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The Effects of KW-3902, an Adenosine A1-Receptor Antagonist, on Diuresis and Renal Function in Patients With Acute Decompensated Heart Failure and Renal Impairment or Diuretic Resistance

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Objectives This study sought to evaluate the dose-dependent effects of adenosine A1-receptor blockade on diuresis and renal function in patients with acute decompensated heart failure (ADHF) and renal impairment or diuretic resistance.

Background Intravenous loop diuretics are the mainstay of therapy for patients with ADHF. Treatment, however, may be complicated by diuretic resistance and/or worsening renal function.

Methods We carried out a pair of randomized, double-blind, placebo-controlled, proof-of-concept studies in 2 clinically challenging ADHF populations.

Results In the ADHF protocol, 146 patients with volume overload and an estimated creatinine clearance (CrCl) of 20 to 80 ml/min were randomized to placebo or 1 of 4 doses of KW-3902 (rolofylline) infused over 2 h daily for up to 3 days. On day 1, KW-3902 monotherapy increased urine output during the first 6 h (445, 531, 631, and 570 ml in the 2.5-, 15-, 30-, and 60-mg groups, respectively) compared with placebo (374 ml; $p = 0.02$). On day 2, serum creatinine decreased in all KW-3902 groups and increased with placebo ($p = 0.04$). By day 4 or day of discharge if earlier, intravenous furosemide administration tended to be lower in the KW-3902 groups compared with placebo ($p = 0.10$). In the diuretic-resistant protocol, 35 patients with an average CrCl of 34 ml/min were randomized to a single infusion of placebo, 10, 30, or 60 mg of KW-3902. Compared with placebo, KW-3902 increased hourly urine volume and estimated CrCl with peak effects occurring at 2 to 3 h and at 24 h, respectively. Adverse events were not different between placebo and KW-3902.

Conclusions In patients with ADHF and volume overload, KW-3902, an adenosine A1-receptor antagonist, enhances the response to loop diuretics and may have a renal protective effect. (J Am Coll Cardiol 2007;50:1551–60)

Heart failure is responsible for a large and still growing proportion of cardiovascular morbidity and mortality. It is the leading cause of hospitalization in patients over the age of 65 years, with a large attendant cost. Most patients with acute decompensated heart failure (ADHF) are admitted with volume overload, and at least one-third have moderate or severe baseline renal impairment (1). Practice guidelines recommend that ADHF patients with evidence of volume overload be treated with escalating doses of diuretics (2), although it is recognized that such therapy can be associated with worsening renal function. An increase in serum creatinine (SCr), whether linked to diuretic use or not, is associated with increased risk of adverse short-term and long-term morbidity and mortality (3). Preservation of renal function, on the other hand, has been associated with improved prognosis (4).

Loop diuretics may adversely affect renal function through tubuloglomerular feedback within the medulla of the nephron. Increased concentrations of $Na+$ and $Cl-$

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Abbreviations and Acronyms

ADHF = acute decompensated heart failure
CrCl = creatinine clearance
GFR = glomerular filtration rate
IV = intravenous
NYHA = New York Heart Association
SBP = systolic blood pressure
SCr = serum creatinine

at the macula densa stimulate local generation of adenosine (5). Adenosine then acts on specific receptors in the nephron, with the predominant A1-mediated effect being constriction of the afferent arteriole resulting in reductions in renal blood flow and glomerular filtration rate (GFR). This, in turn, reduces delivery of filterable ions to the distal nephron (6). In addition, adenosine has direct luminal effects, enhancing sodium reabsorption in the proximal tubule. In the setting of heart failure, as GFR declines, higher doses of diuretics are required to effect natriuresis and diuresis. Normally adaptive paracrine mechanisms at the juxtaglomerular apparatus are further stimulated, leading to additional reductions in renal blood blow and GFR. Thus, adenosine A1-receptor antagonists may be useful in the treatment of ADHF by inhibiting proximal tubular reabsorption and tubuloglomerular feedback.

KW-3902 (rolofylline) is a novel, specific adenosine A1-receptor antagonist shown in animal models to cause diuresis and natriuresis (7), in large part by inhibiting sodium reabsorption at tubular sites. Additional experimental studies show that KW-3902 attenuates renal injury by improving renal blood flow (8). In phase I trials in normal subjects, intravenous (IV) doses of KW-3902 ≥2.5 mg produced a significant natriuretic effect with a half-life of approximately 12 to 14 h and an acceptable safety profile (9). We sought to test the hypothesis that adenosine A1-receptor blockade improves the response to diuretics and preserves renal function in patients with ADHF. Two clinically challenging patient populations were studied in randomized, double-blind, placebo controlled, proof-of-concept protocols: patients with ADHF with accompanying renal impairment (ADHF protocol) and patients who were diuretic refractory or resistant (diuretic-resistant protocol). We report the results of both protocols.

Methods

ADHF protocol. This was a randomized, double-blind, placebo-controlled, parallel-group study conducted at 44 sites in the U.S. The principal objectives were to determine the optimal dose range of IV KW-3902 given initially as monotherapy and subsequently in combination with IV furosemide in improving urine output in heart failure patients with renal impairment who required hospitalization for fluid overload. Secondary objectives were to assess the effects of each dose of KW-3902 on renal function and safety. Eligible patients were at least 18 years of age with New York Heart Association (NYHA) functional class II to IV heart failure and renal impairment defined as an estimated creatinine clearance (CrCl) between 20 and 80 ml/min using the Cockcroft-Gault equation (10). There was no ejection fraction criterion for inclusion. Patients were hospitalized with at least 2 of the following signs or symptoms of fluid overload: jugular venous distension, pitting sacral or pedal edema, dyspnea, or documented weight gain.

