Chronic Eczematous Eruptions in the Aging
Further Support for an Association
With Exposure to Calcium Channel Blockers

Erika M. Summers, MD; Colby S. Bingham, BS; Kevin W. Dahle, MD; Carol Sweeney, PhD; Jian Ying, PhD, MStat; Richard D. Sontheimer, MD

IMPACTANCE Dermatologists frequently encounter patients of advanced age presenting with chronic eczematous eruptions of uncertain etiology. When a drug-induced cutaneous eruption is suspected, identifying the responsible drug(s) is a complex clinical challenge.

OBJECTIVE To determine whether certain drug classes, and in particular calcium channel blockers, are associated with chronic eczematous eruptions in the aging (CEEA) in the United States.

DESIGN Retrospective case-control study.

SETTING Ambulatory patients from the Department of Dermatology, University of Utah School of Medicine, Salt Lake City.

PATIENTS The cases consisted of 94 patients 50 years and older presenting with otherwise unexplainable symmetrical eczematous eruptions of at least 2 months’ duration between January 1, 2005, and December 31, 2011. Inclusion criteria also included histopathologic changes of spongiotic and/or interface dermatitis and clinical suspicion for a drug-induced cutaneous eruption. The controls consisted of 132 age-, sex-, and race-matched patients presenting with benign dermatologic conditions. A subgroup analysis on cases whose skin biopsy specimens showed a pattern of inflammation that is conventionally thought to be associated with eczematous drug eruptions (ie, eczematous and interface dermatitis) was also performed.

MAIN OUTCOMES AND MEASURES Specific drug classes associated with otherwise unexplainable CEEA.

RESULTS A statistically significant difference in drug class use between cases and controls for calcium channel blockers and thiazides was noted. For calcium channel blockers and thiazides, the matched odds ratios were 4.21 (95% CI, 1.77-9.97; P = .001) and 2.07 (95% CI, 1.08-3.96; P = .03) respectively. The histopathological pattern subgroup analysis failed to show any statistically significant associations.

CONCLUSIONS The findings of this study further support an association of calcium channel blockers, as well as thiazides, with CEEA in the United States.

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Dermatologists frequently encounter patients of advanced age presenting with chronic eczematous eruptions of uncertain etiology. The intense, persistent, difficult-to-treat pruritus that typically accompanies chronic eczematous eruptions in the aging (CEEA) can be extremely disabling for the patient and frustrating for the clinician to manage. The various causes of CEEA have been previously commented on by others. Morin et al found that of 83 elderly patients 65 years or older who presented with chronic or recurrent eczematous eruptions, no cause of the eruption could be identified in 35 (42%). In the remaining 48 patients (58%), the most common causes were extensive contact dermatitis, eczema-like mycosis fungoides, atopic dermatitis, eczema-like bullous pemphigoid, and scabies.

A growing body of evidence in recent years has implicated long-term prescription drug use as a common cause of CEEA. Older adults are the largest per-capita consumers of prescription medications with rates continuing to increase over the past several decades. A majority of adults aged at least 18 years in the United States take at least 1 prescription medication per day, with medication use increasing with age. Kaufman et al noted that the highest prevalence of medication use was in women 65 years and older, of whom 12% had taken 10 medications in the past week.

In a French case-control study in 2007, Joly and colleagues demonstrated a significant association between calcium channel blocker (CCB) intake in patients older than 60 years with eczematous eruptions that had evolved continuously or recurrently for more than 3 months without a reliable cause. Long-term intake of CCBs was reported in 26% of cases and 12% of controls, corresponding with a matched odds ratio of 2.29 (95% CI, 1.27-4.15; P = .006). The causative nature of this association was strongly suggested by the high rate of recovery from these eruptions after CCB withdrawal and reappearance of eruptions after rechallenge. While these findings are robust, the prescribing patterns of French physicians may differ significantly from that of their American colleagues, making interpretation of their data difficult to extrapolate to the US population.

To address this issue, we conducted a retrospective case-control study to characterize the epidemiology of otherwise unexplainable CEEA seen within our department over the past 6 years. We also wanted to further test the hypothesis that CCBs are more strongly associated etiologically with CEEA than are other drug classes. In addition, a subgroup analysis of a possible association between cases with a skin biopsy pattern of spongiotic and interface dermatitis (thought to indicate drug hypersensitivity changes in the skin) and CEEA was performed.

