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# Adverse Reactions to Dipyridamole in Patients Undergoing Stress/Rest Cardiac Perfusion Testing

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**Objective:** A reaction scale was used to assess noncardiac adverse reactions exhibited by nuclear medicine outpatients receiving intravenous dipyridamole for pharmacological stress testing.

**Methods:** The study included 933 patients referred to 2 cardiac outpatient centers for assessment. All patients evaluated in this study were unable to perform treadmill stress testing and underwent pharmacological intravenous dipyridamole stress testing. Dual-isotope <sup>201</sup>Tl rest/<sup>99m</sup>Tc-sestamibi stress imaging was performed. An analysis of adverse reactions exhibited by patients given dipyridamole was tabulated.

**Results:** Of the 933 patients, 520 (55.7%) demonstrated no adverse reaction to intravenous dipyridamole; 413 patients (44.3%) had adverse reactions of some type. Many of these patients had multiple types of reactions, and a total of 604 reactions were recorded. The most prevalent adverse reaction was headache (224 reactions; 37.1%), followed by chest pain (73 reactions; 12.1%), and nausea (67 reactions; 11.1%). A sex comparison revealed 271 of 454 male patients (59.7%) and 249 of 479 female patients (52%) demonstrated no adverse reaction to intravenous dipyridamole. An evaluation of the most prevalent adverse reaction (headache) demonstrated a significant difference between males (37.9%) and females (62.1%).

**Conclusion:** An adverse reaction scale characterizing common noncardiac side effects of dipyridamole in nuclear medicine cardiac patients demonstrated the most prevalent adverse reaction was headache. Analysis by sex revealed that significantly more females than males complained of headaches.

**Key Words:** dipyridamole; pharmacological stress testing; <sup>99m</sup>Tc-sestamibi; <sup>201</sup>Tl; noncardiac side effects

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Myocardial perfusion imaging using a rest/stress protocol with either <sup>201</sup>Tl or <sup>99m</sup>Tc-sestamibi has proven to be a valuable tool in the early detection of coronary artery disease (CAD). Gated SPECT acquisition has also proven to be successful in assessing cardiac wall motion abnormalities (1,2).

Several studies have demonstrated that separate acquisition, dual-isotope myocardial perfusion SPECT imaging using <sup>99m</sup>Tc-sestamibi stress and <sup>201</sup>Tl rest can accurately assess CAD. The results correlate well with rest/stress <sup>99m</sup>Tc-sestamibi studies for assessing defect reversibility, and the image quality is good to excellent (1,3). The introduction of pharmacological alternatives to exercise stress for patients unable to perform treadmill exercise has affected the growth of nuclear stress testing. Dipyridamole stress imaging is a useful alternative to exercise stress testing in patients with ischemic heart disease (4).

Dipyridamole, adenosine, and dobutamine have been used successfully as alternatives to treadmill stress testing in patients with compromised peripheral vascular or cardiovascular status, prohibitive physical disabilities, or frailty, and in patients receiving concurrent pharmacological therapy such as  $\beta$ -blockers. Research into the effective use of dipyridamole pharmacological stress agents has shown this agent to be relatively safe. Many articles have indicated that high-dose dipyridamole is safe and easily reversed with intravenous aminophylline (4–9).

The purpose of this study was to evaluate the frequency of noncardiac (non-ECG-related) reactions to dipyridamole experienced by patients undergoing dual-isotope perfusion stress testing. Furthermore, this study evaluated the possibility of sex differences with regard to the type and frequency of adverse reactions after the administration of intravenous dipyridamole within this patient population.

## MATERIALS AND METHODS

The study group consisted of 933 patients referred to either of 2 outpatient nuclear medicine laboratories for

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assessment of myocardial viability and regional wall motion between September 1, 2000, and April 31, 2001. All of the patients involved in this study were unable to perform treadmill stress testing and underwent pharmacological stressing with intravenous dipyridamole. The data were then analyzed to determine the frequency of adverse reactions.

