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ORIGINAL PAPER

Attenuation of the side effect profile of regadenoson: a randomized double-blind placebo-controlled study with aminophylline in patients undergoing myocardial perfusion imaging and have severe chronic kidney disease—the ASSUAGE-CKD trial

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Abstract A subgroup analysis of the ASSUAGE trial suggested that the standardized intravenous aminophylline administration following regadenoson-stress leads to substantial attenuation of regadenoson adverse-effects in patients with severe chronic kidney disease (CKD). In a randomized, double-blinded, placebo-controlled clinical trial of patients with stage 4 and 5 CKD, we compared the frequency and severity of regadenoson adverse-effects in those who received 75 mg of intravenous aminophylline versus a matching placebo administered 90 s post-radioisotope injection. Consecutive 300 patients with severe CKD (36 % women; 86 % end-stage renal disease; age 55 (±13) years) were randomized to receive aminophylline ($n = 150$) or placebo ($n = 150$). In the aminophylline arm, there was 65 % reduction in the incidence of the primary endpoint of diarrhea (9 (6.0 %) vs. 26 (17.3 %), $P = 0.002$), 51 % reduction in the secondary endpoint of any regadenoson adverse-effect (47 (31.3 %) vs. 96 (64 %), $P < 0.001$) and 70 % reduction in headache (16 (10.7 %) vs. 54 (36 %), $P < 0.001$). The stress protocol was better tolerated in the aminophylline group ($P = 0.008$). The quantitative summed difference score, as a measure of stress-induced ischemic burden, was similar between the study groups ($P = 0.51$). In conclusion, the routine standardized administration of intravenous aminophylline in patients with severe CKD substantially reduces the frequency and severity of the adverse-effects associated with regadenoson-stress without changing the ischemic burden. [NCT01336140]

Keywords ASSUAGE-CKD · Aminophylline · Regadenoson · Diarrhea · Chronic kidney disease (CKD)

Introduction

Regadenoson is a selective A_{2A} adenosine receptor agonist; used as a vasodilator pharmacological stress agent with SPECT myocardial perfusion imaging (MPI) [1, 2]. The main elimination mechanism of regadenoson is renal, with approximately 58 % of the drug excreted unchanged in the urine [3]. Pharmacokinetic analyses showed delayed clearance of the drug in subjects with impaired renal function [4]. Despite that, it seems that regadenoson can be safely administered in patients with severe chronic kidney disease (CKD), including those with end-stage renal disease (ESRD) [5–7].

The ADVANCE-MPI clinical trials demonstrated, among patients with preserved renal function, that regadenoson is associated with fewer side effects of flushing and chest pain than adenosine but more frequent symptoms of headache and gastrointestinal (GI) discomfort [8, 9]. Diarrhea and stool incontinence were recognized as additional adverse effects of regadenoson in post-marketing experience and were consequently added to the package insert [10]. In an effort to improve the tolerability of regadenoson, our group conducted the ASSUAGE trial (attenuation of the side effect

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profile of regadenoson: a randomized double-blind placebo-controlled study with aminophylline in patients undergoing myocardial perfusion imaging), which demonstrated that the standardized administration of 75 mg of IV-aminophylline following regadenoson reduced the primary endpoint of diarrhea and abdominal discomfort, which was primarily derived from a lower incidence of diarrhea [11]. The study also demonstrated that aminophylline use reduced the incidence of headache as well as the composite endpoint of any regadenoson adverse-effect. In a prespecified subgroup analysis, patients with severe CKD (stage 4 and 5) seemed to receive a greater reduction in the incidence of diarrhea with aminophylline use [11]. However, the number of patients with severe CKD in the study was too small to draw a definitive conclusion.

In this investigation, we sought to investigate whether the standardized administration of IV-aminophylline as part of regadenoson-stress can reduce the frequency and severity of regadenoson-related adverse-effects among patients with CKD—stage 4 and 5. We also sought to prospectively evaluate the safety and tolerability of regadenoson-stress in patients with ESRD.

