Vismodegib-Induced Muscle Cramps

Effect of Calcium Channel Blockade on Vismodegib-Induced Muscle Cramps

Aberrant hedgehog (HH) pathway signaling is the pivotal molecular abnormality in all basal cell carcinomas whether occurring sporadically or as part of the rare autosomal dominant disease basal cell nevus (Gorlin) syndrome (OMIM 109400). Vismodegib (Erivedge, GDC-0449), an oral HH pathway inhibitor, is approved by the Food and Drug Administration for the treatment of locally advanced and metastatic basal cell carcinomas.

One of the major adverse effects of vismodegib is severe muscle cramps. Currently, there is no treatment for this adverse effect, often resulting in drug therapy discontinuation. Teperino et al4 suggested that vismodegib acts not only to antagonize canonical HH signaling but also to agonize noncanonical HH signaling, causing cell membrane calcium channel activation and inducing muscle cramps. These investigators proposed that calcium channel blockers might abrogate this adverse event. Our objective was to evaluate the course of muscle cramps in our cohort of vismodegib-treated patients and to investigate whether the calcium channel blocker amiodipine besylate would alter the self-reported severity and frequency of these cramps.

Methods | This was an ancillary study of 43 patients enrolled in 2 clinical trials testing vismodegib, 150 mg/d, for basal cell carcinoma prevention.5,6 We treated 9 patients with basal cell nevus syndrome with amiodipine, 10 mg/d, for 8 weeks based on their willingness to take a daily medication for cramps. We queried them using telephone-administered questionnaires at 4 weeks, baseline, and 2, 4, and 8 weeks after amiodipine therapy initiation about cramp frequency, severity (scale of 0 [none] to 10 [severe]), and duration (minutes); frequency of night awakenings due to muscle cramps; and common adverse effects associated with amiodipine. We excluded 34 patients from amiodipine treatment who had completed the study (n = 3), were not currently using vismodegib (n = 11), were expected to stop taking vismodegib within the ensuing 4 weeks (n = 7), were already using amiodipine at baseline (n = 2), were unwilling to take amiodipine or had contraindications to its use (n = 9), or were unavailable to complete baseline questionnaires (n = 2). This study was approved by the Children’s Hospital Oakland Research Institute Institutional Review Board. Oral informed consent was received from all patients.

Our primary end point was the percentage change in muscle cramp frequency from baseline to week 8 of amiodipine treatment. Our secondary outcomes were changes in muscle cramp severity, cramp duration, and frequency of night awakenings. On the basis of an effect size of 30% reduction in muscle cramp frequency (SD, 20%) at week 8 from baseline and a power of 80%, a sample size of 6 patients would be required to detect a statistically significant (α = .05) difference before and after amiodipine treatment.

Results | We included 8 amiodipine-treated patients in the analysis; one patient was excluded because of incomplete questionnaires after baseline. Study participants included 5 men and 3 women with a mean (SD) age of 54 (11) years who were treated with a mean (SD) of 11 (12) months of vismodegib at baseline.

During a period of 8 weeks, the percentage change in cramp frequency was significantly reduced by −5.81% per week (95% CI, −10.15% to −1.48%; P = .009) with amiodipine treatment (Table and Figure). There was no significant change in muscle cramp severity (P = .48), cramp duration (P = .85), or frequency of night awakenings (P = .47) over time (Figure).

As a comparison, we followed up 9 patients who did not take amiodipine but who were taking vismodegib and answered regular telephone questionnaires about muscle cramps.

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During a period of 8 weeks, there was a nonsignificant increase in cramp frequency by 5.13% per week (95% CI, −7% to 17%; \( P = .42 \)) in control patients. There was no change in muscle cramp severity (\( P = .37 \)), cramp duration (\( P = .42 \)), or frequency of night awakenings (\( P = .43 \)) over time.

One patient reported mild intermittent dizziness, one noted new grade 1 peripheral edema, and none reported increased headaches or hypotension with amlodipine treatment.

