Regadenoson, a selective A_{2A} adenosine receptor agonist, causes dose-dependent increases in coronary blood flow velocity in humans

Hsiao D. Lieu, MD, FACC,[a] John C. Shryock, PhD,[b] Gregory O. von Mering, MD,[c] Toufigh Gordi, PhD,[d] Brent Blackburn, PhD,[b] Ann W. Olmsted, PhD,[b] Luiz Belardinelli, MD,[b] and Richard A. Kerensky, MD, FACC[e]

Background. **Regadenoson is a selective A_{2A} adenosine receptor agonist and vasodilator used to increase the heterogeneity of distribution of coronary blood flow during myocardial perfusion imaging. This study characterized the dose dependence of regadenoson-induced coronary hyperemia.**

Methods and Results. **An open-label, dose-escalation study of regadenoson (10-500 μg, rapid intravenous bolus) was performed in 34 subjects; in 4 additional subjects, the effect of aminophylline to reverse the response to regadenoson was determined. Intracoronary peak blood flow velocity in either the left anterior descending or left circumflex artery was measured by continuous Doppler signal recording, heart rate, central aortic blood pressure, and adverse effects were recorded. Regadenoson increased peak blood flow velocity by up to 3.4-fold in a dose-dependent manner. The mean duration of the increase in flow velocity of 2.5-fold or greater caused by 400 to 500 μg of regadenoson was 2.3 to 2.4 minutes. Regadenoson (400-500 μg) increased heart rate by up to 21 ± 6 beats/min and decreased systolic blood pressure (−5 ± 8 mm Hg to −24 ± 16 mm Hg) and diastolic blood pressure (−8 ± 4 mm Hg to −15 ± 14 mm Hg). Aminophylline (100 mg) attenuated the increase in peak flow velocity but not tachycardia caused by 400 μg of regadenoson.**

Conclusion. **The results of this study demonstrate the utility of regadenoson as a coronary vasodilator for myocardial perfusion imaging. (J Nucl Cardiol 2007;14:514-20.)**

Key Words: Regadenoson • coronary flow velocity • myocardial perfusion imaging • A_{2A} adenosine • Doppler • pharmacologic stress agent

Myocardial perfusion imaging using radionuclide agents for the detection and characterization of coronary artery disease is an integral part of cardiology practice.[1] Exercise stress remains the preferred stress modality in conjunction with myocardial perfusion imaging, but for those individuals who cannot exercise adequately, pharmacologic vasodilator stress caused by adenosine or dipyridamole is commonly used.[2] The technique is based on the principle that myocardial uptake of radionuclide is dependent on myocardial blood flow. During myocardial perfusion imaging, adenosine increases blood flow and radionuclide uptake in myocardium with a normal coronary flow reserve by up to 3- to 5-fold, whereas in myocardium with an impaired flow reserve—as a result of coronary stenosis, for example—the adenosine-mediated increases in blood flow and radionuclide uptake are much reduced.[2]

Regadenoson, a pyrazole derivative of adenosine that is selective for the A_{2A} adenosine receptor,[3] is currently being developed as a coronary vasodilator for myocardial perfusion imaging.[4,5] Regadenoson, unlike adenosine, is not a substrate for either adenosine deaminase or the cell membrane nucleoside transporter and thus is not rapidly metabolized in plasma. In awake dogs an intravenous bolus of 5 μg/kg of regadenoson caused a near-maximal (twice baseline) increase in coronary blood flow that was sustained for 247 ± 39 seconds.[6] In contrast, the effect of an intravenous bolus of 267 μg/kg

From the Portola Pharmaceuticals, South San Francisco, Calif[a]; CV Therapeutics, Palo Alto, Calif[b]; Division of Cardiology, College of Medicine, University of Florida, Gainesville, Fla[c]; Depomed, Menlo Park, Calif[d]; and Archbold Medical Center, Thomasville, Ga.[e]

This research was supported by a grant from CV Therapeutics, Palo Alto, Calif.

Drs Lieu and Shryock contributed equally to the manuscript.

Received for publication Oct 23, 2006; final revision accepted Feb 26, 2007.

