Attenuation of Nephrotoxic Acute Renal Failure in the Dog with Angiotensin-Converting Enzyme Inhibitor (SQ-20,881)

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SUMMARY. Angiotensin-converting enzyme inhibitor was used in dogs with uranyl nitrate-induced acute renal failure to evaluate (1) a possible protective effect of angiotensin blockade and (2) the role of angiotensin II in the generation of renal failure in this model. Angiotensin-converting enzyme inhibitor treatment attenuated the fall in glomerular filtration rate and renal blood flow during the first 6 hours after injection of the nephrotoxic agent. A protective effect of similar magnitude was observed whether angiotensin-converting enzyme inhibitor treatment preceded, or shortly followed, the administration of uranyl nitrate. This indicates that angiotensin-converting enzyme inhibitor delivery to its intrarenal site of action remains effective after administration of the nephrotoxin. In addition, protection of glomerular filtration rate correlated with sodium and renal solute excretion. However, combined treatment with angiotensin-converting enzyme inhibitor and furosemide enhanced solute excretion but did not further improve the protection of renal function. Finally, the protective effects of angiotensin-converting enzyme inhibitor on renal function and hemodynamics were abolished by intravenous indomethacin. In conclusion, early, continuous blockade of angiotensin II protects partially against the initiation of acute renal failure. These findings support a major pathogenic role for angiotensin II in the generation phase of acute renal failure in this model. Furthermore, they suggest that an imbalance between vasoconstrictive (angiotensin II) and vasodilator factors (prostaglandins) may be operative in the early phase of uranyl nitrate-induced acute renal failure in the dog. (Circ Res 51: 216-224, 1982)

THE multiple mechanisms involved in the pathophysiology of acute renal failure have been extensively reviewed (Stein et al., 1978). These mechanisms may be different during the generation and the maintenance phases of acute renal failure, and may differ in hemodynamic and nephrotoxic models. One mechanism, the activation of a tubuloglomerular feedback reduction in glomerular filtration, possibly mediated by the renin-angiotensin system, has been proposed (Thurau and Boylan, 1976; Mason, 1976). The role of renin in the generation of acute renal failure, however, remains controversial (Stein et al., 1978).

The supporting evidence in favor of renin as a mediator of vasoconstriction and reduced GFR in the generation of ARF includes (1) the findings of high plasma renin activity at the onset of ARF in several experimental models (Di Bona and Sawin, 1971a; McDonald et al., 1969), including the uranyl nitrate model in the dog (Flamenbaum et al., 1972a); in man (Tu, 1965, Kokot and Kuska, 1969); and (2) the attenuation of the renal functional impairment by chronic salt loading, a maneuver that depresses plasma and renal renin content (McDonald et al., 1969; Di Bona et al., 1971b). On the other hand, Thiel et al. have found that a high solute excretion per se, without renin suppression, attenuates the renal failure in the mercuric chloride model (Thiel et al., 1976). Further evidence against renin is suggested by the failure to protect renal function when rats were immunized against circulating renin (Flamenbaum et al., 1972b) and after passive or active immunization against angiotensin II (Oken et al., 1975). In addition, recent work with saralasin, an angiotensin antagonist (Baranowski et al., 1975; Ishikawa and Hollenberg, 1976), and SQ-20,881, a converting enzyme inhibitor (Ishikawa and Hollenberg, 1976), failed to affect blood urea nitrogen levels or animal mortality after glycerol administration in the rat. We feel these findings are inconclusive, since adequate renal function measurements were not obtained in these studies. Moreover, duration of treatment was short and the completeness of angiotensin blockade was not assessed (Baranowski et al., 1975; Ishikawa and Hollenberg, 1976). Therefore, a role for the renin-angiotensin system in the early phase of ARF cannot be excluded with the available evidence.

In the present study, we evaluated the effect of continuous angiotensin blockade with SQ-20,881 (CEI, converting enzyme inhibitor) before and after uranyl nitrate-induced ARF in the dog. To investigate...
a possible role of prostaglandins, one group of dogs received indomethacin, a prostaglandin synthesis inhibitor.

