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Effects of BG9719 (CVT-124), an A_1-Adenosine Receptor Antagonist, and Furosemide on Glomerular Filtration Rate and Natriuresis in Patients With Congestive Heart Failure

Stephen S. Gottlieb, MD, FACC,* Sandra L. Skettino, MD,† Andrew Wolff, MD,† Evan Beckman, MD,‡ Michael L. Fisher, MD, FACC,* Ronald Freudenberger, MD, FACC,* Tim Gladwell, PHARMD,* Joanne Marshall, RN,* Michelle Cines, RN,* Donald Bennett, PHD,‡ Elizabeth B. Liittschwager, BA†

Baltimore, Maryland; Palo Alto, California; and Cambridge, Massachusetts

OBJECTIVES To determine the effects of furosemide and the selective A_1 adenosine receptor BG9719 on renal function in patients with congestive heart failure (CHF).

BACKGROUND Studies suggest that adenosine may affect renal function by various mechanisms, but the effects of blockade of this system in humans is unknown. In addition, the effects of a therapeutic dose of furosemide on glomerular filtration rate (GFR) and renal plasma flow (RPF) in heart failure patients are controversial.

METHODS On different days, 12 patients received placebo, BG9719 and furosemide. Glomerular filtration rate, RPF and sodium and water excretion were assessed immediately following drug administration.

RESULTS Glomerular filtration rate was 84 ± 23 ml/min/1.73m^2 after receiving placebo, 82 ± 24 following BG9719 administration and a decreased ($p < 0.005$) 63 ± 18 following furosemide. Renal plasma flow was unchanged at 293 ± 124 ml/min/1.73m^2 on placebo, 334 ± 155 after receiving BG9719 and 374 ± 231 after receiving furosemide. Sodium excretion increased from 8 ± 8 mEq following placebo administration to 37 ± 26 mEq following BG9719 administration. In the six patients in whom it was measured, sodium excretion was 104 ± 78 mEq following furosemide administration.

CONCLUSIONS Natriuresis is effectively induced by both furosemide and the adenosine A_1 antagonist BG9719 in patients with CHF. Doses of the two drugs used in this study did not cause equivalent sodium and water excretion but only furosemide decreased GFR. These data suggest that adenosine is an important determinant of renal function in patients with heart failure. (J Am Coll Cardiol 2000;35:56–9) © 1999 by the American College of Cardiology

The impact of a diuretic on glomerular filtration rate (GFR) is dependent both upon direct nephron effects and indirect consequences of volume depletion. Not surprisingly, varying the dose of a diuretic, the model studied or using drugs with different efficacy or mechanism of action lead to conflicting conclusions about the renal effects of diuretics. In patients with congestive heart failure (CHF), a group likely to experience adverse renal effects with a diuretic, even the impact of a therapeutic dose of furosemide on GFR is controversial.

Selective A_1 adenosine receptor blockade could theoretically cause diuresis by a novel mechanism that minimizes the renal effects of volume depletion. The direct renal actions of adenosine include reduced glomerular filtration, perhaps by dilation of postglomerular vessels (1) or by vasoconstrictive effects (2). Similar effects have been seen when intravenous adenosine is given (3). Conversely, selective A_1 receptor blockade has been shown to decrease afferent arteriole pressure and increase urine flow and sodium excretion (4). With these actions, it is possible that an adenosine antagonist may both be able to cause diuresis and maintain or improve glomerular filtration.

We therefore evaluated in a randomized, double-blind, crossover trial, the effects of the selective A_1 antagonist BG9719 on GFR, renal plasma flow (RPF) and sodium and

From the *Division of Cardiology, Department of Medicine, University of Maryland School of Medicine, Baltimore, Maryland and the D.V.A. Medical Center, Baltimore, Maryland; †CV Therapeutics, Palo Alto, California; and ‡Biogen, Cambridge, Massachusetts. This study was supported by a grant from Biogen, Cambridge, Massachusetts. Dr. Evan Beckman and Dr. Donald Bennett are employees of Biogen. Dr. Stephen Gottlieb has served as a consultant to Biogen.

