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To cite this article: Brian S. Liddell DO, John M. Oberlin MD & Daniel P. Hsu MD (2017) Inhaled corticosteroid related adrenal suppression detected by poor growth and reversed with ciclesonide, Journal of Asthma, 54:1, 99-104, DOI: [10.1080/02770903.2016.1196370](https://doi.org/10.1080/02770903.2016.1196370)

To link to this article: <http://dx.doi.org/10.1080/02770903.2016.1196370>



Accepted author version posted online: 10 Jun 2016.
Published online: 10 Jun 2016.



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PHARMACOTHERAPY

Inhaled corticosteroid related adrenal suppression detected by poor growth and reversed with ciclesonide

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ABSTRACT

Introduction: This case series intends to highlight the association between decreased linear growth velocity and adrenal suppression in patients receiving inhaled corticosteroids for asthma. A potential treatment option is also discussed. Adrenal suppression secondary to inhaled corticosteroids has previously been reported and is often underrecognized. A decrease in linear height velocity has also been associated with inhaled corticosteroids. However, a decrease in height velocity has not been shown to predict adrenal suppression. **Case study:** This case series of 15 patients receiving inhaled corticosteroids for control of asthma were noted to have a decrease in linear growth velocity ultimately associated with adrenal suppression. A change in inhaled corticosteroid to ciclesonide led to recovery of adrenal function without impacting asthma control. **Results:** Chart review from a pediatric pulmonology clinic was performed. Growth parameters and laboratory studies were recorded and analyzed. A mean decrease in height standard deviation score in the year prior to diagnosis of adrenal suppression was -0.59 , -0.11 , and -0.18 , in pre-puberty, peri-puberty, and post-puberty patients, respectively. After ciclesonide therapy was initiated, a mean change in height standard deviation score of $+0.40$, $+0.13$, and -0.13 , was noted for pre-puberty, peri-puberty, and post-puberty patients, respectively. A change in growth velocity of $+5.3$ cm/yr, $+2.1$ cm/yr, and -1.9 cm/yr, was noted for pre-puberty, peri-puberty, and post-puberty patients, respectively, after starting ciclesonide. **Conclusions:** Height velocity should be monitored closely during routine asthma visits to identify potential adrenal suppression associated with inhaled corticosteroids use. Ciclesonide is a good option for asthma treatment that allows for adrenal recovery.

ARTICLE HISTORY

Received 10 February 2016
Revised 23 May 2016
Accepted 27 May 2016

KEYWORDS

Asthma; inhaled corticosteroids; adrenal suppression; hypothalamic-pituitary-adrenal axis dysfunction; ciclesonide; growth velocity

Introduction

Hypothalamic-pituitary-adrenal axis (HPAA) suppression has been reported secondary to inhaled corticosteroids (ICS), particularly with moderate- or high-dose therapy [1,2]. It is believed that chronic exposure to ICS may cause a secondary adrenal suppression (AS) via negative feedback upon the hypothalamus and pituitary gland. It is not common practice to screen for AS in asthma patients; therefore, the prevalence of ICS-induced AS is unknown. Although symptomatic adrenal insufficiency (AI) from ICS has been reported, it is considered rare [3].

ICS has also been reported to impact linear growth velocity in children [4]. The National Heart Lung and Blood Institute's (NHLBI) asthma guideline recommends monitoring growth in children receiving ICS; however, monitoring linear growth velocity has not been previously shown to predict AS [4,5]. Biochemical evidence of AS, including decreased levels of morning cortisol and dehydroepiandrosterone-sulfate (DHEA-s), has been correlated with growth suppression [6,7]. There are currently

no guidelines to screen for AS in children who have shown a decrease in linear growth velocity.

Once AS has been identified, adequate treatment of asthma along with simultaneous adrenal recovery remains a therapeutic challenge. Ciclesonide is a prodrug ICS that is activated in the lung and is highly protein bound once absorbed. Theoretically, it is inaccessible to the glucocorticoid receptor outside of the lungs, leading to less systemic side effects. Ciclesonide has been shown to have fewer side effects compared to budesonide [8]. Two case reports have described patients with AS whose adrenal function was restored after asthma treatment was changed to ciclesonide [9,10].

Case study

We present 15 children with asthma who developed AS, while receiving long-term ICS therapy. The evaluation of AS was prompted by decreased linear growth velocity (GV) noted during routine asthma care visits with a

Table 1. Growth prior to diagnosis of adrenal suppression and following recovery of adrenal function.