Exclusion criteria included acute myocardial infarction within 30 days; clinical evidence of ongoing ischemia causing worsening heart failure; uncorrected primary valvular, restrictive, or hypertrophic cardiomyopathy or pericardial disease; implantation of a cardioverter-defibrillator or cardiac resynchronization device within 7 days; need for mechanical ventilation, dialysis or ultrafiltration; active pulmonary, vascular, renal, hepatic, cerebrovascular or systemic disease; or a recent surgical or diagnostic procedure that would confound heart failure management or interpretation of study results. Pregnant or breastfeeding women were excluded, as were patients with a serum potassium level <3.0 mEq/l or systolic blood pressure (SBP) <85 mm Hg.

The primary efficacy end point was total urine output during the 6 h after the first dose of KW-3902 or placebo. Secondary efficacy end points included change in urine flow rate over the first 6 h, change in SCr level at day 4 (or early termination), proportion of patients with worsening renal function at day 4/early termination, defined as an increase from baseline in SCr ≥0.3 mg/dl, mean cumulative dose of IV furosemide, and number of subjects withdrawn from the study because of treatment failure, defined as requirement for further treatment after all protocol-specified increases in diuretic therapy were administered. Adverse events were monitored during and after the treatment period up to 30 days.

Eligible patients were enrolled within 48 h (days −2 to −1) before the first dose of study drug (Fig. 1A). After written informed consent, patients were randomized to receive placebo or 1 of 4 doses of KW-3902 (2.5, 15, 30, or 60 mg). All patients received 40 mg IV furosemide on the evening of day −1, 12 h before the first dose of study drug. Subjects who were no longer fluid overloaded after the 40 mg dose or for whom this dose was clinically insufficient (and thus required prompt, additional diuretic therapy) were withdrawn from the study before the first dose of study drug. Patients were maintained on a 2-g sodium diet throughout the study period.

On day 1, a single dose of KW-3902 or placebo was administered in a blinded fashion as a 2-h IV infusion at a rate of 1 ml/min. Administration of loop diuretic was prohibited for 6 h after the initiation of study drug. An investigator-defined need for additional diuretic therapy during the course of the infusion was considered a treatment failure and precipitated patient withdrawal. After 6 h, subjects could receive furosemide as clinically indicated by the investigator or treating physician. Use of oral diuretics, except aldosterone antagonists, was prohibited from the −12 h time point through 6 h after study drug infusion.

Metolazone could subsequently be added if the investigator judged it medically necessary. On days 2 and 3, study drug was administered as a 2-h infusion at approximately the same time as on day 1; IV furosemide could be given at any time at the investigator's discretion.

Continuous urine collection, recording of fluid intake, and Holter monitoring were performed beginning with the administration of IV furosemide on day −1. Vital signs, signs and symptoms of heart failure, and laboratory values were determined before each study drug infusion and on day 4 or day of discharge, whichever came first. Patients were withdrawn from the study if they required mechanical ventilation, ultrafiltration, hemodialysis, IV vasodilators, or positive inotropic support; if treatment was successful before day 4, or if they experienced a serious adverse event. Subjects were contacted by telephone at 30 days to assess general status and serious adverse events.

Diuretic-resistant protocol. This was a randomized, double-blind, placebo-controlled, dose-escalation study conducted at 11 sites in the U. S. The principal objectives were to compare 3 doses of KW-3902 and placebo with measures of their effects on urine volume and CrCl, and to assess safety. Eligible patients had NYHA functional class III or IV heart failure and were currently hospitalized and receiving diuretic therapy (and, if necessary in the view of the treating physician, IV inotropic or vasodilator therapy). In the opinion of the investigators, the patients had to have reached the point where a further increase in diuretic therapy was unlikely to be effective or would worsen renal function and where the investigator was considering more aggressive management of fluid overload, including the use of further IV vasoactive medications, mechanical circulatory support, ultrafiltration, or dialysis. Examples of diuretic refractoriness included: the combination of 160 mg IV furosemide plus 5 mg oral metolazone given 1 or more times in a day, or an infusion of furosemide at more than 20 mg/h that does not yield any significant increase in urine output or reduction in edema, weight, or fluid volume status. Other inclusion/exclusion criteria were similar to the ADHF protocol with the exception that there was no requirement for CrCl to fall within a defined range.

The primary efficacy end point was the change in hourly urine output at intervals over a 24-h period after administration of KW-3902 or placebo, with the average hourly urine output from −3 to 0 h serving as a baseline. The principal secondary end point was the change in CrCl from baseline at 3, 6, 9, 12, and 24 h after dosing. Additional efficacy end points included other measures of cumulative and hourly urine output, use of additional IV furosemide after study drug administration, and use of IV vasoactive agents, ultrafiltration, and mechanical ventilation. Change in heart failure signs and symptoms, and adverse events were also recorded.

Hospitalized subjects who met entry criteria and provided written informed consent were randomized 2:1 to receive a single dose of KW-3902 (10, 30, or 60 mg) or placebo administered as a 2-h IV infusion (Fig. 1B). Current diuretic therapy was discontinued at least 5 h before administration of study drug to allow baseline urine volume and CrCl to be measured for the 3-h period before study drug administration. After study drug infusion, IV diuretics were administered at the investigator's discretion. Urine volume was measured hourly between 1 and 12 h and at 24 h after study drug infusion. CrCl was measured at 3-h intervals up to 12 h, and between 12 and 24 h. Fluid intake was measured continuously.

