**Zenhale Inhaled Corticosteroid Therapy: Useful Second Line Therapy for Asthma in Children but be Wary of Adrenal Suppression**

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**INTRODUCTION**

- Inhaled corticosteroids (ICS) are the most effective treatment of chronic persistent asthma in adults and children.1  
- Children with Asthma who do not respond to first-line therapy may need ICS-Long-Acting Beta Agonist (ICS-LABA) combination therapy.  
- Adrenal insufficiency (AI) due to adrenal suppression is a recognized side effect of ICS therapy2,3 but clinically significant suppression is rare.4  
- An increase in suspected cases of AI associated with one particular ICS-LABA, mometasone-formoterol (Zenhale) was observed at a tertiary care Asthma clinic over a 6-month period.

**OBJECTIVE**

To identify the prevalence of adrenal insufficiency in children treated with Zenhale.

**METHODS**

**Patients**

- After confirmation of AI in the index patients by low-dose synthetic ACTH stimulation testing (LDST) all children attending the Asthma Clinic at Alberta Children’s Hospital (ACH) treated with Zenhale were identified using the respiratory database.  
- Subjects were then contacted by Respiratory clinic staff and screened for possible symptoms of AI and requested to perform an 8 am plasma cortisol.

**Children with symptoms suggestive of adrenal insufficiency and/or low 8 am plasma cortisol levels (<200 nmol/L) were reviewed by Endocrinology and underwent a LDST.**

**Biochemistry**

**Plasma Cortisol**

- Measured using Roche Modular Analytics E170 platform (Roche Diagnostics) with chemiluminescent competitive assay: functional sensitivity 0.5 nmol/L and coefficient of variation (CV): mean of 110 nmol/L CV, 6.4%; mean of 595 nmol/L CV, 3.3% and for mean of 900 nmol/L CV, 3%. Reference range: 200-690 nmol/L.

**LDST**

- 1 microgram of Cosyntropin was administered, after serial dilution, by IV injection and plasma cortisol samples obtained at baseline, 30 and 60 minutes post-injection.  
- Peak cortisol level of <500 nmol/L was considered an impaired response.

**Statistics**

SPSS Version 19  
Groups were compared using independent t-tests.  
Receiver operating characteristic (ROC) curve  
Generated to assess 8 am cortisol as a diagnostic screening test.

**RESULTS**

- 170 children in the Asthma clinic were prescribed Zenhale.  
- 12 children prescribed Zenhale were not included: as they never started or had previously discontinued the medication.

**Screening has been completed in 111 children; 39 had LDST of which 16 (14.4 %) had adrenal insufficiency (see Table).**

- In the 6 years sub-group, 9 of 21 children screened (42.9%) had adrenal insufficiency; and 9 of 10 children (90%) screened on high dose Zenhale (800 mcg/day) had AI.

**Table:** Characteristics of all subjects described as median (range)  
*Denotes P<0.01 vs. no suppression (N=96)

<table>
<thead>
<tr>
<th>N</th>
<th>8 am Plasma Cortisol (nmol/L)</th>
<th>Peak Cortisol on LDST (nmol/L)</th>
<th>Age (y)</th>
<th>Zenhale Dose (mcg/day)</th>
<th>Duration (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low 8 am Cortisol &amp;/or AI symptoms</td>
<td>Adrenal suppression</td>
<td>16</td>
<td>12 (2-255)</td>
<td>216 (11-398)</td>
<td>5.7 (3-12.6)*</td>
</tr>
<tr>
<td>No adrenal suppression</td>
<td>24</td>
<td>147 (3-321)</td>
<td>654 (509-890)</td>
<td>9.4 (9-14.0)</td>
<td>400 (200-800)</td>
</tr>
<tr>
<td>Normal 8 am Cortisol &amp; no AI symptoms</td>
<td>32</td>
<td>372 (203-747)</td>
<td>N/A</td>
<td>10.9 (2.5-17.5)</td>
<td>400 (200-800)</td>
</tr>
<tr>
<td>No screening performed</td>
<td>46</td>
<td>N/A</td>
<td>N/A</td>
<td>11.1 (2.4-17.3)</td>
<td>400 (200-800)</td>
</tr>
</tbody>
</table>

**RESULTS cont.**

- Relative Risk of adrenal insufficiency with Dose ≥ 600 mcg/d was 11.3 (95% CI: 2.7-47.4)  
- Relative Risk of adrenal insufficiency in Age <6yr was 6.5 (95 % CI: 2.6-16.3)

8 am Plasma Cortisol as a diagnostic screening test?

- ROC curve was generated using various cut-offs of plasma cortisol to assess its use as a diagnostic screening test (see Figure)  
- According to ROC curve best cut-off was 50 nmol/L with the following characteristics:
  - Sensitivity: 0.86 (95% CI: 0.79-0.92)  
  - Specificity: 0.95 (95% CI: 0.90-0.99)  
  - Positive predictive value: 0.71  
  - Negative predictive value: 0.98  
  - Likelihood ratio: 16.1 (95% CI: 6.69-38.82)

**CONCLUSIONS**

- Zenhale is an effective second-line Asthma medication but its use in children has been complicated by adrenal suppression in 14% of a pediatric population.  
- The relative risk is unacceptably high with a dose ≥ 600 mcg/day and children <6 years.

- We recommend a maximum daily dose of 400 mcg in children <12 years and caution in those <6 years based on these data.

- Children/adolescents using Zenhale <12 years or on high daily doses (>400 mcg) should be advised about: signs and symptoms of AI and to avoid abruptly stopping Zenhale therapy and to discuss any dose changes with their Asthma team.

- 8 am plasma cortisol is an acceptable screening test for adrenal insufficiency in this scenario if the 50 nmol/L cut-off is employed vs. lower limit of normal range but cannot exclude adrenal insufficiency and patients with suggestive symptoms should still be referred to Endocrinology.

**REFERENCES**


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