Dipyridamole-induced adverse effects in myocardial perfusion scans: Dynamic evaluation

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Abstract

Aim and Background: Dipyridamole-induced stress myocardial perfusion scans (MPS) has been widely used for management of coronary artery disease. The adverse effects of dipyridamole and other stress agents have been evaluated. The aim of this research is to confirm the dynamic data on dipyridamole side effects during MPS.

Methods: We collected data of 183 patients who underwent dipyridamole-induced stress MPS by retrospectively reviewing their clinical records, which included the severity of dipyridamole side effects in 3 min, 10 min, and 20 min after infusion. The incidence and severity at all three points, including the effect of age and gender, were obtained.

Results: Adverse effects occurred in 96 patients (69.6%). The most frequent symptoms were dizziness (42.8%), chest tightness (24.6%), abdominal pain (18.1%), and headache (15.2%). Most symptoms were Grade 1 to 2, according to the grading system for common terminology criteria. The median duration of symptom persistence was 36 min, not significantly different among age and gender.

Conclusion: This study demonstrates that the adverse effects of dipyridamole were generally minimal and its duration was acceptable for clinical usage.

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Keywords: Dipyridamole, Myocardial perfusion scan, Adverse effects

1. Introduction

Cardiovascular disease has been the second most common mortality since 2000 in Taiwan [1]. Myocardial perfusion imaging (MPI) is a useful tool in diagnosing and follow up care for coronary artery disease [2]. According to current clinical guidelines for better sensitivity and specificity, the exam is performed with a stress test [2–4]. Dipyridamole, a vasodilator, is one of the most widely used agents in stress tests in Taiwan. According to prior literature, up to 70% of patients undergoing dipyridamole stress suffer from adverse effects such as flush, chest pain, headache, dizziness, hypotension, abdominal pain, or diarrhea [5–9]. However, severity and duration of adverse effects have not been analyzed. As stated, the aim of this study is to examine dynamic data of dipyridamole side effects during MPS.

2. Materials and methods

2.1. Patients and data collection

In our institute, symptoms of patients receiving dipyridamole-stress MPI for 3 min, 10 min, and 20 min were recorded, according to the Common Terminology Criteria of Adverse Effects v4.0 (CTCAE) [10]. Records were written and maintained by physicians and technicians. Symptoms recorded included: chest tightness, palpitation, abdominal pain, diarrhea, nausea, headache, dizziness, neck pain, dyspnea, weakness, and flush. If symptoms persisted for more than 20 min after administration, we recorded timing of recovery. In the case of aminophylline use to relieve adverse effects, we also recorded administration timing.

From July 2nd 2013 to July 19th 2013, there were 183 patients receiving MPI. There were 138 complete records of symptoms after delivery of dipyridamole. For an evaluation of confounding factors, we collected the following parameters: age, gender, and frequency of regular exercise. These comorbidities were recorded in the clinical chart review: hypertension, diabetes, dyslipidemia, prior myocardial infarction (MI), documented coronary artery disease (CAD), and congestive...
Results

males and females, the age groups, and the exercise groups. The Kaplan-Meier curve and Cox regression test were used for comparison between evaluation of confounding factors, e.g., gender and age, the Kaplan-Meier curve was used to highlight persistent symptoms. The frequency and severity of adverse effects are listed in Table 2 and Fig. 1. Adverse effects occurred in 96 patients (69.6%), with the most frequent symptoms being dizziness (42.8%), chest tightness (24.6%), abdominal pain (18.1%), and headache (15.2%). These effects accompany dyspnea (8.7%), nausea (8.0%), neck pain (7.2%), weakness (5.1%), palpitation (3.6%), and flush (2.9%). No patients had diarrhea in our study population, while most symptoms were Grade 1 and 2. Seven patients receiving aminophylline treatment due to adverse effects. For patients with symptoms at 3 min, the persistent symptoms can be seen in the Kaplan-Meier curve (Fig. 2). The median duration of persistent symptoms was 36 min (95% confidence interval [CI]: 30–46 min). Fifty-six patients (40.6%) did not recover from side effects at 20 min, while 32 of them were female.

