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An Unintended Case Control Study: Corticosteroid Growth Restriction in a Monozygotic Twin

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Abstract

Medication errors are an important cause of morbidity and mortality in children, occurring roughly every 8 minutes for children under 6. Among all medical errors, medication dosing errors are very common. In this context, we present the case of amonozygotic twin girl with severe, persistent asthma, who erroneously received a double dose of nebulized budesonide (2 mg/day) for a period of 23 months. Although the patient's height and weight tracked along the 50thpercentile before starting budesonide, these growth measures fell to the 5th and 10thpercentile respectively following the initiation of this prescription error, despite having improved asthma control over this period. In contrast, during the same time period, the patient's twin sister experienced normal growth along the 50th centile. Furthermore, this patient experienced long-term harm: three years after discontinuing the erroneous budesonide dose, growth did not return to the 50thpercentile and a DEXA scan documented persistent osteopenia, a known side effect of corticosteroids.

This case highlights key considerations to reduce harm using ICS medications: First, any changes in growth trajectory should prompt a review of inhaled corticosteroid medications being used. Second, corticosteroid medications should be reviewed at any hospital visit. The use of clinical standard work pathways in primary care and the emergency department can help to standardize medical management and reduce the risk of medical errors. Finally, minimal effective doses of corticosteroids (and all medications) should be prescribed.

Abbreviations

Inhaled corticosteroids (ICS), Dual-energy X-ray absorptiometry (DEXA), Medication taken inhaled (INH), Medication taken as needed (PRN), Metered dose inhaler (MDI), Actuation (ACT)

Introduction

It is estimated that in the United States, a medication error occurs every 8 minutes for a child under 6 years of age [1]. Following medication omission, the second most commonly cited medication error is incorrect dosage [2]. Here we present the case of a pre-pubertal girl who received an unintended double dose of nebulized corticosteroid for 23 months and experienced substantial growth restriction as compared to her monozygotic twin.

While inhaled corticosteroids (ICS) are recommended as first-line therapy for the control of asthma and have a clear benefit in reducing related morbidity and mortality, [3] chronic ICS use has the potential to reduce growth velocity [4-6]. While ICS doses above 100 mcg offluticas one or equivalent result in minor improvements to asthma control, adverse impact on growth restriction is dose-dependent, with minimal effects at therapeutic doses [4].

This case report ascertains the need for regular medication review and robust practices to monitor both benefit as well as potential risks of long-term corticosteroids administered to pre-pubertal children.

Case Presentation

This is the case of a monozygotic twin girl, born at 34weeks, 4 days estimated gestational age, who was evaluated at the age of 3.5 years for severe, uncontrolled asthma in a respiratory clinic at a Canadian tertiary pediatric centre. The referral had been requested one-month prior by an emergency department physician following a severe asthma exacerbation in this toddler. At the time of her initial clinic assessment, the patient's parents reported a series of episodes consisting of acute-onset shortness of breath in the absence of viral symptoms or identified environmental triggers, which responded to nebulized salbutamol. Despite a 1-month tapered course of oral prednisolone, initially 2mg/kg/day, the parents reported that the patient required a rescue dose of inhaled salbutamol every four hours to control her symptoms. At this time the patient's regular medications included salbutamol metered-dose inhaler (MDI) as required, vitamin D6000 IU by mouth once daily, montelukast 4mg by mouth at bedtime, and mometasone nasal spray 50mcg once daily. The therapeutic outcome of this visit was addition of a fluticasone/salmeterol 25/125 mcg/actuation (ACT) MDI dosed twice daily.

A complicating factor in the control of this patient's asthma was an underlying diagnosis of mannose-binding lectin (MBL) deficiency. This condition was diagnosed after a referral to immunology following a series of lower respiratory tract infections and recurrent otitis media requiring antibiotic treatment from the age of two years.