Methods

Studies were done in 30 mongrel dogs of either sex weighing 15-20 kg. Dogs were anesthetized with pentobarbital (30 mg/kg) and ventilated with a Harvard respirator. Cannulas were inserted in the femoral arteries for blood collection and continuous blood pressure recording. Both ureters were cannulated through a suprapubic incision. The kidneys were exposed via a medial incision and the renal pedicle carefully dissected. A well-fitting electromagnetic flowmeter probe was placed around each renal artery for continuous monitoring of renal blood flow. Zero flow was obtained by temporary occlusion of the renal artery. Flow meter calibration was performed at the end of the experiment using in vivo perfusion of blood in each renal artery at different rates with an infusion pump and simultaneous timed collections of renal venous outflow.

A water load (20 mg/kg) was given intravenously over 30 minutes in the form of 5% dextrose in water to ensure adequate urine flow. After baseline blood samples had been obtained, a priming dose of creatinine was given, and a maintenance infusion was used to maintain a plasma concentration about 10 mg/ml. Urine collection periods averaged 30 minutes and started after 1 hour post surgical stabilization. Ringer's lactate solution was infused continuously at a rate to approximate urine losses.

All studies were done with each dog serving as its own control. After equilibration, at least two 30-minute renal clearance periods and baseline measurements of mean RBF were obtained. Acute renal failure then was induced with anhydrous uranyl nitrate in a dose of 10 mg/kg, intravenously. Thirty-minute renal clearance periods were obtained for 6 hours after uranyl nitrate injection. RBF was measured at 1, 3, and 6 hours after administration of the nephrotoxic agent to coincide with the initiation phase of ARF, analogous with the experimental design in previous studies (Kleinman et al., 1975; Lindner et al., 1979). The average of several RBF determinations made in and around these specific times was used.

Six groups of studies were performed as follows: Group A: Acute renal failure, untreated dogs (n = 6). No therapeutic intervention was used after induction of ARF with uranyl nitrate. Group B: Angiotensin-converting enzyme inhibitor (CEI) administration in normal, control dogs (n = 5). Group C: CEI treatment 15 minutes after administration of uranyl nitrate (n = 5). Group D: CEI treatment 15 minutes prior to induction of ARF with uranyl nitrate (n = 6). Group E: Combined treatment with CEI and furosemide after administration of uranyl nitrate (n = 5). Group F: CEI treatment, followed by indomethacin, prior to induction of ARF with uranyl nitrate (n = 6). Because of an unreliable flow probe, renal blood flows were not available from the animals in groups A-E. Therefore, two additional groups were studied. Group A-2: (n = 5), was identical to Group A; and Group C-2: (n = 5), identical to group C. In these last two groups and in group F, renal blood flow (RBF) was measured with brand new flow probes, and GFR was measured withulin clearance. Only these values for RBF and GFR are reported.

Dogs in groups B, C, D, E, F, and C-2 received CEI (also known as Bradykinin-potentiating factor, SQ-20,881, or the nonapeptide: pGlu-TRP-PRO-ARG-PRO-Gln-Ile-Pro-Pro). A 300 μg/kg intravenous dose was given slowly over 3-5 minutes. This minimized the initial, transient hypoten-

Results

A summary of the sequential findings in renal function (group mean ± SEM) is shown in Table 1.
### Table 1

