Cutaneous adverse reactions to calcium channel blockers

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Summary

Background: **Previous studies have shown that calcium channel blockers can cause cutaneous adverse reactions; however, the amounts of data collected are limited. Recently, there have been new drugs available for which only a few reports have been published with regard to cutaneous adverse reactions.**

Objective: **The purpose of our study was to estimate the rate and to study clinical patterns of cutaneous adverse drug reactions to calcium channel blockers.**

Methods: **Medical records of patients who had cutaneous adverse reactions to calcium channel blockers between January 2004 and December 2010, at the Adverse Drug Reaction Center of Siriraj hospital, Mahidol University, Bangkok, Thailand were reviewed.**

Results: **From 996,583 prescriptions of calcium channel blockers, forty six patients developed cutaneous adverse effects. Diltiazem was the drug that showed the highest rate of cutaneous reactions per million prescriptions. Maculopapular rash was the most common dermatologic manifestation (41.7%), followed by ankle/pedal edema (18.8%). Three patients (6.2%) developed Stevens-Johnson syndrome due to amlodipine and 1 patient (2.1%) developed toxic epidermal necrolysis due to manidipine. Four patients (8.7%) had renal or cardiovascular involvement.**

Conclusions: **It is important to keep in mind that some patients may develop cutaneous adverse reactions, including severe reactions, from calcium channel blockers.** ***(Asian Pac J Allergy Immunol 2014;32:246-50)***

Keywords: *Allergy, calcium channel blockers, cutaneous, hypersensitivity, reaction*

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Introduction

Calcium channel blockers (CCBs) are frequently used to treat cardiovascular diseases such as hypertension.[1] These drugs can be classified into several subgroups, based on receptor binding properties, tissue selectivity, and pharmacokinetic profiles. However, only three main subgroups, dihydropyridine (eg. nifedipine, nimodipine, felodipine, manidipine, and amlodipine), benzothiazepine (eg. diltiazem), and phenylalkylamine (eg. verapamil) are widely used in clinical treatment.[2] Both allergic and non-allergic adverse drug reactions (ADRs) have been reported, such as flushing, gingival hyperplasia, gynaecomastia and also cutaneous ADRs.[3,4] Serious adverse events such as anaphylaxis, Steven-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) have occasionally been reported.[3-6] However, previous studies of CCB-induced cutaneous ADRs are limited, and most of them are case reports.[6-18] Recently, there have been new drugs available on the market, such as amlodipine and manidipine, and only a few reports have been published about cutaneous ADRs from these new drugs. Therefore, the purpose of our study weas to estimate the rate and to study updated clinical patterns of cutaneous ADRs to CCBs, including amlodipine and manidipine.

Methods

Patients who had cutaneous ADRs to CCBs were reported to the Adverse Drug Reaction (ADR) Center by attending physicians and dermatologists. Well-trained and experienced ADR Center pharmacists and dermatologists then reviewed the event and assessed the culprit drugs, based on

history, clinical manifestations, and investigations. The culprit drugs in the cases were classified into 6 levels (certain, probable, possible, unlikely, unclassified, and unclassifiable) according to World Health Organization-Uppsala Monitoring Centre (WHO-UMC) Categories. [19, 20]

Patients 18 years of age and above, who had cutaneous ADRs to CCBs and were reported to the ADR center from January 2004 to December 2010 at Faculty of Medicine Siriraj Hospital, a medical school and a tertiary referral center in Thailand, were enrolled. This study was approved by the Siriraj Institutional Review Board, Mahidol University.

Statistical analysis

Descriptive statistics were used for demographic data, underlying diseases, previous drug allergies, and characteristics of cutaneous ADRs. All statistical analyses were performed using *SPSS* version 17.0 (SPSS Inc., Chicago, IL).

