

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 therapy²⁻⁵ but clinically significant suppression is rare.⁶
- 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.



RESULTS cont.

- Relative Risk of adrenal insufficiency with Dose \geq 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)

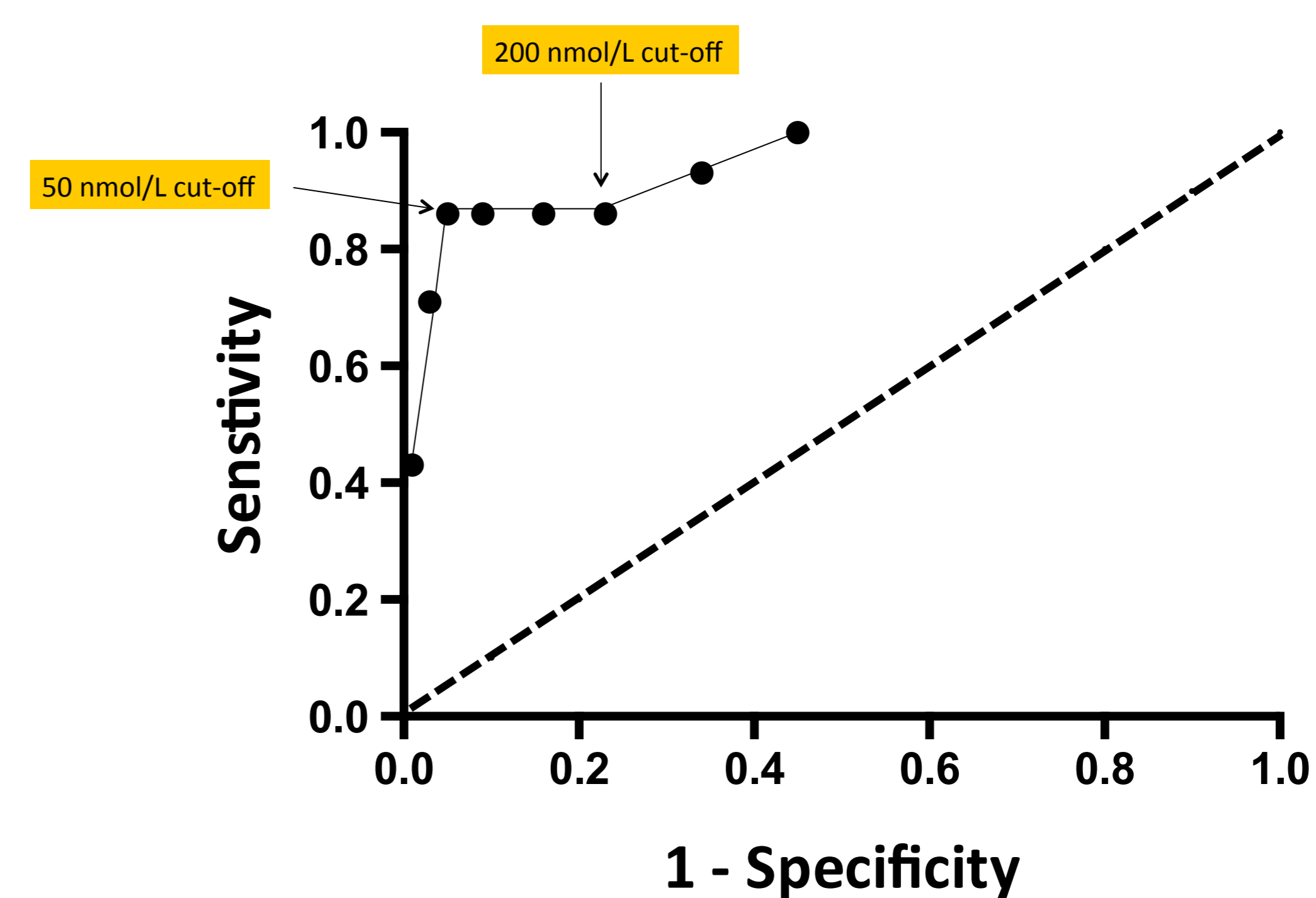


Figure: ROC curve for 8am Plasma Cortisol

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 remaining 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 plasma cortisol as a diagnostic screening test.

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 \geq 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.

RESULTS

- 170 children in the Asthma clinic were prescribed Zenhale.
- 12 children prescribed Zenhale are 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.

	N	8am Plasma Cortisol (nmol/L)	Peak Cortisol on LDST (nmol/L)	Age (y)	Zenhale		
					Dose (mcg/day)	Duration (y)	
Low 8am Cortisol &/or AI symptoms	Adrenal suppression	16	12 (2-255)	216 (11-398)	5.7 (3.3-12.6)*	800 (400-800)*	0.7 (0.3-2)
	No adrenal suppression	24	147 (3-321)	654 (503-890)	9.4 (3.9-14.0)	400 (200-800)	0.8 (0.3-2)
Normal 8am Cortisol & no AI symptoms	72	372 (203-747)	N/A	10.9 (2.5-17.5)	400 (200-800)	1.1 (0.02-2.6)	
No screening performed	46	N/A	N/A	11.1 (2.4-17.3)	400 (200-800)	1.2 (0.2-3.3)	

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

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