In comparison, the patient's monozygotic twin sister had two presentations to the emergency department for laryngotracheo bronchitis between 2 -3 years of age, she did not have a history of recurrent infections, persistent asthma symptoms, and was never diagnosed with MBL deficiency. The parents did however report the twin sister was referred to pulmonology for recurrent symptoms consistent with reactive airway disease (RAD) and was prescribed

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inhaled fluticasone 50 mcg (roughly equivalent to 95 mcg budesonide) [7], dosed once daily to be taken with exacerbations. This medication was used infrequently (fewer than 30 days over the year) and was discontinued after 6 months (Figure 1 and 2).

Between clinic visits, which occurred annually with the patient's pediatrician and roughly every 6 months with the pediatric pulmonology clinic, the patient continued to experience asthma exacerbations, with roughly one ED visit per month, one of which was severe enough to warrant a one-week prescription of PO prednisone dosed 2mg/kg/day.

At the first follow-up visit following this enteral course of prednisone, the patient's height and weight tracked along the 50th percentile. At this time her medications included fluticasone/salmeterol 125/25mcg/ACTMDI two inhalations twice daily, lansoprazole 15mg by mouth once daily, nebulised ipratropium bromide every 6 hours as needed, and salbutamol MDI 100 mcg every 4 hours as needed taken once a day when well.

Due to the recurrent nature of her asthma exacerbations, a decision was made to start nebulized budesonide at a dose of dosed 500 mcg twice daily when the patient was 3 years 11 months old. However, the pharmacy erroneously dispensed nebulised budesonide at a dose of 1000 mcg twice daily, double the highest budesonide dose recommended by the FDA [8]. After 8 months, the pharmacy noticed the error and contacted the prescribing physician. Despite a correction from the prescribing physician, the pharmacy continued to dispensetheerroneous higher dose of 1000 mcg twice daily. Budesonide 2000 mcg daily was continued for a period of 23 months from 4 to 6 years of age. During this time, the patient remained on fluticasone/salmeterol 125/25mcg MDI twice daily until 4 years 8 months of age, when this was exchanged in favor of mometasone/formoterol 200mcg/5mg/ACT twice per day. During this time, she experienced improved asthma symptom control per parental report, with a single substantial exacerbation at 4 years 6 months that required a 5th day course of oralprednisolone, dosed 1.2mg/kg/day.

At the age of 6 years 0 months, 23 months after starting nebulised budesonide at the erroneous dose, the patient presented to the emergency department following a one-day history of lethargy, vomiting, loss of balance, frontal headache, and poor oral intake, identified as concerning for adrenal failure per the emergency department discharge summary. A review of the patient's medications was performed at that time, which revealed the underlying prescription error. On discharge, the nebulised budesonide discontinued entirely.

Within one month of the cessation of the inhaled budesonide, a growth chart assessment indicated that the patient's height and weight tracked at the 5th and 10th centiles respectively. In contrast, on this date, the patient's identical twin tracked at the 50th percentile for both height and weight. A DEXA scan of the patient revealed bone mineral density loss in the lumbar spine, corresponding to an age-matched Z-score of -2.5.

Three years after discontinuing budesonide, the patient was diagnosed with steroid-induced osteoporosis with at Z-score of -1.7. At this time, her height and weight corresponded to the 5th and 13th centiles respectively. In contrast, her twin sister continued to track along the 50th centiles for height and weight. Between the age of 4-5,

