Influence of hemodialysis on regadenoson clearance in an *in vitro* hemodialysis model

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Background. **Regadenoson is a novel pharmacological stress agent whose disposition during hemodialysis is not known. The purpose of this study was to determine the clearance of regadenoson under varying dialytic conditions using an in vitro hemodialysis model.**

Methods and Results. **Whole human blood was used to analyze the effect of hemodialysis on the clearance of regadenoson. Regadenoson transmembrane clearance (CL_D) was assessed for both a standard permeability and a high permeability polysulfone hemodialyzer with blood/dialysate flow rates of 300/600 and 400/800 mL/min. A two-tailed, paired Student's *t* test was used to compare regadenoson CL_D between hemodialyzer types and flow rates. The mean ± SD regadenoson CL_D values ranged between 62.5 ± 11.8 and 89.1 ± 24.0 mL/min for all dialytic conditions. There was no significant difference in regadenoson CL_D between hemodialyzer types and flow rates ($p > .05$).**

Conclusions. **Hemodialysis enhances the clearance of regadenoson independent of hemodialyzer permeability and blood/dialysate flow rate. This clearance is modest relative to total body clearance and is unlikely to produce a clinically significant outcome. (J Nucl Cardiol 2018;25:234–9.)**

Key Words: Regadenoson • chronic kidney disease (CKD) • hemodialysis • clearance

Abbreviations			
CAD	Coronary artery disease	SPECT	Single-photon emission computed tomography
MPI	Myocardial perfusion imaging		

INTRODUCTION

Regadenoson, a selective adenosine 2A receptor agonist, was approved by the United States Food and Drug Administration in April 2008 for use as a pharmacologic stress agent with radionuclide myocardial perfusion imaging (MPI), including single-photon emission computed tomography (SPECT) MPI.[1,2] Regadenoson primarily acts on arteriolar smooth muscle cells to induce hyperemia via coronary vasodilation, aiding in the detection of coronary artery disease (CAD) and other perfusion abnormalities.[3-5] Following intravenous administration of a single 0.4 mg bolus dose, regadenoson undergoes rapid distribution (peak plasma concentration within 1-3 minutes) followed by slower elimination with a half-life of approximately 2 hours. It is primarily eliminated via renal tubular secretion (58% excreted unchanged) and has a prolonged half-life of

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approximately 4 hours in patients with severe renal impairment (creatinine clearance <30 mL/min).[6,7]

Cardiovascular disease, including CAD, is a leading cause of mortality in chronic kidney disease (CKD) patients receiving dialysis (stage 5D).[8,9] In 2013, over half the deaths among CKD stage 5D patients were attributed to this disease.[9] Consequently, most CKD patients on dialysis, including those seeking renal transplantation, are routinely evaluated for CAD, often with regadenoson stress SPECT MPI.[10-12] Despite its prevalent use, few studies on regadenoson have been conducted in patients with CKD on hemodialysis. Studies by Doukky and AlJaroudi et al used a subset of CKD stage 5D patients from the ASSUAGE and ASSUAGE-CKD trials and other databases to show the safety and prognostic value of regadenoson in this population.[12-17] No studies, however, have yet evaluated the pharmacokinetics of regadenoson in patients with CKD stage 5D to show how hemodialysis may influence the clearance of regadenoson. Based on its small molecular weight (408 Da) and low plasma protein binding (30%), regadenoson has the potential to be removed by hemodialysis. However, its relatively large volume of distribution (63-75 L) may offset this potential.[2,7] In this study, we assessed the effect of hemodialysis on the clearance of regadenoson under varying dialytic conditions using an in vitro hemodialysis model.

METHODS

Our in vitro model used a commercially available Fresenius 2008K dialysis machine (Fresenius Medical Care, Waltham, MA) to assess regadenoson clearance during hemodialysis. This model used, as a patient surrogate, one liter of continuously stirred, sodium heparin-anticoagulated, whole human blood (BioreclamationIVT, Westbury, NY) placed in an Erlenmeyer flask and warmed to 37 °C in a water bath. The dialysis circuit was connected using a compatible Fresenius hemodialysis blood tubing set primed with 0.9% NaCl and one of two hemodialyzers (filters): a standard permeability (low flux) polysulfone hemodialyzer (Fresenius Hemoflow™ F8; ultrafiltration coefficient (K_{uf}) = 7.5 mL/h/mmHg; surface area = 1.8 m^2) and a high permeability (high flux) polysulfone hemodialyzer (Fresenius Optiflux® F160NR; K_{uf} = 50 mL/h/mmHg; surface area = 1.5 m^2). Dialysate was prepared using manufacturer-recommended Naturalyte® 4000 sodium bicarbonate concentrate (Fresenius Medical Care) and Centrisol® calcium-free acid concentrate (Minntech, Minneapolis, MN) diluted with deionized water in a 1:45 ratio.