2.3. Statistics

R project version 3.1.2 was used for statistical analysis. The continuous parameters were expressed in terms of mean and standard deviation (SD). The categorical variables were expressed as count and percentage. Severity of each symptom at 3 min, 10 min, and 20 min were also expressed as count and percentage. No patients had diarrhea in our study population, while most symptoms were Grade 1 and 2. Seven patients receiving aminophylline treatment due to adverse effects. For patients with symptoms at 3 min, the persistent symptoms can be seen in the Kaplan-Meier curve (Fig. 2). The median duration of persistent symptoms was 36 min (95% confidence interval [CI]: 30–46 min). Fifty-six patients (40.6%) did not recover from side effects at 20 min, while 32 of them were female.

3. Results

Data from 138 patients were analyzed and listed in Table 1. The average age was 66.1 ± 13.4 years (range 32–90). Seventy-five were male (54.3%) and 60 study subjects exercised more than 3 times per week (43.5%). There were 96 patients (69.6%) suffering from symptoms of heart failure. The laboratory data over 3 months were also recorded: creatinine level, lipid profile, and hepatic enzyme glutamate pyruvate transaminase (GPT).

These methods were approved by our institutional review board.

2.2. Stress protocol

All patients underwent the Thallium-201 (Ti-201) stress and early-redistribution MPI with the diprydamole stress test, on the recommendation of the Society of Nuclear Medicine and Molecular Imaging (SNMMI and EANM). Heart rate, blood pressure, and ECG monitoring were performed throughout the stress test.

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Table 1

| Total | Symptomatic | Asymptomatic | P-value |
|-------|-------------|--------------|---------|
| Number 138 | 96 | 42 | 0.002141 |
| Gender Male | 75 (54.3%) | 41 (42.7%) | 33 (78.6%) | 0.009262 |
| Female | 63 (45.7%) | 55 (57.3%) | 9 (21.4%) |
| Age (years old) 66.1 ± 13.4 (32-90) | 64.2 ± 13.24 (32-90) | 70.6 ± 12.88 (41-90) | 0.009262 |
| Frequency of exercise (times per week) | Range 0-7 | Median 2.8 | 2.5 | 0.4626 |
| Using aminophylline | 18 | 60 (43.5%) |
| Timing (min) 22.2 ± 8.5 |
| Comorbidity Hypertension | 85 (61.6%) | 56 (58.3%) | 29 (69.0%) | 0.317 |
| Diabetes | 37 (26.8%) | 24 (25.0%) | 13 (31.0%) | 0.6048 |
| Dyslipidemia | 51 (37.0%) | 34 (35.4%) | 17 (40.5%) | 0.7077 |
| Prior MI | 22 (15.9%) | 14 (14.6%) | 8 (19.0%) | 0.6844 |
| Documented CAD | 39 (28.3%) | 23 (24.0%) | 16 (38.1%) | 0.1358 |
| Congestive heart failure | 10 (7.2%) | 7 (7.3%) | 3 (7.1%) | 1.0000 |
| Creatinine (n = 125) 1.37 ± 0.17 (0.57–6.87) | 1.19 ± 0.77 (0.57–6.69) | 1.79 ± 1.49 (0.81–6.06) | 0.02368 |
| HDL (n = 111) 40.3 ± 10.52 (19–77) | 40.8 ± 10.63 (22–77) | 39.17 ± 9.88 (19–59) | 0.4284 |
| LDL (n = 111) 97.52 ± 29.16 (41–218) | 97.17 ± 27.07 (41–195) | 98.29 ± 33.69 (48–218) | 0.8642 |
| TG (n = 106) 155.95 ± 113.54 (35–769) | 162.07 ± 108.49 (35–552) | 142.42 ± 124.68 (35–552) | 0.438 |
| GPT (n = 119) 29.77 ± 26.98 (4–261) | 29.66 ± 17.7 (6–161) | 30.03 ± 41.48 (4–261) | 0.9597 |
| Pretest SBP 150.95 ± 22 (101–214) | 150.25 ± 23.32 (101–214) | 152.57 ± 18.82 (110–183) | 0.5392 |
| Pretest DBP 86.88 ± 12.3 (57–126) | 86.87 ± 13.43 (57–126) | 86.90 ± 9.75 (61–106) | 0.9876 |
| Post test SBP 130.8 ± 18.27 (94–188) | 128.02 ± 15.20 (94–184) | 128.02 ± 15.20 (94–184) | 0.1971 |
| Post test DBP 75.21 ± 11.87 (49–113) | 75.8 ± 12.37 (52–113) | 73.86 ± 11.06 (49–95) | 0.3505 |