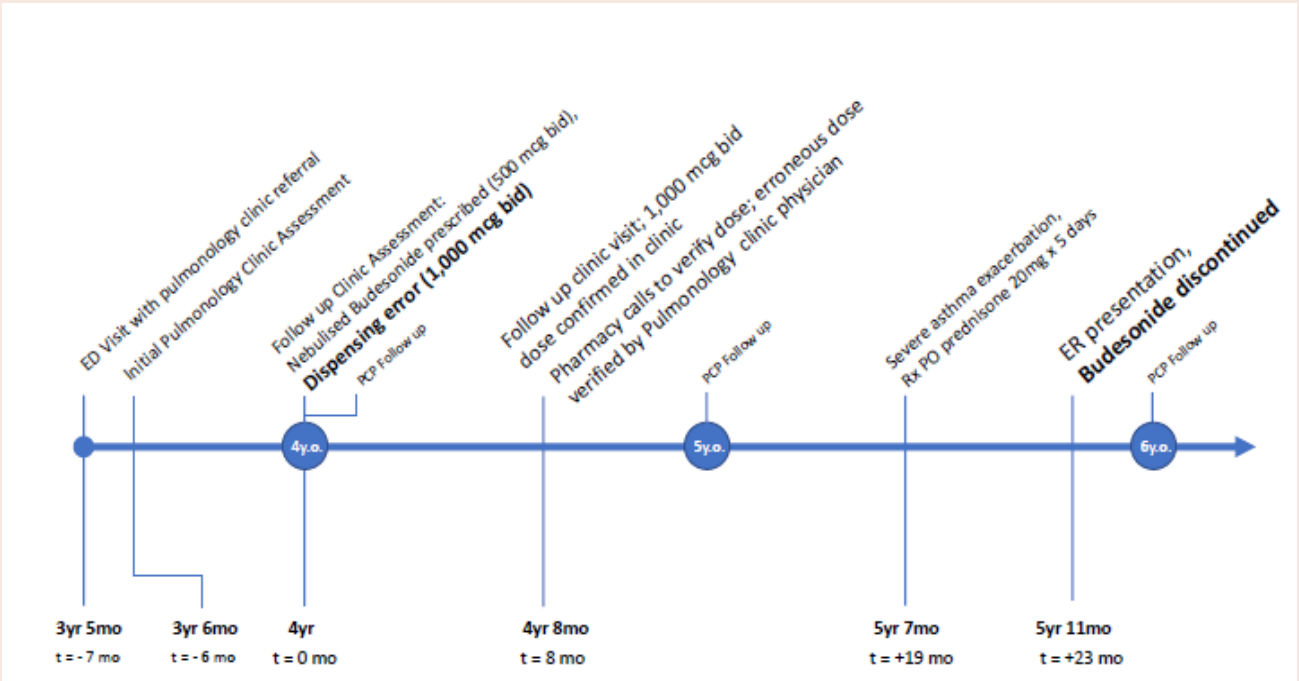

Figure 1: Timeline of key events related to the patient's ICS prescriptions. At 3 years 11 months of age, the patient was prescribed nebulised budesonide at a dose of 500 mcg bid, which was erroneously dispensed as 1000 mcg bid. This dose was continued for 23 months until the dossing error was identified at an ED visit.

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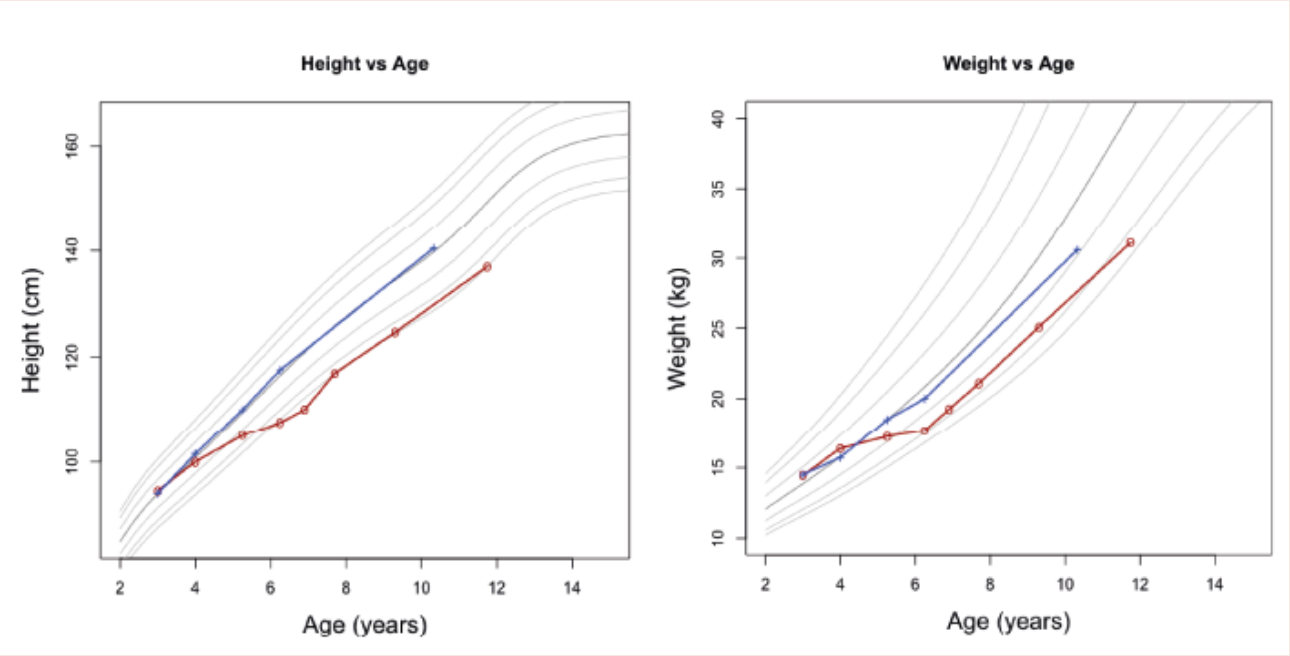

