Journal of the American College of Cardiology
© 2005 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 46, No. 11, 2005
ISSN 0735-1097/05/$30.00
doi:10.1016/j.jacc.2005.07.061

EDITORIAL COMMENT

Impact of Selective Adenosine A_{2A} Receptor Agonists on Cardiac Imaging

Feeling the Lightning, Waiting on the Thunder*

D. Douglas Miller, MD, CM, FACC
St. Louis, Missouri

Approximately equal numbers of thunderstorms and cardiac stress imaging studies occur daily around the world (approximately 40,000). The U.S. National Center for Health Statistics reported 1,318 deaths from lightning from 1980 to 1995 (1). In the same era, multi-center registries of 89,973 adenosine (2) and dipyridamole (3,4) testing reported only nine cardiac deaths (0.0001%). As such, one is more likely to be killed by a random lightning strike than to die during a vasodilator stress imaging study.

See page 2069

Despite this reassuring mortality tilt in favor of pharmacological stress, there continues to be test tolerability issues that reduce patient comfort during cardiac drug stress imaging—let's call these troublesome side effects the thunder. In other reports (4,5), more than one-third of patients note flushing, dyspnea, and chest pain after adenosine, whereas 10% to 20% of patients receiving either of the Food and Drug Administration (FDA) approved agents experience headache, dizziness, or transient electrocardiographic changes. The most feared non-lethal complications—myocardial infarction (MI) and bronchospasm—occurred in <0.15% of tests.

THE LITERATURE

In this issue of the *Journal*, Hendel et al. (6) report the findings of a Phase 2 study designed to establish the safest and most efficacious bolus dose of new selective A_{2A} receptor agonist (regadenoson) in subjects with clinically-indicated adenosine single-photon emission computed tomography (SPECT) scans. The requirement for a predominantly reversible myocardial perfusion defect suggests a study population with a high pre-test likelihood of coronary artery disease (CAD). The open-label, unblinded trial design compared patient tolerability of two randomly selected intravenous (IV) boluses (400 or 500 μg). On the basis of the side effect profile of the higher dose, the better-tolerated 400-μg bolus was selected for the subsequent Phase 3 trial, despite two serious adverse events (SAEs).

Although the statistical rigor of the study was limited, owing to small sample size, adenosine-regadenoson SPECT image agreement was good (86%) and comparable to that reported when sequential dipyridamole and adenosine SPECT scans were compared in the same patients (87% [7] and 90% [8], respectively). The reproducibility of two serial adenosine SPECT studies in the same patient has never been established. As such, the equivalency of a regadenoson bolus to an adenosine infusion for reversible SPECT perfusion defect detection could not be determined.

The current study is comparable to a previous study (9) in which another A_{2A} agonist (binodenoson) was administered as either a 3-min 1.5-μg/kg IV infusion or as a range of 30-s IV boluses. Of the subjects, 98% had known CAD (90%) or high pre-test CAD likelihood (8%). Overall, binodenoson-adenosine SPECT concordance was good-to-excellent for defect extent and severity (79% to 87%). Kappa statistics in this larger population ranged from 0.69 to 0.85, supporting binodenoson's SPECT comparability to adenosine. Patient-reported adverse effects (AEs) were similar with both agents, but AE severity was less with binodenoson. High-degree atrioventricular (AV) block only occurred with adenosine. Separate pharmacokinetic studies in healthy volunteers showed good tolerability, with dose-dependent and generally mild AEs occurring over a range of binodenoson boluses (10).

THE DRUG APPROVAL AGENDA

Under the Federal Food, Drug and Cosmetic Act, the FDA's Center for Drug Evaluation and Research has a responsibility to assure the safe and effective use of approved drugs by prescribers and patients (11). What does the FDA's Cardio-Renal Panel want from the *−denoson* clinical trialists and sponsors before approving a Phase 3 clinical trial? Although the panel reviews the pre-clinical data and human subject AEs in Phases 1 and 2, it is more appropriately concerned about the SAEs that threaten patient safety than nuisance complaints that limit tolerability. Investigational new drugs (INDs) must prove to be as safe as or safer than drugs already in clinical use. Binodenoson (9) and regadenoson (6) Phase 2 trials were free of feared cardiopulmonary SAEs that are rarely observed after adenosine and dipyridamole (i.e., stroke, MI, death, and bronchospasm).