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Abbreviations and Acronyms

CHF = congestive heart failure
GFR = glomerular filtration rate
RPF = renal plasma flow

water excretion in patients with CHF. In addition, we investigated the renal effects of open label furosemide in patients with CHF.

METHODS

Patient population. We studied the renal response to furosemide, BG9719 and placebo in 12 male patients with CHF ages 42 to 73 years (mean 59 ± 11). Nine patients were classified as New York Heart Association functional class III and three patients as class IV but all were clinically stable and receiving constant daily doses of digoxin (mean dose 0.21 ± 0.06 mg), furosemide (66 ± 58 mg) and lisinopril (26 ± 16 mg). The lisinopril dose was stable for at least six weeks before the study. Patients were not hypertensive or orthostatic. Baseline serum creatinine was <2.5 mg/dL and baseline serum sodium was greater than 131 mEq/L. One patient was receiving beta-adrenergic blocking agents and one patient was receiving spironolactone. Patients abstained from xanthine or chocolate containing foods for three days before the first dosing day and during study participation. Patients refrained from solid food for at least 10 h before initiation of the study drug. All medications were given as prescribed except on the dosing days of study when they were held until after renal function assessment.

Study protocol. After written informed consent was obtained, patients were admitted to a clinical research unit, where they were stabilized for at least three days on a 30 mEq sodium, 60 mEq potassium and 1 to 1.5 g/kg protein diet and no diuretics. When the patient's weight did not change by more than 1 kg on two sequential days, the patient was randomized in a double blind manner to receive either study drug (1 mg/kg of BG9719) or placebo (dosing day 1). Drug was administered over 60 min. Renal plasma flow and GFR were determined as were 2 h electrolyte and water excretion.

Patients were then again stabilized on the same diet. When weight did not change >1 kg for two consecutive days and at least 72 h after dosing day 1, patients were restudied. The protocol was the same as on dosing day 1, except that patients received placebo if BG9719 was previously given or BG9719 if placebo was previously administered.

At least two days after the second dosing day, the patient received an intravenous dose of furosemide, equal to the patient's usual daily oral dose. For the one patient who was not receiving a daily dose of furosemide, 40 mg was given.

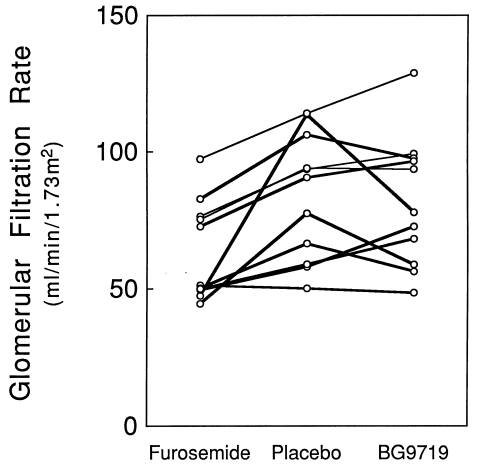

Figure 1. The GFR for 11 patients following administration of placebo, furosemide and BG9719. The mean GFR was 63 ± 18 ml/min/1.73m^2 following furosemide, 84 ± 23 after receiving placebo and 82 ± 24 ml/min/1.73m^2 following BG9719 administration. The difference between furosemide and both placebo and BG9719 was significant, $p < 0.005$. GFR = glomerular filtration rate.

The dose of furosemide given ranged from 20 to 200 mg (mean 63 ± 49 mg). Glomerular filtration rate and RPF were then assessed. Glomerular filtration rate was not obtained in one patient because of technical problems. On the furosemide dosing day, sodium and water excretion were measured for 2 h in six of the 12 patients.

Measurements of renal hemodynamics. Renal plasma flow was measured by assessing the disappearance from the serum of 60 μCi of ^{131}I-orthodihippurate at precisely 44 min after the injection, as described by Tauxe and colleagues (5). Glomerular filtration rate was determined by the serum disappearance of ^{99m}Tc DTPA (6). ^{99m}Tc DTPA was injected 1 h before study drug administration and blood samples collected 0, 1 and 2 h after injection. ^{131}I-hippuran was injected at the same time as study drug administration and RPF determined 0 to 44 min after isotope injection.