Figure 2: Timeline of corticosteroid medication use. At 3 years 11 months, the patient was prescribed nebulised budesonide at the erroneous dose of 1000 mcg bid in addition to her MDI controller therapies, which was continued for 23 months. During this time, she also received a course of PO prednisolone due to an asthma exacerbation.

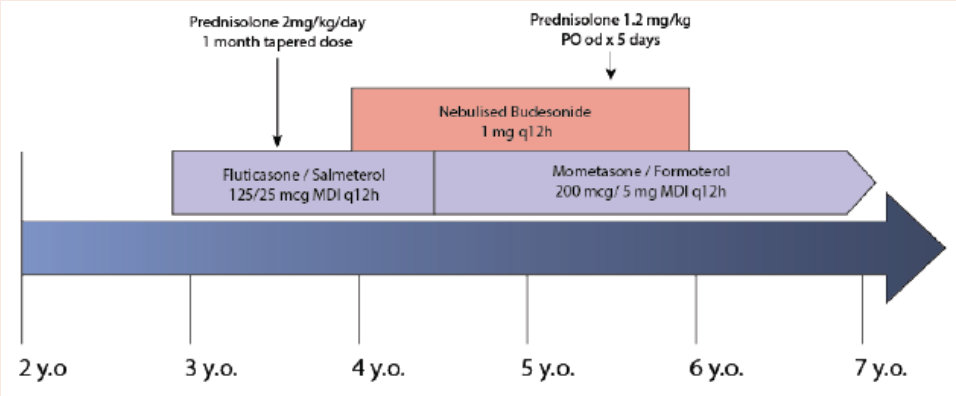

Figure 3: Height and weight growth curves for the patient (red) and her twin sister (blue) superimposed against standard percentile lines from the CDC23. After starting nebulised budesonide at the incorrect dose, the patient's height and weight fall from 50thpercentile to 5th and 13th percentiles, while her monozygotic twin sister continuing growth along the 50th percentile. Once nebulised budesonide is discontinued, the patient initially experiences a period of catch-up growth, with subsequent plateau.

while receiving 2000 mcg of budesonide daily, the patient experienced eight asthma exacerbations resulting in emergency department visits. However, between the ages of 5-11 years, the patient experienced at most 1 exacerbation per year, while undergoing accelerating growth velocity (Figure 3).