Evaluation of each patient included a rest perfusion  $^{201}\text{Tl}$  test followed by an intravenous dipyridamole pharmacological stress test with  $^{99\text{m}}\text{Tc}$ -sestamibi. Patients that were able to perform treadmill stress testing or required the use of adenosine or dobutamine were not included in this study. The resting protocol began with an injection of 130 mBq (3.5 mCi)  $^{201}\text{Tl}$ . Imaging was performed using a low-energy, high-resolution collimator on one of two single-head gamma cameras (SPX4; Elscint, Haifa, Israel, or FX830; Picker, Cleveland, OH). At both facilities, patients were imaged in a supine position with arms extended overhead. Imaging acquisition required approximately 20 min.

All 933 patients in this study were pharmacologically stressed using dipyridamole. Dipyridamole dose calculation was based on patient weight (kg) times 0.57 mg/kg. The maximum dipyridamole dose was 60 mg. The dipyridamole dose was diluted in 45–50 mL saline and administered over 4 min through a continuous pump. Blood pressure was monitored continuously during the infusion. If a 10-point drop in diastolic blood pressure was noted, patients were immediately injected with 925 mBq (25 mCi)  $^{99\text{m}}\text{Tc}$ -sestamibi. If diastolic blood pressure did not drop by 10 points, patients were injected with the radiopharmaceutical 8 min after the start of the infusion. Patients that demonstrated an adverse reaction to dipyridamole were given 75–150 mg intravenous aminophylline. Patients that indicated they were having chest pain were given nitroglycerin spray (400 mg) under the tongue. Imaging at both sites began 30 min after  $^{99\text{m}}\text{Tc}$ -sestamibi injection.

A reaction scale was developed before patient information was gathered and was designed to gather information on the types of adverse reactions the patients experienced. Patient information included sex, age, date of examination, and any adverse reaction recorded by the nuclear medicine technologist at the facility. The reaction scale included the following reactions: 1 = no reaction, 2 = shortness of breath, 3 = nausea, 4 = flushing sensation, 5 = headache, 6 = lightheadedness, 7 = dizziness, 8 = chest pain, 9 = tightness in neck or arm, and 10 = any other reaction not listed. Certified nuclear medicine technologists gathered pertinent data and identified on the reaction scale the type, if any, of adverse reactions the patients exhibited.

After 7 mo of data collection, the data from both outpatient cardiology centers were analyzed. The total number of reactions was tabulated and sex differences (if any) were assessed.

## RESULTS

Patient adverse reactions to dipyridamole were tabulated and analyzed based on the 10 categories in the

reaction scale. Of the 933 patients that underwent dipyridamole stress testing, 520 did not exhibit any identifiable noncardiac adverse side effect. Many patients that did complain of adverse reactions had multiple symptoms. Of the 933 patients, 413 (44%) complained of some form of adverse reaction to dipyridamole stress testing, and a total of 604 observed adverse reactions were recorded. Of the 604 adverse reactions recorded, headache was the most frequent complaint (224 reactions; 37.1%). Chest pain (73 reactions; 12.1%) and nausea (67 reactions; 11.1%) were the second and third most common adverse reactions recorded. All other adverse reactions exhibited by patients to dipyridamole occurred in fewer than 10% of patients (Table 1).

This study also evaluated sex differences in regard to the amount and type of adverse reactions to dipyridamole exhibited by patients at both outpatient cardiology centers. The total patient population consisted of 454 males and 479 females. Of the 540 patients that did not experience any adverse side effects, 271 were male and 249 were female (Table 2). A sex comparison found the higher number of females than males exhibiting adverse reactions to dipyridamole to be statistically significant (Table 3). The largest discrepancy between the sexes was exhibited when comparisons were made regarding the most predominant adverse reaction, headache. Of the 224 patients that complained of headache, 85 (37.9%) were male and 139 (62.1%) were female (Table 4).