Methods

Patient population

All consecutive adult patients with severe CKD defined as stage 4 or 5 (GFR < 30 ml/min/1.73 m^2 or ESRD) referred to undergo a clinically-indicated regadenoson-stress MPI at the stress testing laboratories of Rush University Medical Center and John H. Stroger, Jr. Hospital of Cook County (Chicago, IL, USA) were candidates for the study. Exclusion criteria included: GFR ≥ 30, inability to provide an informed consent, known allergic reaction to aminophylline, pre-existing headache or GI symptoms, systolic blood pressure (SBP) < 90 mmHg, unstable cardiac arrhythmias, pulmonary edema, acute coronary symptoms, active dipyridamole, aminophylline or theophylline use, pregnancy and any contraindication to aminophylline according to the package insert: uncontrolled seizure disorder, sepsis with multi-organ failure and liver impairment [12]. The GFR was calculated using the Cockcroft-Gault formula [13]. Subjects were then classified into Stage 4 CKD defined as GFR 15–29 but not on dialysis; and stage 5 CKD (ESRD) defined as GFR < 15 or dialysis therapy [14]. Compliance with 8-hour fasting and 24-hour abstinence from caffeinated foods or beverages was verbally verified. A written HIPAA authorization and informed consent were obtained from all participants.

Design

A randomized double-blinded, placebo-controlled clinical trial design was implemented. At enrollment, the patients were randomized in a 1:1 ratio into an intervention (aminophylline) or control (placebo) arm using randomly-sequenced opaque, sealed envelopes. Patients, supervising physicians, technologists, and outcome assessors remained strictly blinded to the study-arm assignment. Open-label IV-aminophylline was permitted (up-to 250 mg) to treat suspected regadenoson adverse-effects, which was not considered a cross-over and the affected subjects were analyzed in their original study arm based on the intention-to-treat principle.

Experimental protocol

A 1-day, Tc-99m tetrofosmin protocol was implemented [15–18]. Following the resting MPI acquisition and under continuous ECG monitoring, 0.4 mg of regadenoson was administered intravenously in 10 s, followed by 5 ml of normal saline flush. Thirty-seconds following the completion of the regadenoson injection, the stress dose of Tc-99m tetrofosmin was injected and followed by a normal saline flush. Ninety-seconds post-radioisotope injection (approximately 2 min following regadenoson), 75 mg of IV-aminophylline or a matching placebo (normal saline) was administered intravenously over 30 s and followed by 5 cc normal saline flush. During the protocol, patients were in sitting position and leg lifting exercise was encouraged with all subjects except for those with left bundle branch block or ventricular pacemaker. The blood pressure and heart rate were recorded at baseline then at 30 s and 3 min post-regadenoson injection. Following the stress protocol, subjects underwent stress MPI acquisition as per usual protocol.

Subsequently, subjects underwent two identical questionnaires: *the first* was conducted right before the patient's dismissal from the laboratory after completing the stress MPI acquisition and it inquired about the patient's experience in the period between the stress test termination and questionnaire execution. *The second* questionnaire was conducted by telephone the next day and it inquired about the patient's experience in the subsequent 24 h. Each questionnaire surveyed for regadenoson adverse-effects of flushing or feeling hot, chest pain or discomfort, angina, headache, dizziness, nausea, abdominal discomfort and diarrhea. Each symptom was graded on a scale from 0 to 3 (0: absent, 1: mild, 2: moderate, 3: severe). The Bristol stool scale was used to quantify stool consistency (0: none; 1: hard formed stool through 7: completely liquid) [19].

Endpoints

All end-points relate to events occurring prior to patient's dismissal from the laboratory. The primary endpoint was diarrhea, defined as patient-reported loose bowel movement occurring while the patient is in the laboratory. The Bristol scale and number of bowel movements were used as additional more objective tools to assess stool consistency and diarrhea severity. The secondary endpoints were: (1) the composite endpoint of any regadenoson adverse-effect; (2) the Global Symptom Score which is calculated from the sum of the individual regadenoson-related adverse-effects weighted by severity (0: absent, 1: mild, 2: moderate, 3: severe); (3) the composite GI adverse-effects of diarrhea, abdominal discomfort, nausea or vomiting; (4) patient tolerability score (1: very comfortable, 2: somewhat comfortable, 3: somewhat uncomfortable, 4: very uncomfortable); and 5) patient willingness to take the test again score (1: definitely, 2: probably, 3: probably not; 4: definitely not). The safety endpoint was a composite of serious aminophylline related adverse events of seizure, tachyarrhythmia and systemic hypotension (SBP $\leq$80 or $<$ 90 mmHg with symptoms).