Statistical analysis. Data from all subjects treated with at least 1 dose of study drug were included in the analyses. Safety data were summarized with descriptive statistics and are presented for the combined study populations. Data are presented as mean ± standard deviation (unless otherwise noted). All statistical analyses were performed using SAS version 8.2 or higher (SAS Institute Inc., Cary, North Carolina). A result was considered statistically significant when the associated 2-sided statistical test yielded a p value of 0.05 or less. No p value adjustment was made for multiple comparisons because these were dose-ranging pilot studies.

ADHF PROTOCOL. Sample size (for the primary end point) was calculated using the assumption that the observed difference would be 400 ml with a standard deviation of 500 ml. At 80% power, this yielded 26 patients per treatment group. For the primary efficacy end point, mean cumulative urine volume in the first 6 h aftere initial infusion of study drug, as well as the secondary end points of change in SCr from baseline and mean daily cumulative dose of IV furosemide, data were summarized and treatment groups were compared using a one-way analysis of variance model with factor treatment. Normality (Shapiro-Wilk) and homogeneity of variances (Bartlett) were tested before analysis, and the distributions of these variables were found to be significantly non-normal and/or were not valid for the assumption of homogeneity of variance. Therefore, the rank transformation was performed and data were analyzed using a nonparametric analysis of variance (analysis of covariance). For change in SCr, SCr at baseline was used as the covariate. The proportion of subjects with an increase in SCr ≥0.3 mg/dl from baseline or with a reduction in or discontinuation of diuretics because of worsening renal function during the treatment period were determined by dichotomizing data into binary responses (outcome present or not present) and then performing a pairwise comparison for each time point and overall for each dose to placebo using the Fisher exact test.

DIURETIC-RESISTANT PROTOCOL. This study was exploratory, and not powered for statistical significance. All data were summarized using descriptive statistics.

Results

ADHF protocol. A total of 159 subjects were randomized. Thirteen subjects did not receive study drug (4 randomized to placebo, 3 to 2.5 mg, 1 to 15 mg, 2 to 30 mg, and 3 to 60 mg KW-3902) because they were not volume overloaded

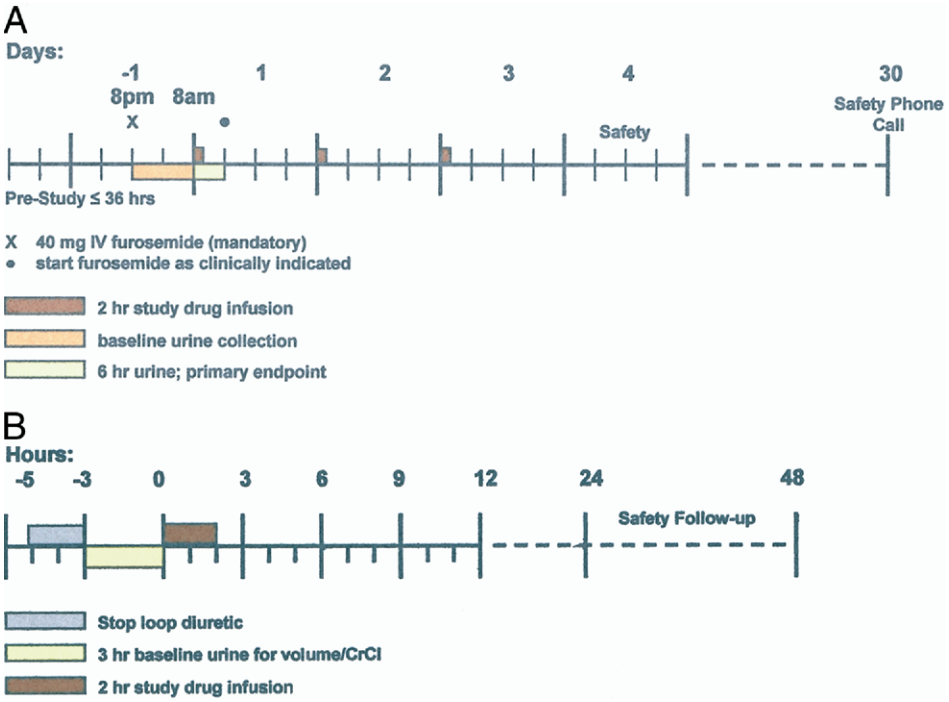

Figure 1 Flow Diagrams Depicting Study Protocols

(A) Acute decompensated heart failure (ADHF) patients with renal impairment.
(B) ADHF patients who were resistant or refractory to diuretics. CrCl = creatinine clearance; IV = intravenous.

or had required rescue therapy, including supplemental furosemide, during the 12-h baseline period. Thus, a total of 146 subjects were treated with at least 1 dose of study drug. Demographic and baseline characteristics were similar across treatment groups (Table 1). The study population was older and predominantly male (69%), and approximately one-half had heart failure of ischemic etiology. Mean ejection fraction ranged from 26% to 37% across study groups. At baseline, patients had at least moderate renal impairment with mean SCr and CrCl of 1.8 mg/dl and 48 ml/min, respectively.

URINE OUTPUT IN FIRST 6 H. In all dose groups, KW-3902 monotherapy resulted in higher cumulative urine output during the first 6 h compared with placebo (Fig. 2). This difference was statistically significant for the 30-mg group (631 ± 506 ml vs. 374 ± 190 ml, p = 0.02). By 24 h, cumulative urine volumes were similar for all treatment groups. Between 1 h and 2 h after initiation of infusion, statistically significant, transient increases in urine flow rate relative to baseline were observed for the 30- and 60-mg KW-3902 groups (from 123 ± 60 ml/h to 139 ± 149 ml/h [p = 0.02] and 124 ± 111 ml/h to 133 ± 149 ml/h [p = 0.03], respectively). From baseline to 6 h, there were no significant differences in the change in SBP or heart rate among the 5 treatment groups (−6.1 ± 14 mm Hg, 2.1 ± 16 mm Hg, −2.6 ± 14 mm Hg, −6.6 ± 14 mm Hg, and −3.8 ± 18 mm Hg and −2.8 ± 7 beats/min, 1.0 ± 8 beats/min, 0.9 ± 12 beats/min, −0.3 ± 9 beats/min, and −0.8 ± 12 beats/min in the placebo and KW-3902 2.5-, 15-, 30-, and 60-mg groups, respectively).