Sequential Changes in Renal Function after Urinary Nitrate

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>V (ml/min)</th>
<th>UNaV (µEq/min)</th>
<th>EFSNa (%)</th>
<th>UOsm (mOsm/liter)</th>
<th>UOsmV (µOsm/min)</th>
<th>Clc (ml/min)</th>
<th>Clc (% of control value)</th>
<th>BP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.27</td>
<td>15.8</td>
<td>0.20</td>
<td>957</td>
<td>253</td>
<td>54.4</td>
<td>128</td>
<td>±7</td>
</tr>
<tr>
<td></td>
<td>±0.09</td>
<td>±3.5</td>
<td>±0.06</td>
<td>±57</td>
<td>±76</td>
<td>±10.2</td>
<td>±7</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.42</td>
<td>55.4</td>
<td>3.9</td>
<td>665</td>
<td>279</td>
<td>18.3</td>
<td>34%</td>
<td>±8</td>
</tr>
<tr>
<td></td>
<td>±0.08</td>
<td>±20</td>
<td>±2.2</td>
<td>±54†</td>
<td>±58</td>
<td>±0.3*</td>
<td>±8</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.33</td>
<td>40.4</td>
<td>35</td>
<td>425</td>
<td>146</td>
<td>2.3</td>
<td>4%</td>
<td>±0.06†</td>
</tr>
<tr>
<td></td>
<td>±0.08</td>
<td>±11</td>
<td>±22‡</td>
<td>±23‡</td>
<td>±40</td>
<td>±0.8‡</td>
<td>±5</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0.22</td>
<td>23.9</td>
<td>72</td>
<td>386</td>
<td>124</td>
<td>1.2</td>
<td>2%</td>
<td>±2</td>
</tr>
<tr>
<td></td>
<td>±0.07</td>
<td>±8</td>
<td>±53‡</td>
<td>±36€</td>
<td>±36</td>
<td>±0.6‡</td>
<td>±8</td>
<td></td>
</tr>
</tbody>
</table>

**Values are the mean changes ± SEM.**

* P < 0.05; † P < 0.01; ‡ P < 0.001.
Group A: Acute renal failure, untreated dogs (n = 6). In all dogs, administration of uranyl nitrate resulted in a severe fall in creatinine clearance which was present by the 1st hour and continued to worsen throughout the experiment. By the 3rd hour creatinine clearance was 4% of control, and it was 2% of control by the 6th hour (P < 0.001 in each case). Urine flow rate remained unchanged. The fraction of filtered sodium excreted (EFFNa) rose within 1 hour (P < 0.001), and was maximally elevated at 6 hours (P < 0.001). Sodium excretion, on the other hand, was not significantly increased during the experiment reflecting the near total fall in glomerular filtration rate. Urine osmolality fell from 957 during control to as low as 386 mOsm/liter at 6 hours (P < 0.001). On the other hand, osmolar excretion (UosmolV) was not significant different in any study period. Arterial blood pressure (BP, mm Hg) was not significantly different from control at 1, 3, and 6 hours after uranyl nitrate. BP, however, showed wide fluctuations, and a tendency to decrease as much as 30 mm Hg for the first 5-10 minutes after injection of the nephrotoxic agent, and then returned to control levels.

Group A-2: Acute renal failure, untreated dogs (n = 7). As in group A using creatinine clearance, there was a progressive fall in inulin clearance which reached a minimum of 12% of control by the 6th hour (Table 2). Urine flow rate remained unchanged, except for a mild, transient increase at 3 hours. Mean RBF appeared to fall by the 1st hour and reached a minimum of 71% of control by the 6th hour. Blood pressure remained unchanged. Thus, the mean calculated renal vascular resistance (RVR, mm Hg/ml per min) rose from 0.94 to a peak of 1.16 at 6 hours.

Group B: CEI administration in normal, control dogs (n = 5). Administration of CEI to normal, control dogs was not associated with measurable changes in urine flow rate or creatinine clearance. On the other hand, there was a clear trend toward rising sodium excretion (UNaV, µEq/min) which doubled from 7.6 to 14.8 after 6 hours of treatment. Similarly, the fraction of filtered sodium excreted (EFFNa) rose from 0.14 to 0.32 at 6 hours. Both changes, however, were marginally significant statistically, P < 0.07 and P < 0.16, respectively. The small number of dogs studied, however, may explain these statistical values. In addition, potassium excretion (UKV, µEq/min), not shown on the table, rose from a control of 10.5 to 15.6, 24.0, and 42.8 after 1, 3, and 6 hours, respectively. All these changes were statistically significant (P < 0.01 at 1, 3, and 6 hours). Urine osmolality rose progressively from 948 mOsm/liter during control to a maximum of 1490 (P < 0.05) after 6 hours. Changes in osmolar excretion, however, were not significant. Blood pressure fell transiently in most dogs between 5 and 20 mm Hg; then it stabilized at control values within 5-10 minute after CEI injection. Blood pressure values at 1, 3, and 6 hours were unchanged for the group.