## DISCUSSION

Data related to patient adverse reactions to intravenous dipyridamole during a nuclear medicine stress/rest myocardial perfusion study were quantified by the participating cardiac outpatient facilities. Overall, the data showed a 44% adverse reaction rate to the administered intravenous dipyridamole. Many research articles have investigated and concluded that the use of dipyridamole is a relatively safe alternative to treadmill stress testing (4,8–15). Some of these studies have reported adverse reaction rates of any-

**TABLE 1**  
Types of Adverse Reactions to Dipyridamole

Reaction scale	Type of reaction	No. of reactions		Percentage of total reactions
		Site 1	Site 2	
1	No adverse reaction	233	287	
2	Shortness of breath	17	10	4.5
3	Nausea	48	19	11.1
4	Flushing sensation	25	26	8.4
5	Headache	126	98	37.1
6	Lightheadedness	27	25	8.6
7	Dizziness	22	9	5.1
8	Chest Pain	50	23	12.1
9	Tightness in neck or arm	21	16	6.1
10	Other	39	3	7.0

**TABLE 2**  
Adverse Reactions by to Dipyridamole Sex

Patient category	Site 1		Site 2		Total, no. (% of total patients)	
	Male	Female	Male	Female	Male	Female
All patients	252	235	202	244	454 (48.7)	479 (51.3)
No adverse reaction	141	89	130	160	271 (29.0)	249 (26.7)
Adverse reaction	111	146	72	84	183 (19.6)	230 (24.7)

where between 25% and 60% for their particular patient populations (10–15).

In our study of 933 patients, the total adverse reaction rate of 44% agrees well with other studies. However, the most prevalent adverse noncardiac reaction in our study was headache, followed by chest pain and nausea. A recent article by Jacobsen and Lassen found that headache was an important side effect to administration of dipyridamole. Although many of these studies found headache as a noncardiac side effect to dipyridamole use, it was not the most common side effect identified.

A number of studies reported the most frequent adverse reaction to dipyridamole administration to be chest pain. Studies by Miller and Scott (8) reported chest pain to comprise approximately 30% of all adverse reactions. Zhu and Chung (16) reported that 44% of their patients with known or suspected unstable angina experienced chest pain. Several large studies on dipyridamole stress testing (11–13) reported that chest pain occurred in approximately 20% of their patients. Most of these studies reported that headache occurred in about 10% of patients. In this study, because the most common adverse reaction to dipyridamole was headache, the researchers investigated possible differences related to sex.

Many studies have concluded that dipyridamole is safe for both men and women, but few have investigated sex-related differences in the types of reactions observed. Cardiologists involved in this study have postulated that the higher percentage of female patients complaining of

headache may be due to a greater willingness among female patients to express their adverse physical status to the technologist, in contrast to their male counterparts, who may be less willing to state they had a problem.

#### Limitations of the Study

This study was limited to the patient populations at the 2 cardiac outpatient facilities in the time-frame studied. Generalizations of results beyond the sample must be made with caution. The different technologists that documented results at the time of testing may have inadvertently influenced the data collected and recorded over the 7-mo evaluation period. Therefore, accurate interpretation by the authors may have been limited in this study.

#### CONCLUSION

This retrospective study evaluated noncardiac adverse reactions in 933 patients who were administered intravenous dipyridamole for nuclear medicine stress testing at 2 outpatient cardiology centers over a 7-mo period. In this study, 413 patients (44.3%) demonstrated some form of adverse reaction. The most prevalent of these adverse reactions was headache. A statistically significant difference was found between males and females relating to adverse reactions to dipyridamole. Overall, females demonstrated a higher rate of adverse reactions, and substantially more women than men complained of headache after the administration of dipyridamole.

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**TABLE 3**

Observed and Expected Adverse Reaction Rates to Dipyridamole

Patient category	No. observed (expected)		Total
	Male	Female	
No adverse reaction	271 (253)	249 (267)	520
Adverse reaction	183 (201)	230 (212)	413
Total observed	454	479	933

$\chi$ -square value 5.61 > 3.84 is the critical value at  $P = 0.05$ .

**TABLE 4**

Male and Female Patients with Headache as an Adverse Reaction to Dipyridamole

	Male	Female
Site 1	45	78
Site 2	40	61
Total, no. (%)	85 (37.9)	139 (62.1)

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