Case	HtSDS prior to AS	HtSDS at time AS identified	δ HtSDS prior to AS	HtSDS at time of adrenal recovery	δ HtSDS after adrenal recovery	GV at time diagnosed with AS(cm/yr)	GV after adrenal recovery(cm/yr)	δ GV after adrenal recovery(cm/yr)
GROUP 1a (Pre-Pubertal Females)								
5	0.43	0.07	−0.36	0.33	+0.26	3.5	6.2	+2.7
6	−1.15	−1.54	−0.39	−1.12	+0.42	2.4	8.2	+5.8
7	0.24	−0.64	−0.88	−0.18	+0.70	1.3	9.0	+7.7
4	−0.11	−1.09	−0.98	−0.66	+0.44	1.4	7.7	+6.3
GROUP 1b (Pre-Pubertal Males)								
9	−1.11	−1.62	−0.51	−1.00	+0.62	2.9	8.4	+5.5
10	−0.84	−1.01	−0.17	−1.11	−0.10	4.5	4.6	+0.1
12	−0.43	−0.93	−0.50	−0.82	+0.11	2.1	7.4	+5.3
14	0.48	−0.30	−0.78	0.30	+0.60	2.2	9.7	+7.5
15	−0.86	−1.62	−0.76	−1.10	+0.52	3.5	9.9	+6.4
GROUP 2 (Peri-Pubertal)								
8	−1.45	−1.68	−0.23	−1.39	+0.29	5.2	8.4	+3.2
11	−0.35	−0.59	−0.24	−0.55	+0.04	4.5	7.6	+3.1
13	−2.38	−2.23	+0.15	−2.18	+0.05	7.5	7.6	+0.1
GROUP 3 (Post-Pubertal)								
1	0.42	0.07	−0.35	−0.21	−0.14	3.5	2.5	−1.0
2	−0.85	−1.46	−0.61	−1.67	−0.21	0.8	1.5	+0.7
3	−1.33	−0.90	+0.43	−0.95	−0.05	7.8	2.4	−5.4

Note. HtSDS-Height standard deviation score, GV-growth velocity, AS-adrenal suppression.

pediatric pulmonologist. The diagnosis of asthma was confirmed by a pediatric pulmonologist, in accordance with the NHLBI asthma guidelines, with other etiologies of chronic respiratory illness ruled out [4]. All patients had a history of receiving treatment for allergic rhinitis initiated by a primary care physician or allergist. Eight of the 15 patients had a history of eczema. All patients had a family history of atopic disease. Stepwise management of asthma was dictated by the pediatric pulmonologist in accordance with the NHLBI asthma guidelines [4].

In all 15 cases, recovery of adrenal function was achieved after ICS therapy was changed to ciclesonide, and asthma control remained excellent. Height standard deviation scores (HtSDS) were calculated using World Health Organization (WHO) z-score tables for growth [11]. GV was calculated based on height measurements obtained during clinic appointments. Changes in height standard deviation scores (δ HtSDS) and growth velocity (δ GV) were calculated over 12 months preceding the diagnosis of AS and after recovery of adrenal function (Table 1).

Results

Eleven out of 12 pre-pubertal or peri-pubertal patients had an increase in HtSDS, and all 12 patients had an increase in GV. The 3 post-pubertal patients had an expected decrease in HtSDS associated with completion of puberty, although one patient did have an increase in GV. In the year prior to AS diagnosis, a mean decrease in δ HtSDS was -0.59 , -0.11 , and -0.18 ,

in pre-puberty, peri-puberty, and post-puberty patients, respectively. HtSDS and GV were measured 1 year after ciclesonide was initiated. A mean change in δ HtSDS of $+0.40$, $+0.13$, and -0.13 , was noted for pre-puberty, peri-puberty, and post-puberty patients, respectively. A δ GV of $+5.3$ cm/yr, $+2.1$ cm/yr, and -1.9 cm/yr, was noted following initiation of ciclesonide for pre-puberty, peri-puberty, and post-puberty patients, respectively. The δ GV was also plotted against the 50th percentile longitudinal standards for height based upon gender (Figure 1) [12]

Laboratory evidence of AS was based on a low morning cortisol level, with or without a low DHEA-s level. Following initiation of ciclesonide for treatment of asthma, recovery of adrenal function was demonstrated within 5 to 14 months (Table 2). Use of cosyntropin stimulation testing was determined by an attending pediatric endocrinologist, and was not performed on all patients.

Exposure to inhaled, oral and nasal corticosteroids was obtained from the electronic medical record. The prescribed daily dose of ICS, the duration of treatment with ICS, last prescribed dose of oral corticosteroids and prescription for nasal corticosteroids were recorded (Table 3).