Methods

Cases

This study was approved by the institutional review board of the University of Utah and adhered to the Declaration of Helsinki Principles. Cases were selected retrospectively from patients who had received care at any of the outpatient clinics of the Department of Dermatology, University of Utah School of Medicine, from January 2005 to December 2011. Cases were found using 2 methods: electronically searching departmental pathology reports for “spongiotic and interface dermatitis” and “drug,” along with departmental billing records that were electronically searched for “drug eruption-internal” (ICD-9 [International Classification of Diseases, Ninth Revision] code 693.0), “drug eruption-external” (ICD-9 code 692.3), “adverse effect of drug” (ICD-9 code 995.2), and “dermatitis unspecified” (ICD-9 code 682.9). Inclusion criteria for cases were (1) 50 years or older; (2) taking a least 1 prescription medication at the time of presentation; (3) at least 2 months’ duration of the eruption; (4) a symmetric eczematous eruption based on physical examination findings and clinical suspicion for drug eruption; and (5) skin biopsy histopathologic features consistent with “spongiotic” and/or “interface” dermatitis. Exclusion criteria included (1) a history of atopic dermatitis; (2) no prescription medication use at the time of presentation; (3) a positive direct immunofluorescence skin biopsy result; (4) a reliable cause of eczematous eruption based on clinical judgment or histopathologic features (ie, contact dermatitis, bullous pemphigoid); (5) receiving chemotherapy at the time of onset of the eruption; (6) a lichenoid eruption or photodistributed eruption based on physical examination description; and (7) having a cutaneous eruption that persisted despite stopping all medication use for 3 months.

Relevant data collected included age, sex, ethnicity, physical examination description, and biopsy results. Medication information was obtained from both the physician’s notes and from “intake sheets” filled out and updated by medical staff at each appointment. Owing to a lack of conformity in reporting across our department, over-the-counter medications and herbal supplements were not included in the study.

Controls

Controls were selected retrospectively based on billing records from patients 50 years and older who had visited one of our outpatient dermatology clinics for common dermatologic conditions from 2007 to 2012. Departmental billing records were searched for “actinic keratosis” (ICD-9 code 702.0), “basal cell carcinoma” (ICD-9 code 173), “impetigo” (ICD-9 code 684), and “seborrheic keratosis” (ICD-9 codes 702.11 and 702.19). Controls were sex, race, and age matched within 5 years of controls. Each case was matched with 1 or 2 controls. Cases with unknown ethnicity were matched with controls of white descent, given the overwhelming prevalence of white patients in our population. Patients were excluded if any diagnosis of dermatitis or eczema had been made previously in the patient’s records. Pertinent characteristics and medication information for controls was gathered in the same manner as the cases.

Case Subgroup

Cases with a pathology report showing features of both spongiotic and interface dermatitis were included in the subgroup analysis. Controls who had been previously assigned to these cases were used as the control subgroup.
Statistical Analysis

Subject characteristics between case and control groups were compared using either the χ² or t test. A logistic regression was used to assess the odds ratios of subjects using more classes of medication (4-6 and ≥7 vs ≤3). A conditional logistic regression matched on sex, age, and race was adjusted for the number of medications used by subjects to assess the association of usage of each medication class with chronic eczematous eruptions. Only drug classes with a prevalence of at least 10% in cases were considered. The same conditional logistic regression was also applied to a subgroup analysis described in the previous subsection. In the subset analysis, only medications used by at least 15 patients in the subset were analyzed.

Results

The study included 94 cases and 132 controls. Descriptive characteristics of the case and control groups are reported in Table 1. Controls were matched to cases, with differences of mean age and sex lacking statistical significance. The mean (SD) number of prescription medications taken was 6.6 (3.6) for cases and 4.8 (4.1) for controls (P < .001).

The cases included 79 white patients, 10 patients of unknown race, 2 Hispanics, 2 Asians, 1 Native American, and 1 African American. Two controls presented with seborrheic keratoses, 128 with actinic keratoses, 1 with basal cell carcinoma, and 1 with impetigo. Of the controls, 105 (80%) were patients with visits in the calendar year 2011, 24 (18%) from 2012, 2 (2%) from 2009, and 1 (1%) from 2007. The control for the 1 African American patient was age matched within 10 years because a suitable control age matched within 5 years could not be identified. The controls included 126 white patients, 2 Hispanics, 2 Asians, 1 Native American, and 1 African American. Of the 132 controls, 124 (93%) were using at least 1 prescription medication at presentation.

