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SHORT COMMUNICATION

Younger Females Are at Greater Risk of Vasodilation-Related Adverse Symptoms Caused by Dihydropyridine Calcium Channel Blockers: Results of a Study of 11,918 Japanese Patients

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Abstract

Background and Objective Adequate control of blood pressure in younger females is of crucial importance, because they are at higher risk of hypertensive target organ damage compared with males of similar age. In addition, female sex is a risk factor for adverse effects of antihypertensive drugs, especially dihydropyridines. This study set out to assess the incidence of adverse reactions during dihydropyridine use in a real-life clinical setting, focusing on the influence of female sex and age.

Methods The incidence of adverse reactions to dihydropyridine calcium channel blockers were investigated in 11,918 Japanese patients who participated in the Drug Event Monitoring project of the Japan Pharmaceutical Association conducted in Kumamoto prefecture. A multiple logistic regression analysis was used to determine the association between the incidence of adverse symptoms and female sex, with adjusted odds ratios (ORs) and 95 % confidence intervals (95 % CIs).

Results Vasodilation-related adverse symptoms occurred significantly more often in females than in males (OR 1.87, 95 % CI 1.28–2.71, $p = 0.001$). Furthermore, among females only, the younger age group (<50 years) complained of vasodilation-related symptoms more frequently (OR 2.39, 95 % CI 1.02–5.59, $p = 0.045$) and the older age group (≥80 years) complained of vasodilation-related symptoms less frequently (OR 0.56, 95 % CI 0.33–0.95, $p = 0.030$) than the middle age group (50–79 years).

Conclusion To the best of our knowledge, this is the first report showing that younger females are at high risk for vasodilation-related adverse symptoms during dihydropyridine use in a real-life clinical setting. These results should be verified in clinical studies using larger samples of young patients and more parameters.

Key Points

Vasodilation-related adverse symptoms during dihydropyridine use occurred significantly more often in females than in males in a real-life clinical setting.

This is the first report showing that younger females are at high risk for vasodilation-related adverse symptoms.

1 Background and Objective

Recently, Hadaegh et al. [1] reported that the effects of hypertension on incident cardiovascular disease (CVD)

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were stronger in younger patients than in the elderly (≥60 years). In particular, premenopausal females are indicated to have an increased risk of hypertensive target organ damage compared with males of similar age [2]. Although adequately controlling blood pressure (BP) in high-risk patients is of crucial importance, female sex is a risk factor for adverse effects of antihypertensive drugs [3, 4]. As for dihydropyridine calcium channel blockers (dihydropyridines), females exhibit a twofold higher incidence of vasodilation-related adverse reactions (flushing, headaches, dizziness and peripheral oedema) [4]. Among these adverse reactions, flushing and headaches appear to be more common in young females [4] and are a major reason for the discontinuation of these drugs [3]. However, there are currently no data available regarding adverse reactions of dihydropyridines among younger females.

We therefore aimed to investigate the incidence of adverse reactions during dihydropyridine use in a real-life clinical setting, with particular attention devoted to the influence of female sex and age.

2 Patients and Methods

The Drug Event Monitoring (DEM) project, initiated by the Japan Pharmaceutical Association (JPA) in February 2003, is an annual nationwide surveillance program designed to monitor adverse drug events (ADEs) in cooperation with JPA member pharmacies [5]. Three dihydropyridines—amlodipine besylate, nifedipine including the sustained-release preparation, and benidipine hydrochloride—were investigated in 2007. Every patient who visited a pharmacy affiliated with the JPA DEM project with a prescription for a target drug during 1 week of surveillance was asked to participate in the project. The participants were interviewed by pharmacists using structured questionnaires to assess the self-perception of adverse symptoms after the last prescription of the target drug. The questionnaires included open questions regarding demographic information and adverse symptoms and a checklist of symptoms that can be caused by the target drugs (Supplemental Table 1). A total of 484 (70.0 %) pharmacies in Kumamoto prefecture, Japan, responded to the survey, and the survey results of 12,146 participants were collected via a web-based system linked to a reporting portal in the KUMAYAKU Network for Community Pharmacies in Kumamoto [5]. This protocol was approved by the institutional ethics committee of the Faculty of Life Sciences at Kumamoto University.

A multiple logistic regression analysis was used to determine the association between the incidence of adverse symptoms and female sex, with adjusted odds ratios (ORs) and 95 % confidence intervals (95 % CIs). In the analysis, the ORs were adjusted for the potential confounding factors (i.e. age, daily dose and number of concomitant antihypertensive agents). We also calculated the ORs in the patients stratified by age (<50 years, 50–79 years and ≥80 years). In order to assess the daily dose of three different drugs in the same way, we divided the prescribed daily dose for each subject by the defined maximum daily dose approved in Japan, i.e. 10 mg for amlodipine besylate, 40 mg for nifedipine and 8 mg for benidipine hydrochloride. Categorical and continuous variables were compared using Fisher's exact test and Student's *t* test, respectively. A p value of <0.05 was considered to be statistically significant. All statistical analyses were performed using the SPSS software package for Windows (Version 17.0, IBM Japan Ltd, Tokyo, Japan).