Discussion

The potential side effects associated with corticosteroid therapy have long been a concern. However, these side effects are believed to be minimal with ICS in comparison to higher dose oral steroids [13]. One controversial side effect of ICS is HPA suppression, often

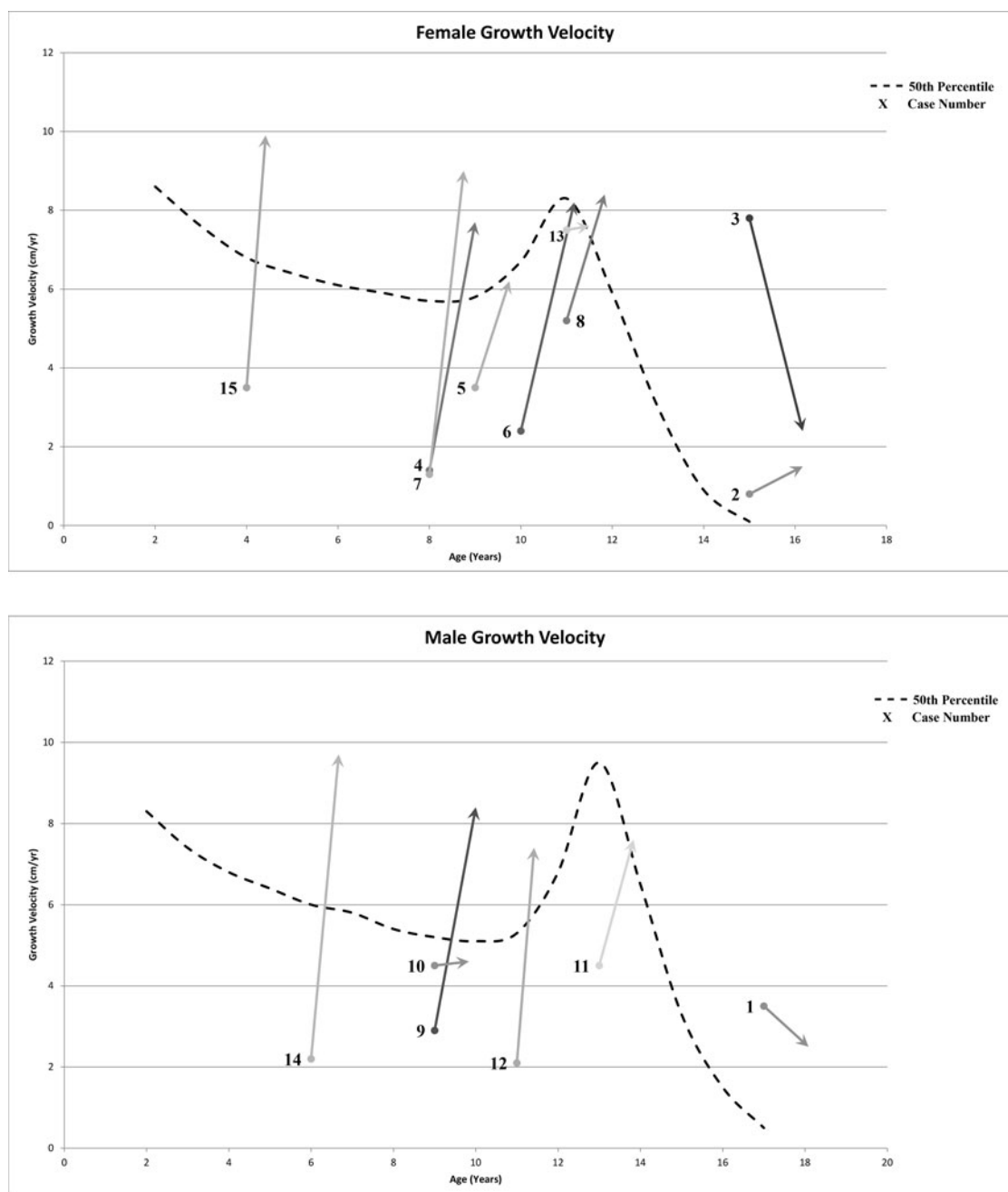


Figure 1. Growth velocity chart, 50th percentile shown by dashed line. Demonstrated is growth velocity at time of diagnosis of adrenal insufficiency (circle) and after initiation of asthma treatment with ciclesonide and lab evidence of full adrenal recovery (arrow).

leading to asymptomatic AS with a reported incidence of 12 to 66% [2,14]. Although there have been case reports of adrenal crisis associated with the use of ICS, this is a rare clinical scenario [14–16]. There are no specific guidelines regarding monitoring for HPA axis suppression in asthmatic children who are receiving ICS. However, expert opinion and consensus suggests children receiving ICS should be observed for possible signs or symptoms of HPA axis suppression, and screening for asymptomatic AS should be based on risk factors. It had previously been recommended only to screen for AS in asthmatic child with a

low BMI, who are being treated with both ICS and nasal corticosteroids, and are adherent to therapy [14].