Reprint requests: Richard A. Kerensky, MD, FACC, Archbold Medical Center, Gordon Avenue, Thomasville, GA 31792; *rakerensky@archbold.org.*

1071-3581/$32.00

Copyright © 2007 by the American Society of Nuclear Cardiology.

doi:10.1016/j.nuclcard.2007.02.016

Table 1. Characteristics of study subjects

	Regadenoson (n = 34)	Regadenoson and aminophylline (n = 4)
Age (± SD)	54.3 ± 11.1	57.5 ± 14.9
Male	16 (47%)	1 (25%)
Race		
Caucasian	30 (88%)	4 (100%)
Black	4 (12%)	
Weight (kg)	89.7 ± 20.2	81.2 ± 28.3
Study vessel		
LAD	29	4
LCX	5	
LVEF	57.4 ± 8.6	53.5 ± 5.0
CAD	14 (41%)	1 (25%)
Angina	15 (44%)	1 (25%)
PTCA	7 (21%)	0
Previous MI	3 (9%)	1 (25%)
HTN	23 (68%)	3 (75%)

CAD, Coronary artery disease; *HTN,* hypertension; *LAD,* left anterior descending; *LCX,* left circumflex; *LVEF,* left ventricular ejection fraction; *MI,* myocardial infarction; *PTCA,* percutaneous transluminal coronary angioplasty; *SD,* standard deviation.

of adenosine was sustained for only 24 ± 2 seconds.[6] Regadenoson (400-500 μg, intravenous bolus) was found to be as effective as a 6-minute adenosine infusion for detecting and quantifying the extent of myocardial ischemia observed with single photon emission computed tomography (SPECT) imaging.[5]

The effect of regadenoson to increase coronary blood flow velocity was determined in this study by use of an intracoronary Doppler-tipped guidewire. The goals of the study were to confirm the utility and tolerability of regadenoson as a coronary vasodilator for use in myocardial perfusion imaging and to identify a dose of regadenoson that causes an increase in blood flow velocity of 2-fold or greater of a suitable duration for imaging (ie, ≥2 minutes). The magnitude, dose dependence, duration of coronary hyperemia, and adverse events observed with regadenoson were characterized. Furthermore, the action of aminophylline (which is a dissociable complex of theophylline with ethylenediamine) to reverse the coronary hyperemic effect of regadenoson was assessed to confirm the reversibility of, and the role of adenosine receptors in, the hyperemic response to regadenoson.

METHODS

Study Population

Thirty-eight subjects were enrolled at four sites from September 2001 through January 2005 into an open-label, phase 2 study of the dose dependency, duration, and reversibility of regadenoson's coronary hyperemic effect (Table 1). Thirty-four patients were enrolled in a dose-escalation substudy, wherein each subject received a single injection of drug. Four additional patients were enrolled in a substudy to demonstrate the action of aminophylline to reverse the hyperemic effect of 400 μg of regadenoson. The study protocol was approved either by the institutional review board at a given site or by a central review board. Informed consent was obtained from each subject. Subjects aged 18 years or greater and undergoing clinically indicated cardiac catheterization for the evaluation or treatment of suspected ischemic heart disease were considered for enrollment. Subjects were excluded if they were found to have a 70% stenosis or greater in any coronary vessel, recent (within 1 month) myocardial infarction or unstable ischemic syndromes, coronary bypass or interventions within the last 6 months, left ventricular ejection fraction of less than 35%, decompensated or New York Heart Association class IV heart failure, moderate to severe aortic stenosis (<1.5 cm^2), a history of cardiac transplantation, known hypersensitivity to adenosine, a history of asthma, or chronic obstructive pulmonary disease. In addition, a positive response to intracoronary adenosine was a prerequisite for inclusion of each subject in the study. A positive response to adenosine was defined as an increase in average peak flow velocity by 2.5 or greater above baseline after an intracoronary (either the left anterior descending artery [n = 33] or left circumflex artery [n = 5]) 1.5-mL bolus injection of 18 μg of adenosine, as determined by pulsed-wave Doppler sonography. Medications with long-acting vasodilator agents (eg, calcium channel blockers and long-acting nitrates) and adenosine receptor antagonists (eg, theophylline and caffeine) were discontinued 24 hours before the study, and medications with short-acting nitrates were discontinued 2 hours before the study.

Download English Version:

https://daneshyari.com/en/article/2977067

Download Persian Version:

https://daneshyari.com/article/2977067

Daneshyari.com