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Chronic Eczematous Eruptions of the Elderly Are Associated with Chronic Exposure to Calcium Channel Blockers: Results from a Case–Control Study

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It has been suggested that chronic eczematous eruptions of the elderly could be associated with chronic drug exposure. To determine the drugs associated with these eruptions, we conducted a case–control study on 102 cases and 204 controls. Cases were consecutive patients older than 60 years presenting with an eczematous eruption that had evolved continuously or recurrently for more than 3 months without a reliable cause. Two controls were matched to each case on age, sex, in/outpatient origin, and center. Information about drug exposure was obtained from patients and their pharmacists. Drug use for more than 3 months within the year preceding the eruption was compared between cases and controls. An association was found between calcium channel blockers (CCB) and eczema, with a matched OR (odds ratio) of 2.5 (95% CI (confidence interval): 1.3–4.6). To ascertain the course of patients after CCB withdrawal, two ancillary studies were performed on 74 patients with eczematous eruptions from our department before the case–control study period, and on 101 patients registered in the French "Pharmacovigilance" database. Healing of these eruptions after CCB withdrawal occurred in 83 and 68% of these cases, respectively. The long-term use of CCB is a risk factor for chronic eczematous eruptions of the elderly.

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INTRODUCTION

Eczematous eruptions are quite common in the elderly (Kligman, 1979; Beauregard and Gilchrest, 1987; Thivolet and Nicolas, 1990). Some cases correspond to contact dermatitis or atopic dermatitis, whereas other cases correspond to atypical forms of various dermatoses such as bullous pemphigoid, mycosis fungoides, or scabies (Honig *et al.*, 1991; Scolo *et al.*, 1995). Additionally, some cases cannot be related to a reliable cause. We recently reported findings from a retrospective series of 83 elderly patients referred to our Department of Dermatology for chronic or recurrent extensive eczematous eruptions (Morin *et al.*, 2002). At least a reliable cause could be identified in 48 patients (58%), namely extensive contact dermatitis in 19 patients (23%), eczema-like mycosis fungoides in 10 patients (12%), atopic dermatitis in seven patients (8%), eczema-like bullous pemphigoid in six patients (7%), and scabies in six patients (7%). For the remaining 35 patients (42%), no cause could be determined. Comparison of clinical and histological features of patients with or without an identified cause showed a more frequent localization of skin lesions on sun-exposed areas ($P=0.004$), and a higher frequency of sparse keratinocyte necrosis on biopsy specimens ($P=0.007$) among patients without an identified cause. Moreover, patients without an identified cause had a higher frequency of chronic (i.e., $\geqslant 3$ months) drug intake ($P=0.02$). These findings suggested that some of these eruptions of unknown cause could be caused by chronic drug intake. The most frequently recorded drugs were diuretics, calcium channel blockers (CCB), angiotensin-converting enzyme inhibitors, nitrates, and benzodiazepines. We conducted a multicenter case–control study to ascertain the risks of chronic eczematous eruptions in relation with chronic drug intake in the elderly.

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Abbreviation: CCB, calcium channel blockers

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RESULTS

Cases and controls

During the study period, 255 cases were assessed for eligibility. One hundred and forty-one patients were excluded because a reliable cause of their eczematous eruption was identified, namely contact dermatitis ($n=62$), eczema-like mycosis fungoides ($n=26$), atopic dermatitis ($n=21$), scabies ($n=18$), or eczema-like bullous pemphigoid ($n=14$). Additionally, 12 patients were excluded because the information on their drug intake could not be elicited or verified from their pharmacist. Of the remaining 102 cases (66 males and 36 females), there were 49 inpatients and 53 outpatients. Their mean age was 76.6±7.6 years. Preferential localization of skin lesion on sun-exposed areas was noted in 17 cases (17%). However, no clear-cut seasonality in the onset of these eruptions was evidenced. All but two cases (98%) complained of pruritus. The mean delay since initial onset of skin lesions was 12.5±4.5 months.

Two hundred and four patients were selected as controls from a series of 245 patients of whom 21 refused to participate in the study, and 20 could not have their drug intake elicited or verified. Seventy-six control patients (37%) presented with the following common dermatological conditions: actinic keratosis, basal cell carcinoma, seborrheic keratosis, nevi, seborrheic dermatitis, or cutaneous xerosis. The remaining 128 control patients (63%) presented with acute non-dermatological conditions including pneumonia, hip fracture, peritonitis, and various other acute medical or surgical conditions.