Regadenoson (Lexiscan®, Astellas Pharma Inc., Northbrook, IL) was obtained and used in its commercially available form (0.4 mg/5 mL syringe for injection, Lot Nos. 49-048-EV and 50-028-EV). Based on findings from an initial dose-finding experiment, 24 μg (0.3 mL) of regadenoson was added to the flask of warmed blood to target the average peak plasma concentration of 17.5 ng/mL that is observed after a single 0.4 mg dose in patients with severe kidney dysfunction (creatinine clearance <30 mL/min).[7] Urea (750 mg, Lot No. 30K0221; Sigma, St. Louis, MO) and creatinine (100 mg, Lot No. 072K0094; Sigma) were added to the blood as control markers. Solutes were allowed to mix continuously in the blood for 10 minutes to ensure even distribution of all solutes. The blood was recirculated through the dialysis circuit for an additional 20 minutes to allow for uniform coating of the tubing and hemodialyzer. Dialysis and ultrafiltration were turned off during recirculation.

Hemodialysis was performed in single-pass mode at blood flow rates (Q_b) of 300 and 400 mL/min and dialysate flow rates (Q_d) of 600 and 800 mL/min, respectively. Each hemodialyzer was tested for both flow rate pairs. Ultrafiltration flow rate was set to zero for all runs of hemodialysis. Blood samples were collected simultaneously from the prefilter and postfilter ports of the dialysis circuit approximately 90 seconds after initiation of hemodialysis. The filtered blood was collected in an empty flask for disposal. This procedure was repeated eight times for each hemodialyzer flow rate pair. A new hemodialyzer and blood tubing set was used for each run of hemodialysis.

Collected blood samples were centrifuged at 3000 rpm for 10 minutes, and the separated plasma was transferred to 2.0 mL polypropylene cryogenic vials (Fisher Scientific, Pittsburgh, PA), labeled, and stored at −80 °C until analysis.

Sample Analysis

Regadenoson concentration was determined using a validated high-performance liquid chromatography assay. Plasma samples containing regadenoson were extracted with ammonium acetate (solid phase extraction). The eluate was evaporated and reconstituted and an aliquot was analyzed on an API 5000 LC system with tandem mass spectrometric detection (AB Sciex LLC, Framingham, MA). Blood urea nitrogen and creatinine concentrations were analyzed on a Siemens Advia 1800 chemistry system (Tarrytown, NY). The lower limits of detection for BUN and creatinine were 5 and 0.1 mg/dL, respectively, with a coefficient of variation (precision) of ≤4.7%. Blood hematocrit was measured using a microcapillary centrifuge (Model MB, IEC, Needham Heights, MA) and a dial reader.

Calculations

The extraction ratio (E) and transmembrane clearance during hemodialysis (CL_D) for regadenoson, urea, and creatinine were calculated for each hemodialyzer using the following equations:

$$E = \frac{(C_a - C_v)}{C_a},$$

$$CL_D = Q_b * (1 - Hct) * E,$$

where C_a is the prefilter solute concentration, C_v is the postfilter solute concentration, Q_b is the blood flow rate in mL/min, and Hct is the blood hematocrit.

Statistical Analysis

A power analysis indicated that 8 experiments were required to detect a 20% difference in the dialytic clearance of regadenoson between filter types. Assumptions used in these calculations included: a power of 90% and a standard deviation of 10% with a significance level of $p < .05$. A two-tailed, paired Student's *t* test was used to compare extraction ratio and solute clearance between hemodialyzer types and flow rates. A value of $p < .05$ was regarded as statistically significant.

RESULTS

The mean ± standard deviation (SD) of the extraction ratio for regadenoson ranged between 0.30 ± 0.08 and 0.32 ± 0.06 for the F8 hemodialyzer and 0.36 ± 0.09 and 0.41 ± 0.06 for the F160NR hemodialyzer (Table 1). The larger regadenoson molecule had a significantly smaller extraction ratio than urea and creatinine in all hemodialyzer types and flow settings ($p < .001$).

