BG9719 (CVT-124), an A<sub>1</sub> Adenosine Receptor Antagonist, Protects Against the Decline in Renal Function Observed With Diuretic Therapy

Stephen S. Gottlieb, MD; D. Craig Brater, MD; Ignatius Thomas, MD; Edward Havranek, MD; Robert Bourge, MD; Steven Goldman, MD; Farere Dyer, MD; Miguel Gomez, MD; Donald Bennett; Barry Ticho, MD, PhD; Evan Beckman, MD; William T. Abraham, MD

Background—Adenosine may adversely affect renal function via its effects on renal arterioles and tubuloglomerular feedback, but effects of adenosine blockade in humans receiving furosemide and ACE inhibitors is unknown.

Methods and Results—This was a randomized, double-blind, ascending-dose, crossover study evaluating 3 doses of BG9719 in 63 patients with congestive heart failure. Patients received placebo or 1 of 3 doses of BG9719 on 1 day and the same medication plus furosemide on a separate day. Renal function and electrolyte and water excretion were assessed. BG9719 alone caused an increase in urine output and sodium excretion (P<0.05). Although administration of furosemide alone caused a large diuresis, addition of BG9719 to furosemide increased diuresis, which was significant at the 0.75-μg/mL concentration. BG9719 alone improved glomerular filtration rate (GFR) at the 2 lower doses. Furosemide alone caused a decline in GFR. When BG9719 was added to furosemide, however, creatinine clearance remained at baseline at the 2 lower doses.

Conclusions—In patients with congestive heart failure on standard therapy, including ACE inhibitors, BG9719 increased both urine output and GFR. In these same patients, furosemide increased urine output at the expense of decreased GFR. When BG9719 was given in addition to furosemide, urine volume additionally increased and there was no deterioration in GFR. A<sub>1</sub> adenosine antagonism might preserve renal function while simultaneously promoting natriuresis during treatment for heart failure. (Circulation. 2002;105:1348-1353.)

Key Words: adenosine antagonist • renal function • congestive heart failure • diuretics

Renal function is exceedingly important in patients with chronic congestive heart failure. Although it has long been known that good fluid balance is essential for symptomatic control of heart failure, recent studies have demonstrated that worsening renal function is associated with poorer clinical outcome among hospitalized patients with heart failure.1 Indeed, renal function is one of the most important determinants of survival in patients with heart failure.2 Furthermore, renal impairment is an important cause of suboptimal prescription of medications known to be beneficial, such as diuretics and ACE inhibitors.

Renal function can be modulated by extracellular levels of adenosine acting on specific cell-surface receptors. Adenosine binding to receptors on the afferent arteriole causes local constriction, thereby reducing renal blood flow. Stimulation of A<sub>1</sub> adenosine receptors also increases sodium reabsorption in the proximal and distal tubules. An acute increase in the delivery of sodium in the distal tubule causes an increase in adenosine concentrations, which reduces glomerular filtration rate (GFR) via tubuloglomerular feedback at the macula densa and afferent arterioles. Antagonism of A<sub>1</sub> adenosine receptors therefore maintains renal function by vasodilatation of the afferent arteriole and disruption of the tubuloglomerular feedback loop while causing natriuresis.

BG9719 is a selective A<sub>1</sub> adenosine receptor antagonist with the potential to improve renal function in patients with heart failure. In animal studies, BG9719 has caused a potassium neutral diuresis while maintaining renal function.3 Prior human studies have also suggested that it promotes diuresis while maintaining glomerular function.4 However, there have been no previous evaluations in humans of the effects of A<sub>1</sub> antagonism in combination with standard heart failure therapy that includes furosemide and ACE inhibitors.
Study Design

The purpose of the present study was to compare the effects of BG9719 alone, furosemide alone, and BG9719 in combination with furosemide in patients with congestive heart failure. We evaluated renal function, urine volume, and urinary electrolyte excretion.

Methods

This was a randomized, double-blind, crossover study evaluating 3 doses of BG9719 and placebo (Figure 1). The study compared the renal actions of BG9719 (or placebo) alone and in combination with furosemide in 63 edematous patients with symptomatic heart failure. The study enrolled patients at 8 clinical sites over 14 months. Inclusion criteria included New York Heart Association class II through IV heart failure with an ejection fraction ≤40% and the presence of edema despite a daily furosemide dose of at least 80 mg. All patients were taking ACE inhibitors. Two patients were receiving spironolactone. Baseline GFR, as measured by creatinine clearance, was at least 30 mL/min per 1.73 m² or serum creatinine was <1.9 mg/dL. The study protocol was approved by all participating institutional review boards, and all patients gave written informed consent for participation in this study.