Comparison of drug intakes between cases and controls

Controls appeared well matched to cases for age, sex, in/outpatient status, and center (Table 1). Ninety-two cases (90%) and 186 controls (91%) had taken at least one drug for a period of at least 3 months during the year preceding the onset of the eruption in cases and the corresponding period in controls. Mean number of drugs chronically taken was 4.7±3.3 per patient in cases and 4.5±3.2 in controls (Table 1). Among cases, the main drugs used were diuretics (37%), converting enzyme inhibitors (28%), CCB (26%), hypolipidemic drugs (25%), and salicylates (22%) (Table 2).

Comparison of the prevalence of chronic drug intake between cases and controls showed a significant association between the occurrence of eczematous eruptions and chronic intake of CCB. Twenty-six cases (26%) and 25 controls (12%) reported chronic intake of CCB, respectively, corresponding to a matched odds ratio (OR) of 2.29 (95% confidence interval (CI): 1.27–4.15; $P=0.006$). Among the 26 cases with intake of CCB, 20 had taken dihydropyridine, whereas three and three had taken verapamil and diltiazem, respectively. Among the 25 control patients with intake of CCB, corresponding figures were 16, 8, and 1, respectively. The OR of the association of verapamil with chronic eczematous eruption was 2.72 (95% CI: 1.40–5.28; $P=0.003$). Interestingly, no significant associations were found with any other drug classes (Table 2).

Drug classes that showed a separate association with eczematous eruptions at the 0.15 level in univariate analysis, namely antidepressants ($P=0.09$), nitrates ($P=0.10$), and antiarrhythmics ($P=0.14$) were retained in multivariate analysis. Upon adjusting for chronic intake of these drugs, the association between CCB and eczematous eruptions remained significant, with a slightly increased OR of 2.45 (95% CI: 1.30–4.61; $P=0.0049$). In this analysis, chronic intakes of antidepressants, nitrates, and antiarrhythmics showed again no significant associations with eczematous eruptions ($P=0.31$, 0.08, and 0.16, respectively).

These analyses were repeated after excluding 19 cases with elevated serum IgE levels (>500 IU/L) and their 38 matched controls. Indeed, although these patients had no documented history of atopic dermatitis, their eczematous eruption could potentially correspond to a late form of atopic dermatitis in view of their high IgE levels. A significant association of eczematous eruptions with CCB intake was further evidenced, with about the same magnitude as on the whole case–control sample (OR=2.21; 95% CI: 1.15–4.24; $P=0.02$) in univariate analysis. Again, no association was found with any other drugs and further adjusting for chronic intake of antidepressants, nitrates, and antiarrhythmics, and did not modify results appreciably (adjusted OR=2.41; 95% CI: 2.20–4.83; $P=0.01$).

Table 1. Main characteristics of case and control patients

	Case patients			Control patients			
	Total (*n*=102)	Inpatients (*n*=49)	Outpatients (*n*=53)	Total (*n*=204)	Inpatients (*n*=98)	Outpatients (*n*=106)	*P*-value*
Mean age±SD (years)	76.6±7.6	78.2±7.6	75.0±7.3	76.5±3.7	77.9±7.3	74.4±7.5	0.99**
Male/female sex ratio	1.83	1.23	2.79	1.83	1.23	2.79	1.00***
Mean number of drugs with chronic intake (≥3 months in reference year)±SD	4.7±3.3	5.6±3.6	4.1±2.7	4.5±3.2	4.9±3.0	4.1±3.3	0.56**

*Comparisons between all case patients and all control patients (irrespective of in/outpatient status).
**From Student's *t*-test.
***From Pearson's χ^2 test.

Table 2. Univariate analysis of the association between chronic intake of drug classes and chronic or recurrent eczematous eruptions