3 Results

Of the 12,146 participants, 228 were excluded because of missing data for age, sex, adverse symptoms and/or the name of the surveyed drug, leaving 11,918 patients (98.1 %) (5,057 males and 6,861 females) for the analyses. The mean age of the subjects was 71.5 ± 11.2 years (17–101 years). The females were older and were treated with lower doses of dihydropyridines in addition to more frequent monotherapy and fewer concomitant antihypertensive drugs than the males (Table 1). Amlodipine besylate and benidipine were more likely to be prescribed to females, while controlled-released nifedipine was more likely to be prescribed to males.

Adverse symptoms occurring after previous prescriptions were reported by 258 (2.2 %) of the 11,918 subjects. Symptoms that can be caused by vasodilation and/or excessive depression of BP (i.e. dizziness, hot flashes, headaches, palpitations and peripheral oedema) were the most common complaints (Table 2).

Females complained of adverse symptoms more frequently than males (2.4 vs 1.9 %), and female sex was found to be a statistically significant risk factor for symptoms (OR 1.31, 95 % CI 1.01–1.69, $p = 0.045$). Vasodilation-related symptoms were significantly more frequent in females than in males (OR 1.87, 95 % CI 1.28–2.71, $p = 0.001$) (Table 3), whereas other symptoms were not, after adjustment. Among females only, the younger age group (<50 years) complained of vasodilation-related symptoms more frequently (OR 2.39, 95 % CI 1.02–5.59, $p = 0.045$) and the older age group (≥80 years) complained of vasodilation-related symptoms less frequently (OR 0.56, 95 % CI 0.33–0.95, $p = 0.030$) than the middle age group (Table 4). Younger females receiving combination therapy with an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB)

Table 1 Patient characteristics and demographics according to sex[a]

Variable	Total ($N = 11,918$)	Male ($N = 5,057$)	Female ($N = 6,861$)	p value
Age (years)	71.5 ± 11.2	69.1 ± 11.4	73.2 ± 10.6	<0.001
Calcium channel blocker currently using				
Amlodipine besylate (%)	65.3	63.6	66.6	0.001
Nifedipine				
Controlled-release drugs (%)	17.1	19.5	15.3	<0.001
Long-acting drugs (%)	11.2	11.2	11.3	0.860
Non-sustained release drugs (%)	0.2	0.2	0.2	1.000
Benidipine hydrochloride (%)	6.1	5.6	6.6	0.023
Ratio of daily dose to maximum dose	0.53 ± 0.24	0.55 ± 0.25	0.51 ± 0.23	<0.001
Antihypertensive therapy[b]				
Monotherapy (%)	50.6	47.2	53.2	<0.001
With ARB (%)	31.4	34.0	29.5	<0.001
With alpha- and/or beta-blocker (%)	11.4	12.8	10.4	<0.001
With ACEI (%)	9.7	11.1	8.7	<0.001
With diuretic (%)	8.5	8.1	8.8	0.196

ACEI angiotensin-converting enzyme inhibitor, *ARB* angiotensin II receptor blocker

[a] The values are presented as the percentage of subjects or the mean ± SD

[b] Multiple answers allowed

Table 2 Reported adverse symptoms[a]

Symptom	N (male/female)
Dizziness	63 (23/40)
Hot flush	32 (9/23)
Headache	29 (7/22)
Constipation	28 (10/18)
Rash and itching	23 (10/13)
Palpitation	17 (4/13)
Nausea	13 (6/7)
Thirst	10 (4/6)
Gingival hypertrophy	7 (4/3)
Drowsiness	6 (2/4)
Peripheral oedema	5 (1/4)
Muscle or joint pain	5 (1/4)
Others	47 (23/24)

[a] More than one symptom was reported in some cases

reported fewer vasodilation-related adverse symptoms than those receiving monotherapy, but the frequency did not differ significantly (1.6 vs 5.6 %, $p = 0.370$) (Supplemental Table 2).