Group C: CEI treatment after uranyl nitrate (n = 8). Administration of uranyl nitrate was followed by a progressive fall in creatinine clearance, which was unchanged at 1 hour and fell to 47 and 33% of control values at 3 and 6 hours, respectively. This fall was markedly attenuated when contrasted with group A (untreated dogs). Urine flow rate increased progressively from 0.19 ml/min to a maximum of 0.72 at 6 hours (P < 0.01). EFFNa was markedly increased at all

### Table 2

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>V (ml/min)</th>
<th>CIN (ml/min)</th>
<th>CIU (%) of control</th>
<th>RBF (ml/min)</th>
<th>RBF (%) of control</th>
<th>BP (mm Hg)</th>
<th>RVR (mm Hg/ml per min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.14±0.01</td>
<td>27.0±2.2</td>
<td>151±32</td>
<td>119±6</td>
<td>0.94±0.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 hr</td>
<td>0.12±0.03</td>
<td>14.3±2.64</td>
<td>53</td>
<td>133±35</td>
<td>88</td>
<td>116±7</td>
<td>1.04±0.25</td>
</tr>
<tr>
<td>3 hr</td>
<td>0.22±0.03†</td>
<td>6.3±1.24</td>
<td>23</td>
<td>131±37‡</td>
<td>87</td>
<td>114±7</td>
<td>1.15±0.33</td>
</tr>
<tr>
<td>6 hr</td>
<td>0.19±0.03</td>
<td>4.8±1.04‡</td>
<td>12</td>
<td>107±23‡</td>
<td>71</td>
<td>108±4</td>
<td>1.16±0.24</td>
</tr>
</tbody>
</table>

(Group A-2) untreated dogs (n = 7)

| Control   | 0.06±0.01  | 28.1±3.7     | 155±20             | 129±2        | 0.89±0.11           |            |                        |
| 1 hr      | 0.19±0.06  | 44.6±7.7     | 158                | 126±30       | 77                  | 104±72     | 0.97±0.19              |
| 3 hr      | 0.48±0.09‡ | 22.8±7.5     | 81                 | 179±23       | 115                 | 109±8‡     | 0.70±0.15              |
| 6 hr      | 0.40±0.07‡ | 14.8±4.9     | 52                 | 166±39       | 107                 | 106±5‡     | 0.77±0.17              |

(Group C-2) CEI-treated dogs (n=5)

| Control   | 0.07±0.01  | 21.9±2.9     | 129±21             | 128±7        | 1.24±0.24           |            |                        |
| Post-CEI  | 0.10±0.02† | 24.4±5.6     | 111                | 144±26†      | 112                 | 110±3‡     | 0.97±0.19†             |
| Post-indomethacin | 0.07±0.02 | 17.9±3.8     | 82                 | 123±22       | 95                  | 124±5      | 1.26±0.23              |
| 1 hr post uranyl nitrate | 0.02±0.02 | 1.5±0.6‡    | 7                  | 97±23        | 65                  | 123±6      | 3.09±2.0               |

Values are the mean change ± SEM; P values represent difference from control. RVR = calculated renal vascular resistance, group means.

* P < 0.05; † P < 0.01; ‡ P < 0.001.
Groups C-2: CEI treatment after uranyl nitrate (n = 5).

Addition of the diuretic resulted in marked progressive increases in urine flow rate, sodium excretion, and the fraction of filtered sodium excreted. The largest increases in osmolar excretion (\(U_{in}V\)) were observed in this group, with a peak at 3 hours, 1310 \(\mu\)Osm/min, falling to 972 at 6 hours (\(P < 0.01\) in each case). \(U_{in}V\) was shown to decrease and approximate plasma levels within the 1st hour and it remained at this level throughout the study. Blood pressure remained statistically unchanged at all study periods.