Patients were enrolled into 1 of 3 dosing cohorts of ascending doses of BG9719. Within each cohort, patients were randomized to receive either active investigational drug (BG9719) or placebo (Figure 1). After an equilibration period, baseline urine was collected to determine urine volume, electrolyte determinations, and creatinine clearance. On the following day, subjects received investigational drug (BG9719 or placebo) and either a bolus of intravenous furosemide or placebo. On the second dosing day after another equilibration period, urine was collected to determine urine volume, electrolyte excretion, and creatinine clearance for the first 8 hours after drug administration. Because of creatinine washout, creatinine clearance was measured during the 7 hours of the infusion. Creatinine clearance was determined from serum creatinine and urinary creatinine excretion and adjusted for body surface area. Serum creatinine was measured at each urine collection.

Renal Function

Urine was collected to determine urine volume, electrolyte excretion, and creatinine clearance on the day before the first dosing day and on both dosing days. Patients were instructed to urinate after the following time intervals with respect to dosing: 0 to 1, 1 to 2, 2 to 4, 4 to 6, and 6 to 8 hours; a Foley catheter was used in 3 patients. The data presented are cumulative for the first 8 hours after drug administration. Because of creatinine washout, creatinine clearance was measured during the 7 hours of the infusion. Creatinine clearance was determined from serum creatinine and urinary creatinine excretion and adjusted for body surface area. Serum creatinine was measured at each urine collection.

Statistics

Analysis of dose effects was based on mixed-effect ANOVA and ANCOVA. Two-sided tests were used with statistical significance at P < 0.05. Multiple covariates were considered, including baseline renal function, severity of heart failure, and demographic information.

Response variables were calculated as change from baseline measurements during the same time interval on the predosing day.

Results

Patient Population

The patients in this study reflect a typical heart failure study population (Table 1). The patients were elderly, predominantly male, and racially mixed. Patients receiving placebo were slightly younger, although this was not statistically significant. 33% of patients were classified as NYHA class II and 65% as class III. One patient was class IV. Mean ejection fraction was 28 ± 7%. Forty-three percent of the patients had diabetes mellitus, and 57% had ischemic heart disease.

Mean baseline urine volume (before any intervention) was 758 mL for 8 hours. Sodium excretion was 20.3 mEq for this time. Creatinine clearance for 1 to 8 hours was 87.5 ± 43 mL/min per 1.73 m². Although the mean baseline creatinine clearance was higher in patients who received placebo, this was not statistically significant.

Urine Output and Sodium Excretion

The urine output during the infusion of BG9719 (or placebo), with or without furosemide bolus, is shown in Figure 2. BG9719 caused a statistically significant dose-dependent increase in urine output and sodium excretion, with no additional effect of the 2.5 µg/mL concentration compared with the 0.75 µg/mL concentration. Both the trend and the 2 higher doses were significant (P < 0.05). Furosemide alone caused a large diuresis. The addition of BG9719 caused an additional increase, which was significant at the 0.75 µg/mL concentration.
Creatinine Clearance
BG9719, when given without furosemide, tended to improve GFR at the 2 lower doses, with a P value of 0.055 at the 0.75-µg/mL concentration (Figure 3). Furosemide alone caused a significant decline in GFR. When BG9719 was added to furosemide, however, creatinine clearance remained at baseline at the 2 lower doses. BG9719 at 2.5 µg/mL did not prevent the decline in creatinine clearance associated with furosemide.

The relationship between change in urine volume and change in creatinine clearance is shown in Figure 4 for patients receiving the 0.75-µg/mL concentration. BG9719 increased both urine output and GFR compared with placebo. Furosemide increased urine output at the expense of decreased GFR. When BG9719 was given in addition to furosemide, urine volume additionally increased, and there was no deterioration in GFR seen.

Electrolyte Excretion
Potassium and sodium excretion is shown in Table 2. Alone, BG9719 did not significantly increase potassium excretion despite increasing sodium excretion. In combination with furosemide, sodium excretion increased, as did potassium excretion. Magnesium and uric acid excretion are also shown in Table 2.