Imaging analysis

The 4DM-SPECT software (INVIA; Ann Arbor, MI) was used for image processing and analysis. MPI scans were processed and analyzed by technologists who were blinded to the patients' study-assignment. A *quantitative* interpretation of MPI was performed using the 17-segment model [20]. The segmental radiotracer activity was scored according to the standard 5-point scale (0: normal; 1: equivocal; 2: moderate; 3: severe; 4: absence). The quantitative summed stress (SSS), summed rest scores (SRS), summed difference score (SDS) and gated-SPECT left ventricular ejection fraction were tabulated.

Statistical analysis

We calculated that a minimum of 248 subjects are needed to attain 80 % power to detect 70 % reduction in the incidence of the primary endpoint (diarrhea), assuming an event rate of 15 % in the control group (2-tailed $\alpha = 0.05$). We targeted enrolling 300 patients to allow some room for error in our assumptions which were based on the findings of the ASSUAGE trial [11].

The Chi square (χ^2) test was used to compare dichotomous variables. The Breslow-Day test was used to evaluate for homogeneity of odds-ratio of regadenoson adverse-effects between subgroup strata. The independent sample Student's T test was used to compare normally distributed continuous variables. The Mann-Whitney-Wilcoxon test was used to compare nonparametric variables. The Mantel–Haenszel extension of the χ^2 test for trend was used to compare graded responses. The analysis of covariance (ANCOVA) method was used to study the impact of baseline characteristics covariates on the SDS. All P values were 2-tailed and were considered statistically significant if $P < 0.05$. The SPSS 18.0 software (SPSS, Inc, Chicago, IL, USA) was used for data analysis.

A blinded safety data monitoring procedure and predetermined triggers for study termination were in place. The study was approved by the institutional review boards of the participating institutions. An investigational new drug application (IND 110129) for aminophylline use to attenuate regadenoson adverse-affects was obtained. The study was registered on clincialtrials.gov (NCT01336140).

Results

A consecutive 427 subjects with history of severe CKD referred for a clinically-indicated regadenoson-stress MPI were recruited in the period from June 14, 2011 to May 14, 2012. Out of those, 122 subjects were excluded: 50 refused; 10 were unable to provide an informed consent; 6 had GFR $>$ 30; 20 had pre-existing acute GI illness; 9 had pre-existing headache; 1 was previously enrolled in the same trial; 26 subjects had a contraindication to IV aminophylline. Five consenting subjects were excluded: 3 had their regadenoson-stress cancelled for a clinical reason; 2 had a treatment assignment that could not be verified due to a labeling error. The remaining 300 patients were randomized: 150 received aminophylline and 150 received placebo. The baseline characteristics of the study population were well matched between the two arms, except for higher prevalence of history of myocardial infarction (MI) and diabetes and lower-trending left ventricular ejection fraction in the placebo arm (Table 1). Notably, 74 % of the study subjects were undergoing kidney transplant evaluation.

Unless otherwise specified, all the reported adverse-effects relate to those occurring before the patient's dismissal from the laboratory. The primary endpoint of diarrhea was significantly less frequent in the aminophylline group; occurring in 9 (6.0 %) vs. 26 (17.3 %) subjects ($P = 0.002$) (Fig. 1). There were no events of stool incontinence reported in either study group. However, the incidence of severe diarrhea, defined as Bristol stool scale of $\geq$ 6 (7 is maximum score) was also reduced with aminophylline (6 (4 %) vs. 17 (11.3 %), $P = 0.02$). Concordantly, patients in the aminophylline arm reported milder diarrhea ($P = 0.02$), more formed stool on the Bristol scale ($P = 0.03$) and fewer bowel movements ($P < 0.001$). Furthermore, the incidence of abdominal discomfort was

