When to re-dose regadenoson?

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Since FDA approval in 2008, regadenoson, an A2A adenosine receptor agonist, has become the most commonly used pharmacological stress testing agent in the U.S.[1] In this issue of the *Journal*, Townsend et al[2] address the important question of how to manage re-dosing of regadenoson if it were to become necessary. This information would be helpful, for example, if the FDA approved 0.4 mg (400 μg) dose of regadenoson were administered intravenously (IV) but the radiotracer became inadvertently unavailable or in the case of an infiltrated IV line resulting in the subcutaneous administration of regadenoson.

Townsend et al[2] evaluated the pharmacokinetics (the study of the time course of the drug's absorption, distribution, metabolism, and excretion) and pharmacodynamics (the study of the biochemical and physiological effects of a drug on the body) of different doses of regadenoson administered every 10 minutes (min). To do so, they randomized 36 healthy men and women, mean age 38 years, who were not on any medications, to receive either 3 separate doses of 0.1 mg 10 minutes apart, 3 doses of 0.2 mg 10 minutes apart, 2 doses of 0.4 mg 10 minutes apart or 2 or 3 doses of placebo 10 minutes apart. In addition to measuring plasma concentrations of regadenoson, they studied the pharmacodynamic effect on blood pressure and heart rate as primary endpoints.

Work by Lieu et al[3] evaluated the pharmacodynamic effect of escalating doses of regadenoson on coronary velocity using a coronary Doppler flow wire. They found that regadenoson doses of 0.1 mg, 0.3 and 0.4 mg increased peak velocity above baseline by 3.0 ± 0.6 (SD), 3.4 ± 0.8, and 3.1 ± 0.5 times, respectively. As flow increases linearly with velocity, by the formula [Flow = πr^2 (average velocity)(0.5) × 60] with r equal to vessel radius, peak myocardial blood flow would thus increase to a similar degree with either 0.1 or 0.4 mg of regadenoson. However, the 0.4 mg dose was selected for use with MPI as it produced a sustained velocity 2.5 times above baseline for 2.3 minutes compared to <2 minutes for smaller doses.[3,4]

Townsend et al[2] found 0.4 mg of regadenoson to result in mean plasma concentrations of ≈18 and ≈9 ng·mL^{-1} at 3 and 9 min, respectively. Given earlier findings of Lieu et al[3] that coronary velocity remains ≥2 times baseline for a mean of 9 minutes, a concentration of 9 ng·mL^{-1} would correlate with a ≈twofold increase in velocity.

Using the 0.1 mg dose, which Lieu et al[3] found to increase coronary velocity threefold, Townsend et al[2] found 0.1 mg to result in a mean concentration of ≈5 ng·mL^{-1} measured 3 minutes post dosing. This was the first time of measurement in their study. Correlating this dose with coronary velocity in the study of Lieu et al[3] is difficult, as coronary velocity had decreased to <2 times baseline by 3 minutes with this dose. Nonetheless, the coronary velocity curves Lieu et al[3] observed are consistent with a significant impact on coronary velocity remaining at 3 minutes in relation to a plasma concentration of ≈5 ng·mL^{-1}.

Thus, clinically re-dosing 0.4 mg of IV regadenoson 10 minute after an initial 0.4 mg IV dose as performed in

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the study of Townsend et al[2] would be re-administering regadenoson at a time when the initial dose still has a considerable pharmacodynamic effect on coronary velocity and flow.

As well, as Townsend et al[2] demonstrate in Figure 4, a 10 minutes re-dosing interval resulted in a concentration of $\approx$24 ng·mL^{-1} at 3 minute following the second dose of 0.4 mg administered at 10 minutes compared to $\approx$18 ng·mL^{-1} 3 minutes after the first dose. As a single dose of 0.4 mg is adequate to achieve the necessary pharmacodynamic effect at a concentration of $\approx$18 ng·mL^{-1}, a higher concentration of $\approx$24 ng·mL^{-1} is unnecessary. Consistent with this concern, Hendel et al[5] observed more adverse events during their dose ranging study when 0.5 mg of regadenoson was used compared to 0.4 mg.

While the vasodilatory effects of regadenoson are understood to be a direct effect on the A2A receptor in the vessel wall, the heart rate increase is most consistent with an indirect effect, mediated through stimulation of the A2A receptors in the carotid body resulting in an increase in plasma norepinephrine.[6] This sympathetic stimulatory effect is observed with adenosine and dipyridamole, as well.[7] This presumably causes the brief ''mini-panic attack'' feeling that patients often experience beginning 30-90 seconds after administration of regadenoson or adenosine. As observed in other studies,[3,8] heart rate increases with escalating doses of regadenoson, although the incremental increase is not directly proportional to dose. Figure 3 and Appendix 2 of Townsend et al[2] demonstrate an additional 5 bpm heart rate increase with a second dose of 0.4 mg of regadenoson over and above the 45 bpm heart rate increase observed with the first dose.