Results

During the six-year period, there were 996,583 prescriptions of CCBs in Siriraj Hospital but only 46 patients (48 times) developed cutaneous ADRs; the rate was thus 48 per million prescriptions. All except one of the patients were Thai. The other was Chinese. Females were more likely to develop cutaneous ADRs than males, with a 3:1 ratio. The mean age was 58 years (range, 30-92 years, SD±19.7 years). A history of atopy was detected in two cases. Two of these patients had a previous history of amlodipine-induced pedal edema. (Table 1) The reason for prescribing CCBs was hypertension in 43 cases (93.5%), aortic aneurysm in 2 cases (4.3%), and cluster headaches in 1 case (2.2%). The routes of administration and the daily dosages are shown in Table 2.

Table 1. Demographic and clinical data for patients with cutaneous reactions to calcium channel blockers

Characteristic	No. (%) of patients (n=46)
Gender	
Male	13 (28.3)
Female	33 (71.7)
Personal history of atopy	2 (4.3)
History of adverse drug reactions of any medications	12 (26.1)
Other antihypertensive drugs	5
Antibiotics	4
Calcium channel blockers	2
Aspirin	1
Underlying diseases (some patients have several underlying diseases)	
Hypertension	43 (93.5)
Cardiovascular related diseases	7 (15.2)
Autoimmune diseases	4 (8.7)
Others	18 (19.5)

Table 2. Dosage and routes of administration of calcium channel blockers

Calcium channel blockers	Routes of administration	Dosage
Amlodipine	Oral	2.5-10 mg/day
Diltiazem	Oral	60-180 mg/day
	Intravenous	3 mg/hour
Felodipine	Oral	2.5-5 mg/day
Manidipine	Oral	5-20 mg/day
Nifedipine	Oral	20-120 mg/day
Nimodipine	Oral	240 mg/day
Verapamil	Oral	120 mg/day

According to WHO-UMC Guidelines,[19,20] 17 patients (37%) were diagnosed as probable ADRs and 29 patients (63%) were diagnosed as possible ADRs. No patient was diagnosed as having a certain reaction to CCBs due to concern about doing challenge testing. After excluding anaphylaxis that caused the reactions occurring within 2 hours of CCBs administration, the mean duration of developing cutaneous ADRs was 14.6 days (range, 1-111 days, SD±21.6 days). The rates of cutaneous ADRs to CCBs per million prescriptions are shown in Table 3. The most common dermatologic manifestation was maculopapular rash (41.7%) caused by amlodipine, diltiazem, and manidipine, respectively. The second most common cutaneous ADRs was ankle/pedal edema (18.8%) which was caused by amlodipine, manidipine, and nifedipine, respectively. Although less common, CCBs can also cause severe skin reactions in some individuals. Three patients (6.2%) developed SJS due to amlodipine (possible ADR). One patient (2.1%) developed TEN due to manidipine (possible ADR) (Table 4).

Nine patients (18.8 %) were admitted due to their adverse drug reactions and had life threatening conditions ie anaphylaxis, SJS or TEN. All patients survived and made a full recovery without lasting

Table 3. Rate and number of cutaneous adverse reactions to calcium channel blockers

	Amlodipine	Manidipine	Felodipine	Diltiazem	Nifedipine	Verapamil	Nimodipine
No. of prescriptions	423,527	183,279	136,378	98,576	93,941	18,878	516
No. of reactions*	21	9	2	9	5	1	1
Rate (cases per million prescriptions)	49.6	49.1	14.7	91.3	53.2	53.0	1,937

* Two patients developed 2 cutaneous adverse reactions to calcium channel blockers

severe adverse effects. Four patients (8.7%) had systemic involvement which was renal or cardiovascular. All of them showed full recovery.

Discussion

Previous studies of ADRs associated with antihypertensive drugs have shown that CCBs were the most common cause of ADRs, followed by diuretics and β-blockers.[21] In this study, we focused on CCB-induced cutaneous ADRs. Females appear more likely than males to develop drug reactions, which is similar to other published data. However, the mechanism is not clear.[21-23] Previous reports suggest that pedal edema is the most common cutaneous ADR (up to 30%).[3,7] Many mechanisms have been proposed in order to explain pedal edema, such as fluid-volume retention, effects on the renin-angiotensin-aldosterone system and precapillary arteriolar vasodilatation.[3,24] In this study, only 18.8% of our patients developed pedal edema, less than those who developed maculopapular rash. This may be due to cases being under-reported to the ADR Center.