DISCONTINUATION OF TREATMENT. Treatment was discontinued before day 3 in 64 subjects (44%). The primary reason for early discontinuation was adequate diuresis, observed most frequently in the 3 highest KW-3902 dose groups (30% to 39% of subjects) (Table 2). Early discontinuation of treatment because of adequate diuresis was reported for 1 subject (4%) in the placebo group. Few subjects (6% overall) had discontinued treatment because of treatment failure. Other reasons for early discontinuation included adverse events (2 subjects in the placebo group; 1 each in the 2.5- and 60-mg KW-3902 groups), death (1 subject in the 60-mg group), investigator discretion (2 subjects in the placebo group; 1 each in the 2.5-, 15-, and 30-mg KW-3902 groups), and subject request (1 in the 2.5-mg and 3 in the 15-mg KW-3902 groups).

CHANGE IN SERUM CREATININE. On Day 2 of therapy, SCr had decreased in all KW-3902 groups relative to baseline (−0.08, −0.03, −0.06, and −0.03 mg/dl for the 2.5-, 15-, 30-, and 60-mg groups, respectively), whereas placebo subjects had a mean increase in SCr of +0.04 mg/dl (p = 0.04 for 30 mg KW-3902 vs. placebo). With the exception of the 60-mg KW-3902 group, all treatment groups had decreased SCr levels on Day 4 or the day of discharge. Although not significantly different, larger mean decreases

Table 1 ADHF Protocol Baseline Characteristics

		KW-3902			
	Placebo (n = 27)	2.5 mg (n = 29)	15 mg (n = 31)	30 mg (n = 30)	60 mg (n = 29)
Age, yrs	67 ± 14	64 ± 14	69 ± 12	66 ± 15	67 ± 13
Male, %	74	66	65	70	69
Race/ethnicity, n (%)					
Caucasian or Hispanic	19 (70)	24 (83)	22 (71)	22 (73)	23 (79)
Black	7 (26)	5 (17)	9 (29)	8 (27)	5 (17)
Other	1 (4)	0 (0)	0 (0)	0 (0)	1 (3)
NYHA functional class, n (%)					
III	14 (52)	12 (41)	18 (58)	14 (47)	15 (52)
IV	12 (44)	17 (59)	13 (42)	15 (50)	12 (41)
LVEF, % (n)	34 ± 18 (20)	37 ± 17 (17)	28 ± 12 (18)	34 ± 16 (23)	26 ± 15 (22)
Weight, kg	92 ± 19	103 ± 29	87 ± 29	97 ± 24	92 ± 32
HF etiology, n (%)					
Ischemic	15 (56)	11 (38)	18 (58)	15 (50)	15 (54)
Idiopathic	5 (19)	6 (21)	4 (13)	2 (7)	3 (11)
Hypertensive	1 (4)	3 (10)	3 (10)	4 (13)	5 (18)
Medications, n (%)					
ACE inhibitor/ARB	24 (89)	25 (86)	29 (94)	19 (63)	27 (93)
Beta-blocker	21 (78)	26 (90)	26 (84)	23 (77)	25 (86)
Digoxin	15 (56)	12 (41)	10 (32)	10 (33)	16 (55)
Aldosterone inhibitor	0 (0)	0 (0)	0 (0)	2 (7)	0 (0)
HR, beats/min	80 ± 16	77 ± 13	77 ± 14	81 ± 13	76 ± 16
SBP, mm Hg	121 ± 23	124 ± 22	122 ± 19	131 ± 22	121 ± 26
Serum Cr, mg/dl	1.9 ± 0.6	1.6 ± 0.8	1.8 ± 0.7	1.7 ± 0.6	1.8 ± 0.7
CrCl, ml/min	41 ± 22	47 ± 27	42 ± 22	59 ± 55	49 ± 36

ACE = angiotensin-converting enzyme; ADHF = acute decompensated heart failure; ARB = angiotensin receptor blocker; Cr = creatinine; CrCl = creatinine clearance; HF = heart failure; HR = heart rate; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SBP = systolic blood pressure.

in SCr were observed for subjects in the 2.5-, 15-, and 30-mg KW-3902 groups (−0.07, −0.04, and −0.09 mg/dl, respectively) compared with placebo (−0.01 mg/dl). For subjects who received 60 mg KW-3902, SCr was increased relative to baseline (+0.03 mg/dl). By day 4/day of discharge, the percentages of subjects with worsening renal function (defined as an increase in SCr ≥ 0.3 mg/dl) were not significantly different between the treatment groups: 7%, 3%, 7%, and 17% in the 2.5-, 15-, 30-, and 60-mg KW-3902 groups, respectively, compared with 19% in the placebo group.