		Case patients			Control patients			
Drug class	Total (*n*=102) no (%)	In-patients	Outpatients	Total (*n*=204) no (%)	In-patients	Outpatients	Odds ratio (95% confidence interval)*	*P*-value*
Hypokalemic diuretics	29 (28)	15 (31)	14 (26)	67 (33)	39 (40)	28 (26)	0.80 (0.45–1.38)	0.39
Angiotensin-converting enzyme inhibitors	29 (28)	15 (31)	14 (26)	58 (28)	33 (34)	25 (24)	1.00 (0.61–1.65)	1.00
Calcium channel blockers	**26 (26)**	**14 (29)**	**12 (23)**	**25 (12)**	**14 (14)**	**11 (10)**	**2.29 (1.27–4.15)**	**0.006**
Hypolipidemic drugs	25 (25)	14 (29)	11 (21)	38 (19)	15 (15)	23 (22)	1.39 (0.80–2.43)	0.25
Salicylates	23 (22)	11 (22)	12 (23)	40 (20)	26 (27)	14 (13)	1.22 (0.66–2.25)	0.53
Antiarrhythmics	20 (20)	8 (16)	12 (23)	27 (13)	13 (13)	14 (13)	1.64 (0.85–3.15)	0.14
Vasodilatators	19 (19)	9 (18)	10 (19)	40 (20)	20 (20)	20 (19)	0.94 (0.52–1.71)	0.84
β-Blockers	19 (19)	10 (20)	9 (17)	32 (16)	14 (14)	18 (17)	1.24 (0.65–2.35)	0.51
Nitrates	17 (17)	9 (18)	8 (15)	21 (10)	13 (13)	8 (8)	1.89 (0.89–3.99)	0.10
Benzodiazepines	16 (16)	10 (20)	6 (11)	32 (16)	16 (18)	16 (15)	1.00 (0.51–1.96)	1.00
Hyperkalemic diuretics	9 (9)	4 (8)	5 (9)	18 (9)	12 (12)	6 (6)	1.00 (0.44–2.26)	1.00
Antiulcers	9 (9)	5 (10)	4 (8)	18 (9)	8 (8)	10 (9)	1.00 (0.42–2.38)	1.00
Antidepressants	6 (6)	5 (10)	1 (2)	24 (12)	11 (11)	13 (12)	0.47 (0.80–1.19)	0.09

*From conditional logistic regression with no further adjustment considering all case and control patients (i.e., irrespective of in/outpatient status).

When using a permutation-based (i.e., $n=13$) correction for multiple comparisons, the association between CCB and eczematous eruptions was borderline significant ($P=0.058$). Finally, upon fitting an interaction term between in/outpatient status and CCB intake, we obtained an OR for interaction of 1.01 (95% CI: 0.31–3.32), meaning that the association between CCB intake and eczematous eruption was almost identical in outpatients (OR = 2.28, 95% CI: 0.98–5.30) and inpatients (OR = 2.31, 95% CI: 1.00–5.30).

Ancillary studies: Course of the eruptions after stopping CCBs

To ascertain the relationship between intake of CCB and eczematous eruptions, we evaluated response to drug withdrawal on two independent series of patients with chronic eczematous eruptions. First, we retrospectively analyzed a series of 74 patients older than 60 years who had been referred to our department for chronic eczematous eruptions without a known cause before the case–control study period from January 1995 to January 2000. The main clinical features of patients at baseline and main drugs used are shown in Table 3. Some drugs were stopped in 54 patients, whereas 20 patients did not have any drug withdrawal. Among the 54 patients with drug withdrawal, CCBs were stopped in 12 cases and other drugs in 42 cases. Long-lasting (i.e., >6 months) recovery from the eruption was observed in 10 of the 12 patients (83%) who had stopped taking CCB after a mean time of 3.4 ± 1.8 months, as compared with 14 of 42 (33%) who had stopped other drugs, and four of the 20 patients (20%) who did not stop taking any drug ($P=0.001$, Fisher's exact test). Interestingly, among the 42 patients who had stopped taking various drugs other than CCB, eight patients were taking CCB. Only one of them (12%) recovered from his eruption while continuing to take CCB ($P=0.0045$, Fisher's exact test for the comparison with the 12 patients who had stopped CCB intake).

Second, we analyzed the main characteristics and follow-up data of 101 patients having presented with eczematous eruptions while being treated with CCB, who were registered in the French National ''Pharmacovigilance'' database. The keywords used were ''eczema'', ''eczematous eruption'', and each of the CCB that are on the market in France. Their main clinical features are displayed in Table 3. Twenty-two of them (22%) had been hospitalized because of the severity of their eruption. The median delay from their initial CCB intake to the occurrence of their eczematous eruption was 91 days (range: 30–3,600 days). Follow-up data were available for 67 cases. Thirty of the 53 patients (68%) who stopped taking CCB recovered from their eczema, as compared with five of the 14 (36%) who continued taking CCB ($P=0.03$).

Rechallenge with CCB was performed in six cases from the pharmacovigilance database and in three cases from authors. Drugs involved were nicardipine ($n=6$), amlodipine ($n=2$), and felodipine ($n=1$). Drugs were taken for a mean time of 5.7 ± 4.1 months before the onset of eruption. Mean delay to resolution after drug withdrawal was 21.5 ± 13.1 days. Rechallenge was performed after a mean time of 5.0 ± 4.3 months after resolution of the eruption. It resulted in the reoccurrence of the eruption in five of the six cases from the pharmacovigilance database, and in the three cases from the authors, after a mean time of 3.8 ± 1.9 days.