Table 2

| Symptomatic Asymptomatic P-value |
|---------------------------------|---------|---------|
| Total 3rd minute 10th minute 20th minute Any time |
| Chest tightness 26 (18.8%) 24 (17.4%) 17 (12.3%) 34 (24.6%) 0.002141 |
| Palpitation 4 (2.9%) 2 (1.4%) 2 (1.4%) 5 (3.6%) |
| Abdominal pain 13 (9.4%) 19 (13.8%) 7 (5.1%) 25 (18.1%) |
| Dyspnea 10 (7.3%) 7 (5.1%) 4 (2.9%) 12 (8.7%) |
| Diarrhea 0 0 0 0 |
| Nausea 5 (3.6%) 7 (5.1%) 7 (5.1%) 11 (8.0%) |
| Headache 16 (11.6%) 13 (9.4%) 11 (8.0%) 21 (15.2%) |
| Dizziness 52 (37.7%) 45 (32.6%) 30 (21.7%) 59 (42.8%) |
| Neck pain 5 (3.6%) 5 (3.6%) 8 (5.8%) 10 (7.2%) |
| Weakness 3 (2.2%) 6 (4.3%) 7 (5.1%) 7 (5.1%) |
| Flush 3 (2.2%) 1 (0.7%) 1 (0.7%) 4 (2.9%) |
| Overall 84(60.9%) 79 (57.2%) 56 (40.6%) 96 (69.6%) |

"S.-D. Lee et al. / IJC Heart & Vasculature 14 (2017) 14–19"
There was a significantly higher incidence of adverse effects in the female population than the male population at all points (Tables 1 and 3). There is a higher incidence in women for the three time points of dizziness, chest tightness, abdominal pain, headache, dyspnea, nausea, weakness, and palpitation. However, there is a significant difference between genders for dizziness only at 10 min.

There is no significant difference of symptom duration between genders (Fig. 3), as the p value of the Cox regression is 0.421. The median time for symptom-relief took 33 min for women and 36 min for men. Women tend to have a higher incidence of adverse effects, and more severe symptoms. There is a significant difference in dizziness between the two groups at 10 min ($p = 0.003724$).

Younger patients (age <65) tended to have a higher probability of adverse effects than older patients, which was the only statistically significant difference at 3 min (Table 4). The younger group had a greater risk for all symptoms except dizziness. Symptom duration was similar between age groups (Fig. 4), and $p = 0.374$. The median time of symptom-relief took 33 min in older people and 48 min in younger people. Younger people also had a higher incidence of adverse effects and more severe symptoms. There was not a significant difference for chest tightness and nausea between the two groups at 3 min ($p = 0.000162$). Exercise did not interfere with adverse dipyridamole effects in our study. (See Table 5.)

