The Safety of Intravenous Dipyridamole Thallium Myocardial Perfusion Imaging

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Clinical data on 3,911 patients were collected from 64 individual investigators to evaluate the safety of intravenous dipyridamole-thallium imaging as an alternative to exercise thallium imaging for the evaluation of coronary artery disease. There were two deaths because of myocardial infarctions, two nonfatal myocardial infarctions, and six cases of acute bronchospasm. Chest pain occurred in 770 patients (19.7%). Headache and dizziness were reported by 476 patients (12.2%) and 460 patients (11.8%), respectively. ST-T changes on the electrocardiogram were seen in 292 patients (7.5%). Use of parenteral aminophylline to treat adverse events associated with intravenous dipyridamole brought complete relief of symptoms in 439 of 454 patients (96.7%). There is a potential for increased risk for serious ischemic events in patients with a history of unstable angina who are administered intravenous dipyridamole. In patients with acutely unstable angina (i.e., continuing chest pain) or in the acute phase of myocardial infarction, use of intravenous dipyridamole in thallium scintigraphy should be avoided. There is also an increased risk for bronchospasm in patients with a history of asthma; acute bronchospasm can be relieved immediately by administration of aminophylline. These results demonstrate that intravenous dipyridamole-thallium scintigraphy is a relatively safe, noninvasive technique for the evaluation of coronary artery disease. (Circulation 1990;81:1205-1209)

In 1978, several studies reported the clinical usefulness of performing thallium myocardial perfusion imaging in conjunction with pharmacological vasodilation, using an infusion of intravenous dipyridamole to increase coronary blood flow. In the early 1980s, additional studies reported the usefulness of intravenous dipyridamole as an adjunct to thallium scintigraphy. With the publication of further studies and the recognition of the clinical usefulness of intravenous dipyridamole as an alternative to exercise in evaluating coronary artery disease (CAD) with thallium myocardial perfusion imaging, it was decided to seek regulatory approval to market intravenous dipyridamole for use as an adjunct to thallium scintigraphy. After the collection of clinical data for submission to regulatory authorities in the United States, additional studies were published that demonstrate the diagnostic usefulness of dipyridamole-thallium scintigraphy. This study focuses on the safety of dipyridamole-thallium scintigraphy with an analysis of the clinical safety data that were collected from investigators in the United States who had performed thallium myocardial imaging using intravenous dipyridamole.

Methods

Study Plan and Design

A total of 70 investigators who had received supplies of intravenous dipyridamole for thallium imaging studies were contacted to participate in this study. Of these, 64 investigators who had conducted intravenous dipyridamole-thallium imaging tests under their own Investigational New Drug applications between September 19, 1978, and August 1, 1985, contributed patient data to the study. Although these individual studies differed in design and had different goals, safety information common to all of them was collected retrospectively on standardized forms. Specifically, all adverse events that occurred within 24 hours after the administration of intravenous dipyridamole were recorded; the use and the degree of effectiveness of parenteral aminophylline or nitroglycerin for the treatment of adverse events associated with intravenous dipyridamole were recorded (note that investigators did not always identify the specific adverse events requiring treat-
ment with aminophylline); and pulse rate and blood pressure, both during and for up to 10 minutes after the infusion of dipyridamole, were recorded.

Two groups of patients were identified, and they were 1) those who had both intravenous dipyridamole-thallium scintigraphy and coronary angiography performed within a 1-year period and had the two tests interpreted blindly, that is, without knowledge of the patient's medical history or the results of other tests, and 2) those who had intravenous dipyridamole-thallium scintigraphy performed more than 1 year before or after coronary angiography or who had either test interpreted in an unblinded fashion.

Information concerning patient characteristics, intravenous dipyridamole dosage, and vital sign changes was collected for all patients in the former group but only for a subgroup of the patients in the latter group, specifically those who had an adverse event within 24 hours after the administration of intravenous dipyridamole. These data were not collected for all patients in this latter group because of time and resource constraints. The data for the former group provide some idea of the attributes of patients who are candidates for intravenous dipyridamole-thallium imaging and what happens to their vital signs when undergoing this procedure.

Informed consent from all patients and institutional review board approval were obtained by the individual investigators before initiation of clinical studies with intravenous dipyridamole.

Study Limitations

Although information was collected on the diagnostic usefulness (i.e., sensitivity and specificity) of dipyridamole-thallium scintigraphy as part of this study, this information is not presented here. The interpretation of the sensitivity-specificity data is complex because the data were collected retrospectively; there was no uniform protocol, no standard test procedures or equipment, and no uniform experience in conducting the test for all investigators (e.g., some investigators provided data from only one patient, whereas others provided data from more than 100 patients).