Another concerning side effect that has been reported is the potential impact of ICS on height velocity in children and final adult height. Several previous studies suggested that the effect of ICS on final adult height was negligible [17–21]. However, more recent research has shown that budesonide was associated with a deficit in adjusted mean adult height of 1.2 cm when compared to placebo [22]. In addition, intermittent high dose fluticasone use at the time of viral upper respiratory illness in preschool

Table 2. Biochemical assessment of adrenal function before and after initiation of asthma treatment with ciclesonide.

Case	Before ciclesonide		After ciclesonide	
	AM cortisol (mcg/dL)	DHEA-s (mcg/dL)	AM cortisol (mcg/dL)	Stimulated cortisol (mcg/dL)
1	5.3	37	11.8	26.9
2	0.1	11.9	14.7	27.6
3	3.7	28.3	13.7	not done
4	0.9	0.1	6.1	31.8
5	0.19	1.85	4.5	24.5
6	0.7	0.2	20.4	15
7	0.1	<0.1	16.5	23.7
8	0.3	not done	8.6	24.1
9	<0.1	not done	30	not done
10	0.1	1.2	14.1	28.1
11	8.7	21.7	19.1	not done
12	0.6	6.4	12.7	not done
13	0.1	not done	13.2	24.2
14	0.4	0.4	5.8	24.7
15	0.1	0.2	14.8	30.1

children has been shown to lead to a decrement of -0.24 Z scores in height over 40 weeks [23]. A recent Cochrane review also concluded that daily use of low-to-medium dose ICS was associated with a decrease in growth velocity in children during the ensuing year [24]. Despite these studies that report a potential impact on linear growth in children, monitoring growth in asthmatic children treated with ICS has not previously been shown to predict AS [5].

A review of the literature for this case series notes confusion regarding use of the terms HPAA suppression, AS, and AI. HPAA suppression implies a secondary adrenal dysfunction, involving a relative deficiency of adrenocorticotrophic hormone and/or corticotropin-releasing hormone. AS is a generic term for adrenal dysfunction, although usually asymptomatic, whereas AI is more specifically utilized to describe adrenal dysfunction associated with clinical signs and symptoms, such as adrenal crisis. A low morning plasma cortisol can indicate AS or AI, but does not distinguish between a primary or secondary mechanism. In our case series, the subsequent normalization of adrenal laboratory values was interpreted to suggest a secondary mechanism for AS, which was consistent with ICS suppression of the HPAA.

We present 15 cases of ICS-related HPAA suppression, each identified by decreased linear growth at routine asthma visits and verified with laboratory testing. Each patient was receiving an ICS for treatment of asthma as recommended by their pediatric pulmonologist. The majority of patients were prescribed a moderate-to-high daily dose of ICS to adequately control asthma symptoms. In all of the cases, complete HPAA recovery was demonstrated by laboratory tests, following initiation of ciclesonide for asthma treatment. In addition, 13 of the

15 cases had an increase in GV following initiation of ciclesonide. Asthma symptoms remained well controlled for all patients while receiving ciclesonide, with or without formoterol. Only one patient required a short course of systemic corticosteroids for an acute asthma exacerbation. Also of note, HPAA recovery was noted in each case where nasal corticosteroids were continued after AS was identified.

In our cases, linear growth proved to be essential in detecting otherwise asymptomatic AS, which has not been previously reported. This correlation suggests a decrease in linear GV is an indicator of AS in children receiving ICS, and should be part of any screening guidelines. Previous studies have mainly focused on linear growth changes in pre-pubertal patients to limit the confounding effect of puberty [5]. Interestingly, we found 1 of 3 post-pubertal patients had an increased δ GV following treatment with ciclesonide. In the pre-pubertal children, all patients had an increased δ GV, and 7 of the 8 patients had an increased δ HtSDS, following initiation of ciclesonide. In addition, all three peri-pubertal patients had increased δ HtSDS and δ GV following initiation of ciclesonide.

Demonstration of adrenal function recovery in suspected ICS-related AS has previously been reported after discontinuation of fluticasone and initiation of ciclesonide [10]. Our report confirms this finding and also shows that the associated decrease in linear growth recovers following initiation of ciclesonide.