4. Discussion

The purpose of the MPI stress test is to induce a distinction in blood flow between normal coronary arteries and those with stenosis. Dipyridamole has been used as a pharmaceutical method of stress testing. Dipyridamole infusion blocks reabsorption and metabolism of endogenic adenosine [11,12], elevates extra-cellular adenosine concentration [12,13], non-selectively activates all types of adenosine receptors [12], induces vascular resistance of normal coronary artery decrease, and creates myocardial blood flow increase up to 5-fold [11–13]. On the other hand, the blood flow of the myocardium, which is supplied by stenosed coronary arteries, was unable to increase blood flow from the stress due to compensatory dilation at rest [11, 12]. Dipyridamole-stress MPI is able to detect coronary artery disease as accurately as exercise stress tests, and provides prognostic information regarding cardiac death and myocardial infarction [11].

Using dipyridamole in myocardial perfusion is generally safe [5–8, 13,14]. Nevertheless, up to 70% of patients undergoing dipyridamole stress suffer from variable adverse effects, such as flush, chest pain, headache, dizziness, hypotension, abdominal pain, or diarrhea [5–9]. Adverse effects can develop from stimulating different types of adenosine receptors and signal pathways, including peripheral vasodilation and hypotension [12].

In our study population, 69.6% of patients suffered from the adverse effects of dipyridamole. The most frequent symptoms were dizziness, chest tightness, abdominal pain, and headache. Prior literature shows the incidence of adverse effects from dipyridamole can range from 27.9% to 75.36% [5–7,9,15–17]. However, there is a wide variation of the definition of adverse effects among studies.
Table 3
Incidence of symptomatic patients at 3, 10, and 20 min for gender.

| Table 3 | Male (n = 75) | Female (n = 63) | p value |
|---------|--------------|----------------|---------|
| 3rd minute | 35 (46.7%) | 49 (77.8%) | 0.000378* |
| Chest tightness | 10 (13.3%) | 16 (25.4%) | 0.1126 |
| Palpitation | 1 (1.3%) | 3 (4.8%) | 0.4924 |
| Abdominal pain | 6 (8.0%) | 7 (11.1%) | 0.7409 |
| Dyspnea | 3 (4.0%) | 7 (11.1%) | 0.2022 |
| Diarrhea | 0 | 0 | – |
| Nausea | 1 (1.3%) | 4 (6.3%) | 0.2656 |
| Headache | 7 (9.3%) | 9 (14.3%) | 0.5233 |
| Dizziness | 24 (32.0%) | 27 (42.9%) | 0.2546 |
| Neck pain | 1 (1.3%) | 4 (6.3%) | 0.2659 |
| Weakness | 0 | 3 (4.8%) | 0.1853 |
| Flush | 2 (2.7%) | 1 (1.6%) | 1 |
| 10th minute | 32 (42.7%) | 46 (73.0%) | 0.0006497* |
| Chest tightness | 10 (13.3%) | 14 (22.2%) | 0.2515 |
| Palpitation | 1 (1.3%) | 1 (1.6%) | 1 |
| Abdominal pain | 8 (10.7%) | 11 (17.5%) | 0.3651 |
| Dyspnea | 1 (1.3%) | 6 (9.5%) | 0.07271 |
| Diarrhea | 0 | 0 | – |
| Nausea | 2 (2.7%) | 5 (7.9%) | 0.3097 |
| Headache | 6 (8.0%) | 7 (11.1%) | 0.7409 |
| Dizziness | 16 (21.3%) | 29 (46.0%) | 0.003724* |
| Neck pain | 3 (4.0%) | 2 (3.2%) | 1 |
| Weakness | 1 (1.3%) | 5 (7.9%) | 0.14 |
| Flush | 1 (1.3%) | 0 | 1 |
| 20th minute | 24 (32.0%) | 32 (50.8%) | 0.03888* |
| Chest tightness | 7 (9.3%) | 10 (15.9%) | 0.3658 |
| Palpitation | 1 (1.3%) | 1 (1.6%) | 1 |
| Abdominal pain | 1 (1.3%) | 6 (9.5%) | 0.07271 |
| Dyspnea | 1 (1.3%) | 3 (4.8%) | 0.4924 |
| Diarrhea | 0 | 0 | – |
| Nausea | 2 (2.7%) | 5 (7.9%) | 0.3097 |
| Headache | 5 (6.7%) | 5 (7.9%) | 1 |
| Dizziness | 12 (16.0%) | 18 (28.8%) | 0.115 |
| Neck pain | 4 (5.3%) | 4 (6.3%) | 1 |
| Weakness | 2 (2.7%) | 5 (7.9%) | 0.3097 |
| Flush | 0 | 0 | – |
| Any time | 42 (56.0%) | 54 (85.7%) | 0.01226* |
| Chest tightness | 46 (73.0%) | 38 (50.7%) | 0.000162* |
| Palpitation | 21 (31.3%) | 5 (6.7%) | 0.4924 |
| Abdominal pain | 8 (12.7%) | 7 (5.7%) | 0.3598 |
| Dyspnea | 6 (9.5%) | 4 (5.3%) | 0.5378 |
| Diarrhea | 0 | 0 | – |
| Nausea | 5 (7.9%) | 0 | 0.04257* |
| Headache | 11 (17.5%) | 5 (6.7%) | 0.08804 |
| Dizziness | 22 (34.9%) | 29 (38.7%) | 0.7817 |
| Neck pain | 4 (6.3%) | 1 (1.3%) | 0.2656 |
| Weakness | 2 (3.2%) | 2 (1.3%) | 0.8785 |
| Flush | 2 (3.2%) | 1 (1.3%) | 0.8785 |

