<td>10.03 ± 1.86</td>
</tr>
<tr>
<td>Baseline</td>
<td>Exp 1</td>
<td>0.04 ± 0.01</td>
<td>8.09 ± 4.19</td>
</tr>
<tr>
<td>Exp 2</td>
<td>0.05 ± 0.01</td>
<td>9.94 ± 4.50</td>
<td>10.50 ± 1.62</td>
</tr>
<tr>
<td>Group 3, normal, Ibu (n = 6)</td>
<td>0.04 ± 0.01</td>
<td>9.45 ± 1.55</td>
<td>5.14 ± 0.63</td>
</tr>
<tr>
<td>Baseline</td>
<td>Exp 1</td>
<td>0.04 ± 0.02</td>
<td>13.93 ± 4.89</td>
</tr>
<tr>
<td>Exp 2</td>
<td>0.04 ± 0.01</td>
<td>16.03 ± 3.22</td>
<td>7.64 ± 0.95*</td>
</tr>
<tr>
<td>Group 4, low sodium, Acet (n = 9)</td>
<td>0.06 ± 0.01</td>
<td>10.72 ± 3.44</td>
<td>12.47 ± 1.85</td>
</tr>
<tr>
<td>Baseline</td>
<td>Exp 1</td>
<td>0.04 ± 0.01</td>
<td>6.29 ± 1.63</td>
</tr>
<tr>
<td>Exp 2</td>
<td>0.06 ± 0.01</td>
<td>12.14 ± 3.06†</td>
<td>14.09 ± 1.80†</td>
</tr>
<tr>
<td>Group 5, low sodium, Ibu (n = 5)</td>
<td>0.04 ± 0.01</td>
<td>1.25 ± 0.38</td>
<td>10.04 ± 1.72</td>
</tr>
<tr>
<td>Baseline</td>
<td>Exp 1</td>
<td>0.01 ± 0.00*</td>
<td>0.50 ± 0.05</td>
</tr>
<tr>
<td>Exp 2</td>
<td>0.03 ± 0.01†</td>
<td>2.25 ± 0.98†</td>
<td>10.42 ± 3.15†</td>
</tr>
</tbody>
</table>
animals were similarly stressed (depleted) or non-stressed (normal, replete) in the various treatment groups, despite the large variability in sodium excretion.

Under the conditions of this study, both Acet and Ibu reduced GFR and RBF in the normal, sodium-replete dogs. Anesthesia and surgical stress may have been the factors involved in this response. Pentobarbital anesthesia stimulates the renin-angiotensin system (7), thus producing a mild renal PG-dependent state. Laparotomy also has been shown to increase renal PG synthesis in dogs (27). The differences between Acet and Ibu were clearly seen in the low-sodium animals. In these animals Acet had effects similar to that in the normal dogs. In contrast, Ibu caused a markedly greater renal vasoconstriction in the low-sodium animals. The declines in both GFR and RBF were significantly greater with Ibu compared with Acet (Figs. 1 and 2). In the low-sodium dogs Ibu increased RVR fourfold, whereas this value increased by only 67% with Acet (Table 2). These data demonstrate that both drugs cause renal vasoconstriction in animals whose renal function is PG dependent; the effects, however, are dramatically more severe with Ibu.

Surprisingly, Acet and Ibu reduced urinary PGE$_2$ excretion to comparable levels in both normal and low-sodium dogs. This response is similar to that reported by Blasingham et al. (5) and Blasingham and Nasjletti (4) using meclofenamate. Although the decrease in PGE$_2$ excretion as a percentage of baseline values was greater in the low-sodium animals, this was a function of their higher baseline PGE$_2$ levels. Ibu tended to have a greater and more prolonged effect on PGE$_2$ excretion in both sodium states. This finding is consistent with in vivo data (10) in which Ibu produced a greater suppression of PGE$_2$ synthesis in rat kidney than did Acet.

When Ibu vs. Acet is compared under these conditions, the issue of dosage is an important factor. The therapeutic dose of Acet can be as high as 4,000 mg/day (22). Nielsen et al. (18) observed that a maximum analgesic effect of Acet was reached 2 h after oral administration of a single therapeutic dose (500–1,000 mg). At maximum effect, plasma concentration of Acet was 8–10 µg/ml. The intravenous dose of Acet used in this study has shown to result in plasma Acet concentrations in this therapeutic range (22, 23). Because the half-life of Acet after intravenous administration has been shown to be <30 min (22, 25), a sustaining solution of Acet (5 mg·kg$^{-1}$·h$^{-1}$) was utilized to maintain therapeutic levels of the drug throughout the full duration of the experiment. The dose of Ibu used (10 mg/kg) was selected on the basis of our prior work using this compound. In an earlier study (29), 20 mg/kg of Ibu were utilized, and this dose decreased renal PGE$_2$ excretion by >90%, an effect similar to what was seen with 10 mg/kg of naproxen. In subsequent tests, it was determined that a 10 mg/kg dose of Ibu achieved renal PG inhibition ranging from 70 to 90%; therefore, we chose to use the lower dose. Table 4 shows that this dose of Ibu was effective, reducing PGE$_2$ excretion by 70–80%.

A methodological concern pertains to the fact that Ibu is an inhibitor of anion transport. As such, Ibu could potentially alter PAH transport, change the PAH clearance values, and thus invalidate the use of PAH clearance to measure RBF. In this study we did not sample renal venous blood to determine PAH extraction. However, we believe that the declines in RBF observed with Ibu are real and not due to this possible artifact. A strong argument in support of this position is that the declines in GFR and RBF, shown in Figs. 1 and 2, are essentially superimposable. Because inulin clearance, unlike PAH clearance, cannot be affected by this potential problem, this suggests that the declines in PAH clearance were reflecting changes in RBF.

This study is the first to show that Acet may compromise renal function in a renal PG-dependent animal model. The renal vasoconstriction observed with Acet in the low-sodium animals was associated with an inhibition of renal PG synthesis, as estimated by PGE$_2$ excretion. Although the effects of Acet were far less than that seen with Ibu, these data do suggest that Acet has the potential to decrease renal PG and possibly adversely affect renal function under certain conditions.

These results suggest that a more careful or closer inspection is warranted concerning the effects of Acet on renal function in humans when the renal sympathetic nerves and the renin-angiotensin system are both maximally activated, either because of environmental conditions such as dehydration, heat stress, or exercise or as a consequence of a disease state, such as congestive heart failure or cirrhosis.

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