Table 1 Baseline characteristics

	Entire study ($n = 300$)	Placebo ($n = 150$)	Aminophylline ($n = 150$)	χ^2 or T test P value
Age (years)	55 (±13)	56 (±13)	54 (±13)	0.12
Women	107 (36 %)	54 (36 %)	53 (35 %)	0.90
End-stage renal disease	259 (86 %)	128 (85 %)	131 (87 %)	0.61
Dialysis therapy	247 (82 %)	126 (84 %)	121 (81 %)	0.45
Hemodialysis	229 (76 %)	116 (77 %)	113 (75 %)	0.68
Peritoneal dialysis	18 (6 %)	10 (7 %)	8 (5 %)	0.63
Post kidney transplant	43 (13 %)	20 (13 %)	23 (15 %)	0.62
GFR[b] (ml/min/1.73 m^2)	21 (± 4)	20 (± 4)	21 (± 4)	0.61
Kidney transplant evaluation	223 (74 %)	110 (73 %)	113 (75 %)	0.69
Race				0.55
African American	157 (52 %)	80 (53 %)	77 (51 %)	
Caucasian	43 (14 %)	24 (16 %)	19 (13 %)	
Hispanic	91 (30 %)	43 (29 %)	48 (32 %)	
Other	9 (3 %)	3 (2 %)	6 (4 %)	
Out-patient testing	263 (88 %)	129 (86 %)	134 (88 %)	0.61
Primary indication for stress MPI				0.41
Chest pain	62 (21 %)	35 (23 %)	27 (18 %)	
Dyspnea	13 (4 %)	4 (3 %)	9 (6 %)	
Evaluation of known CAD	11 (4 %)	7 (5 %)	4 (3 %)	
Pre-operative assessment	203 (68 %)	99 (66 %)	104 (69 %)	
Hypertension	285 (95 %)	141 (94 %)	144 (96 %)	0.56
Diabetes mellitus	166 (55 %)	92 (61 %)	74 (49 %)	0.04
Hypercholesterolemia	155 (63 %)	72 (58 %)	83 (67 %)	0.15
Tobacco use	48 (16 %)	20 (13 %)	28 (19 %)	0.21
Body mass index (kg/m^2)	30 (±7)	30 (±7)	29 (±7)	0.44
Known CAD	81 (27 %)	43 (29 %)	38 (25 %)	0.52
Prior myocardial infarction	43 (14 %)	28 (19 %)	15 (10 %)	0.03
Coronary revascularization	58 (19 %)	29 (19 %)	29 (19 %)	1.0
Congestive heart failure	50 (17 %)	27 (18 %)	23 (15 %)	0.54
Asthma or COPD	38 (13 %)	22 (15 %)	16 (11 %)	0.30
Post-stress ejection fraction[a] (%)	62 (±13)	60 (±14)	64 (±12)	0.05

GFR glomerular filtration rate, *MPI* myocardial perfusion imaging, *CAD* coronary artery disease, *COPD* chronic obstructive pulmonary disease

[a] By gated-SPECT

[b] GFR values are relevant only to patients not on dialysis ($n = 53$)

significantly lower (7 (4.7 %) vs. 22 (14.7 %), $P = 0.003$) and reports of nausea trended to be fewer in the aminophylline arm (15 (10 %) vs. 26 (17.3 %), $P = 0.06$). Consequently, the incidence of the composite of any GI adverse effect was effectively reduced in the aminophylline arm (24 (16 %) vs. 59 (39.3 %), $P < 0.001$).

The secondary endpoint of any regadenoson adverse effect occurred less frequently in the aminophylline than the placebo group (47 (31.3 %) vs. 96 (64.0 %), respectively; $P < 0.001$). The global symptom score (the sum of severity-weighted adverse-effects) was significantly lower in the aminophylline arm (mean score 1.7 ± 0.8 vs. 2.1 ± 1.6; Mann-Whitney-Wilcoxon $P < 0.001$). The incidence of headache in the aminophylline arm was significantly lower (16 (10.7 %) vs. 54 (36 %), $P < 0.001$) and headache events were milder. Furthermore, headache was the only adverse-effect that continued to be significantly less frequent in the aminophylline arm in the subsequent 24-hours (19 (12.7 %) vs. 33 (22 %), $P = 0.03$). Additionally, dyspnea was modestly reduced with aminophylline (18 (12.0 %) vs. 8 (5.3 %), $P = 0.04$). There were no events of angina in either study group. The frequency and severity of hot feeling or flushing, chest pain or discomfort and dizziness were not significantly impacted by aminophylline use (P values = 0.71, 0.19 and 0.14, respectively). Open-label IV-aminophylline to treat suspected regadenoson adverse-effects was less frequently used in the aminophylline arm (2 (1.3 %) vs. 24 (16 %),