In our study, the rate of diltiazem-induced cutaneous ADRs is highest (91.3 cases per million prescriptions) compared to a previous study that indicated that verapamil is the most common cause (16.6 cases per million prescriptions). The previous study did not include amlodipine because amlodipine was approved by the U.S Food and Drug Administration until after their publication.[4] (Table 5) Amlodipine-induced cutaneous ADRs were reported in 21 patients. Because amlodipine was prescribed more frequently than other medications, calculation including the number of prescriptions showed that the rate of amlodipine-induced

Table 4. Cutaneous adverse drug reactions associated with calcium channel blockers

Cutaneous adverse reactions	**Amlodipine**	**Diltiazem**	**Manidipine**	**Nifedipine**	**Felodipine**	**Verapamil**	**Nimodipine**	**No(%) of reactions (n=48)****
Maculopapular rash	8	5	3	1	1	1	1	20(41.7)
Ankle/pedal edema	6	0	2	1	0	0	0	9(18.8)
SJS/TEN*	3	0	1	0	0	0	0	4(8.3)
Erythema multiforme	0	2	0	1	0	0	0	3(6.2)
Nonspecific eczema	1	1	1	0	0	0	0	3(6.2)
Angioedema and/or urticaria	1	1	0	0	1	0	0	3(6.2)
Anaphylaxis	0	0	1	1	0	0	0	2(4.2)
Photosensitivity dermatitis	0	0	1	0	0	0	0	1(2.1)
Erythroderma	1	0	0	0	0	0	0	1(2.1)
Flushing	1	0	0	0	0	0	0	1(2.1)
Vasculitis	0	0	0	1	0	0	0	1(2.1)
No (%) of reactions (n=48)**	21 (43.7)	9 (18.7)	9 (18.7)	5 (10.4)	2 (4.2)	1 (2.1)	1 (2.1)	

*SJS/TEN: Stevens-Johnson syndrome/ Toxic epidermal necrolysis

**Two patients developed two cutaneous adverse reactions to calcium channel blockers

Table 5. Comparison of the rate of cutaneous adverse reactions to calcium channel blockers

	Stern et al.[4] (the rate per 10^6 prescriptions)	Our study (the rate per 10^6 prescriptions)
Diltiazem	6.5	91.3
Nifedipine	5.8	53.2
Verapamil	16.6	53.0
Amlodipine	-	49.6
Manidipine	-	49.1
Felodipine	-	14.7

cutaneous ADRs (49.6 cases per million prescriptions) was less than the rate of diltiazem-, nifedipine-, and verapamil-induced cutaneous ADRs (91.3, 53.2, and 53.0 cases per million prescriptions, respectively). In addition, it should be noted here that we had only a small number of patients who were receiving nimodipine. (Table 2)

Even though ADRs from CCBs were infrequent, our study has shown that these drugs can occasionally cause severe adverse cutaneous ADRs. Considering amlodipine-induced SJS and manidipine-induced TEN, the rates were 7.1 and 5.5 cases per million amlodipine-, and manidipine-prescriptions, respectively. To the best of our knowledge, there has been only one case of amlodipine-induced SJS reported previously and one case report of amlodipine-induced TEN. There were no reports of manidipine-induced severe cutaneous ADRs.[25,26]

Conclusions

Despite enrolling many patients who received CCBs, only a few of them developed cutaneous adverse reactions. In addition, it is important to keep in mind that some patients may develop serious skin reactions from CCBs. The limitation of this study is the small sample size of CCBs-induced cutaneous adverse reactions in spite of the large unber of prescriptions.

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