Among the cases, the drug classes most used were statins (49%), CCBs (34%), angiotensin-converting enzyme inhibitors (3%), thyroid replacement (32%), and thiazides (29%). There was a statistically significant difference in drug class use between cases and controls for CCBs and thiazides. For CCBs and thiazides, the matched odds ratios were 4.21 (95% CI, 1.77-9.97; P = .001) and 2.07 (95% CI, 1.08-3.96; P = .03), respectively. Matched odds ratios for other drug classes are reported in Table 2.

For the subgroup analysis, there were 30 cases and 48 controls selected. The most common prescription medications used by subgroup cases were statins (43%), thyroid replacement (30%), selective serotonin reuptake inhibitors (23%), and CCBs (23%). Thiazides were used by 17% of subgroup cases. In the subgroup controls, 8% used CCBs and 19% used thiazides. No drug class met a statistically significant difference between cases and controls in this subgroup analysis.

Discussion

This study supports the finding by Joly and colleagues2 and gives added evidence establishing the association between the use of CCBs and CEEA. Furthermore, while prescribing patterns seem to differ considerably between French and American physicians, the association between CCBs and chronic eczematous eruptions was also strong among our American population of patients. The prevalence of CCB use among controls was 10% in our study and 12% in the study by Joly and colleagues2; for cases, the prevalence of CCB use in the 2 studies was 34% and 26%, respectively. Although the association appeared to be specific to CCB in the study performed by Joly and colleagues,2 thiazides also met statistical significance in our study. Other classes of medications were also examined. Most other drug classes had small numbers of users, and therefore deviations of odds ratios from the null are likely due to chance.

It is generally believed by dermatopathologists and dermatologists that a skin biopsy specimen showing both spongiotic and interface dermatitis suggests the possibility of a cutaneous drug hypersensitivity reaction.5,6 We therefore performed a subgroup analysis in our study population to determine whether cases displaying spongiotic and interface dermatitis on biopsy specimens were more likely to have a true drug eruption compared with those without this specific histopathologic pattern. Because the power was low on the subgroup analysis, we believed it would be inappropriate to report a matched odds ratio for thiazides or CCBs. Although no statistically significant associations were made, some interesting trends did appear. For example, subgroup analysis cases used more than twice the amount of CCBs than did controls. Thiazide use was very similar between the 2 subgroups.

Because this is a retrospective case-control study, some weaknesses and a variety of biases are inevitable. In a review of the study by Joly and colleagues,2 Stern7 stated that “obtaining and confirming data on chronic past drug use is very challenging. The steps the investigators took to establish chronic drug use were comprehensive and likely to be impractical in the United States.” Unlike the study by Joly and colleagues,2 a national “pharmacist’s computerized database” was not available to verify drug intake reported by our cases and controls. Instead, case and control medication lists were obtained from both the physician’s notes and from “intake sheets” filled out and updated by medical staff at each appointment. Because the possibility of a drug eruption was likely discussed with some cases, medications may have been added secondarily to the intake sheet, causing a recall bias. In addition, prescription drug intake could not be verified, so it is likely that some of the drug lists reported by patients are incomplete. Moreover, owing to the retrospective nature of the study, we were unable to reliably confirm the duration of time a patient had been using a particular medication.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Controls (n = 132)</th>
<th>Cases (n = 94)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male to female ratio</td>
<td>1.03</td>
<td>1.09</td>
<td>.84</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>72.9 (9.7)</td>
<td>72.7 (9.6)</td>
<td>.87</td>
</tr>
<tr>
<td>Prescription medications, mean (SD), No.</td>
<td>4.8 (4.1)</td>
<td>6.6 (3.6)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
Selection of controls in a study in which cases are obtained from a very specific group, such as is the case in our study, is difficult, to say the least, and is a potential source of bias. Although controls were matched by age, sex, and race to avoid a selection bias, we were unable to control for other variables. Most of the controls were patients who presented to our clinics in the 2011 calendar year. Although the drug classes examined are well established and a large change in physician prescribing patterns is not likely over a 3- to 4-year average, it is possible that a selection bias is present in the study. Also, a healthier control group may have inadvertently been selected because controls were selected from patients who presented with benign dermatologic conditions. Although all patients with chronic eczematous eruptions of unknown cause were included as case patients in their study, regardless of whether the patients were taking medications.