Group F: CEI treatment, followed by indomethacin, prior to uranyl nitrate (n = 4). Compared to control periods, administration of CEI was associated with a tendency to higher urine flow rate and inulin clearance. These values returned to normal, or slightly below, following indomethacin (Table 2). Changes were not statistically significant, although the number of dogs was small. Administration of uranyl nitrate during prostaglandin synthesis inhibition was followed by a dramatic fall in GFR within 1 hour. Urine output became negligible by 2 hours in all cases and experiments terminated. Sodium and solute excretion rates were not significantly changed after CEI or indomethacin administration (Table 1). After uranyl nitrate was given, EFFNa rose from 0.28 to 1.23% at 1 hour. Administration of CEI induced a mild renal vasodilatation and decreased blood pressure and renal vascular resistance. These changes returned to normal following indomethacin injection. When uranyl nitrate was given in the presence of prostaglandin synthesis inhibition, RBF was markedly decreased with a concurrent increase in renal vascular resistance (Table 2). The vasoconstriction worsened and RBF was nearly or completely abolished at 2 hours in all cases. Thus, indomethacin completely prevented the protective effects of CEI on renal function and hemodynamics following administration of uranyl nitrate.

With untreated dogs as a comparison (group A),
two-way analysis of variance (Table 3) indicated a specific effect of CEI treatment (groups C to E) in maintaining creatinine clearance and increasing urine flow rate and sodium excretion. All these differences were highly significant and were present in all experimental periods. Only sodium excretion at 1 hour (group C) was not different from values in group A. The protective effect of CEI on creatinine clearance was statistically significant in all treated groups whether the peptide was administered following (group C) or preceding uranyl nitrate (group D) and when CEI was given in combination with furosemide (group E). Simultaneous treatment with CEI and furosemide (group E) was not significantly more protective of creatinine clearance than the use of CEI alone (group C). As expected with the addition of the diuretic, a significant enhancement of urine flow rate, sodium excretion, and osmolar excretion were present in group E, as compared to untreated (group A) and CEI treated dogs (group C). In contrast, only when furosemide was used concomitantly with CEI (group E) was osmolar excretion significantly larger in comparison with untreated dogs.

When clearance data for all time periods (1, 3, and 6 hours) were examined together, there was a modest correlation between protection of glomerular filtration and osmolar excretion \((r = 0.453, P < 0.001, \text{d.f.} = 67)\) and, less strongly, with sodium excretion \((r = 0.28, P < 0.02, \text{d.f.} = 67)\). When creatinine clearance was specifically examined at 6 hours only, it was highly correlated with the osmolar excretion \((r = 0.654, P < 0.001, \text{d.f.} = 21)\) and with sodium excretion \((r = 0.56, P < 0.005; \text{d.f.} = 21)\).

Renal prostaglandin secretion rates in two dogs are shown in Table 4. Following uranyl nitrate, PGE\(_2\) and PGF\(_{2\alpha}\) secretion rates were markedly reduced for at least 3 hours and began to recover toward the end of the experiment at 6 hours. Secretion of 6-keto F\(_{1\alpha}\) (a PGI or prostaglandin metabolite, largely produced in the lungs) was variable and generally of negative value, indicating either renal metabolism or urinary excretion of this substance. The effects of CEI and indomethacin in another dog with ARF are also shown in Table 4. PGE\(_2\) and PGF\(_{2\alpha}\) secretion rates were largely enhanced by CEI, despite the concomitant administration of uranyl nitrate. In contrast, following indomethacin, there is a profound inhibition of PGE\(_2\) and PGF\(_{2\alpha}\) secretion rates, which remain at low or negative values for the rest of the study. Again, secretion of 6-keto F\(_{1\alpha}\) was quite variable and had no discernible pattern.