Discussion

Several factors implicate the patient's corticosteroid prescription in her growth restriction noted between 4-6 years of age. Most importantly, the patient's growth velocity notably increased once the incorrect budesonide prescription was discontinued. In addition, osteopenia noted in the lumbar spine is a typical adverse effect of long-term corticosteroid use [9-11]. However, lansoprazole, prescribed in the setting of high dose corticosteroid administration, may have also contributed to the osteopenia [12]. Finally, the substantial difference in the growth curves of the two girls, with the patient falling to the 5th and 13th percentiles for height and weight, while her monozygotic twin sister continuing growth along the 50th centiles, provides a

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strong argument that differences in inhaled corticosteroid dosing played a major role (Figure 3). While the patient was administered 2000 mcg inhaled budesonide and 400 mcg fluticasone (equivalent to 900 mcg budesonide) [7] per day, her twin sister received 50 µg of inhaled fluticasone (equivalent to 95 mcg budesonide) [7] per day for fewer than 30 days annually.

The most compelling alternative reason for the patient's growth restriction is the patient's poorly controlled asthma. The patient's MBL deficiency should be considered in this context, as it has been postulated this condition may contribute to airway inflammation and thus increase the risk of developing asthma [13]. However, the patient experienced poorly controlled asthma for two years before the start of the budesonide prescription at the erroneous dose, during which time the patient's growth velocity closely followed that of her sister and remained along the 50th percentile. In addition, rather than growth velocity increasing following improved symptomatology between 5-6 years of age, the patient continued to experience lower than expected growth velocity, falling from the 50th centile to the 5th centile for height.

While data remains conflicting regarding the effects of ICS medications on linear growth at regular dosing, a 2014 Cochrane review suggested low or medium-dose ICS use was associated with a reduction in linear growth velocity of 0.48 cm/year, particularly in the first year of ICS therapy [14]. In addition, it should be noted some studies have reported a decrease in final adult height in the range of 1.2cm on average, even at moderate ICS dosing [15].Effects on growth have been reported to be dose dependent, and are most significant above a dose of 0.4mg/day, a threshold far surpassed by this patient over a period of two years [15]. By age 6, the patient's height was nearly 10cm less than her twin sister, which further widened to 15cm at 10 years of age, suggesting a long-lasting difference in final adult height is likely.

This case highlights the importance of regular review of medications and assessment of growth for children with asthma, particularly those prescribed corticosteroids [16]. In many cases, inhaled corticosteroid dose responses plateau at 200 mcg fluticasone per day or equivalent, and few children benefit from dose increases beyond 500 mcg day [17] (equivalent to 1000 mcg budesonide) [7]. Thus, dosing beyond this threshold was unlikely to provide additional symptom control, which explains why the patient continued to experience severe asthma exacerbations.

From a systems perspective, there are a number of key drivers that contributed to this medication error: 1) faltering growth should have raised concern with the patient's pediatrician; 2) at the time of the error, the pulmonology clinic used paper charts which did not display warnings for doses; 3) the pharmacy should have verified the dose immediately, rather than 8 months later; and finally, 4) the improvement in the patient's asthma control should have prompted a review of her corticosteroid medications.

Implementation of asthma clinical standard work pathways represent potential solutions to increase adherence to NIH asthma guidelines [18]: the "Primary Care Pathway for Childhood Asthma" [19] is an example currently being studied for primary care, and many children's hospitals employ clinical pathways to standardize asthma care in their emergency department and following hospital discharge [20]. In hospital, mandatory reconciliation of admission/discharge medications can identify errors or concerns [21]. These medication safety exercises and standardized treatment algorithms may have been particularly useful for this patient and may have prevented harm.

In summary, while inhaled corticosteroids remain the most effective therapy available for maintenance treatment of childhood asthma, it is imperative that clinicians use the lowest-effective corticosteroid dose for treating asthma (or other corticosteroid-responsive conditions). Importantly, growth charts should be regularly reviewed in the context of chronic corticosteroid administration, and a full medication review should occur if growth begins to falter [22].

Contributors' Statement Page

Dr Magder obtained the consent from the patient's family for publishing, created the figures, and drafted the initial manuscript.

Dr Zimmerman supported the drafting of the initial manuscript by providing expert advice on the interpretation of clinical data, supported the creation of the figures and revised the initial manuscript for accuracy.

Dr Magder and Dr Zimmerman critically reviewed and edited the revised manuscript.

Ethics approval and consent to participate:

Approval granted by the Royal College of Surgeons Research Ethics Board.

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