In our study, the mean numbers of medications used by the control group was significantly lower than the cases, which may be partly a result of the study design in which part of the case definition was use of at least 1 medication. The logistic model was adjusted for total number of medications used, with the odds ratios in Table 2 reflecting this adjustment. The adjustment would account for the tendency for physicians to more carefully document drug intake by cases compared with controls and for the restriction of cases to those using at least 1 medication. Two specific drug classes, CCBs and thiazides, remained statistically significant when adjusted for total number of medications used. In addition, the number of medications taken by the control group do seem to accurately represent the aging population in the United States when the prevalence of drug intake among the control group is compared with a study by Qato et al, in which 3005 adults aged 57 to 85 years across the United States were sampled about their prescription drug use.

Another critique made by Stern was that “a clearer definition of “cases” with more information about the extent, distribution, morphology, and perhaps pathology of the eruption” would help with the application and utilization of findings. The retrospective nature of this study also precluded a report on the exact physical examination findings of cases. Joly and colleagues describe that many of their patients had a photodistributed cutaneous eruption. We, however, did not note that finding in review of the physical examination descriptions of our patients. One of our case patients, illustrated in the Figure, demonstrates these nonspecific eczematous skin changes. Nevertheless, many of the patients we excluded from the study had descriptions of lichenoid eruptions in a photodistributed pattern. One may therefore speculate whether some of the patients in the study by Joly and colleagues had a photolichenoid eruption.

### Table 2. Matched Odds Ratio by Drug Class

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>No. (%)</th>
<th>Odds Ratio (95% CI)a</th>
<th>P Valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin</td>
<td>55 (49)</td>
<td>1.01 (0.56-1.82)</td>
<td>.98</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>32 (34)</td>
<td>4.21 (1.77-9.97)</td>
<td>.001</td>
</tr>
<tr>
<td>Thyroid replacement</td>
<td>30 (32)</td>
<td>1.86 (0.93-3.72)</td>
<td>.08</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>29 (31)</td>
<td>1.32 (0.68-2.57)</td>
<td>.42</td>
</tr>
<tr>
<td>Thiazide</td>
<td>27 (29)</td>
<td>2.07 (1.08-3.96)</td>
<td>.03</td>
</tr>
<tr>
<td>Angiotensin II receptor blocker</td>
<td>19 (20)</td>
<td>1.51 (0.69-3.33)</td>
<td>.30</td>
</tr>
<tr>
<td>Warfarin</td>
<td>15 (16)</td>
<td>1.50 (0.60-3.73)</td>
<td>.38</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>15 (16)</td>
<td>0.47 (0.21-1.09)</td>
<td>.08</td>
</tr>
<tr>
<td>Loop diuretic</td>
<td>15 (16)</td>
<td>2.80 (0.85-9.29)</td>
<td>.09</td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>13 (14)</td>
<td>1.54 (0.54-4.41)</td>
<td>.43</td>
</tr>
<tr>
<td>Bisphosphonate</td>
<td>12 (13)</td>
<td>1.25 (0.47-3.32)</td>
<td>.65</td>
</tr>
<tr>
<td>α/β Antagonist</td>
<td>11 (12)</td>
<td>1.72 (0.63-4.66)</td>
<td>.29</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitor</td>
<td>11 (12)</td>
<td>0.47 (0.18-1.27)</td>
<td>.14</td>
</tr>
<tr>
<td>Potassium-sparing diuretic</td>
<td>9 (10)</td>
<td>1.60 (0.53-4.83)</td>
<td>.40</td>
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Abbreviation: ACE, angiotensin-converting enzyme.

a Adjusted for matching variables (age, sex, race) and for total number of medications used.

b Values in bold are statistically significant.

<table>
<thead>
<tr>
<th>Abbreviations and Acronyms</th>
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<tbody>
<tr>
<td><strong>ACE</strong></td>
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**Figure. Case Patient**

Patient demonstrating eczematous skin changes on his torso and upper extremities. Note a lack of photodistribution.
In conclusion, identifying the drug(s) responsible for a suspected drug-induced cutaneous eruption in CEEA is a complex clinical challenge. Patch testing, prick testing, and intracutaneous tests have an overall low sensitivity for detecting reactivity to a drug, even in patients with a firm clinical diagnosis of a drug hypersensitivity reaction. Drug withdrawal and rechallenge, which is a gold standard for confirming a drug hypersensitivity reaction, carries the risk for severe clinical reactions in patients. Although the causative nature of CCBs and thiazides on CEEA cannot be confirmed with case-control studies, epidemiologic studies such as this are important in helping clinicians better pinpoint which drugs to stop in patients of advanced age presenting with these eczematous eruptions.

REFERENCES