Data analysis. Renal hemodynamic response was assessed by comparing differences obtained after placebo, BG9719 and furosemide administration. The differences were evaluated for normality with the Shapiro-Wilk test. A paired *t* test was used to evaluate whether differences deviated significantly from zero. All tests were two sided. P values <0.05 without adjustment for multiple comparison were considered statistically significant.

RESULTS

Renal hemodynamic response to therapy. The mean GFR was 84 ± 23 ml/min/1.73m^2 for the 2 h after receiving placebo, 82 ± 24 ml/min/1.73m^2 after BG9719 administration and 63 ± 18 ml/min/1.73m^2 after furosemide (Fig. 1). The difference between furosemide and

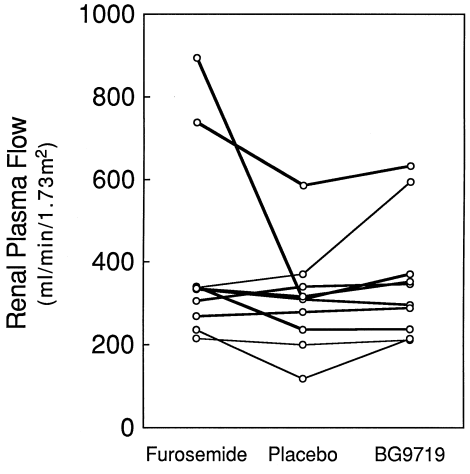

Figure 2. The renal plasma flow for each patient following administration of placebo, furosemide and BG9719. There were no significant differences among the groups.

both placebo and BG9719 was significant, $p < 0.005$. Ten of 11 patients showed a decline in GFR after furosemide.

The mean RPF was 293 ± 124 ml/min/1.73m^2 on placebo, 334 ± 155 ml/min/1.73m^2 after receiving BG9719 and 374 ± 231 ml/min/1.73m^2 after receiving furosemide (Fig. 2). None of the differences were statistically significant.

Sodium excretion. The mean sodium excretion increased from 8 ± 8 mEq in the 2 h following placebo administration to 37 ± 26 mEq in the 2 h following BG9719 administration (Fig. 3, $p < 0.005$). In the six patients in whom it was measured, sodium excretion was 104 ± 78 mEq in the 2 h following furosemide administration, increasing markedly in one patient. This was significant as compared with placebo ($p < 0.05$) but not as compared with BG9719.

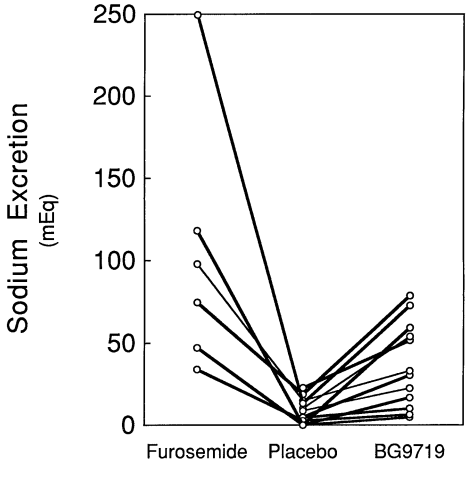

Figure 3. The sodium excretion for each patient for the 2 h following administration of placebo, furosemide and BG9719. Sodium excretion increased with both BG9719 ($p < 0.005$) and furosemide ($p < 0.05$).

Urine volume. Similarly, urine volume increased from 156 ± 107 ml after placebo to 501 ± 293 ml for the 2 h following BG9719 ($p < 0.0005$). Following furosemide administration, urine volume was 1,080 ± 529 ml ($p < 0.0005$ vs. placebo and $p < 0.006$ vs. BG9719).

DISCUSSION

This study demonstrated that the adenosine A_1 antagonist BG9719 causes sodium and water excretion in patients with CHF while maintaining GFR. Doses of furosemide that caused even more diuresis produced clear evidence of decreased renal function in patients with CHF.