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the Department of Internal Medicine, Saint Louis University School of Medicine, St. Louis, Missouri. The department of internal medicine at Saint Louis University has received or is receiving research support for studies of all three A_{2A} receptor agonists from King Pharmaceuticals, Cardiovascular Therapeutics (CVT), and Bristol-Myers Squibb (BMS). Dr. Miller was the local site principal investigator on the Phase III CVT study and is a sub-investigator for the Phase III BMS study. In the context of these multi-center studies, Dr. Miller has participated in required investigator meetings. He is a member of the BMS Speakers Bureau.

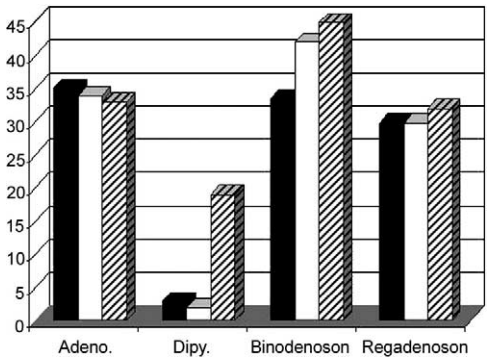

Figure 1. Published rates of the most common vasodilator side effects of adenosine and dipyridamole (5), binodenoson (9), and regadenoson (6), demonstrates similar patient tolerability for A_{2A}selective agonists to adenosine. **Black bars** = flushing; **white bars**= dyspnea; **ruled bars** = chest pain.

Data gathered during pre-clinical and clinical trials become part of the New Drug Application (NDA), which must be FDA-approved before U.S. commercialization. Different regulations and requirements exist under the aegis of the European Union's Agency for Evaluation of Medicinal Products (12).

Sponsors of *−denoson* INDs primarily seek a product-labeling claim on the package insert of comparable safety and efficacy to adenosine. Better safety might be achievable on the basis of highly selective coronary vascular A_{2A} receptor agonism, without A_1-mediated AV conduction effects and A_{2B}-mediated bronchoconstriction. Approval of a better tolerability claim would require that the *−denoson* compounds reduce the frequency and/or severity of less serious AEs. Reported rates of the three commonest vasodilator AEs do not differ among adenosine, binodenoson, and regadenoson; so, available data do not yet support a "better tolerability" labeling claim for the A_{2A} selective agonists (Fig. 1).

No safety or tolerability claim would be meaningful unless the FDA was assured that the new A_{2A} agonists are at least as efficacious as adenosine for the detection of reversible myocardial hypoperfusion ("ischemia"). The FDA requires multiple scoring approaches for the core lab comparison of SPECT studies. The current study (6) used blinded experts to score regadenoson and adenosine SPECT scans twice, in both random order and in side-by-side fashion. Despite reader expertise, regadenoson SPECT was 11% to 18% discordant with adenosine overall and 11% to 24% discordant in the rating of myocardial "ischemia." Normal-versus-abnormal scan classification and degrees-of-defect abnormality classification also produced different concordances. No angiographic "gold standard" comparison was required by the FDA in Phase 2 to confirm *−denoson* scan accuracy for detecting coronary stenoses (6,9); the FDA is seeking this information in one ongoing Phase 3 trial.

Flow- and pressure-wire devices are widely used in the clinical setting to assess whether intermediate coronary lesions are flow-limiting (13). "In-cath. lab." physiological testing of drug-induced coronary hyperemia emerged as a valuable means of establishing the dose-dependent potency of these new *−denoson* agents (Fig. 2), and for determining the timeline of drug effect (14).