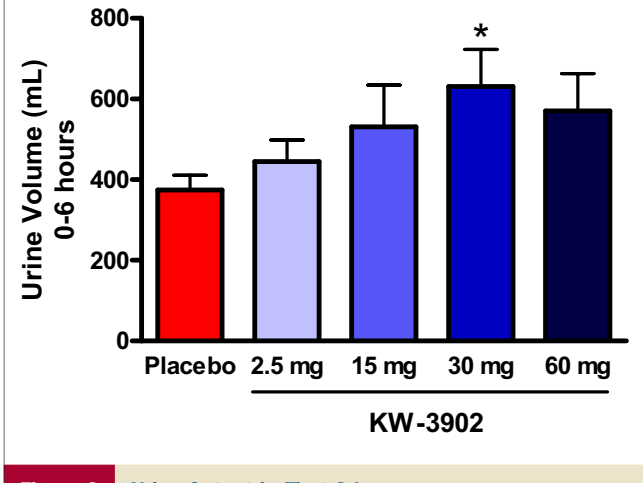

Figure 2 Urine Output in First 6 h

Cumulative urine volume (mean ± SEM) 6 h after initiation of placebo or KW-3902 in acute decompensated heart failure patients with renal impairment (*p = 0.02 vs. placebo).

DIURETIC ADMINISTRATION. Daily furosemide administration tended to be lower for the 3 highest doses of KW-3902 (Fig. 3). The difference between the 30-mg dose of KW-3902 and placebo was statistically significant on day 2 ($p < 0.05$). Cumulative IV furosemide administration through Day 4/day of discharge was lower in all KW-3902 dose groups (353 ± 67 mg, 256 ± 39 mg, 223 ± 26 mg, and 215 ± 30 mg for 2.5-, 15-, 30-, and 60-mg groups, respectively) compared with placebo (393 ± 73 mg) ($p < 0.0997$ by Kruskal-Wallis test). Daily urine volume for the first 3 days and total urine volume and body weight at day 4/day of discharge were not significantly different among the 5 treatment groups (data not shown).

Diuretic-resistant protocol. A total of 35 subjects were randomized, and all were treated with study drug (Table 3). One subject in the placebo group discontinued treatment because of transient hypotension after study drug infusion. There were differences among treatment groups in demographic and baseline characteristics, presumably because of small subject numbers. The baseline SCr level ranged from

Table 2 ADHF Protocol Patient Disposition

	Placebo (n = 27)	KW-3902 2.5 mg (n = 29)	KW-3902 15 mg (n = 31)	KW-3902 30 mg (n = 30)	KW-3902 60 mg (n = 29)
Disposition, n (%)					
Completed treatment	20 (74)	21 (72)	13 (42)	15 (50)	13 (45)
Prematurely discontinued	7 (26)	8 (28)	18 (58)	15 (50)	16 (55)
Reason for premature discontinuation, n (%)					
Adequate diuresis	1 (4)	4 (14)	12 (39)	9 (30)	11 (38)
Treatment failure	1 (4)	0 (0)	2 (7)	3 (10)	2 (7)
Adverse event	2 (7)	1 (3)	0 (0)	0 (0)	1 (3)
Death	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)
Other	3 (11)	3 (10)	4 (13)	3 (10)	1 (3)

ADHF = acute decompensated heart failure.

1.9 ± 0.4 mg/dl in the 60-mg KW-3902 group to 2.6 ± 0.7 mg/dl in the 15-mg KW-3902 group, and the calculated CrCl ranged from 30 ± 15 ml/min in the 30-mg group to 41 ± 22 ml/min in the placebo group. For the entire population, concomitant medications included renin-angiotensin system inhibitors in 37%, beta-blockers in 60%, and digoxin in 34%. Use of parenteral vasoactive agents was common, including milrinone (23%), nesiritide (23%), dobutamine (17%), and dopamine (11%).

CHANGE IN URINE OUTPUT. Overall, subjects treated with placebo had decreased hourly urine output relative to baseline through 24 h (Fig. 4). By contrast, increased urine output was observed for all KW-3902 dose groups within the first 6 h after study drug administration, with the peak effect occurring at 2 h to 3 h in the 30-mg dose group. This early effect on urine output was associated with increased sodium excretion (Table 4). By 5 h to 6 h, there was no difference among KW-3902 groups, and thereafter, there was no consistent pattern of increases or decreases from baseline in any KW-3902 group. The absolute change in urine flow rate at 6 h compared with baseline was positive in all KW-3902 groups, ranging from +22 ml/h to +24 ml/h, whereas subjects treated with placebo had a decrease in urine flow rate of 29 ml/h (Fig. 5). Administration of loop diuretics within the first 4 h after start of study drug was similar between treatment groups (7 of 12, 7 of 8, 4 of 8, and 5 of 7 for placebo, 10-, 30-, and 60-mg KW-3902, respectively).

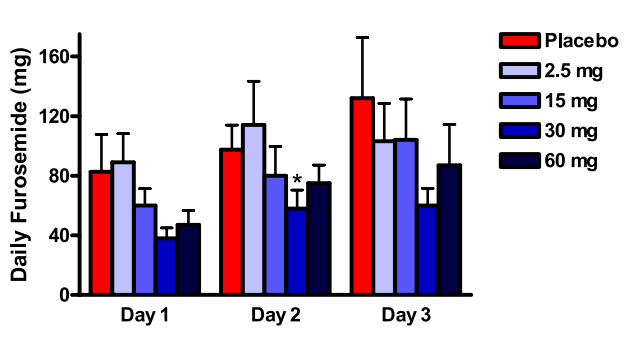

Figure 3 Daily Administration of IV Diuretics

Daily dose of intravenous (IV) furosemide (mean ± SEM) administered to the placebo and 4 KW-3902 groups over the first 3 days of the study (*$p < 0.05$ vs. placebo).