Additionally, demographic and baseline data were not collected on all patients who underwent intravenous dipyridamole-thallium imaging. Thus, estimation of mortality or morbidity rates for select subgroups of patients is not possible (e.g., the mortality rate in patients without a history of unstable angina).

Despite these problems in design, however, this study presents data for the largest collection of patients, to date, who have undergone dipyridamole-thallium scintigraphy, which allows evaluation of the safety of the procedure.

Patient Characteristics and Intravenous Dipyridamole Dosage

Of the 3,911 patients in this study, 1,096 (28.0%) were patients who had intravenous dipyridamole-thallium scintigraphy and coronary angiography performed within a 1-year period and whose tests were interpreted in a blinded fashion. Patient characteristics and dosage information were collected for all these 1,096 patients. Approximately two thirds of these 1,096 patients were male. The mean age of the patients was 57.7 years (SD, 10.4 years), with a range of 26–88 years. Almost 88% of the patients had a history of chest pain before undergoing thallium imaging. Nineteen patients (1.7%) had a history of nonanginal pain, 420 (38.3%) had stable angina, 505 (46.1%) had a history of unstable angina (i.e., chest pain at rest or recent acceleration of chest pain), and 16 (1.5%) had a history of nonspecific chest pain. Approximately 42% of the patients had a history of myocardial infarction, 9.0% had previous coronary artery bypass graft surgery, and 3.0% had a previous coronary angioplasty. The two most frequently reported concurrent diseases other than CAD were hypertension and cardiovascular disease, which were reported in 45.0% and 29.0% of the patients, respectively.

The most frequently reported concomitant medications included nitroglycerin (46.0%), isosorbide dinitrate (32.0%), propranolol hydrochloride (30.0%), and nifedipine (22.0%). The mean dosage of intravenous dipyridamole administered to these patients was 0.567 mg/kg (SD, 0.030 mg/kg), with a range of 0.14–0.79 mg/kg. Almost 93% of the patients were administered doses in the range of 0.55 to less than 0.65 mg/kg. The dipyridamole was always administered as a 4-minute infusion.

Results

Of the 3,911 patients in this study, a total of 10 patients (0.26%) had major adverse events and 1,820 (46.5%) had minor adverse events. Of the 10 patients with major adverse events, two patients had fatal myocardial infarctions (0.05%), two additional patients (0.05%) experienced nonfatal myocardial infarctions, and six patients (0.15%) experienced acute bronchospasm with wheezing. In each of these six patients, the bronchospasm was readily reversed with parenteral aminophylline. One of the patients who had a fatal myocardial infarction and both patients who experienced nonfatal infarctions had a history of unstable angina (chest pain at rest or recent acceleration of chest pain) before thallium imaging.

A complete listing of minor adverse events experienced by at least 1.0% of the patients in the study, in descending order of incidence, is contained in Table 1. The most common adverse events included chest pain, headache, dizziness, and ST-T changes on the electrocardiogram. In the subgroup of 1,096 patients, there were 420 patients with a history of stable angina pectoris, 124 (29.5%) of whom had chest pain associated with the administration of intravenous dipyridamole. Of the 505 patients with a history of unstable angina, 124 (24.6%) developed chest pain after administration of intravenous dipyridamole.

In the subgroup of 1,096 patients, 1,008 patients (92.0%) had vital sign data measured in a nonstand-
of intravenous dipyridamole-thallium imaging for the largest collection of patients available to date. It is important to emphasize that 46.5% of the patients within the study experienced a minor adverse event. Major adverse events (fatal and nonfatal myocardial infarction and acute bronchospasm) occurred in 0.26% of patients. Mortality, in this study of patients suspected of having CAD, was 0.05%. The two deaths occurred as a result of myocardial infarctions, whereas two other patients sustained nonfatal myocardial infarctions. Three of these four patients had a history of unstable angina (i.e., history of chest pain at rest or recent acceleration of chest pain). As reported by other investigators,6,10 such patients might be at an increased risk for cardiac complications, similar to the above-average risk for such complications seen with exercise stress testing.10 In a survey conducted on approximately 170,000 exercise stress tests, in which patients with unstable angina were specifically excluded, the crude mortality and morbidity were 0.01% and 0.02%, respectively.11 Although this crude mortality rate is less than the 0.05% rate found in the current study, the current study had many patients with a history of unstable angina. Nearly half (46.1%) of the group of 1,096 patients reported a history of unstable angina. The incidence of chest pain associated with the administration of intravenous dipyridamole in this subgroup of patients was approximately the same as in the subgroup of patients who reported stable angina pectoris (24.6% vs. 29.5%, respectively). Despite the apparent equal risk for chest pain in these two subgroups of patients, we strongly believe that a history of unstable angina might increase the risk of severe cardiac ischemic events. This conclusion is based on the fact that three of the four patients with severe ischemic events had a history of unstable angina. In patients with acutely unstable angina (i.e., continuing chest pain) or in the acute phase of myocardial infarction, it seems prudent to avoid the use of intravenous dipyridamole with thallium scintigraphy,12 and preferable to wait 2 or 3 days after symptoms have subsided.