4 Discussion

Providing effective and persistent antihypertensive therapy is crucial for preventing cardiovascular events [6–9]. Hypertensive females, however, have a lower BP control rate [10] and worse quality of life under drug treatment [11], and younger females, in particular, have a higher likelihood of drug switching and a poorer rate of persistence [7, 9]. Furthermore, younger females have an increased risk of hypertensive target organ damage compared with males of similar age [1], indicating that they require strict BP control. In the present study, vasodilation-related adverse symptoms were significantly more frequent in younger females, suggesting that such patients also require meticulous and adequate safety evaluations. Although a possible influence of menopausal symptoms on the incidence of vasodilation-related adverse symptoms cannot be ruled out, these symptoms were more pronounced in females less than 40 years of age, with an incidence of 15.4 %. On the other hand, females were more likely to be treated with monotherapy and to not use concomitant antihypertensive drugs than males, and the number of drugs did not increase the risk of adverse symptoms. It has been reported that peripheral oedema was much less common when a dihydropyridine was given with an inhibitor of the renin–angiotensin system [12–14]. Although we could not show any beneficial effect of the concomitant use of an ACEI or ARB with a dihydropyridine, the efficacy and safety have previously been demonstrated in studies of both sexes [6, 15] and females [8]. Therefore combination therapy using a dihydropyridine and an ACEI or ARB can be valuable for controlling the BP, especially in younger females whose antihypertensive treatment is insufficient.

Endothelium-derived hyperpolarizing factor (EDHF) relaxes vascular smooth muscle, consequently playing a

Table 3 Distribution of the characteristics of the patients with or without vasodilation-related symptoms

Variable	Without symptoms[a] ($N = 11,782$)	With symptoms[a] ($N = 136$)	Adjusted OR[b] (95 % CI)
Sex			
Male (%)	42.6	30.9	1
Female (%)	57.4	69.1	1.87 (1.28–2.71)
Age (years)	71.5 ± 11.2	69.4 ± 11.5	0.98 (0.97–0.99)
Ratio of daily dose to maximum dose	0.53 ± 0.24	0.57 ± 0.29	2.31 (1.22–4.38)
Antihypertensive therapy			
Monotherapy (%)	50.6	53.7	1
With one concomitant agent (%)	39.1	35.3	0.81 (0.56–1.18)
With two concomitant agents (%)	9.0	8.8	0.86 (0.46–1.61)
With more than two concomitant agents (%)	1.3	2.2	1.32 (0.40–4.31)

CI confidence interval, *OR* odds ratio

[a] The values are presented as the percentage of subjects or the mean ± SD

[b] Adjusted for other factors listed in this table

Table 4 Association between the risk of vasodilation-related symptoms and age according to sex

Age (years)	Male			Female		
	Without symptoms[a] ($N = 5,015$)	With symptoms[a] ($N = 42$)	Adjusted OR[b] (95 % CI)	Without symptoms[a] ($N = 6,767$)	With symptoms[a] ($N = 94$)	Adjusted OR[b] (95 % CI)
<50	285 (5.7)	3 (7.1)	1.22 (0.37–4.01)	162 (2.4)	6 (6.4)	2.39 (1.02–5.59)
50–79	3,846 (76.7)	33 (78.6)	1	4,610 (68.1)	71 (75.5)	1
≥80	884 (17.6)	6 (14.3)	0.77 (0.32–1.85)	1,995 (29.5)	17 (18.1)	0.56 (0.33–0.95)

CI confidence interval, *OR* odds ratio

[a] The values are presented as the number (percentage) of subjects

[b] Adjusted for the ratio of daily dose to maximum dose and antihypertensive therapy

fundamental role in the regulation of vascular tone [16, 17]. Fisslthaler et al. [16] demonstrated that nifedipine enhances EDHF-mediated relaxation. EDHFs are upregulated by oestrogen and more prominently contribute to vascular reactivity in females than males [17]. Therefore, the EDHF-mediated vasodilatory effects of dihydropyridines are considered to be significant in younger females.

This pilot study is associated with some obvious limitations. First, a cross-sectional design does not allow causality between the drugs and the adverse symptoms to be established. Second, the adverse symptoms reported largely on the basis of the patient's memory may have been under/overestimated, and we could not assess adverse symptoms using objective parameters, e.g. the ankle–foot volume and pretibial subcutaneous tissue pressure, to assess the peripheral oedema [12–14]. Third, the absolute number of females with adverse effects was small (94 of 6,861; 1.4 %) and the confidence interval of the adjusted OR was large. Finally, we did not have adequate information regarding the duration of the drug use, co-medication(s), complications or BP. We also did not have information regarding the menopausal status, and could not investigate the association between menopause and the risk of adverse symptoms directly.

5 Conclusion

To the best of our knowledge, this is the first report showing that younger females are at high risk for vasodilation-related adverse symptoms during dihydropyridine use in daily practice. These results should be verified in clinical studies using more objective methods and parameters to assess the adverse reactions in a larger number of patients.

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