### Table 4

Renal Prostaglandin Secretion Rate in One dog after Uranyl Nitrate

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>PGE(_2)</th>
<th>PGF(_{2\alpha})</th>
<th>6-Keto PGF(_{1\alpha})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>14.2</td>
<td>9.0</td>
<td>-6.45</td>
</tr>
<tr>
<td>1*</td>
<td>0.55</td>
<td>0.55</td>
<td>0</td>
</tr>
<tr>
<td>3*</td>
<td>-6.6</td>
<td>0.55</td>
<td>-6.6</td>
</tr>
<tr>
<td>6*</td>
<td>3.85</td>
<td>11.6</td>
<td>0</td>
</tr>
</tbody>
</table>

**Effect of CEI and indomethacin in one dog after uranyl nitrate**

<table>
<thead>
<tr>
<th></th>
<th>PGE(_2)</th>
<th>PGF(_{2\alpha})</th>
<th>6-Keto PGF(_{1\alpha})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1.9</td>
<td>5.6</td>
<td>15.0</td>
</tr>
<tr>
<td>CEI + uranyl nitrate</td>
<td>44.0</td>
<td>24.0</td>
<td>-2.0</td>
</tr>
<tr>
<td>15 min post-indocin</td>
<td>20.4</td>
<td>3.7</td>
<td>-11.0</td>
</tr>
<tr>
<td>2*</td>
<td>-4.0</td>
<td>6.0</td>
<td>+26.6</td>
</tr>
<tr>
<td>4*</td>
<td>-34.0</td>
<td>-14.0</td>
<td>0</td>
</tr>
<tr>
<td>6*</td>
<td>-22.0</td>
<td>-10.0</td>
<td>-8.0</td>
</tr>
</tbody>
</table>

* Hours after uranyl nitrate.

### Discussion

The purpose of this study was to evaluate the role of angiotensin II during the generation phase of acute renal failure (ARF) in the uranyl nitrate nephrotoxic model in the dog. In this model, early elevations of plasma renin activity have been observed (Flamenbaum et al., 1972a), analogous to findings in clinical ARF (Tu, 1965; Kokot and Kuska, 1969), and studies in other experimental animals (McDonald et al., 1969; Di Bona and Sawin, 1971a). It has been proposed that a tubuloglomerular feedback reduction in glomerular filtration, possibly mediated by the renin angiotensin system, may occur early in ARF (Thurau and Boylan, 1976; Mason, 1976). The role of angiotensin II in ARF (Mason et al., 1977; Stein et al., 1978), as well as a mediator of tubuloglomerular feedback (Wright and Briggs, 1977), however, remain to be proven.

Maneuvers affecting plasma and renal renin content, such as chronic salt loading, have been shown to attenuate the renal functional impairment in several experimental models of ARF (McDonald et al., 1969; Di Bona et al., 1971b). These maneuvers, however, are not specific for renin blockade. Thiel et al. (1976) have found that a high solute excretion per se without renin suppression attenuates the renal failure in the mercuric chloride model. Additional evidence against renin was obtained in studies in which rats were immunized against circulating renin (Flamenbaum et al., 1972b) and after passive or active immunization against angiotensin II (Oken et al., 1975).

Recently, several agents have become available to interrupt the renin angiotensin system pharmacologically (Keim et al., 1972; Turker et al., 1972). Specific analogs of angiotensin II, such as saralasin, have a partial agonistic action that interferes with proper evaluation of their angiotensin blocking effects (Turker et al., 1972). Angiotensin-converting enzyme inhibitors, such as SQ-20,881, that prevent the conversion of angiotensin I to angiotensin II seem particularly useful to evaluate the renal effects of this hormone (Meggs and Hollenberg, 1980). The observed effects of CEI in our normal dogs (group B and initially in group F) included a significant increase in potassium excretion and a trend toward a larger sodium excretion, fractional sodium excretion, and GFR. These changes were not statistically significant. Systemic blood pressure was either unchanged (group B) or slightly decreased (group F), concomitant with a small renal vasodilation and a fall in renal vascular
resistance. These findings agree with the expected response to CEI in dogs when the renin-angiotensin system is only partially activated (Kimbrough et al., 1977; Meggs and Hollenberg, 1980).