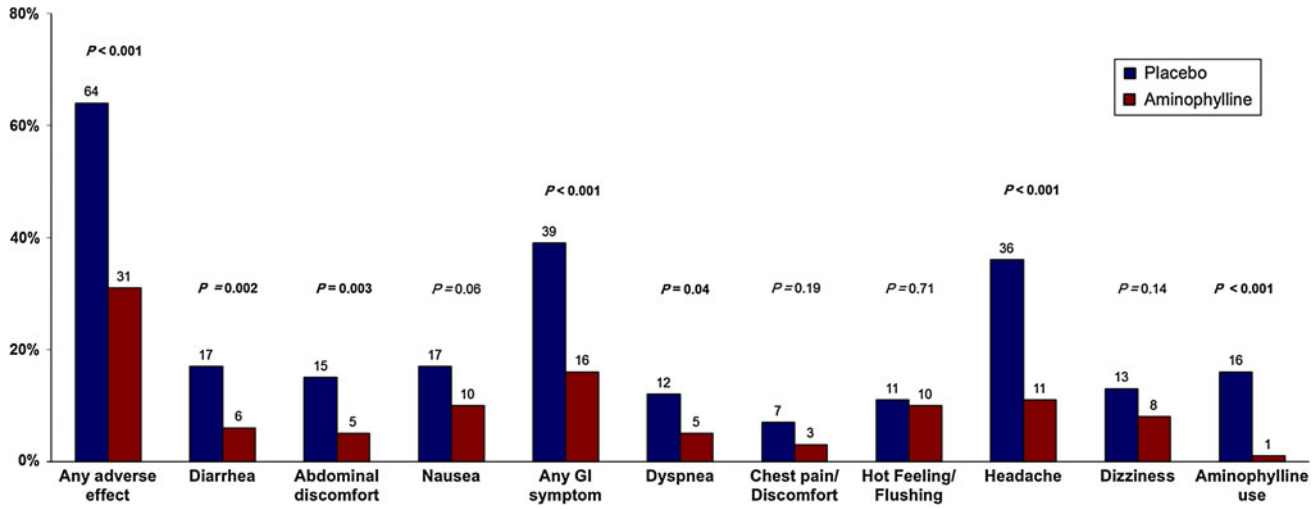

Fig. 1 Rates of regadenoson related adverse effects

$P < 0.001$). Open-Label aminophylline trended to be more frequent in women (11.2 vs. 7.3 %) but the difference was not statistically significant ($P = 0.24$).

Patient tolerability was significantly better in the aminophylline group; as more patients reported that they felt "very or somewhat comfortable" than those who were in the placebo arm (Table 2). Despite that, there was no statistically significant difference in the proportion of patients who indicated that they would "definitely" or "probably" take this test again if recommended (Table 2).

Subgroup analysis of gender (men vs. women), age ($\geq$ 60 vs. $<$ 60 years), ethnicity (Blacks or Hispanics vs. other) and CKD-stage (4 vs. 5) demonstrated concordant reduction of the incidence of diarrhea, headache and the composite of any regadenoson adverse-effect; as all odds-ratios were < 1 and not statistically different between the subgroup strata (odds-ratio homogeneity P values > 0.05).

Table 2 Tolerability and acceptability of regadenoson stress

	Placebo ($n = 124$)	Aminophylline ($n = 124$)	P value*
How did you feel?			0.008
Very comfortable (1)	115 (76.7 %)	135 (90.0 %)	
Somewhat comfortable (2)	17 (11.3 %)	11 (7.3 %)	
Somewhat uncomfortable (3)	14 (9.3 %)	3 (2.0 %)	
Very uncomfortable (4)	4 (2.7 %)	1 (0.7 %)	
Mean score (±SE)	1.39 (0.07)	1.14 (0.04)	
Would you take this test again?			0.23
Definitely yes (1)	119 (79.3 %)	125 (83.1 %)	
Probably yes (2)	24 (16.0 %)	22 (14.7 %)	
Probably not (3)	5 (3.3 %)	2 (1.3 %)	
Definitely not (4)	2 (1.3 %)	1 (0.7 %)	
Mean score (±SE)	1.29 (0.05)	1.20 (0.04)	

SE standard error

* Mantel–Haenszel extension of the χ^2 test for trend

Hemodynamic and ECG changes

Aminophylline use seems to blunt the hemodynamic response to regadenoson at 3 min post-regadenoson injection; as the SBP and DBP, respectively, dropped from baseline by 8 (±20) and 6 (±10) mmHg in the placebo group versus 2 (±18) and 3 (±9) mmHg in the aminophylline group ($P = 0.02$ and 0.003, respectively). The concomitant increase in heart rate was slightly greater in the placebo group (15 (±10) vs. 13(±9); $P = 0.02$) (Fig. 2). There were no events of systemic hypotension in either group.