CHANGE IN CRCL. We assessed the absolute change from baseline in CrCl during 3-h time intervals. For each 3-h interval, mean CrCl in the KW-3902 30-mg group increased compared with baseline (Fig. 6). Conversely, the mean CrCl for placebo decreased compared with baseline at all time intervals. Notably, CrCl at 24 h was substantially increased compared with baseline for both 10- and 30-mg KW-3902 groups (+25 and +65 ml/min, respectively; $p < 0.05$ for 30 mg vs. baseline).

Safety. ADHF PROTOCOL. Adverse events occurred in 85% of placebo-treated patients and from 73% to 87% of KW-3902–treated patients. Serious adverse events through 30 days were reported for 54 subjects (37%) (Table 5). Cardiac disorders were the most commonly reported, and although more frequent among subjects treated with KW-3902, the incidence was not dose-related or significantly different compared with placebo. The most common cardiac event was acute exacerbation of heart failure. In 14 of 24 cases (58%), this occurred 2 to 4 weeks after study drug discontinuation. Acute respiratory distress and a simple partial seizure were reported for a single subject in the 60-mg KW-3902 group. Among patients with serious adverse events leading to premature discontinuation of study drug, 2 occurred in placebo patients, 2 each in the 2.5- and 60-mg KW-3902 groups, 3 in the 15-mg KW-3902 group, and 0 in the 30-mg KW-3902 group.

There were a total of 10 deaths reported during the study period from initiation of study drug to 30 days. An additional 2 patients died after completing the 30-day follow-up. Of these 12 deaths, 1 occurred in the placebo group and 11 were distributed among the 4 KW-3902 groups. All but 1 event in the KW-3902 group occurred at least 13 days after the last dose of study drug. In the single

Table 3 Diuretic-Resistant Protocol Baseline Characteristics

		KW-3902		
	Placebo (n = 12)	10 mg (n = 8)	30 mg (n = 8)	60 mg (n = 7)
Age, yrs	68 ± 16	66 ± 14	63 ± 12	72 ± 10
Male, %	67	63	25	71
Race/ethnicity, n (%)				
Caucasian or Hispanic	10 (83)	4 (50)	5 (63)	7 (100)
Black	2 (17)	4 (50)	3 (38)	0 (0)
NYHA functional class, n (%)				
III	7 (58)	2 (25)	5 (63)	2 (29)
IV	5 (42)	6 (75)	3 (38)	5 (71)
Weight, kg	105 ± 31	109 ± 29	91 ± 17	95 ± 21
HF etiology, n (%)				
Ischemic	9 (75)	4 (50)	2 (25)	6 (86)
Idiopathic	2 (17)	2 (25)	4 (50)	1 (14)
IV medications, n (%)				
Vasodilators	1 (8)	4 (50)	1 (13)	2 (29)
Positive inotropes	4 (33)	5 (63)	5 (63)	4 (57)
HR, beats/min	75 ± 12	77 ± 12	81 ± 14	76 ± 10
SBP, mm Hg	114 ± 23	107 ± 17	113 ± 27	109 ± 18
Serum Cr, mg/dl	2.4 ± 1.0	2.6 ± 0.7	2.2 ± 0.7	1.9 ± 0.4
CrCl, ml/min	41 ± 22	31 ± 12	30 ± 15	35 ± 15

IV = intravenous; other abbreviations as in Table 1.

case in which a patient died while on treatment, the cause of death was superior mesenteric artery occlusion related to underlying vascular disease.

DIURETIC-RESISTANT PROTOCOL. There were no differences among groups in adverse events. There were no clinically significant differences in mean laboratory values or frequency of outliers for laboratory or Holter data. Serious adverse events were reported for 5 subjects (9%): 2 in the placebo group, and 1 and 2 in the 30- and 60-mg KW-3902 groups, respectively.

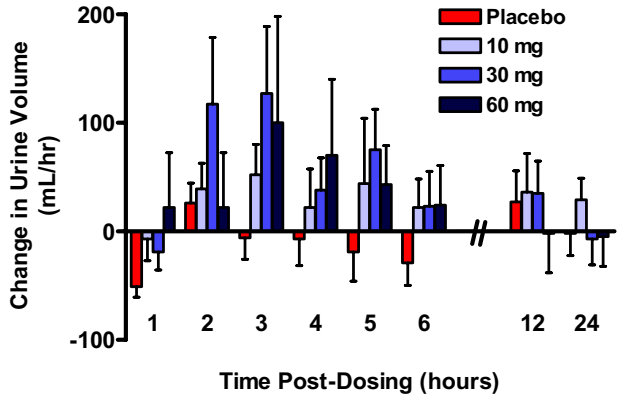

Figure 4 Change in Urine Output over 24 h

Change in hourly urine volume (mean ± SEM) through 24 h after dosing with placebo or KW-3902 in acute decompensated heart failure patients refractory/resistant to diuretics.

Discussion

In these proof-of-concept studies, we sought to determine the effects of adenosine A1-receptor blockade on diuresis and renal function in patients with ADHF and renal impairment or diuretic resistance. In the ADHF protocol, KW-3902 at all 4 doses was associated with increases in urine output during the 6-h period after the first dose. KW-3902 also seemed to have a similar effect on urine output over at least 6 h in a sicker group of patients enrolled in the diuretic-resistant protocol. Importantly, enhanced diuresis with KW-3902 was associated with the use of lower doses of loop diuretics. In the larger ADHF protocol, which allowed for up to 3 days of study drug dosing, early discontinuation of IV loop diuretics as a result of investigator-classified successful diuresis occurred in a substantially greater proportion of KW-3902–treated patients (30%) than placebo-treated patients (4%).

