Prevalence of Adrenal Insufficiency Following Systemic Glucocorticoid Therapy in Infants With Hemangiomas

Jefferson P. Lomenick, MD; Kent L. Reifschneider, MD; Anne W. Lucky, MD; Denise Adams, MD; Richard G. Azizkhan, MD; Jessica G. Woo, PhD; Philippe F. Backeljauw, MD

Objective: To determine the prevalence of adrenal insufficiency in infants with hemangiomas following treatment with systemic glucocorticoids (GCs).

Design: Prospective study for 18 months.

Setting: Hemangioma and vascular malformation center at a tertiary care children’s hospital.

Patients: Sixteen infants with hemangiomas had an adrenal axis evaluation as soon as possible following the completion of GC therapy. Ten healthy control infants were also evaluated for comparison.

Interventions: Prednisolone at a starting dose of 2 to 3 mg/kg/d for 4 weeks, followed by a tapering period. The mean duration of GC treatment was 7.2 months.

Main Outcome Measure: Prevalence of adrenal insufficiency in GC-treated subjects as assessed by a combination low-dose/high-dose corticotropin stimulation test.

Results: Subjects underwent corticotropin testing at a mean of 13 days after the completion of therapy. Only 1 of the 16 GC-treated infants (6%) had adrenal insufficiency. This subject was tested 1 day after GC treatment was stopped, and results from retesting 3 months later were normal. All control subjects had normal adrenal function.

Conclusion: Infants with hemangiomas are at low risk of adrenal insufficiency following the completion of GC therapy, as used in our hemangioma center.

Arch Dermatol. 2009;145(3):262-266

Hemangiomas are common tumors of the vascular endothelium found in approximately 10% of infants. While sometimes present at birth, they more typically appear in the first 2 months. Most superficial hemangiomas then undergo a proliferative phase lasting 6 to 12 months. Approximately 60% of these lesions involute completely by 5 years, with 90% to 95% by 9 years. Because most lesions resolve spontaneously, no specific therapy is required. However, large, disfiguring, or functionally debilitating lesions require medical intervention, often with high-dose systemic glucocorticoids (GCs).

A well-known adverse effect of GC therapy is hypothalamic-pituitary-adrenal (HPA) axis suppression due to decreased hypothalamic corticotropin-releasing hormone (CRH) and pituitary corticotropin secretion, leading to adrenal cortex atrophy. However, the development of adrenal insufficiency (AI) following systemic GC treatment can be idiosyncratic and difficult to predict. Several tests are available to assess the HPA axis, including the CRH test, metyrapone test, insulin tolerance test, and corticotropin test. Many clinicians favor the corticotropin test because of its availability, low cost, safety, and reliability. If AI occurs, the rate of recovery of the HPA axis is variable and depends on the method of adrenal function testing. In addition, HPA axis recovery has been shown to correlate poorly with the dose and duration of GC treatment. A paucity of data exists on adrenal function in infants with hemangiomas following treatment with systemic GCs. A retrospective study and 1 pro-

For editorial comment see page 319
spective report\textsuperscript{13} suggest a high prevalence of adrenal suppression (87\% and 71\%, respectively) in this population using a first-morning cortisol level measurement as the diagnostic test. However, we previously reported a low prevalence of AI (10\%) in a retrospective analysis of a small cohort based on low-dose corticotropin stimulation testing.\textsuperscript{14}

Because of the limited information on HPA axis recovery in infants and the importance of detecting AI, we prospectively evaluated the prevalence of AI following systemic GC therapy in infants with hemangiomas using a combination low-dose/high-dose corticotropin stimulation test.

**METHODS**

**SUBJECTS**

Sixteen infants (12 female and 4 male) were recruited from the Hemangioma and Vascular Malformation Center (HVMC) at Cincinnati Children's Hospital Medical Center (CCHMC), Cincinnati, Ohio, during an 18-month period. All subjects were treated with systemic GC therapy. The infants were otherwise healthy and had no prior exposure to GCs or interferon alfa. The initial GC dose and titration regimen was determined by HVMC clinicians independent of study enrollment. The GC protocol included a starting dose of oral prednisolone of 2 to 3 mg/kg/d for 4 weeks, followed by an approximately 10\% dose decrease biweekly. The duration of the GC tapering period was 5 to 7 months. Ten healthy control infants (6 female and 4 male) were also enrolled from the CCHMC general pediatric clinic (no history of GC use or recent illnesses and unremarkable medical history). All parents or guardians gave informed consent. Institutional review board approval was obtained before the initiation of the study.