In this study, converting enzyme inhibition markedly attenuates the fall in GFR (creatinine and inulin clearances) during the generation of ARF seen with uranyl nitrate administration in the dog. The degree of preservation of GFR at 6 hours was of a magnitude similar to that found with dopamine and furosemide in this model (Lindner et al., 1979). Maintenance of renal function was observed whether the angiotensin inhibitor was given prior to or shortly after administration of the nephrotoxic agent. This suggests that CEI delivery to its intrarenal locus is adequate early in the course of ARF, and this observation may have implications for its possible use in a clinical situation.

It has been postulated that hemodynamic alterations may initiate the renal insufficiency in this model (Stein et al., 1978). Thus, it would be expected that GFR changes would be accompanied by simultaneous changes in renal hemodynamics. Findings in untreated dogs (group A-2) confirmed that early after uranyl nitrate there is a renal vasoconstriction (Flamenbaum et al., 1972a; Lindner et al., 1979). Moreover, in dogs pretreated with indomethacin, the very rapid fall in GFR was accompanied by intense renal vasoconstriction and high renal vascular resistance. On the other hand, the preservation of higher GFR in CEI-treated dogs was characterized by a fall in renal vascular resistance and maintenance of RBF at close to control values. These findings are consistent with a role of angiotensin II-mediated vasoconstriction in the generation of ARF in this model. However, the indirect evidence suggests that factors additional to the vasoconstriction contributed to initiate the renal failure. First, despite the maintenance of RBF with CEI, the protection of GFR was incomplete and temporary. Second, previous studies failed to protect GFR with vasodilators alone, i.e., prostaglandins or dopamine, in dogs given uranyl nitrate (Mauk et al., 1977; Lindner et al., 1979).

Several mechanisms may explain the temporary protection of GFR with CEI treatment in four different groups of dogs. First, GFR protection may be the result of intrarenal blockade of angiotensin II. Angiotensin II has been shown to reduce GFR, SNGFR, and Kf, the glomerular ultrafiltration coefficient (Blantz et al., 1976; Schor et al., 1981a). The fall in Kf may result primarily from a decrease in glomerular surface area due to stimulation of mesangial cell contraction by angiotensin II (Ausiiello et al., 1980). The effect of angiotensin II on Kf in the rat is reversed by verapamil and manganese ion, known blockers of smooth muscle contraction (Ichikawa et al., 1979). Recently, Blantz and Gushwa (1981) showed that the reduction of Kf after uranyl nitrate in the rat is functional in nature and can be reversed by angiotensin blockade with CEI or by plasma volume expansion. Similarly, CEI largely abolished the toxic effects of gentamycin on SNGFR, afferent arteriolar blood flow, and Kf in the rat (Schor et al., 1981b). In contrast to the GFR protection noted in these studies, others have reported that an angiotensin II analog (Baranowski et al., 1975; Ishikawa and Hollenberg, 1976) or a converting enzyme inhibitor, SQ-20,881 (Ishikawa and Hollenberg, 1976) failed to prevent the rise in blood urea nitrogen after glycerol administration in the rat. The evidence from these previous studies is inadequate to exclude a role for the renin-angiotensin system. Persistent azotemia may have been due to a glycerol-induced hypercatabolic state. Unfortunately, no other measurements of renal function were done. The dose and duration of treatment with angiotensin antagonists may have been insufficient to effectively block intrarenal angiotensin II. These agents were used for only 3 hours (Ishikawa and Hollenberg, 1976) or 6 hours (Baranowski et al., 1975), while the duration of follow-up and timing of the functional measurements were at 48 hours in each case. At this late time, other mechanisms may be involved in the maintenance of ARF (Stein et al., 1978). This may explain the difference with our findings in the first 6 hours after uranyl nitrate. Furthermore, in our study, full blockade of angiotensin II was confirmed repeatedly, as shown by the absence of vascular response to intravenous angiotensin I, as compared to the normal response prior to treatment with CEI.