THE MARKETPLACE

By design, Phase 2 studies of these new selective A_{2A} agonists excluded patients with asthma or known bronchospasm, high-degree AV block, recent MI, and depressed left ventricular ejection fraction. By design, and to maximize "ischemic" defects, the majority of Phase 2 subjects had either known CAD or a high pre-test CAD likelihood. Some Phase 3 studies are limiting enrollment of subjects with a <10% pre-test CAD likelihood to increase the likelihood of coronary angiographic correlations. By design, the current study (6) excluded subjects weighing >250 lbs. Both studies enrolled mostly men (64% [9] and 75% [6]), and both included patients with an average age of 65 to 67 years. These pre-determined exclusions appropriately reduced the risk to research subjects. They also increased the

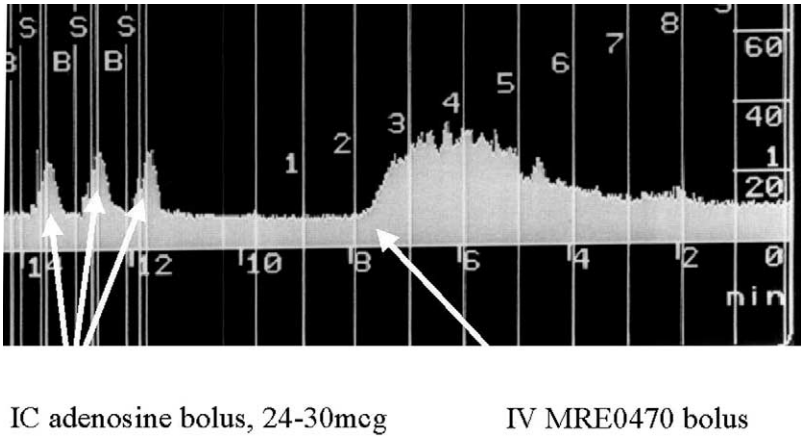

Figure 2. Intracoronary Doppler flow-wire average peak velocity (APV) measurements after three successive intracoronary (IC) adenosine boluses, followed four minutes later by an IV bolus of MRE0470 (binodenoson). A two-fold increase in APV is observed after an IV binodenoson bolus, comparable to an IC adenosine bolus. Coronary hyperemia after IV binodenoson bolus administration lasts three to four minutes. Reprinted with permission (14).

JACC Vol. 46, No. 11, 2005
December 6, 2005:2076–8

potential for differences in the anticipated *−denoson* experience in the clinical setting. Safety, tolerability, SPECT defect detection, and angiographic correlates could vary in real-world referral populations.

Sponsors marketing these agents might exploit the patient throughput and technical advantages of bolus dosing. Such diagnostic utilities could eventually be a basis for competitive product positioning. Although field use must be consistent with the package insert, wider practical experience and technical advances in drug delivery systems have previously led clinicians to modify the FDA-approved drug dosing and imaging protocols. "Off-label" applications have proven useful by shortening adenosine infusion times, augmenting demand stress, or accentuating myocardial defect reversibility with nitroglycerine pre-treatment. Similar modifications intended to improve testing efficiency and/or diagnostic yield of selective A_{2A} agonists should ideally be supported by evidence-based modifications to the package insert.

THE FORECAST

It is a truism, long held by Midwestern farmers, that "lightning doesn't strike twice in the same spot;" however, with the recent advent of highly selective coronary A_{2A} receptor agonists with the *−denoson* suffix, three of which are in the process of passing the obstacles on the way to FDA approval, industry's new drug development efforts in response to patient safety and test tolerability concerns will cause lightning to strike. . .not once, not twice, but thrice!!! Another *−denoson* (i.e., Bristol-Myers Squibb apadenoson) has also entered Phase 3, after demonstrating dose-dependent potency, safety, and efficacy in Phase 2.

Clinicians and the FDA want to know if the *−denosons* will outperform the approved "old standards" (adenosine and dipyridamole). Pilot studies (6,9) suggest that the safety and test tolerability attributes of these A_{2A} receptor agonists are a class effect. The rigor with which these novel pharmacological stress agents are each being studied is unparalleled. This bodes well for patients and doctors who, after a torrential burst of clinical investigation, should have a choice of safer and better-tolerated new drugs to assist in CAD diagnosis and risk stratification.