Table 3. Main characteristics and drugs taken by patients with chronic or recurrent eczematous eruptions included in the two ancillary studies evaluating patient outcome after drug withdrawal

	Monocenter study (*n*=74)	Study of patients in the French "Pharmacovigilance" National Drug Survey database (*n*=101)
Mean age±SD (years)	78.1±9.0	70.0±8.7
Male/female sex ratio	1.55	1.60
Past history of atopic dermatitis no (%)	14 (19)	9 (9)
Preferential localization of skin lesions on sun-exposed areas no (%)	12 (16)	9 (9)
Mean number of drugs with chronic intake (⩾3 months)±SD	5.3±2.4	5.3±2.5
Main drug class no (%)		
Converting enzyme inhibitors	29 (39)	9 (9)
Calcium channel blockers	27 (36)	101 (100)
β-Blockers	22 (30)	6 (6)
Hypolipidemic drugs	22 (30)	5 (5)
Hypokalemic diuretics	17 (23)	9 (9)

DISCUSSION

This study showed an association between chronic intake of CCB and chronic or recurrent eczematous eruptions of the elderly with no known cause, whether patients with elevated serum IgE levels, who could have a late yet undocumented form of atopic dermatitis, were excluded or not. This association appeared specific to CCB, as no associations were found with any of the other 12 drug classes considered. The role of CCB was difficult to suspect *a priori* in this context where most patients had been taking many drugs often for a long time (Bégaud *et al.*, 1985; Moore *et al.*, 1985), a situation that is rather similar to that of nicorandil-induced giant aphthous ulcers, another drug-induced reaction that mainly occurred in the elderly that we reported previously (Agdo-Godeau *et al.*, 1998).

The causative nature of this association is strongly suggested by the high rate of recovery from these eruptions after CCB withdrawal and the reappearance of eruption*s* after rechallenge. A possible mechanism by which CCB might induce eczematous dermatitis can be proposed. It has been recently demonstrated that photodegraded nifedipine stimulates uptake and retention of iron in human epidermal keratinocytes (Gruen *et al.*, 2001). Such a mechanism can induce apoptosis and spongiosis of keratinocytes (Trautmann *et al.*, 2001), which may account for the histological picture associating spongiosis and sparse keratinocyte necrosis seen in skin biopsies from most patients with eczematous eruptions who had taken CCB, as well as for the long delay of recovery of these eruptions after drug withdrawal.

Chronic eczematous eruptions of the elderly seem to correspond to an original skin disorder. Indeed, the main characteristics of patients included in the case–control study essentially confirmed the characteristics reported in our preliminary study (6): (1) old age (mean age: 76 years); (2) male predominance (sex ratio: 1.8); (3) substantial delay from initial take of CCB to the occurrence of skin lesions (3 months median delay); (4) occasional preferential localization of skin lesions on sun-exposed areas (17%); and (5) histological picture of eczema and sparse keratinocyte necrosis. Similar characteristics were found in the two ancillary studies. Despite a frequent good initial response to topical corticosteroids, these eruptions can be severe because of the intensity of pruritus, extent of cutaneous lesions, and their relapsing course after topical corticosteroid withdrawal. Indeed, 22% of patients registered in the French National "Pharmacovigilance" database had been hospitalized because of the severity of their eruption.

As in all case–control studies, various biases are possible in this study. To avoid selection bias of cases, we aimed at recruiting exhaustively all consecutive incident cases from five regions in France, by relying both on office- and hospital-based dermatologists. Indeed, recruiting only hospitalized case patients could have led to the selection of more severe forms, yielding bias in the event of a differential association of drug exposure with eczema depending on disease severity. The absence of major selection bias in our control patients is supported by the similarities in the prevalence of the most frequently used drugs in our control population as compared with that observed in a series of 187 retired people in France (Colomes *et al.*, 1990) as well as with that observed in a control series of 216 patients used in another case–control study of elderly patients in France (Bastuji-Garin *et al.*, 1996). In particular, prevalences of cardiovascular drug intake in these two series (64 and 54%, respectively) were rather similar to that in our control series (48%), and the prevalence of CCB intake (14% in both series) was very close to that in our control series (12%).

Recall bias is a common problem in case–control studies, especially those involving elderly subjects who may suffer from memory impairment. However, because no specific hypotheses had been raised before this study regarding associations of chronic drug intake with chronic eczematous eruptions of the elderly, differential recall bias is unlikely in this study. Moreover, drug intake information provided by case and control patients was systematically verified from their pharmacist's computerized database. Patients whose eruptions had evolved for more than 18 months were not included in this study to make this verification possible for all patients. Indeed, the French pharmacists' database only covers the 18 months before the present time, information before that period being erased on a continual basis. Finally, the fact that the mean number of drugs was similar among case and control patients supports the absence of major

information bias in our study and supports the specificity of the association with CCB.