**CORTICOTROPIN STIMULATION TESTING**

All subjects underwent a combination low-dose/high-dose corticotropin stimulation test at the completion of GC treatment. Because the frequency and degree of AI in this patient population was not known, our goal was to test the subjects within 1 week of the discontinuation of GC therapy. For the low-dose test, a 250-µg vial of synthetic corticotropin (Cortrosyn; Amphastar Pharmaceuticals Inc, Rancho Cucamonga, California) was reconstituted in 250-mL 0.9\% sodium chloride solution, yielding a concentration of 1 µg/mL. For the high-dose test, another 250-µg vial of Cortrosyn was reconstituted with 1 mL of 0.9\% sodium chloride solution, yielding a concentration of 250 µg/mL. An intravenous (IV) line was placed, and baseline cortisol level was measured. The infants were then administered the 1-µg/m² Cortrosyn (low-dose) IV line for 1 to 2 minutes. The peak cortisol level was measured 20 minutes after the administration of Cortrosyn. Immediately after measuring the 20-minute cortisol level, infants were administered the 250-µg/m² Cortrosyn (high-dose) IV line for 1 to 2 minutes. A third serum cortisol level measurement was collected 60 minutes later (80 minutes after baseline).

If the 20-minute peak cortisol level was 18 µg/dL or higher (to convert to nanomoles per liter, multiply by 27.588), the subject was considered to have a normal HPA axis.\textsuperscript{15,16} If the 20-minute and 80-minute peak cortisol levels were both lower than 18 µg/dL but the 80-minute peak cortisol level was 18 µg/dL or higher, the subject was considered to have AI with partial HPA axis recovery.\textsuperscript{16} If the subject was found to have AI, families were instructed on “stress-dosing” with GCs during illness, and corticotropin testing was repeated every 3 months until a normal result was found.

**CORTISOL ASSAY**

Serum cortisol level was measured by radioimmunoassay using a double-antibody technique (MP Biomedicals, Solon, Ohio). The intraassay and interassay coefficients of variation were less than 5\% and less than 10\%, respectively. The sensitivity was 0.1 µg/dL.

**STATISTICAL ANALYSIS**

The primary outcome variable was the percentage of infants treated with systemic GCs who developed AI. Baseline characteristics of the 2 groups were compared using unpaired t tests for continuous variables or Fisher exact tests for categorical variables. Correlations between end points were based on Spearman correlation coefficients. Differences in variability of cortisol level measurements between the groups at each time point tested were compared using the F statistic. Results are expressed as mean (SD), with P \leq .05 considered significant.

Clinical characteristics of the 2 groups are summarized in the Table. At the time of the corticotropin stimulation test, the control subjects were significantly older than the GC-treated infants (P < .001), but there were no other differences between the groups.

Of the 16 GC-treated infants with hemangiomas, 14 completed both the low-dose and high-dose phases of the test, with the other 2 subjects completing only the low-dose phase owing to lost IV access. The cortisol response is given in the Table and shown in Figure. A. Only 1 of the 16 GC-treated infants (6\%) was found to have

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>GC-Treated Infants (n = 16)</th>
<th>Control Infants (n = 10)</th>
<th>P Value \textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, %</td>
<td>75</td>
<td>60</td>
<td>.66</td>
</tr>
<tr>
<td>Age at start of GC treatment, mo</td>
<td>2.3 (0.5)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Duration of GC treatment, mo</td>
<td>7.2 (2.2)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Age at time of corticotropin test, mo</td>
<td>9.9 (2.5)</td>
<td>15.1 (2.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Days since last GC treatment</td>
<td>13.0 (11.2)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Baseline cortisol level, µg/dL</td>
<td>11.0 (5.3)</td>
<td>12.8 (8.6)</td>
<td>.51</td>
</tr>
<tr>
<td>20-min Cortisol level, µg/dL</td>
<td>36.4 (10.4)</td>
<td>39.8 (4.1)</td>
<td>.25</td>
</tr>
<tr>
<td>80-min Cortisol level, µg/dL</td>
<td>46.7 (13.2)</td>
<td>56.2 (12.2)</td>
<td>.09</td>
</tr>
<tr>
<td>Subjects with AI, %</td>
<td>6</td>
<td>0</td>
<td>&gt;.99</td>
</tr>
</tbody>
</table>

Abbreviations: AI, adrenal insufficiency; GC, glucocorticoid; NA, not applicable.