Plasma adenosine levels are elevated in patients with heart failure (11), and adenosine A1 receptors in the kidney mediate vasoconstriction of afferent arterioles, reabsorption of sodium and water in proximal tubules, and tubuloglomerular feedback in the juxtaglomerular apparatus (6).

Table 4 Urinary Sodium Concentrations (mEq/l) in the Diuretic-Resistant Protocol

		KW-3902		
	Placebo	10 mg	30 mg	60 mg
Baseline	67 ± 32	63 ± 37	62 ± 49	42 ± 37
Hour 3	72 ± 28	64 ± 41	80 ± 33	49 ± 25
Change, baseline to hour 3	6 ± 13	10 ± 16	18 ± 22	4 ± 31

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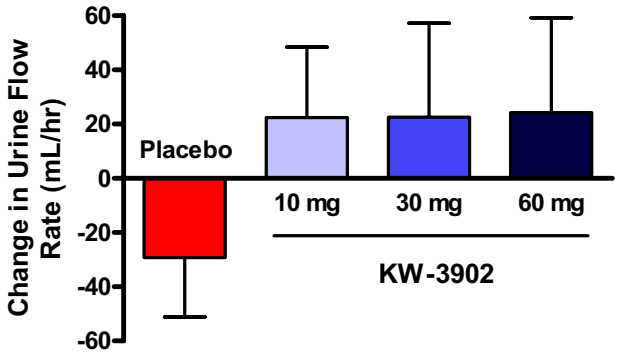

Figure 5 Change in Urine Flow Rate at 6 h

Change in urine flow rate (mean ± SEM) between 5 h and 6 h after administration of placebo or KW-3902 compared with baseline.

Accordingly, inhibition of these receptors would be expected to increase renal blood flow and enhance diuresis. The effects of KW-3902 on renal function are consistent with those obtained with another adenosine A1-receptor antagonist in both experimental (12) and human (13) heart failure. In a pacing-induced model of heart failure, BG9719 increased urine flow and sodium excretion 6- to 10-fold, while exerting a beneficial effect on CrCl (12). Gottlieb et al. (13) studied patients with chronic heart failure and found that although furosemide and the adenosine A1-receptor antagonist each produced diuresis when given alone, furosemide monotherapy was associated with a decline in CrCl. The 2 lower doses of adenosine A1-receptor antagonist as monotherapy improved CrCl, and when given concomitantly with furosemide, enhanced diuresis and blunted the decline in CrCl observed with the loop diuretic alone.

In the ADHF protocol, although furosemide requirements were lower in the 60-mg KW-3902 group at day 4/day of discharge, the percentage of patients in this group with worsening renal function approximated that seen in the placebo group. Similarly, in the diuretic-resistant protocol, although CrCl improved in both the 10- and 30-mg KW-3902 groups, it seemed to deteriorate in the 60-mg group. Taken together, these findings suggest that a dose of 15 mg or 30 mg is appropriate for further investigation in a phase III study. Furthermore, the suggestion of a descending limb of the KW-3902 dose response with regard to renal function is compatible with effects observed with the highest dose of BG9719 (13). This phenomenon might reflect the multiple actions of adenosine in the kidney, acting through at least 4 classes of receptor (A1, A2a, A2b, and A3) (6). It cannot be excluded that KW-3092 at higher doses acts at other receptors (with a resulting countervailing effect on renal function) or that greater degrees of specific A1-receptor antagonism are responsible for a worsening of renal function. In addition, adenosine receptors are ubiquitous and adenosine has effects on multiple organs. Based on the data available from these studies, it is impossible to exclude an extrarenal mechanism for some of these findings, although preclinical studies of adenosine A1-receptor antagonists have not indicated such a mechanism (12). In both the ADHF and diuretic-resistant protocols, KW-3902 had no effect on heart rate or blood pressure; lack of systemic effects also was observed with BG9719 in patients with chronic heart failure (13).

Clinical implications. Renal function is a strong, independent predictor of short-term and long-term prognosis in patients with heart failure, and acute worsening of renal function predicts poor outcomes, regardless of baseline renal function. Approximately 70% of hospitalized patients with heart failure experience an increase in serum creatinine of at least 0.1 mg/dl and up to 45% experience an increase of ≥0.3 mg/dl (14,15). Regardless of the definition used, worsening renal function has been associated with longer lengths of stay, more complications, higher in-hospital mortality, and higher post-discharge rates of death and readmission (3,16). Higher diuretic doses have been associated with more frequent and greater increases in serum creatinine, and such changes often lead physicians to reduce or withhold diuretic and other vasoactive therapy (e.g., renin-angiotensin system inhibitors), which may contribute to worsening heart failure and prolongation of hospitalization. Therefore, an agent that facilitates diuresis with lower doses of loop diuretics or prevents worsening renal function during the management of volume overload could be very useful in the treatment of patients with ADHF. Given the association between higher oral diuretic doses and adverse outcomes in advanced heart failure (17), the role of chronic adenosine receptor blockade in the ambulatory setting also deserves study.