Because we did not collect data on drugs used for a short time, we cannot exclude the possibility that some drugs could induce these eczematous reactions after short-term use. However, this seems unlikely because most documented drug-induced chronic skin disorders such as drug-induced lupus erythematosus, pemphigus foliaceus, lichenoid reactions, or psoriasis necessitate chronic drug exposure (Verdier-Sevrain *et al*., 1994; Tsankov *et al*., 2000; Callen, 2001).

In conclusion, this study suggests that some chronic or recurrent eczematous eruptions of the elderly may be due to CCB. Although further studies would be necessary to confirm this association and investigate further its causative nature, a prudent attitude may be to discontinue CCB in elderly patients with chronic eczema of unknown cause.

MATERIALS AND METHODS

This case–control study was conducted from 1 January 2000 to 31 December 2002 in five dermatology departments in University Hospitals and in 35 private dermatology practices of five regions in France.

Cases

Consecutive in- and outpatients older than 60 years at the onset of cutaneous lesions were included. Inclusion criteria were (1) eczematous eruptions corresponding to pruritic, erythematosus, and vesicular lesions; (2) involving more than 20% of the body surface; (3) having evolved continuously or recurrently (with more than two recurrences) during a period from 3 to 18 months before the study period; (4) without an identified cause, that is, excluding patients with an history of atopic or contact dermatitis, eczema-like mycosis fungoides, bullous pemphigoid, scabies, or nutritional deficiency; (5) with histological features of eczema; and (6) a negative direct immunofluorescence examination. All skin biopsies were assessed by the same pathologist (PC). To detect a possible atopic dermatitis in patients who had no history of atopic dermatitis, serum total IgE level was determined in all patients, but patients were not excluded on the basis of their IgE levels. Biological and histological exams including blood cell count, albumin and total IgE levels, and skin biopsy for standard histological and DIF examinations were performed in all patients.

Controls

Two control patients were individually matched to each case based on sex, age (within 5 years), origin (in- or outpatient), and center. For cases recruited in private dermatology practices, matched controls were selected from patients in the same practice presenting with any dermatosis other than eczema or a documented drug-induced reaction. These two controls were identified as the next two patients fulfilling the matching criteria who were seen after the recruitment of the case by the same dermatologists. For cases recruited in dermatology departments, controls were selected from patients referred the same day as the case to the emergency department of the same hospital for an acute non-dermatological condition. The next two patients fulfilling the matching criteria were identified from the list of hospital admissions. If they agreed to participate in the study, they were examined by investigators and used as controls if they did not have a current or past history of eczema. The proportions of in- and outpatient cases and controls were not significantly different among centers.

Assessment of drug intake

Based on the findings from our preliminary study (Morin *et al*., 2002), we postulated that an association between chronic eczematous eruptions and drug intake, if any, would require several months of treatment. Therefore, we collected data on drugs used for at least 3 months within the year preceding the onset of the first eczematous eruption in cases, and during the same calendar period in controls. Drug information was obtained first by asking patients to name the drugs they had taken for the past year. Then, they were required to present any available written prescription from their physician. Confirmation was sought systematically by asking each patient's usual pharmacist to verify the patient's drug use from their computerized database. In case of discordance, the information provided by the pharmacist was retained. According to the French law, this type of study in which patients are only asked about their drug intake without any intervention does not require the approval of an Ethics Committee.

Statistical analysis

The target sample size was 106 cases and 212 controls (2:1 matching). It was calculated to detect a matched OR of 2.5 for drugs with a prevalence of chronic intake (i.e., $\geqslant$three months) of 10% among controls, with 80% power, and for a two-sided type I error of 5%.

Only the drug classes used with a prevalence of chronic intake over 5% among the controls were considered. In univariate analysis, matched OR with their 95% CI were estimated using conditional logistic regression. All drugs presenting an association with chronic or recurrent eczema with $P \leqslant 0.15$ was retained for the subsequent multivariate analysis that used conditional logistic regression to assess independent associations with eczematous eruptions.

All analyses were repeated for matched sets, in which there was no elevation of IgE levels (<500 IU) in the case. Statistical analyses were performed using version 2.0.31 of Egret software and version 3.1 of StatXact-3 software (both from Cytel Software Corporation, Cambridge, MA).

CONFLICT OF INTEREST

The authors state no conflict of interest.

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