If 10 minutes is too early to re-dose, when should re-dosing occur? A reasonable re-dosing interval can be considered by an analysis of regadenoson pharmacokinetics and pharmacodynamics. In 2 contributions, Gordi et al[8,9] found regadenoson's pharmacokinetics best described by a 3-compartment model with linear clearance (whereby drug removal is proportional to time) and tri-phasic half-lives. The initial half-life of 2-4 minutes corresponds roughly to the drug's appearance in the vascular space and other tissues following IV injection and has a volume of distribution of 11.5 L. The intermediate half-life of $\approx$30 minutes corresponds roughly to distribution into other tissues with a volume of distribution of 59 L. The combined duration of these 2 half-lives over 4-5 half-lives appears to correspond to its loss of pharmacodynamic effects. Based on pharmacokinetic principles, 4-5 half-lives are required to eliminate 94-97% of a drug from its site of action. The terminal elimination half-life is $\approx$120 minutes and reflects redistribution from tissue compartments into the vascular compartment, as well as loss of drug from the body via the renal system.[8,10,11]

The major elimination pathway is renal with 58% of the dose cleared by the kidneys both by glomerular filtration and tubular secretion.[8] In patients with creatinine clearance $<$80 mL·min^{-1}, regadenoson's clearance decreases with a corresponding increase in plasma concentration and prolongation of the terminal half-life.[9]

Throughout the 3 distinct half-lives, regadenoson is distributed from the vascular compartment into various tissues and redistributed back, resulting in mean plasma concentrations of $>$2 and $>$1 ng·mL^{-1} at 1 and 2 hours following 0.4 mg of regadenoson, respectively (estimates obtained from Figure 3 of Gordi et al).[9] Townsend et al[2] observed similar mean concentrations at 1 and 2 hours, $\approx$3 and $\approx$2 ng·mL^{-1}, respectively, following 2 doses of 0.2 mg of regadenoson 10 minutes apart (for a total of 0.4 mg). Assessing the effect on heart rate in 24 subjects 1 and 2 hours following 0.4 mg of regadenoson, Gordi et al[9] found 2 of the 24 subjects to have heart rates that remained $>$10 bpm above baseline at 1 hour. By 2 hours, heart rates in all subjects were within 10 bpm of baseline.

Another consideration of re-dosing is the potential for tachyphylaxis. Desensitization of A2A receptors has been reported in experimental models.[12-14] Trochu et al[15] measured coronary blood flow in the dog model over 3 consecutive regadenoson injections (1 mcg·kg^{-1}, a relatively low dose) administered 5-10 minutes apart. Coronary blood flow (mL·min^{-1}) decreased with each successive dose, 229 ± 14, 218 ± 13, 192 ± 14. As this decrease did not reach significance, the authors interpreted the finding as not consistent with tachyphylaxis. The trend could be interpreted as a signal of tachyphylaxis, however. To our knowledge, tachyphylaxis has not been evaluated in humans with coronary flow measurements. In the study of Townsend et al[2] there is also a signal of a tachyphylaxis effect as subjects described fewer adverse events with repeated doses of 0.2 and 0.4 mg of regadenoson. Alternatively, however, the decrease in adverse effects could have been secondary to familiarity with symptoms observed with regadenoson.

Given the pharmacodynamic effect on coronary vasodilation at relatively low plasma concentrations of regadenoson, the apparent lack of pharmacodynamic properties during the terminal half-life, the unknown potential of tachyphylaxis in humans and application of 4-5 half-lives, a reasonable re-dosing interval may be estimated. Using the sum of the initial and intermediate half-lives of 2-4 and 30 minutes, respectively, 4 and 5 half-lives would be approximately 132-165 minutes. Thus, a re-dosing interval of 150 minutes (2.5 hours) is recommended following an IV dose of 0.4 mg of regadenoson. Estimating a re-dosing interval following

subcutaneous administration of regadenoson is problematic as absorption would differ from IV administration, the route of administration studied by Townsend et al.[2] A pharmacokinetic study evaluating subcutaneous administration of regadenoson is welcomed. Until such a study is performed, a re-dosing interval of 2.5 hours appears reasonable.

As regadenoson is predominately renally excreted and the pharmacokinetics of regadenoson in patients on dialysis have yet to be investigated and reported, further pharmacokinetic investigation is suggested prior to recommendations regarding a re-dosing interval in patients on dialysis.

Thanks are due to Townsend and his colleagues for their important contribution in this issue of the *Journal*.[2] Another pharmacodynamic investigation opportunity is the intriguing potential of decreasing adverse effects with an injection time >10 seconds. Such a study would require measurement of coronary velocity to determine the specific timing of the increase in coronary flow when a longer injection time is used. This would allow a determination of optimal timing of radiotracer injection with a longer injection.

Lastly, as women experience more adverse events than men with all three generations of vasodilators, dipyridamole,[16] adenosine,[17,18] and regadenoson,[19] separately investigating and reporting the pharmacokinetic and pharmacodynamic responses of regadenoson and future pharmacologic stress agents in women is recommended.

Disclosure

Gregory S. Thomas, MD, MPH is a scientific advisor and a member of the speakers bureau for Astellas Pharma US. The other authors have no disclosures.

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