Blood Pressure and Heart Rate
The baseline blood pressure and heart rate and the change in these parameters from pretreatment are shown in Table 3. After 3.5 hours, heart rate (as determined by electrocardiography) did not change significantly in any group. When

![Figure 2](http://circ.ahajournals.org/)

**Figure 2.** The urine volume for 8 hours after BG9719 bolus and subsequent infusion, with and without 80 mg furosemide. Placebo and 3 doses are depicted. BG9719 increased urine volume both alone and in combination with furosemide. *P<0.05 compared with placebo.

![Figure 3](http://circ.ahajournals.org/)

**Figure 3.** Percent change from the baseline day of creatinine clearance for 8 hours after BG9719 bolus and subsequent infusion with and without 80 mg furosemide. BG9719 led to increased creatinine clearance at the 2 lower doses when given alone. In combination with furosemide, creatinine clearance was maintained at the 2 lower doses compared with furosemide alone and the 2.5-µg/mL concentration. *P=0.055 compared with baseline, **P<0.05 compared with baseline.

**TABLE 1. Baseline Characteristics by Randomization Group**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=16)</th>
<th>BG9719, 0.1 µg/mL (n=15)</th>
<th>BG9719, 0.75 µg/mL (n=15)</th>
<th>BG9719, 2.5 µg/mL (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>61±10</td>
<td>64±14</td>
<td>65±12</td>
<td>64±15</td>
</tr>
<tr>
<td>Sex, % male</td>
<td>81</td>
<td>87</td>
<td>93</td>
<td>71</td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White or hispanic</td>
<td>44</td>
<td>80</td>
<td>47</td>
<td>71</td>
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<tr>
<td>Black</td>
<td>56</td>
<td>20</td>
<td>53</td>
<td>29</td>
</tr>
<tr>
<td>NYHA class, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>19</td>
<td>27</td>
<td>47</td>
<td>41</td>
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<tr>
<td>III</td>
<td>81</td>
<td>73</td>
<td>47</td>
<td>59</td>
</tr>
<tr>
<td>IV</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>28±6</td>
<td>29±9</td>
<td>30±7</td>
<td>25±8</td>
</tr>
<tr>
<td>Etiology of heart failure, %</td>
<td>63</td>
<td>67</td>
<td>53</td>
<td>59</td>
</tr>
<tr>
<td>Adjusted creatinine clearance, µg/mL (1–8 h)</td>
<td>108±51</td>
<td>75±40</td>
<td>83±34</td>
<td>83±40</td>
</tr>
<tr>
<td>Urine volume, mL (0–8 h)</td>
<td>798±455</td>
<td>702±435</td>
<td>775±544</td>
<td>720±491</td>
</tr>
</tbody>
</table>
furosemide alone was not seen when BG9719 was given. Given with or without furosemide. The decrease in GFR with increasing urine output during standard heart failure therapy. BG9719 might prevent deterioration in renal function while presence of an effective diuresis. These results suggest that of BG9719, creatinine clearance was maintained in the when furosemide was given in addition to the 2 lower doses furosemide alone caused a decline in creatinine clearance, urine output when given in addition to furosemide. Although furosemide alone caused a decline in creatinine clearance, when furosemide was given in addition to the 2 lower doses of BG9719, creatinine clearance was maintained in the presence of an effective diuresis. These results suggest that BG9719 might prevent deterioration in renal function while increasing urine output during standard heart failure therapy. Moreover, A1 receptor antagonism may protect against the commonly observed decline in glomerular filtration associated with the use of loop diuretics.

Possible Mechanism of Action
Adenosine acts on 2 different receptor subtypes in the kidney (the A1 and A2 receptors). A2 receptor stimulation increases medullary blood flow and would be expected to improve renal function. However, the A1 receptor seems to predominate in the kidney. Adenosine (via stimulation of the A1 receptor) may directly decrease glomerular filtration by dilatation of postglomerular vessels6 or vasoconstriction before the glomerulus.7 The A1 receptor seems to be the mediator of tubuloglomerular feedback, the macula densa mechanism by which increased sodium concentration in the proximal tubule leads to decreased glomerular filtration.8 A1 receptor blockade could therefore inhibit tubuloglomerular feedback and dilate afferent arterioles, leading to improved glomerular filtration.

Selective A1 receptor blockade has also demonstrated a physiological role for adenosine in the control of tubular function.9 A1 adenosine receptor blockade seems to directly impact the proximal and distal tubules, increasing Na+ excretion.10 At the distal tubule, this could lead to a potassium-neutral natriuresis, as was demonstrated in this study. It is thus not surprising that xanthines, which also antagonize adenosine, cause diuresis.11 The highly specific A1 receptor antagonist BG9791 also has been shown to increase natriuresis and diuresis.12 Effects on tubuloglomerular feedback and the proximal and distal tubules could therefore explain the diuretic and natriuretic observations of the present study.