\textsuperscript{a} SI conversion factor: To convert cortisol to nanomoles per liter, multiply by 27.588.
AI. This subject was a full-term infant who was tested 1 day after completing 6.6 months of GC therapy and had abnormal results for both phases of the corticotropin test. When retested 3 months later, this infant had a normal cortisol response (8.0 µg/dL at baseline, 33.6 µg/dL at 20 minutes, and 39.8 µg/dL at 80 minutes). All other subjects tested had a peak cortisol level of 18 µg/dL or higher (to convert to nanomoles per liter, multiply by 27.886).

Figure. Cortisol response to corticotropin stimulation testing in infants with hemangiomas following glucocorticoid treatment (A) and control infants (B). A normal cortisol response is 18 µg/dL or higher (to convert to nanomoles per liter, multiply by 27.886).

Our prospective study evaluated otherwise healthy infants with hemangiomas for the development of AI following long-term GC therapy. Using the corticotropin stimulation test, we found that only 1 of 16 infants (6%) treated with GCs had AI following the completion of therapy. These data are consistent with our previous retrospective analysis, which found a similar low prevalence of AI (10%).14 The 1 infant found to have AI had no specific clinical features to suggest AI, such as a higher dose or longer duration of GC therapy, an unusually large hemangioma, or a more pronounced effect of GC therapy on growth. In our previous study, the only infant with AI had been treated with dexamethasone for a similar duration as the subjects in this study, but there were no clinical characteristics to suggest AI. It is possible that the longer half-life of dexamethasone (36-54 hours compared with 16-36 hours for prednisolone15) contributed to the slower recovery of the HPA axis in that subject.

Our finding that AI is rare following GC treatment in infants with hemangiomas is in contrast to 2 reports12,13 that suggest a relatively frequent occurrence of AI in this patient population. George et al12 retrospectively evaluated the adverse effects of systemic GC treatment in 22 infants with hemangiomas. First-morning serum cortisol concentrations were measured in 15 subjects after they had been administered a tapered physiologic dose of GC, and 13 of them (87%) had a value less than 18 µg/dL. However, the specificity of a single morning cortisol level measurement to diagnose AI is poor,16 and the patients were still receiving treatment. Only 3 of the infants in the report by George et al12 underwent a low-dose corticotropin test, and 2 of these infants had a peak cortisol level lower than 18 µg/dL; however, 1 of these 2 subjects was still receiving GC therapy at the time of the test. A more recent study prospectively compared the effects of oral and IV GC treatment on clinical outcomes and adverse events in infants with hemangiomas.13 In 52 of 73 samples (71%), first-morning serum cortisol levels were lower than 18 µg/dL in the 2 groups, including 13 undetectable values “suggestive of significant AI.”17 Again, the poor specificity of a morning serum cortisol level measurement to diagnose AI should be noted. In addition, cortisol levels were measured at the start of GC treatment and monthly thereafter for 3 months; thus, many of these samples were taken during the peak of GC therapy when one would expect HPA axis suppression.

We used a low-dose (1-µg/m²) corticotropin stimulation test to assess for AI in our study. Several groups have shown that the low-dose corticotropin test has better sensitivity for the diagnosis of AI than the high-dose...
(250 µg/m²) test in both adults and children. Furthermore, a normal cortisol response to the high-dose test but a subnormal response to the low-dose test can indicate initial recovery of endogenous corticotropin secretion. Thus, we chose to do both tests in succession to evaluate the recovery of the HPA axis following long-term treatment with systemic GCs. Of the 16 infants, 15 (94%) had normal adrenal function, with peak cortisol levels of 18 µg/dL or higher for both tests, and 1 of 16 subjects (6%) had AI without evidence of initial recovery of corticotropin secretion (peak cortisol level <18 µg/dL for both tests). No subjects were found to have AI with partial recovery of the HPA axis (peak cortisol level <18 µg/dL for the low-dose test but ≥18 µg/dL for the high-dose test), even though the infants were tested soon (mean, 13 days) after the completion of GC therapy. It appears that most infants treated with our specific GC protocol begin to have endogenous corticotropin secretion sometime during the GC-tapering period, with complete recovery of the HPA axis toward the end of the tapering period or immediately thereafter. However, the variability observed in the 20-minute cortisol levels in the GC-treated infants compared with the controls possibly indicates that adrenal gland recovery is still occurring, even though the response to the low-dose corticotropin test is considered normal.