The summer storm season is upon us. Children anxiously awaking to the crash of thunder will be reassured by watchful parents that additional seconds counted between a lightning flash and the ensuing rumble reflect the storm's passing and safety. It remains to be seen whether the FDA's approval of regadenoson and binodenoson will translate into first-to-market advantages for sponsors or whether the corona of St. Elmo's fire, usually visible after the worst of an electrical storm, will reveal yet another *−denoson's* superiority and signal clearer skies ahead for stress imagers.

Reprint requests and correspondence: Dr. D. Douglas Miller, Professor and Chair, Department of Internal Medicine, Saint Louis University School of Medicine, 1402 Grand Boulevard, St. Louis, Missouri 63104. E-mail: millerdd@slu.edu.

REFERENCES

1. Mercedes Bern-Klug. When Lightening Strikes, Strike Back With CPR. Center on Aging, The University of Kansas Medical Center. Available at: http://www2.kumc.edu/coa/Senior_Press_Article/Article_Index-Prevention.htm. Accessed May 17, 2005.
2. Cerqueira MD, Verani MS, Schwaiger M, et al., and Investigators of the Multicenter Adenoscan Trial. Safety profile of adenosine stress perfusion imaging: results from the Adenoscan Multicenter Trial Registry. J Am Coll Cardiol 1994;23:384–9.
3. Ranhosky A, Kempthorne-Rawson T, for the Intraveneous Dipyridamole Thallium Imaging Study Group. The safety of intravenous dipyridamole thallium myocardial perfusion imaging. Circulation 1990;81:1205–9.
4. Lette J, Tatum JL, Miller DD, et al., for the Multicenter Dipyridamole Safety Study Investigators. Safety of dipyridamole testing in 73,806 patients: the Multicenter Dipyridamole Safety Study. J Nucl Cardiol 1995;2:3–17.
5. Miller DD, Labovitz AJ. Dipyridamole and adenosine vasodilator stress for myocardial imaging: vive la difference! J Am Coll Cardiol 1994;23:390–2.
6. Hendel RC, Bateman TM, Cerqueira MD, et al. Initial clinical experience with regadenoson, a novel selective A_{2a} agonist for pharmacologic stress single-photon emission computed tomography myocardial perfusion imaging. J Am Coll Cardiol 2005;46.2069–75.
7. Taillefer R, Amyot R, Turpin S, et al. Comparison between dipyridamole and adenosine as pharmacologic coronary vasodilators in detection of coronary artery disease with thallium 201 imaging. J Nucl Cardiol 1996;3:281–3.
8. Levine MG, Ahlberg AW, Mann A, et al. Comparison of exercise, dipyridamole, adenosine, and dobutamine stress with the use of Tc-99m tetrofosmin tomographic imaging. J Nucl Cardiol 1999;6:389–96.
9. Udelson JE, Heller GV, Wackers FJ, et al. Randomized, controlled dose-ranging study of the selective adenosine A_{2a} receptor agonist binodenoson for pharmacological stress as an adjunct to myocardial perfusion imaging. Circulation 2004;109:457–64.
10. Barrett RJ, Lamson MJ, Johnson J, et al. Pharmacokinetics and safety of binodenoson after intravenous dose escalation in healthy volunteers. J Nucl Cardiol 2005;12:166–71.
11. Reviewer Guidance: conducting a clinical safety review of a new product application and preparing a report on the review. U.S. Department of Health and Human Services FDA Center for Drug Evaluation and Research (CDER). Good Review Practices Feb. 2005;1–51.
12. Miller DD. Medical Globalization: "A Fin de Siecle Phenomenon." The Multinational Business Review 2004;11:113–42.
13. Miller DD, Donohue TJ, Younis LT, et al. Correlation of pharmacological ^{99m}Tc-sestamibi myocardial perfusion imaging with poststenotic coronary flow reserve in patients with angiographically intermediate coronary artery stenoses. Circulation 1994;89:2150–60.
14. Kern MJ, Hodgson JM, Rossen JD, et al. Hyperemic coronary blood flow induced by a selective adenosine A_{2a} receptor stimulation: first report in patients of a well tolerated novel agent for stress imaging. J Am Coll Cardiol 2001;37A:299A.