Furosemide. The effect of furosemide on GFR has been controversial. One study of seven healthy humans on salt restricted diets demonstrated increased GFR (7), and high dose furosemide increased GFR in a study of rats (8). On the other hand, other animal (9–11) and human (12) studies have demonstrated diuretic induced decreased GFR. The marked findings of this study clearly show that diuresis with furosemide in patients with CHF decreases glomerular filtration.

Many mechanisms of action of furosemide might affect GFR. Intravascular depletion might cause neurohormonal activation, leading to decreased perfusion pressure by afferent arteriolar constriction, efferent arteriolar dilation or effects on renal blood flow. This study does not support RPF as the cause of the marked decrease in renal function caused by furosemide. On the other hand, the effects of furosemide might be secondary to direct renal actions. Indeed, bumetanide, another loop diuretic, appears to induce a biphasic renal response, unrelated to diuresis (13). This suggests that the effects of loop diuretics on prostaglandin E_2 (14), the renin-angiotensin system, adenosine receptors and tubuloglomerular feedback (15) might be important.

BG9719. The importance of adenosine on renal function is just beginning to be explored. Adenosine could be the mechanism of some of the adverse effects of diuretics and some of the decreased renal function seen in patients with heart failure. However, the impact of adenosine administration in people is not clear. While it appears to decrease glomerular filtration, studies report divergent actions. Adenosine decreased renal blood flow by a microvascular vasoconstrictive effect in one study (2), but in nine patients with CHF, adenosine increased renal vascular resistance and decreased both blood flow in and cross section of the renal artery (16). Postglomerular vascular dilation has also been reported (1).

Selective adenosine A_1 antagonists have similarly produced inconsistent renal effects. A_1 antagonists increased urine flow rate but caused no effect on renal blood flow in normal human subjects (17) and dogs (18). However, decreases in renal function caused by radiocontrast media

and cisplatin were attenuated by the adenosine antagonist KW-3902 (19,20).

Some of the varying effects of adenosine and adenosine antagonists might be related to the characteristics of the subjects studied. For example, plasma adenosine levels are increased in patients with CHF (21), and the renal effects in this patient population might be different than in normal subjects or in those with renal dysfunction caused by toxins. The findings of this study suggest that BG9719 can cause increased sodium excretion in patients with heart failure without decreasing GFR. This suggests that adenosine may be an important modulator of renal function in CHF patients.

Study limitations. While furosemide clearly decreased GFR and BG9719 did not, the comparison is limited by the different extent of natriuresis caused by the administered doses of the two agents. Future comparisons should attempt to compare doses that produce equally effective sodium and urine volume excretion.

Urine was not collected by urethral catheters, which could introduce bias because of incomplete collection. Slight differences in sodium excretion and urine volume might result. This study did not have the power to detect small differences in RPF. However, the marked decrease of GFR following furosemide without alteration in RPF to a similar extent suggests that the effect on glomerular filtration is caused by local renal actions rather than by changes in delivery of blood to the kidneys.

This study analyzed patients with CHF. The conclusions should not be extended to other patients, as the renal status of heart failure patients is probably affected both by neurohormonal factors not seen in other subjects and by medications.

Conclusions. Natriuresis is effectively induced by both furosemide and the adenosine A_1 antagonist BG9719 in patients with CHF. The doses of the two drugs used in this study did not cause equivalent sodium and water excretion but only furosemide caused a 25% decrease in GFR. If BG9719 causes a similar maintenance of GFR when used either at higher doses or in combination with other drugs which produce greater diuresis, it would suggest that activation of adenosine A_1 receptors is an important determinant of renal function in diuresed patients with heart failure. Adenosine A_1 receptors have the potential to be clinically useful in the many patients with heart failure who demonstrate decreased renal function with diuresis.

Reprint requests and correspondence: Dr. Stephen S. Gottlieb, Division of Cardiology, University of Maryland School of Medicine, 22 South Greene Street, Baltimore, Maryland 21201. E-mail: sgottlie@medicine.umaryland.edu.

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