Our study has some limitations. A relatively small number of infants with hemangiomas were studied to determine the prevalence of AI, so our estimate may be subject to sampling error. However, the finding of a similar low rate of AI in our previous retrospective study using the same method of testing is reassuring. Second, although a standard approach to GC therapy was attempted, variability in efficacy was observed, as evidenced by the duration of therapy, which ranged from 5.2 to 12.3 months. While some of this variability may be due to the inherent responsiveness of the hemangioma to GC treatment, poor medication compliance may have contributed as well, which could affect the rate of AI. Another limitation was the duration of time between discontinuation of GC therapy and the corticotropin test: 13 of the subjects were tested 1 to 16 days after completing treatment, but 3 subjects had their test 26 to 40 days later. While we attempted to test all subjects within 7 days, many families lived more than 100 miles from our center and could not comply. Thus, some of the subjects with a normal test result may have had AI had the test been done within 7 days. Finally, the use of 18 µg/dL as a cutoff to define normal adrenal function in response to the low-dose corticotropin test is derived from studies of older children and adults. Though we found no difference between the cortisol responses of the infants treated with GCs and the controls, the control subjects were slightly older at the time of their test. However, we found no association between the subjects’ age and cortisol response in either GC-treated infants or controls. In addition, a recent study found the low-dose corticotropin test to be useful in term infants younger than 12 months in demonstrating normal adrenal function.

In conclusion, our study shows that infants with hemangiomas treated with systemic GCs have a low risk of AI at the completion of therapy. The 1 infant found to have AI had no clinical indicator of this condition but recovered completely within 3 months. In the case of significant body stress, such as a febrile illness or surgery, stress dosing with GCs seems prudent in infants with hemangiomas during the latter stages of the GC tapering period through the first 3 months after GC therapy is discontinued. If stress dosing is needed, we suggest administering hydrocortisone, 30 to 50 mg/m²/d, divided into 3 doses (or equivalent dose of prednisolone) orally or intramuscularly if the infant is vomiting. If needed, a low-dose corticotropin stimulation test can be used to evaluate the HPA axis and determine if AI is present.

Accepted for Publication: July 22, 2008.
Correspondence: Jefferson P. Lomenick, MD, Division of Pediatric Endocrinology, Vanderbilt University School of Medicine, 11136 Doctors’ Office Tower, 2200 Children’s Way, Nashville, TN 37232-9170 (jefferson.lomenick@vanderbilt.edu).

Author Contributions: Drs Lomenick, Reifschneider, Woo, and Backeljauw had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Lomenick, Lucky, and Backeljauw. Acquisition of data: Lomenick, Reifschneider, Lucky, Adams, Azizkhan, and Backeljauw. Analysis and interpretation of data: Lomenick, Reifschneider, Woo, and Backeljauw. Drafting of the manuscript: Lomenick, Reifschneider, Woo, and Backeljauw. Critical revision of the manuscript for important intellectual content: Reifschneider, Lucky, Adams, Azizkhan, and Backeljauw. Statistical analysis: Woo. Obtained funding: Lomenick and Backeljauw. Administrative, technical, and material support: Lomenick, Reifschneider, Woo, and Backeljauw. Study supervision: Lucky and Backeljauw.

Financial Disclosure: Dr Lomenick is a consultant for and has received honoraria from Pfizer and Lilly. Dr Backeljauw is a consultant for and has received honoraria from Pfizer.

Funding/Support: This study was supported by a grant from Pfizer Inc.

Role of the Sponsor: The sponsor had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

Additional Contributions: Peggy Sweeney, RN, assisted in the recruitment of control subjects.

REFERENCES

5. Akyüz C, Yarış N, Kuflik MT, Buyukpamukcu M. Management of cutaneous hem-


C ongratulations to the winner of our December quiz, Paula Boggio, MD, Department of Dermatology, Ramos Mejía Hospital, Buenos Aires, Argentina. The correct answer to our December challenge was granulomatous cheilitis. For a complete discussion of this case, see the Off-Center Fold section in the January Archives (Cernik C, Kerns MJ, Moaad JC, Hefferman M. Asymptomatic, edematous upper lip in a 39-year-old woman. Arch Dermatol. 2009;145[1]:77-82).

Be sure to visit the Archives of Dermatology Web site (http://www.archdermatol.com) to try your hand at the interactive quiz. We invite visitors to make a diagnosis based on selected information from a case report or other feature scheduled to be published in the following month’s print edition of the Archives. The first visitor to e-mail our Web editors with the correct answer will be recognized in the print journal and on our Web site and will also receive a free copy of The Art of JAMA II.