It is unlikely that differences in hemodynamics could explain the differences in renal function that were observed between the treatment groups, because no significant changes were noted in heart rate or blood pressure between the groups (Table 3). Prior studies in patients with heart failure treated with BG9719 demonstrated only minor changes in heart rate and blood pressure (unpublished results). Healthy subjects also demonstrated no significant changes in pulse or blood

![Figure 4. The relationship between change in urine volume and change in creatinine clearance for patients receiving the 0.75-μg/mL concentration. BG9719 increased urine output when given without furosemide. The decrease in GFR with furosemide alone was not seen when BG9719 was given.](Image 78x627 to 250x718)

### TABLE 2. Electrolyte Excretion With BG9719, With and Without Furosemide

<table>
<thead>
<tr>
<th>Electrolyte Excretion</th>
<th>Placebo</th>
<th>BG9719, 0.75 μg/mL</th>
<th>BG9719, 2.5 μg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺ excretion, mEq/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without furosemide</td>
<td>9±18</td>
<td>17±24</td>
<td>43±20*</td>
</tr>
<tr>
<td>In addition to furosemide</td>
<td>187±84</td>
<td>188±82</td>
<td>270±93*</td>
</tr>
<tr>
<td>K⁺ excretion, mEq/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without furosemide</td>
<td>9±12</td>
<td>11±14</td>
<td>14±13</td>
</tr>
<tr>
<td>In addition to furosemide</td>
<td>29±14</td>
<td>34±17</td>
<td>45±19*</td>
</tr>
<tr>
<td>Mg excretion, mEq/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without furosemide</td>
<td>0.1±1.9</td>
<td>1.5±1.6*</td>
<td>2.2±1.3*</td>
</tr>
<tr>
<td>In addition to furosemide</td>
<td>3.5±2.9</td>
<td>4.7±2.4</td>
<td>4.9±2.4</td>
</tr>
<tr>
<td>Uric acid excretion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without furosemide</td>
<td>−0.3±0.6</td>
<td>0.0±0.6</td>
<td>0.4±0.5*</td>
</tr>
<tr>
<td>In addition to furosemide</td>
<td>−0.5±0.6</td>
<td>−0.3±0.4</td>
<td>0.1±0.5*</td>
</tr>
</tbody>
</table>

*P<0.05 vs placebo.

Discussion
This is the first study to evaluate the combination of an A1 adenosine receptor antagonist and furosemide in humans. In this study, BG9719 increased urine output and sodium excretion when given without a diuretic in patients with heart failure receiving ACE inhibitors, confirming the diuretic effect of adenosine A1 receptor antagonism. It also increased urine output when given in addition to furosemide. Although furosemide alone caused a decline in creatinine clearance, when furosemide was given in addition to the 2 lower doses of BG9719, creatinine clearance was maintained in the presence of an effective diuresis. These results suggest that BG9719 might prevent deterioration in renal function while increasing urine output during standard heart failure therapy. Moreover, A1 receptor antagonism may protect against the
pressure when treated with BG9719. Animal studies with selective A1 adenosine antagonists did not show an effect on heart rate or blood pressure in dogs. Additional support for the lack of hemodynamic effect comes from animal studies in which arterial blood pressure and heart rates were indistinguishable between A1 adenosine receptor–deficient mice and normal controls.

**Prior Studies in Heart Failure**

Plasma adenosine levels are elevated in patients with heart failure, implying that adenosine antagonism might have physiological or pathologic importance in these patients. A prior study of the effects of BG9719 in patients with heart failure suggested potential beneficial effects of A1 receptor blockade. BG9719 caused a mild diuresis without decreasing glomerular filtration. In contrast, furosemide produced a marked decrease in glomerular filtration. While interpretation of this previous study was limited by differences in the extent of diuresis between the treatment groups, it did raise hope that BG9719 might preserve renal function in the setting of diuresis.

Most studies evaluating the renal effects of furosemide have demonstrated decreased glomerular function. These effects may be mediated by adenosine release in the kidney. The marked furosemide-induced decrease in creatinine clearance in the present study is consistent with the clinical observation that diuresis may be limited by worsening renal function. Considering the known adverse prognostic importance of an increased serum creatinine in the hospital, an intervention that might permit diuresis while maintaining renal function could conceivably have a favorable impact on patients hospitalized for heart failure.