Regadenoson-induced type-1 second degree atrioventricular blocks were uncommon; 3 (2.0 %) in the placebo arm and 4 (2.7 %) in the aminophylline arm ($P = 0.70$). There were no events of first degree, type-2 seconds degree or third degree atrioventricular block in either group. There was only one case of self-limited supraventricular tachyarrhythmia in each study group. Interestingly, there was similarly high incidence of premature ventricular complexes in both arms; observed in 14 (9 %) placebo and 11 (7 %) aminophylline subjects ($P = 0.53$). However, there were no events of ventricular tachyarrhythmias in either group. The incidence of the composite safety endpoint of systemic hypotension, tachyarrhythmias or seizure was identical in both arms; as only one case (0.7 %) of tachyarrhythmia was recorded in each group, but no events of hypotension or seizures were observed ($P = 1.0$). There

were no events of bronchospasm, hospitalization, cardiac arrest or death in either group.

There were 259 patients with ESRD enrolled in the trial, of whom 128 received placebo and 131 received aminophylline. The incidence of adverse events in the ESRD subgroup, within each arm, was similar to that of the entire study population (Table 3).

Impact on perfusion imaging

The mean *quantitative* SDS, as a measure of stress-induced ischemic burden, was 1.8 (±3.8) in the placebo arm versus 1.4 (±2.4) in the aminophylline arm ($P = 0.51$). Similarly, the mean SSS and SRS were similar between the study arms ($P = 0.40$ and 0.96, respectively). ANCOVA determined that prior MI was independently predictive of higher SDS ($P = 0.002$), while the treatment arm (aminophylline vs. placebo) and diabetic status were not ($P = 0.37$ and 0.95, respectively). Similarly, prior MI was independently predictive of lower ejection fraction ($P < 0.001$), while treatment group and diabetic status were not ($P = 0.14$ and 0.72, respectively).

Discussion

This dual-center, randomized, double-blinded, placebo-controlled clinical trial demonstrated, in patients with stage 4 and 5 CKD, that administering 75 mg of IV-aminophylline 90 s post-radioisotope in patients undergoing regadenoson-stress MPI can reduce the incidence of regadenoson-induced diarrhea by nearly two-thirds. Although the determination of diarrhea events was primarily subjective, more quantitative measures such as the number of bowel movements and Bristol stool scale showed concordant attenuation in diarrhea symptoms. Additionally, this intervention reduced the incidence of any regadenoson adverse-effects by one-half, any GI symptoms by 60 % and headache by 70 %. Furthermore, the tolerability of regadenoson-stress was significantly improved. The reduction in regadenoson adverse-effects was consistent across subgroups of gender, age (< 60 vs. ≥ 60 years), ethnicity (Blacks or Hispanics vs. other), and CKD stage (4 vs. 5). These benefits were not at the expense of any increase in aminophylline-related adverse events or an apparent impairment in MPI sensitivity.

Expectedly, there was a modest decline in the mean SBP and DBP at 30 s following regadenoson administration in both study groups, which was reversed at 3 min in the aminophylline arm (Fig. 2). However, there were no events of systemic hypotension, which reflects the safety of regadenoson and aminophylline in patients with severe CKD. It is also plausible that the elevated SBP at baseline in this population helped preventing any events of clinical hypotension.

This investigation represents the first randomized clinical trial to prospectively study regadenoson in a large number of patients with ESRD ($n = 259$), nearly half of whom ($n = 128$) received standard regadenoson-stress protocol followed by placebo. To date, this is the largest experience with regadenoson stress in patients with ESRD in any randomized clinical trial. With the exception of frequent GI symptoms, the incidence of regadenoson adverse-effects in this subgroup was comparable to patients with preserved renal function in the ADVANCE-MPI trials [8, 9]. Furthermore, there were no events of treatment-requiring arrhythmias or hypotension. These findings further support the use of regadenoson in patients with ESRD as it has been suggested in a previous retrospective study [21].

