Use of regadenoson in end-stage renal disease

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See related article, pp. 205–213

Regadenoson has rapidly become the pharmacological stress agent of choice in the United States since its approval by the Food and Drug Administration in April 2008.^{1–5} The effect of regadenoson on myocardial blood flow is rapid necessitating the injection of radio-nuclide tracer 30 seconds after its injection as a bolus. The terminal part of the triphasic half-life is not associated with significant drug effect of any sort, which is important as prolonged monitoring of the patient is unnecessary. Almost 57% of the drug is excreted unchanged in the urine, which begs the question of safety in patients with impaired renal function.^{6,7}

It is against this background that the study of Doukky et al⁸ in this issue of the Journal becomes important. The authors assembled a group of patients with end-stage renal disease (ESRD, $n = 146$) stages 5 (on dialysis or with $\text{GFR} < 15 \text{ mL/minute/1.73 m}^2$ and not yet on dialysis) and compared their responses (see below) to a control group with $\text{GFR} > 30$ ($n = 97$). The 2 groups were selected from identically designed randomized studies that addressed the usefulness of aminophylline in reducing the side effects of regadenoson (one trial was in ESRD patients while the 2nd was open to all patients).^{9,10} The primary end-point of both trials was any adverse event over a 24-hour period after the stress test. The secondary end points were multiple and included hemodynamic responses, ECG changes, aminophylline use, gastro-intestinal symptoms, broncho-spasm, comfort level, and willingness to undergo the test again.

The patients with ESRD are an important group of patients because of the high total and cardiovascular mortality rates especially sudden death. In prior studies, left ventricular (LV) ejection fraction (EF), ischemic burden, scar burden, autonomic neuropathy measured indirectly with the heart rate response to adenosine or regadenoson and LV dyssynchrony (measured with phase analysis of gated SPECT myocardial perfusion imaging) were found to be predictors of outcome in this population.^{11–16}

The main conclusion of the study presented here is that regadenoson is safe in ESRD with an overall side-effect profile comparable to that seen in the control group. Specifically, there were no serious side effects such as death, cardiac arrest, hospitalization, or bronchospasm seen in either group. While a single participant in the control group experienced self-limited hypotension, this was not seen in any subject with ESRD. None of the subjects in either group had ventricular tachyarrhythmia, third-degree or second-degree type-2 atrio-ventricular block. Two participants with ESRD had Mobitz type-1 second-degree atrio-ventricular block (Wenckebach block) and one participant in each group had first-degree block (all these events were rare and not significantly different between groups). Premature ventricular contractions were more common in ESRD than in control subjects (8% vs 1%, $P = .02$) but this finding is of uncertain clinical significance and may have been present before the test as well.

There were more gastro-intestinal symptoms (diarrhea and abdominal discomfort) but less dizziness in the ESRD group than in the control group.⁸ However, more patients in the ESRD group than in the control group felt comfortable with the test and were willing to undergo repeated testing than in the control group. The differences in heart rate and blood pressure responses were minor and of no clinical relevance.

This study therefore supports prior observational studies that showed the safety of regadenoson in ESRD.^{17,18} The precise reason for the higher incidence of diarrhea in ESRD is not clear and the increase in half-life of regadenoson does not appear to fully explain this as these patients had frequent bowel movements while still in the laboratory and not in the subsequent 24 hours.

We obviously do not know the prior history of the bowel habits in these patients before the stress test and

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there was no control over their dietary intake after the test. There were also many differences between the ESRD group and the control group in age, ethnicity, gender, diabetes, and the indications for testing. It should also be pointed out that the patients were given two interviews, one after the stress test and the second 24 hours later and hence many trivial complaints may have been registered. This may explain the higher incidence of side effects in general and the higher rate of use of aminophylline compared to other trials.¹⁹

The drug information package lists diarrhea in <1% and dizziness in 8% of unselected patients receiving regadenoson, clearly much less than the corresponding numbers in the control group in this study. One possible reason for these differences is that these patients were bombarded by questions throughout the procedure and their awareness that they were in a research study with a chance of 1 in 2 of receiving an active drug rather than a placebo.

The strengths of the study by Doukky et al are the prospective nature and the details of safety information collected over a 24-hour period.⁸ The weaknesses include the fact it is not a randomized study with major inequalities in baseline characteristics of the patients and the control group. In the pursuit of completeness many meaningless complaints of mild nature were elicited (not volunteered by the patients) but listed nevertheless as side effects. These minor side effects have no real clinical relevance as seen by the dissociation between them and the comfort score; the ESRD patients had more diarrhea and yet were more comfortable than the control group and more willing to undergo repeated testing if needed! We do not know whether the ESRD patients had more diarrhea, even before the stress test possibly because of diabetic neuropathy.

In summary, this study provides further assurance that regadenoson could be safely used in patients with ESRD.

Conflict of interest

Dr Iskandrian is on the steering committee of Astellas Pharma. Drs. Hage and Iskandrian report investigator-initiated grant support from Astellas Pharma.

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