The six cases of acute bronchospasm with wheezing might be related to the effect of dipyridamole in inhibiting adenosine uptake, resulting in acute elevation of adenosine blood levels.13 Elevated adenosine levels can lead to bronchospasm in patients with a history of asthma because inhaled adenosine has been shown to precipitate bronchospasm in some asthmatic patients but not in patients without such a history.14 Four of the six patients in this study who developed bronchospasm had either a history of asthma or evidence of wheezing on physical examination before administration of dipyridamole. Wheezing is believed to be evidence of reversible airway disease. All episodes of bronchospasm were rapidly reversed after administration of intravenous aminophylline.

### TABLE 1. Adverse Events Reported by Patients Who Underwent Intravenous Dipyridamole Thallium Imaging

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Patients (n) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest pain</td>
<td>770 (19.7)</td>
</tr>
<tr>
<td>Headache</td>
<td>476 (12.2)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>460 (11.8)</td>
</tr>
<tr>
<td>ST-T changes on electrocardiogram</td>
<td>292 (7.5)</td>
</tr>
<tr>
<td>Ventricular extrasystoles</td>
<td>204 (5.2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>180 (4.6)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>179 (4.6)</td>
</tr>
<tr>
<td>Flushing</td>
<td>132 (3.4)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>127 (3.2)</td>
</tr>
<tr>
<td>Pain (nonspecified)</td>
<td>102 (2.6)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>100 (2.6)</td>
</tr>
<tr>
<td>Blood pressure lability</td>
<td>61 (1.6)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>59 (1.5)</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>49 (1.3)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>45 (1.2)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>38 (1.0)</td>
</tr>
</tbody>
</table>

Values are for adverse events reported by at least 1.0% of total (100.0%) number of patients (3,911) studied.

The six cases of acute bronchospasm with wheezing might be related to the effect of dipyridamole in inhibiting adenosine uptake, resulting in acute elevation of adenosine blood levels.13 Elevated adenosine levels can lead to bronchospasm in patients with a history of asthma because inhaled adenosine has been shown to precipitate bronchospasm in some asthmatic patients but not in patients without such a history.14 Four of the six patients in this study who developed bronchospasm had either a history of asthma or evidence of wheezing on physical examination before administration of dipyridamole. Wheezing is believed to be evidence of reversible airway disease. All episodes of bronchospasm were rapidly reversed after administration of intravenous aminophylline.
In nearly all patients who were administered parenteral aminophylline to treat adverse events associated with administration of intravenous diprydramole, use of parenteral aminophylline proved very effective in relieving symptoms. This is in agreement with findings of previous investigations.2–4,6 The study strongly supports the recommendation that parenteral aminophylline be readily available when intravenous diprydramole-thallium scintigraphy is performed.

Intravenous diprydramole-thallium scintigraphy has been shown to be a relatively safe, noninvasive method for the evaluation of CAD. Only appropriately trained physicians who are able to perform advanced life support for any complications that might occur, however, should conduct the test. Potential advantages for intravenous diprydramole-thallium imaging as compared with exercise thallium imaging include the following: less time and equipment necessary to conduct the intravenous diprydramole thallium test, availability of aminophylline to promptly treat adverse events associated with intravenous diprydramole, and satisfactory performance of testing without need to have the patient perform exercise.