The half-life of dipyridamole is approximately 30–45 min [12]. In our study, the median duration of persistent symptoms was 36 min. Duration of symptoms was not significantly different between gender and age group.

In our study population, the most frequent symptom was dizziness, which made up 42.8% of patients. Most of the symptoms were Grade 1, although nobody suffered from severe dizziness (Grade 3). A study by Takeishi et al. revealed similar results, i.e., that the incidence of dizziness from dipyridamole-stress MPI was 51% [17]. In contrast, Colarinha et al. showed that 13 individuals out of 140 patients (9.3%) undergoing...
dipyridamole-stress MPI experienced dizziness [16]. The variation may have resulted from different awareness levels of it.

The second most frequent symptom was chest tightness, with an accumulated incidence of 24.6%. It is much higher than found in prior studies, ranging from 0.68% to 16.4% [5,6,13,15,16], but lower than the results of Takeishi et al. [17]. Most of our patients suffered from mild chest tightness, although only 12 patients (8.7%) had chest tightness greater or equal to Grade 2, and only four people (2.9%) had Grade 3 chest tightness. Dipyridamole-induced chest tightness has been correlated with more severe coronary artery disease [17].

According to our data, females have a greater potential to experience adverse effects (Table 3 and Fig. 2). This phenomenon is revealed in a prior study [6,8,18]. Our data revealed that women have a higher accumulated risk for all symptoms. However, there is a statistically significant difference in dizziness at 10 min, similar to the results of Kong [16]. The gender difference is not yet clear, but could possibly be related to different fat-to-muscle ratio [18].

In our study population, younger subjects have greater potential to have adverse effects, except for dizziness (Table 4). A report from Lette et al. revealed that the frequency of dipyridamole-induced side effects is less in patients older than 70 [8]. Adenosine-related side effects also occur more frequently in younger people [22]. Our data shows, compared to those older than 65, that younger people have higher risk of all symptoms, except dizziness. There is a significant difference of chest tightness and nausea between the two age groups, but only at 3 min.

The limitation of our study includes a retrospective study design with some missing data (24.6%), and a relatively small population. Due to these issues, we did not record symptom onset more than 20 min after the dipyridamole injection, and as such, any delayed adverse effects were not evaluated.

5. Conclusion

Our study reveals that dipyridamole use in MPS is generally safe. Women and younger people tended to have a higher risk of adverse effects. However, there is a trend that the elderly have a higher risk of dizziness than younger people. Duration of adverse effects was not significantly different for gender and age.

Conflicts of interest

No.

Acknowledgement

No.

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