Observed regadenoson, urea, and creatinine transmembrane clearances are shown in Table 2. The mean CL_D for regadenoson ranged between 62.5 ± 11.8 and 76.9 ± 19.7 mL/min for the F8 hemodialyzer and 75.1 ± 17.0-89.1 ± 24.0 mL/min for the F160NR hemodialyzer. Regadenoson clearance did not significantly change when Q_b was increased from 300 to 400 mL/min with the F8 hemodialyzer ($p = .12$) or F160NR hemodialyzer ($p = .22$). There was no significant difference in regadenoson clearance between the two hemodialyzers at a Q_b of 300 mL/min ($p = .11$) or 400 mL/min ($p = .23$) (Figure 1). Although urea and creatinine clearances could not be directly compared with values reported by the manufacturer due to varying flow rates and dialysis methods, results were consistent with expectations for the given conditions.[18,19]

DISCUSSION

Renal excretion is a major elimination pathway for regadenoson. Pharmacokinetic studies in subjects with renal impairment indicate regadenoson clearance decreases in parallel with a reduction in creatine clearance.[7] Several studies have evaluated whether this reduced clearance adversely effects the safety profile and prognostic value of regadenoson in both dialysis-dependent and nondialysis patients with CKD. These studies have shown a generally favorable profile of regadenoson with an increased occurrence of headaches and gastrointestinal adverse effects,[12-15,20] both of which were found to be effectively controlled with aminophylline, a nonselective adenosine receptor antagonist.[16,17] Despite the abundance of these studies supporting its safe and effective use in patients with CKD on hemodialysis, no known studies have yet clarified whether regadenoson is actually removed by hemodialysis. In this study, we evaluated and assessed the effect of hemodialysis on the clearance of regadenoson. Results from this study indicate that regadenoson is cleared by hemodialysis at a rate of approximately 60-90 mL/min with hemodialyzer permeability (flux) and varying Q_b of 300-400 mL/min having no significant effect on clearance. A previous pharmacokinetic study in subjects with severe renal impairment (creatinine clearance <30 mL/min) not on hemodialysis showed that the total body clearance of regadenoson (CL_T) is approximately 250 mL/min, with nonrenal clearance (CL_{NR}) accounting for the majority of this clearance at approximately 200 mL/min.[7] Our findings indicate that hemodialysis would contribute approximately 30-45% to the overall regadenoson clearance, which would shorten the half-life by about 35%. When compared to the total clearance observed in patients with normal renal function (630 mL/min),[6] it becomes evident that the additional clearance by hemodialysis is of relative insignificance (<25%). Typically, drug dosage adjustments are considered when extracorporeal clearance accounts for greater than 30% of total body clearance.[21] However, due to its relatively limited clearance during

Table 1. Regadenoson, urea, and creatinine mean extraction ratios ± SD during hemodialysis with two hemodialyzers and two flow rates

Q_b/Q_d (mL/min)	F8 (n = 8)			F160NR (n = 8)		
	Regadenoson	Urea	Creatinine	Regadenoson	Urea	Creatinine
300/600	0.32 ± 0.06	0.66 ± 0.05	0.63 ± 0.06	0.41 ± 0.06	0.71 ± 0.11	0.75 ± 0.10
400/800	0.30 ± 0.08	0.60 ± 0.13	0.60 ± 0.13	0.36 ± 0.09	0.72 ± 0.08	0.74 ± 0.08

Q_b, blood flow rate; Q_d, dialysate flow rate; *F8*, standard permeability (low flux) hemodialyzer; *F160NR*, high permeability (high flux) hemodialyzer

Table 2. Regadenoson, urea, and creatinine mean transmembrane clearances ± SD (mL/min) during hemodialysis with two hemodialyzers and two flow rates

	F8 (n = 8)			F160NR (n = 8)		
Q_b/Q_d (mL/min)	Regadenoson	Urea	Creatinine	Regadenoson	Urea	Creatinine
300/600	62.5 ± 11.8	132 ± 10	125 ± 13	75.1 ± 17.0	130 ± 25	136 ± 24
400/800	76.9 ± 19.7	151 ± 28	150 ± 28	89.1 ± 24.0	181 ± 26	184 ± 24

Q_b, blood flow rate; Q_d, dialysate flow rate; *F8*, standard permeability (low flux) hemodialyzer; *F160NR*, high permeability (high flux) hemodialyzer