This case series highlights the need for standard guidelines in screening asthmatic children for HPAA suppression. The prevalence of HPAA suppression in asthmatic children receiving ICS therapy is unknown. Instituting universal standard screening for HPAA suppression before and after initiating ICS therapy would be important to determine the true incidence of ICS-related HPAA suppression. It would also provide the incidence of decreased growth velocity in children with normal adrenal laboratory tests. This case series strongly suggests a causal relationship between ICS related HPAA suppression and decreased growth velocity, however more research is required to establish this potential linkage.

One of the challenges to establishing universal HPAA suppression screening is the controversy over the ideal screening test for HPAA suppression. Review of the literature is consistent with the controversy that exists within our pediatric endocrinology division regarding the preferred screening test for HPAA suppression [24,25]. Moreover, all current testing is invasive requiring venipuncture and potentially time consuming if adrenal corticotrophic hormone stimulation testing is performed. A noninvasive screening test for HPAA suppression

Table 3. Exposure to corticosteroids prior to diagnosis of adrenal suppression.

Case	Inhaled Corticosteroids			Oral Corticosteroids Last received(months prior)	Nasal Corticosteroids	
	Medication	ICS Dose(mcg/day)	Duration(months)		Medication	Dose(mcg/day)
1	Fluticasone	440	10	14	Mometasone	100
	*Fluticasone + salmeterol	180–500	48			
2	Fluticasone + salmeterol	500	32	30	Fluticasone	100
	Budesonide + formoterol	640	21			
	*Mometasone + formoterol	800	11			
3	*Fluticasone	440	29	28	Fluticasone	100
4	Fluticasone	176–880	37	20	Mometasone	100
	*Fluticasone + salmeterol	180–920	11			
5	Fluticasone	176–440	39	35	Mometasone	100
	*Fluticasone + salmeterol	460	12			
6	Fluticasone	176	2	2	Fluticasone	100
	*Fluticasone + salmeterol	180–920	18			
7	Fluticasone	440	4	13	None	
	*Fluticasone + salmeterol	460–920	20			
8	Fluticasone	176–440	53	2	None	
	Fluticasone + salmeterol	460	8			
	Mometasone + formoterol	800	37			
	*Fluticasone + salmeterol	920	1			
9	Budesonide	250	4	1	None	
	Fluticasone	440	2			
	*Fluticasone + salmeterol	460–920	22			
10	Fluticasone	176	10	2	Mometasone	100
	Fluticasone + salmeterol	460	39			
	Beclomethasone	320	2			
	*Fluticasone + salmeterol	920	4			
11	Fluticasone	440–880	53	36	Fluticasone	100
	*Fluticasone + salmeterol	920	50			
12	Fluticasone	440	9	None	Fluticasone	100
	*Fluticasone + salmeterol	180	1			
13	Fluticasone	176–440	70	4	None	
	Budesonide + formoterol	640	21			
	*Fluticasone + salmeterol	460	27			
14	Fluticasone	440	20	11	None	
	*Mometasone + formoterol	400	13			
15	Fluticasone + salmeterol	460–920	14	None	None	
	Mometasone + formoterol	400	6			
	*Fluticasone + salmeterol	460–920	7			

*Prescribed ICS at time of diagnosis of adrenal suppression.

would be a welcome adjunct in the treatment of patients with asthma. Recent studies evaluating hair or urinary cortisol level may be a solution for HPAA suppression screening [26,27].

Another important discussion point is the management of patients with asthma. The importance of ICS therapy for management of persistent asthma is incontrovertible. However, it should be emphasized that the lowest dose of ICS should be utilized to maintain asthma control. The patients in this case series had asthma managed primarily by a pediatric pulmonologist who followed the NHLBI stepwise care guidelines. A step down in ICS was frequently attempted if possible. This principle should be a primary point of focus in the management of persistent asthma. Another consideration is the possible benefit of other ICS therapy if AS is identified. Ciclesonide was utilized based upon prior literature report [10]. However, newer ICS formulations have been developed, and may have a similar effect. Research on these newer ICS would be required to determine if this is the case.

Conclusion

Our report suggests a decrease in linear growth velocity may be an important clue to identify the possibility of AS in patients receiving ICS therapy. Linear growth velocity should be followed closely in all asthma patients who are receiving ICS. Once AS is noted, initiation of ciclesonide may be an appropriate treatment for long-term control of asthma that allows for both recovery of adrenal function and linear growth.

Acknowledgements

The authors would like to thank Alicia French, RN, BSN for her review of the manuscript.

Declaration of interest

The views expressed herein are those of the authors and do not reflect the official policy or position of Brooke Army Medical Center, the U.S. Army Medical Department, the U.S. Army Office of the Surgeon General, the Department of the Army or the Department of Defense or the U.S. Government.

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