We observed a high rate of diarrhea in the placebo arm (17.3 %) which seems to be higher than the 10.5 % observed in the placebo arm of the ASSUAGE trial (all comers), but in line with the 15.4 % rate identified in the subset of patients with severe CKD [11]. Furthermore, the rate of any GI symptoms in the placebo arm (39 %) seems higher than the 23 % reported in the population with preserved renal function in ADVANCE-MPI trials [9]. This discrepancy is attributable, in part, to the predominant renal metabolism of regadenoson [4]. Moreover, it is plausible

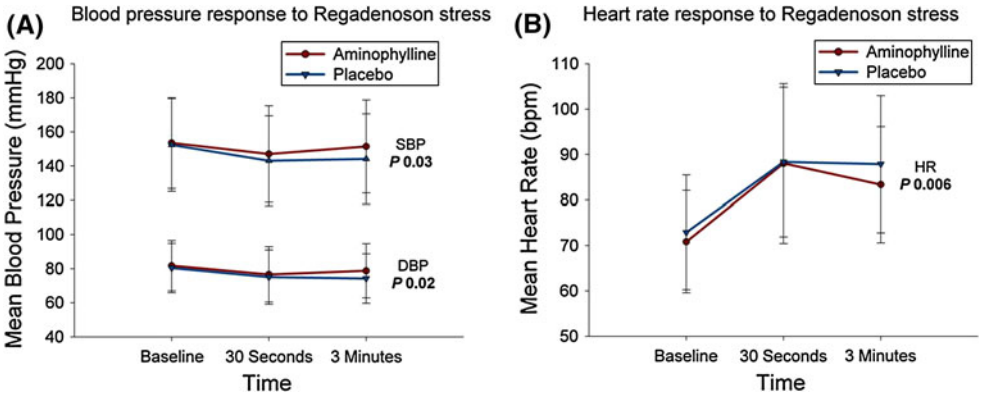

Fig. 2 The hemodynamic response to regadenoson stress. All *P* values are of the repeated measure analysis of variance (ANOVA) with Greenhouse-Geisser correction which compared the within subjects effect of the intervention (aminophylline vs. placebo) on the SBP, DBP and heart rate change over time

Table 3 Tolerability and safety of regadenoson stress in ESRD patients

	Placebo N = 128	Aminophylline N = 131	*P* value
Any adverse effect	82 (64 %)	42 (32 %)	< 0.001
Flushing or hot feeling	16 (13 %)	14 (11 %)	0.65
Chest Pain or discomfort	7 (6 %)	5 (4 %)	0.53
Dyspnea	12 (9 %)	8 (6 %)	0.33
Dizziness	17 (13 %)	11 (8 %)	0.21
Headache			
In laboratory	44 (34 %)	16 (12 %)	< 0.001
From lab departure to 24 h later	30 (26 %)	17 (14 %)	0.02
Nausea	23 (18 %)	12 (9 %)	0.04
Abdominal cramps	20 (16 %)	6 (5 %)	0.003
Diarrhea	22 (17 %)	9 (7 %)	0.01
Any GI adverse effect	51 (40 %)	20 (15 %)	< 0.001
Premature atrial complexes	2 (2 %)	0	0.15
Atrial fibrillation	0	0	NA
Atrial flutter	0	0	NA
Supraventricular tachycardia	1 (1 %)	0	0.31
Premature ventricular complexes	11 (9 %)	10 (7.6 %)	0.78
Ventricular tachycardia	0	0	NA
1st Degree AV block	0	0	NA
2nd Degree AV block	2 (2 %)	0	0.15
3rd Degree AV block	0	0	NA
Hypotension	0	0	NA
Comfortable during the test	116 (91 %)	127 (97 %)	0.04
Would take the test again	124 (97 %)	128 (98 %)	0.68

that diarrhea was under-reported in the ADVANCE-MPI trials since it was not tabulated as a stand-alone adverse effect. We also suspect that diarrhea is under-recognized clinically, since it is rarely inquired about by physicians and often goes unreported by patients due its delayed onset. Interestingly, the increase in GI symptoms was not paralleled with an increase in other adverse effects, as the 64 % rate of any adverse effect observed in the placebo arm is similar to the 67 % reported in the ASSUAGE trial [11]. This may be explained by a better symptom tolerance and higher threshold for reporting subjective side effects in the "sicker" patient population with severe CKD.