Appendix: Investigators Who Contributed Patient Data to This Study

Robert L. Allen, Cleveland, TN; Lewis C. Becker, The Johns Hopkins Medical Institutions, Baltimore, MD; Ruby Bendersky, Maplewood, NJ; Daniel S. Berman, Cedars-Sinai Medical Center, Los Angeles, CA; Eli Botvinik, University of California, San Francisco, CA; Charles Boucher, Massachusetts General Hospital, Boston, MA; Bruce Brent, Pacific Medical Center, San Francisco, CA; Kenneth Brown, University of Vermont, Burlington, VT; Richard J. Butcher, Geisinger Medical Center, Danville, PA; Bernard Chaitman, St. Louis University Medical Center, St. Louis, MO; William H. Clark, Tucson, AZ; J.V. Faris, VA Medical Center, Indianapolis, IN; Martin J. Frank, Medical College of Georgia, Augusta, GA; Myron C. Gerson, Cincinnati, OH; Alan Gladstone, Exeter, NH; Raymundo Go, Cleveland Clinic Foundation, Cleveland, OH; Donald Gordon, Jacksonville Cardiovascular Clinic, Inc, Jacksonville, FL; Edward W. Gott, St. John’s Regional Health Center, Springfield, MO; Joshua Greenberg, Worcester, MA; John Guillemont, Winchester Hospital, Winchester, MA; B.D. Gupta, South Lynnfield, MA; Laurence Hanlin, The Mason Clinic, Seattle, WA; Robert Jaros, Catholic Medical Center, Manchester, NH; Martin Josephson, Wadsworth VA Hospital, Los Angeles, CA; John Kenerson, Virginia Beach General Hospital, Virginia Beach, VA; Marvin A. Konstam, Tufts University School of Medicine, Boston, MA; Edward Kosinski, New England Deaconess Hospital, Boston, MA; Ricky Latham, Brooke Army Medical Center, Fort Sam Houston, TX; Henry LeBost, Brotman Medical Center, Culver City, CA; R. Leighton, Medical College of Ohio, Toledo, OH; Frank Leone, Enloe Hospital, Chico, CA; Jeffrey A. Leppo, University of Massachusetts Medical Center, Worcester, MA; J. E. Logic, University of Alabama Hospital, Birmingham, AL; M.L. Marcus, University of Iowa Hospital and Clinics, Iowa City, IA; Ismael Mena, University of California, Los Angeles, Torrance, CA; Fred Mishkin, Martin Luther King Jr. General Hospital, Los Angeles, CA; Christopher Modic, St. Clair Hospital, Pittsburgh, PA; Warren Moore, St. Luke’s Episcopal Hospital, Houston, TX; Lawrence Moser, Inter-Community Medical Center, Covina, CA; Judith Murphy, Hahnemann University Hospital, Philadelphia, PA; R.M. Murty, Ohio Valley Hospital, Stuebenville, OH; R.W. Myers, Mercy Hospital of Sacramento, Sacramento, CA; F.A. Pizgata, The Malden Hospital, Malden, MA; Steven Reisman, Long Island College Hospital, Brooklyn, NY; Martin Robinson, San Jose, CA; John Rockett, Memphis, TN; Heinrich Schelbert, University of California, Los Angeles School of Medicine, Los Angeles, CA; D.H. Schmidt, Mount Sinai Medical Center, Milwaukee, WI; Robert Schor, Swedish Hospital Medical Center, Seattle, WA; Lon G. Sherman, Newburger, PA; J. Sklar, Greenbrae, CA; Robert M. Sodaro, Western Medical Center, Santa Ana, CA; J. Stolzenberg, Miami Heart Institute, Miami, FL; James L. Tatum, Virginia Commonwealth University, Richmond, VA; E.H. Turbiner, Mercy Hospital, Pittsburgh, PA; G. Michael Uzslar, Santa Monica, CA; Eugene Van Hove, Methodist Hospital of Indiana, Inc, Indianapolis, IN; Ronald Veatch, Wishon Memorial Hospital, Indianapolis, IN; F.J. Wackers, Yale University School of Medicine, New Haven, CT; Richard Wilson, Oregon Health Sciences University, Portland, OR; M.A. Winston, St. Joseph Medical Center, Burbank, CA; Gary Winzelberg, Shadyside Hospital, Pittsburgh, PA; Jason Zielonka, VA Medical Center, Milwaukee, WI; Timm Zimmerman, Mount Vernon, WA.

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and exercise thallium-201 myocardial perfusion imaging. *Am Heart J* 1982;103:1008–1018

**Key Words:** thallium scintigraphy • dipyridamole • coronary angiography • exercise thallium scintigraphy • coronary artery disease
The safety of intravenous dipyridamole thallium myocardial perfusion imaging.

Intravenous Dipyridamole Thallium Imaging Study Group.

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