**Concentration of 2.5 μg**

Creatinine clearance was not maintained when BG9719 at a concentration of 2.5 μg/mL was given in addition to furosemide. It is unclear why no benefit was seen at this concentration when GFR improved with the 2 lower doses. It is possible that the contrasting results are secondary to additional pharmacological activity of the high dose or to cross-reactivity of BG9719 to another receptor system. Interestingly, when BG9719 was given alone, creatinine clearance did not increase as much with the higher dose as it did with the lower doses. This additionally supports the idea of varying effects at different doses.

**Limitations**

This study is a preliminary evaluation of BG9719, having evaluated a limited number of patients. Thus, it is possible that the dose-related findings of the present study were attributable to the relatively small size of the study. It is also possible that the baseline differences (although not statistically different) impacted comparisons of placebo and the different doses of BG9719. There may have been differences in patient characteristics leading to divergent results. Indeed, the placebo group tended to have better baseline renal function. However, this baseline difference would not explain the high-dose observations, because baseline creatinine clearance was similar in all 3 groups that received active drug. Baseline differences also cannot explain the intragroup effects noted when the actions of BG9719 in addition to furosemide were compared with the furosemide-only dosing.

Because this study was performed in stable patients, at this time one must be cautious in extrapolating the findings to unstable patients. Nevertheless, patients in this study did have evidence of fluid overload (edema, dyspnea), even if they did not have an acute change in their clinical status. Although patients in this study were more stable than patients with decompensated heart failure, there is no reason to believe that the renal physiology should differ greatly between these 2 groups.

**Conclusion**

Combining the A1 adenosine receptor antagonist BG9719 (at 0.1 and 0.75 μg/mL) with standard diuretic therapy may increase renal output while protecting renal function. The
present study suggests that treatment with an A1 adenosine receptor antagonist may be useful in the therapy of congestive heart failure. Additional investigation of this mechanism might lead to novel approaches to the treatment of patients with renal dysfunction associated with diuresis and heart failure.

Acknowledgments
This study was supported by a grant from Biogen Inc, Cambridge, Mass.

References
BG9719 (CVT-124), an A<sub>1</sub> Adenosine Receptor Antagonist, Protects Against the Decline in Renal Function Observed With Diuretic Therapy

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/content/106/13/1743.full.pdf

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In the article, “BG9719 (CVT-124), an A1 Adenosine Receptor Antagonist, Protects Against the Decline in Renal Function Observed With Diuretic Therapy,” by Gottlieb et al, which appeared in the March 19, 2002, issue of the journal (Circulation. 2002;105:1348–1353), the units in Table 2 were incorrect. The corrected table appears below.

**TABLE 2. Electrolyte Excretion With BG9719, With and Without Furosemide as Compared With Baseline Day**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>BG9719, 0.1</th>
<th>BG9719, 0.75</th>
<th>BG9719, 2.5</th>
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</thead>
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<tr>
<td><strong>Na⁺ excretion, mEq/8 h</strong></td>
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<td>202±102</td>
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<td><strong>K⁺ excretion, mEq/8 h</strong></td>
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<td></td>
</tr>
<tr>
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<td>34±17</td>
<td>45±19*</td>
<td>34±27</td>
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<tr>
<td><strong>Mg excretion, mEq/8 h</strong></td>
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<td></td>
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<td></td>
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<td>2.2±1.3*</td>
<td>0.8±1.7</td>
</tr>
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<td>In addition to furosemide</td>
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<td>4.7±2.4</td>
<td>4.9±2.4</td>
<td>3.8±2.4</td>
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<tr>
<td><strong>Uric acid excretion, mEq/8 h</strong></td>
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<td></td>
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<td></td>
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</tr>
</tbody>
</table>

*P<0.05 vs placebo.

In the article, “Angiotensin II Type 2 Receptor Overexpression Preserves Left Ventricular Function After Myocardial Infarction,” by Yang et al, which appeared in the July 2, 2002, issue of the journal (Circulation. 2002;106:106–111), an author was omitted from the byline. The corrected author list appears below.

Zequan Yang, MD, PhD; Christina M. Bove, MD; Brent A. French, PhD; Frederick H. Epstein, PhD; Stuart S. Berr, PhD; Joseph M. DiMaria, BA; Jennifer J. Gibson, MS; Hiroaki Matsubara, MD, PhD; Robert M. Carey, MD; Christopher M. Kramer, MD