Aminophylline use was associated with a lower incidence of flushing, chest discomfort and dizziness, but this trend was not statistically significant. This is, in part, explained by the fact that the study was not sufficiently powered to detect a difference in these individual adverse effects. Additionally, these symptoms tend to be brief, occurring shortly after regadenoson administration. Thus, aminophylline injected more than 2 min after regadenoson has little impact on these symptoms. Furthermore, the study suggested that aminophylline use was associated with reduction in the incidence of dyspnea ($P = 0.04$; Fisher's Exact $P = 0.06$). Since dyspnea was not a predefined endpoint, this finding may simply be due to chance given the multiple testing applied in the evaluation of regadenoson adverse-effects.

The demonstrated reduction in the rate of adverse effects with aminophylline use is not only significant statistically but also clinically, as we observed 11 % absolute risk reduction (ARR) in the primary endpoint, which translates to a number needed to treat (NNT) of 9 to prevent a single event of diarrhea. The ARR in the incidence of severe diarrhea (Bristol stool scale $\geq$ 6) was 7.3 % with NNT of 14 patients. Furthermore, the ARR of any GI symptoms was 23 % with NNT of 5. Headache was not only common, but also long lasting. Aminophylline use was associated with an impressive 70 % RRR and 25 % ARR in the incidence of headache, which translates to NNT of 4. The secondary end-point of any regadenoson adverse-effect was significantly reduced (51 % RRR, 33 % ARR) with NNT of 3 to prevent any adverse-effect. These clinical benefits lead to an improved tolerability of regadenoson-stress but did not translate into significant improvement of patients' willingness to receive the test again; suggesting a good tolerance for adverse-effects by this patient population.

This trial, essentially, reproduced the findings of the ASSUAGE trial of all comers in the population of patients with severe CKD. Furthermore, the benefit of aminophylline in these patients seems to be greater than the general population, as the NNT to prevent various adverse effects are generally lower than those reported in the ASSUAGE trial [11]. Considering the very low cost of aminophylline, this intervention is not only clinically beneficial but also economically feasible.

There was a relatively high use rate of open-label aminophylline in the placebo arm (16 %) to reverse regadenoson side-effects. This seems higher than the 5.6 % rate reported in the ASSUAGE trial of all comers and the 9.5 % rate reported by Palani et al. in their retrospective study of patients with GFR < 60 [5, 11]. We suspect that the rate of aminophylline use in this study was somewhat inflated due to bias among the laboratory staff. Being in the midst of a clinical trial investigating the potential benefit of aminophylline in patients with severe CKD undergoing regadenoson-stress, it is plausible that the laboratory staff were more likely to administer aminophylline in response to patient-reported regadenoson-related symptoms.

The timing of aminophylline administration in this trial, 90 s after the radioisotope injection, was based on the best available basic science evidence indicating that myocardial uptake of Tc-99m tetrofosmin plateaus at 100 s after administration [22]. Taking into account circulation time of

the slowly administered IV aminophylline, we determined that 90 s delay after the radioisotope injection is the shortest necessary to insure maximal radioisotope uptake. We suspect that a shorter delay may impair the sensitivity of MPI to detect myocardial ischemia by prematurely reversing the regadenoson-induced hyperemic state, while a longer delay may be less effective in aborting regadenoson adverse effects.

Limitations

Although the aminophylline administration strategy did not seem to impair the sensitivity of stress-MPI, it is important to note that the current study is not powered to detect minimal differences in the SDS between the study groups. Moreover, we recognize that a cross-over study design, in which patients serve as their own controls, is the optimal methodology to address the question of MPI accuracy with the ASSUAGE protocol. Therefore, our group is currently planning the ASSUAGE-MPI trial which addresses this very issue.

The study population was predominantly comprised of African Americans and Hispanics in excess to the proportion of these minorities in the general population of our laboratory [11]. This observation echoes the disproportionate impact of CKD on these minority groups [23]. Nonetheless, subgroup analysis indicated that other racial groups receive similar reduction of major adverse effects with aminophylline use.

In conclusion, this trial indicates that regadenoson is safe and well tolerated in patients with severe CKD, including those with ESRD. Furthermore, the study decisively demonstrates that the administration of aminophylline in the manner described in the ASSUAGE protocol is safe and effective in reducing the frequency and severity of regadenoson adverse-effects in patients with stage 4 and 5 CKD.

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