### Discussion

We found that in a subset of patients with basal cell nevus syndrome, amlodipine, 10 mg daily, reduced the frequency of vismodegib-induced muscle cramps after 8 weeks compared with baseline. In contrast, patients who did not take amlodipine did not have a decrease in muscle cramps during the 8-week observation period. Amlodipine may be effective in vismodegib-induced muscle cramps because it blocks voltage-gated calcium channels and inhibits the transport of extracellular calcium into muscle that is required for contraction.\(^7\)

### Conclusions

In our study, the therapeutic benefit of amlodipine was evident within 2 weeks; therefore, we recommend a 2-week trial of amlodipine treatment for vismodegib-

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**Table. Mean (SD) Change in Muscle Cramp Characteristics Over Time With Amlodipine Treatment**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Amlodipine (n = 8)</th>
<th>( P ) Value(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle cramps(^c)</td>
<td>15 (8)</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Night awakenings due to muscle cramps</td>
<td>5 (6)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Cramp</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity (scale of 1–10)</td>
<td>7 (2)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Duration, min</td>
<td>6 (4)</td>
<td>5 (5)</td>
</tr>
</tbody>
</table>

\(^a\) Values calculated for 8 patients at all time points, including 2 patients who stopped treatment at 2 and 4 weeks, respectively.

\(^b\) We used the generalized estimating equation model to analyze the percentage change in cramps per week for all patients who started amlodipine treatment and completed at least 1 follow-up questionnaire.

\(^c\) Of the 8 amlodipine-treated patients, 5 had reduced cramp frequency during the 8-week trial. The remaining 3 patients experienced increased cramp frequency with amlodipine, 2 of whom stopped amlodipine treatment within 2 and 4 weeks, respectively. Cramp frequency in these 2 did not improve with discontinuation of amlodipine treatment. By contrast, among the 2 patients who derived benefit from amlodipine and continued to take vismodegib after discontinuation of amlodipine treatment, cramp frequency increased to baseline levels within 1 week of cessation of amlodipine.
related muscle cramps with continued use if successful. Further study with a larger randomized clinical trial is warranted.

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Study concept and design: Ally, Tang, Epstein.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Ally, Tang, Lindgren, Acosta-Raphael, Rezae.

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Administrative, technical, or material support: Ally, Lindgren, Acosta-Raphael, Rezae, Chanana.

Study supervision: Tang, Lindgren, Epstein.

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Prevalence and Correlates of Indoor Tanning in Nonsalon Locations Among a National Sample of Young Women

Indoor tanning is a public health threat,1 and the Surgeon General has called for its reduction in adolescents and young adults.2 Research on indoor tanning has not distinguished between tanning-only salons vs other businesses and private residences that provide tanning (ie, nonsalon tanning). For example, gyms often offer free tanning, which may lead to riskier tanning habits.3 Better understanding of nonsalon tanning could have policy, prevention, and clinical implications. Our study addresses this literature gap by examining the prevalence and correlates of nonsalon tanning in a nationally representative sample of young women, who have the highest rates of indoor tanning use.

Methods | Rutgers Institutional Review Board approved the study and all participants signed an online consent form presented prior to the study. A nationally representative sample of 823 women aged 18 to 25 years (mean age, 22.7 years; 463 [56.3%] non-Hispanic white, 118 [14.3%] non-Hispanic black, 174 [21.1%] Hispanic, and 68 [8.3%] non-Hispanic other) was recruited through GfK Knowledge Networks, a research survey firm that uses address-based sampling methods to recruit a probability-based online panel of 55 000 adults from which this sample was drawn. Participants were paid $5 for completing the survey. Measures included demographics, lifetime indoor tanning use (ever used indoor tanning), current indoor tanning frequency (past 12 months), and indoor tanning location (tanning-only salon or location other than a tanning-only salon). Participants who indicated they tanned at a nonsalon location identified the location as a gym or health club, beauty shop, private home, apartment, or other location. Participants who currently use indoor tanning completed measures of indoor tanning patterns4 (event or year-round pattern) and indicated whether they used indoor tanning to improve their mood and how difficult it would be to stop using indoor tanning (proxy measure of tanning dependence5). History of depression and anxiety were also measured. Analysis of categorical variables used χ² difference tests and continuous outcomes used bivariate general linear models in SPSS Complex Samples, version 21 (SPSS Inc).

Results | Forty-one percent (unweighted n = 123) of participants who ever used indoor tanning and 24.6% (n = 34) of current indoor tanning users reported nonsalon tanning (Table 1). Participants who had ever used indoor tanning most commonly used indoor tanning at gyms (64 [18.9%]), beauty shops (39 [13.8%]), and private homes (40 [13.2%]). Participants who were currently using nonsalon indoor tanning most often used indoor tanning at gyms (20 [9.8%]), private homes (13 [7.7%]), and apartment complexes (10 [7.5%]). The number of lifetime indoor tanning sessions was...