Safety. These protocols represent the largest experience to date of adenosine A1-receptor blockade in patients with

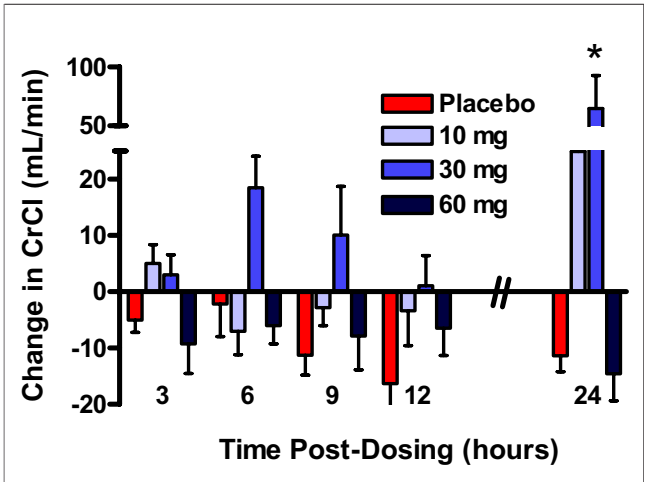

Figure 6 Change in CrCl over 24 h

Change in measured creatinine clearance (CrCl) (mean ± SEM) relative to baseline in acute decompensated heart failure patients refractory/resistant to diuretics (*$p < 0.05$ vs. baseline).

Table 5 ADHF Protocol Serious Adverse Events

		KW-3902			
	Placebo (n = 27)	2.5 mg (n = 29)	15 mg (n = 31)	30 mg (n = 30)	60 mg (n = 29)
Subjects with ≥1 serious adverse event	8 (30)	8 (28)	15 (48)	8 (27)	15 (52)
Cardiac	4 (15)	5 (17)	9 (29)	6 (20)	7 (24)
Renal	3 (11)	1 (3)	2 (6)	0 (0)	4 (14)
Metabolic	1 (4)	0 (0)	3 (10)	0 (0)	0 (0)
Respiratory	0 (0)	0 (0)	2 (7)	0 (0)	3 (10)
Vascular	0 (0)	1 (3)	1 (3)	2 (7)	0 (0)
Gastrointestinal	2 (7)	2 (7)	3 (10)	0 (0)	1 (3)
Other*	2 (7)	0 (0)	1 (3)	1 (3)	3 (10)

Values are expressed as n (%). *Includes 1 simple partial seizure in the 60-mg KW-3902 group.
ADHF = acute decompensated heart failure.

heart failure and the first in vivo study in ADHF. Adverse events were reported in up to 40% of patients, reflecting the severity of illness in the study population, but no differences were observed between KW-3902–treated and placebo-treated patients. In preclinical studies, adenosine A1-receptor blockers have not been associated with adverse cardiovascular or renal effects, and in the prior clinical study by Gottlieb et al. (13), a single dose of BG9719 was well tolerated. However, adenosine receptors in the heart mediate a number of important physiologic effects, including coronary vasodilation, atrioventricular nodal conduction, and anti-inflammatory effects, and inhibition of these receptors carries theoretical risks (18,19). We observed no change in heart rate, heart rhythm, or blood pressure in these protocols, and there was no evidence of excess coronary ischemic events.

Adenosine, acting at A1 receptors in the brain, is also an inhibitory neuromodulator. Because levels of endogenous adenosine are elevated in the brain after seizure, it is considered an endogenous anticonvulsant (20). Although adenosine A1-receptor blockade does not induce seizures in preclinical studies, modulation of A1-receptor activity has been shown to affect seizure activity in animal models of epilepsy, with activation raising the seizure threshold and blockade lowering it (21). In the ADHF protocol, 1 patient who received 60 mg KW-3902 experienced a simple partial seizure. Immediately before the seizure, this patient experienced wide swings in serum glucose concentrations from 34 to 454 mg/dl, and on the preceding day had been started on pseudoephedrine, a known proconvulsant. These observations suggest that KW-3902 might lower the seizure threshold. This could prove clinically significant in patients at risk of seizure, and needs to be considered in the design and choice of dose in future studies with KW-3902 and other agents that share the same mechanism of action.

Study limitations. Phase II protocols are, by design, preliminary in nature. Two primary goals of our study were to show proof of concept with regard to the potential benefits of adenosine A1-receptor blockade and to evaluate a range of doses of KW-3902 from which to further assess clinically relevant dose-response relationships and safety. They were successful in providing important information concerning these objectives in 2 important groups of ADHF patients—those with coexisting renal dysfunction and those that fail to respond adequately to usual approaches to diuresis. However, it is important to recognize the limitations of these data. Although it seems that adenosine A1-receptor blockade is associated with enhanced diuresis, preservation of renal function, and a perhaps lesser need for loop diuretics, these data were acquired in relatively small numbers of patients at limited sites. Furthermore, dosing of concomitant medications, including parenteral diuretics and vasoactive agents, was at the discretion of the treating physician. Importantly, we did not test the diuretic effects of KW-3902 against furosemide. In the case of the diuretic-resistant protocol, because of widely divergent treatment practices and frequent changes, diuretic type and dosing before the study drug were not collected. Lastly, we cannot comment on the differential effects of KW-3902 in heart failure with preserved versus reduced systolic function. These results do provide evidence for greater effects with infusions of KW-3902 ranging from 2.5 to 30 mg and suggest that doses higher than 30 mg do not offer incremental benefit, but they are insufficient in themselves to define an optimal dose, infusion duration, or frequency. Lastly, much greater patient exposure will be required to evaluate the safety of this agent.

Conclusions

These results indicate that adenosine A1-receptor blockade has a potential role as an adjunct to loop diuretics to enhance diuresis in the treatment of ADHF, both reducing the amount of loop diuretic necessary to treat such patients and preventing deterioration of renal function during treatment. Further trials will be required to determine the optimal approach to administering KW-3902 and establish its efficacy and safety in patients with ADHF and accompanying renal dysfunction. Two large-scale trials in this population (PROTECT [A Study of the Selective A1 Adenosine Receptor Antagonist KW-3902 to Assess

Treatment Effect on Heart Failure and Renal Function]-1 and -2) already have commenced, and an additional study will target hospitalized patients with more severe or worsening renal dysfunction.

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