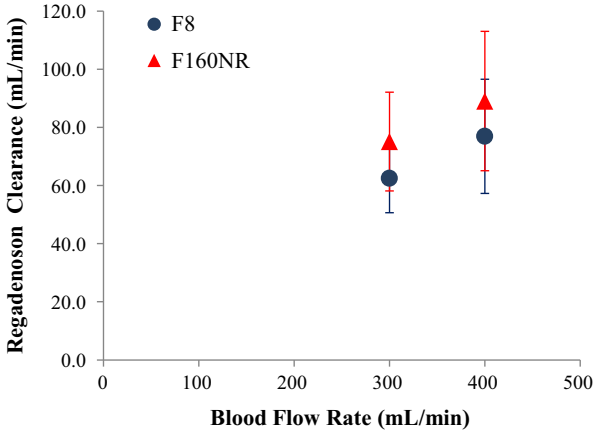

Figure 1. Mean regadenoson transmembrane clearance for two hemodialyzers (F8 and F160NR) at blood flow rates of 300 and 400 mL/min. Error bars represent the standard deviation from the mean. There was no significant difference in regadenoson clearance between the two hemodialyzers and two blood flow rates ($p > 0.05$).

hemodialysis and its relatively safe profile in CKD stage 5D, regadenoson dose adjustments in the dialysis-dependent population may not be warranted as hemodialysis will likely not have a substantial effect on the clinical outcome of a patient receiving regadenoson.

Many factors may affect the efficiency of hemodialysis and the removal of small solutes. A faster flow rate or a hemodialyzer with larger membrane pores will more efficiently clear solutes from blood and may significantly influence solute clearance. For this reason, regadenoson clearance was evaluated using two hemodialyzer types with varying membrane permeability and two common blood and dialysate flow rate pairs. The results reported here suggest that neither of these factors significantly influence regadenoson clearance. In the clinical setting, patient-specific factors such as residual renal function (RRF) and hemodialysis access recirculation may further influence regadenoson clearance. Although the additional clearance, if any, provided by RRF cannot easily be assessed, it would be expected to reduce the half-life to a value closer to that observed in patients with normal renal function and would not have any clinical implications. Recirculation, which occurs when some of the blood returning to the patient (postfilter) is immediately drawn back into the dialysis line (prefilter) without entering systemic circulation, may reduce the total amount of regadenoson removed without affecting the dialytic clearance.[22] Any reduction in dialytic clearance due to recirculation would increase the half-life to a value closer to that observed in patients with CKD stage 5D, a population for which the safety and efficacy of regadenoson has already been established.[11,13-17]

There are several potential clinical applications of this new knowledge. First, although regadenoson may induce myocardial infarction and potentially fatal ventricular arrhythmias in rare cases,[23-25] lesser degrees of myocardial ischemia may occur in response to regadenoson are not uncommon,[26] particularly in patients with advanced coronary artery disease.[27] While initial management generally includes medical therapies such as aminophylline, beta-adrenergic antagonists, and/or nitroglycerin, invasive management may also be required in some cases. These data suggest that there is no clinically relevant role for hemodialysis in cases of regadenoson induced myocardial ischemia, arrhythmia, or other severe side effects.

More commonly, clinicians are faced with uncertainty as to optimum timing of regadenoson stress in relation to hemodialysis. Many patients are relatively hypotensive after hemodialysis and may not tolerate vasodilator stress immediately afterward. Conversely, some laboratories have been hesitant to perform regadenoson stress on nondialysis days under the belief that regadenoson administration immediately prior to dialysis may limit potential adverse effects. These data suggest that timing of regadenoson stress in relation to dialysis can be safely liberalized.

Lastly, an analysis of the ASSUAGE trials suggested that patients with advanced renal disease may particularly benefit from aminophylline administration

after regadenoson stress compared to those with preserved renal function.[28] Unfortunately, aminophylline is contraindicated in patients with seizure disorder. In such patients, early dialysis is likely to have at most a modest effect on symptom control.

STRENGTHS AND LIMITATIONS

The in vitro study design we report in this paper allowed us to easily control for the many variables affecting dialytic clearance, including hemodialyzer type and flow rates. This allowed us to determine and compare the clearance of regadenoson under varying dialytic conditions that would otherwise be difficult to do in the clinical setting. This in vitro design has some important limitations as well. Since we used a hemodialysis model with whole human blood collected from relatively healthy patients supplemented with urea and creatinine, the findings reported here may not translate to patients with CKD stage 5D who have altered pharmacokinetics. However, similar in vitro hemodialysis models have been used for other drugs and found to be a good predictor of in vivo drug clearance.[29-32]

NEW KNOWLEDGE GAINED

Regadenoson is a dialyzable solute that is removed by hemodialysis under common dialytic conditions, albeit at a rate much slower than the nonrenal clearance rate in patients with severe renal impairment. Therefore, hemodialysis is unlikely to hasten significantly the removal of regadenoson from the body.

CONCLUSION

Hemodialysis enhances the clearance of regadenoson independent of hemodialyzer permeability and blood/dialysate flow rate. This clearance is modest relative to total body clearance and is unlikely to produce a clinically significant outcome.

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Disclosure

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