Second, it has been suggested that kinins mediate the renal effects of CEI. Thus, in the dog, Nasjletti and colleagues (1975) documented an increase in kinins in urine and in the renal venous effluent after treatment with SQ-20,881. On the other hand, the evidence favors the view that the effects of CEI depend primarily on angiotensin II inhibition rather than bradykinin production. For instance, both CEI...
and saralasin, an angiotensin analog, are equally effective in attenuating tubuloglomerular feedback (Stowe et al., 1979) and the changes in GFR, RBF, and intrarenal distribution of RBF in sodium-depleted rats (Mimram et al., 1980). Finally, the renal vascular effects of bradykinin may in turn be mediated by prostaglandins (Nasjletti and Malik, 1981). In summary, the precise role of kinins in the renal vascular response to CEI remains controversial and may be subject to species differences.

Third, it has been suggested that some vascular effects of CEI may be mediated by renal prostaglandin production (Swartz et al., 1980). To evaluate this possibility, we pretreated an additional group of dogs with indomethacin, an inhibitor of prostaglandin synthesis. First, in preliminary studies in our laboratory, we confirmed the observation by Terragno et al. (1977) that prostaglandins are essential to maintain GFR and RBF in the anesthetized, laparotomized dog. In this animal, we found that indomethacin decreased RBF by more than 50% and led to a cessation of urine output. This is analogous to the recent finding that indomethacin abolished the effect of prostaglandins to oppose the vasoconstrictor effect of angiotensin II and the renal sympathetic nervous system in sodium-depleted dogs (Oliver et al., 1980). Moreover, in our dogs we found that the effect of indomethacin could be reversed by CEI or prevented by CEI pretreatment. Based on these findings, in group F we pretreated dogs with CEI and later with indomethacin. In this setting of angiotensin II and prostaglandin blockade, addition of uranyl nitrate resulted in a rapid fall in GFR, RBF, and anuria within 1–2 hours in all cases. Further indication that prostaglandins may have modulated the effects of angiotensin II in these studies was given by our measurements in two dogs. Following uranyl nitrate alone, PGE2 and PGF2α secretion rates were markedly reduced. In contrast, secretion rates of these prostaglandins were largely enhanced by CEI, despite the concomitant administration of uranyl nitrate. Finally, indomethacin markedly suppressed prostaglandin secretion. Although these findings are preliminary, they suggest that an imbalance between vasoconstrictor (angiotensin) and vasodilator factors (prostaglandins) may occur during the generation of ARF in this model. Presumably, after uranyl nitrate (Blantz and Gushwa, 1981), GFR progressively decreases, blocking renal function. Arch Int Pharmacodyn 217: 322–331.


In conclusion, uranyl nitrate reduces RBF and GFR in the dog and may reduce prostaglandin secretion. During the generation of ARF in this model, CEI attenuates the fall in RBF and GFR, blocks the renal hemodynamic effects of angiotensin II, and possibly enhances prostaglandin secretion. These protective effects of CEI are abolished by indomethacin. These observations are compatible with a major pathogenetic role for angiotensin II during the initiation of ARF. Furthermore, they suggest that an imbalance between vasoconstrictor (angiotensin II) and vasodilator factors (prostaglandins) may be operative in the early phase of uranyl nitrate-induced ARF in the dog.

Particularly, in the case of nephrotoxic agents like uranyl nitrate or mercury chloride (Kleinman et al., 1977), the initial insults result in biochemical alterations at the molecular level which eventually lead to tubular cell death (1). Despite treatment with CEI or similar agents, these biochemical changes, including impairment of cellular respiration, must continue to progress. In a sense, the temporary protective effects of CEI seem remarkable in this setting of continuous biochemical injury and imply an associated major role for vasoactive factors early in the production of renal failure.

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References


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