

PHARMACOTHERAPY

Problematic severe asthma in children treated at high altitude: tapering the dose while improving controlErik-Jonas van de Griendt, MD^{1,2,3}, Marieke Verkleij, MSc^{2,3}, J. Menno Douwes, MD⁴, Wim M. C. van Aalderen, MD, PhD¹, and Rinie Geenen, PhD^{5,6}¹Department of Pediatric Respiratory Medicine and Allergy, Emma Children's Hospital, Academic Medical Center, Amsterdam, The Netherlands,²Merem Netherlands Asthma Centre, Davos, Switzerland, ³Merem Asthma Centre Heideheuvel, Hilversum, The Netherlands, ⁴Department of Pediatrics, Division of Pediatric Pulmonology, Beatrix Children's Hospital, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands, ⁵Department of Clinical and Health Psychology, Utrecht University, Utrecht, The Netherlands, and ⁶Department of Rheumatology and Clinical Immunology, University Medical Center Utrecht, Utrecht, The Netherlands**Abstract**

Background: Multidisciplinary treatment at high altitude is a possible treatment option for problematic severe asthma (PSA) in children. This management can result in the tapering of inhaled corticosteroids. **Aim:** Our aim was to analyze the effect of multidisciplinary treatment at high altitude, notably the ability to taper corticosteroids. To get an insight into possible factors influencing tapering, we examined whether demographic variables, disease control and quality of life at treatment entrance could predict the tapering of corticosteroids. **Methods:** This prospective open-phase cohort study analyzed the data of 43 children aged 8–17 years referred to a specialized high altitude treatment centre. Lung function (FEV₁, FEV₁/VC), inflammation (FeNO), medication level, asthma control (ACT) and quality of life (PAQLQ(S)) were evaluated on admission and at discharge. **Results:** Thirty-two (74%) children fulfilled PSA criteria. Three (7%) children used daily oral steroids. After 72 ± 30 (mean ± SD) days of treatment, the mean dosage of inhaled corticosteroids (ICS) could be significantly reduced from 1315 µg ± 666 budesonide equivalent to 1132 µg ± 514. Oral steroid maintenance therapy could be stopped in all patients. FeNO, asthma control and quality of life improved ($p < 0.001$) from admission to discharge; FEV₁ was in the normal range on both occasions. Apart from ICS levels at entrance, multiple regression analyses did not show any associated factor predicting the reduction of ICS dosage during treatment. **Conclusion:** The results indicate that high altitude treatment may be a treatment option for children with PSA, but it is not possible to predict ICS tapering off from health status variables at treatment entrance.

Keywords

Asthma control, inhaled corticosteroids, lung function, problematic severe asthma, tapering

History

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Introduction

Asthma is a common chronic respiratory disease in childhood characterized by airway obstruction, airway inflammation and bronchial hyper-responsiveness (BHR). The reported prevalence of asthma in childhood and adolescence ranges from 5% to 15% [1]. A small portion (the precise prevalence is unknown) of pediatric asthma patients can be classified as having problematic severe asthma (PSA), defined as asthma that is not under control despite optimal treatment [2,3]. PSA is characterized by longer periods of unstable asthma, lower forced expiratory flow in 1 s (FEV₁), higher dose of inhaled steroids and more severe airway obstruction at the time of referral to a specialist [4]. Despite the low prevalence, PSA is of major interest as these patients have more morbidity, a larger disease burden, higher treatment costs [5,6] and

a poorer overall quality of life [7]. Insight into the prevalence and characterization of pediatric PSA as well as the response to treatment and long term effects of treatment on quality of life is needed. High doses of inhaled corticosteroids (ICS) or oral steroids may be needed to stabilize PSA in children, which may result in a reduction in growth velocity or bone density. In such a scenario, it is desirable to use the lowest possible level of (inhaled) steroids. High altitude treatment is one of the possible treatment options to reduce the dosage of ICS in children with PSA [8]. Climatologic advantages, the absence of house dust mite allergen and the removal of the child from his daily surroundings may be responsible for stabilization of the disease in the high altitude environment [9]. Whether high altitude treatment can result in successful tapering of ICS remains unknown, however. Moreover, the role of other determinants [such as asthma control, lung function and disease-specific quality of life (QOL)] in successful reduction of ICS is unknown. Asthma control correlates with the need for change in pharmacotherapy as indicated by the specialist's rating of asthma control [10].

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However, we were unable to find studies in children with asthma that show a better quality of life preceding reduced medication use.

Our aim was to investigate the effect of multidisciplinary high altitude treatment on the (minimum) dose of inhaled corticosteroid required to keep the asthma under control. In order to gain insight in possible factors influencing the tapering, we examined whether the reduction in inhaled corticosteroid requirement after high altitude treatment could be predicted by demographic (gender and age), clinical (asthma control or quality of life) or lung function variables at entrance. We hypothesized that a lower dose of ICS could be used at the end of high altitude treatment while gaining stability. We had no clear expectations whether QOL or ACT could be predictors for tapering ICS.

Methods

Patients

From January 2008 to March 2009, patients aged 8–17 years with a confirmed diagnosis of asthma, who were admitted to the Netherlands Asthma Centre in Davos, Switzerland, were invited to participate in this prospective cohort study. This center, specialized in the treatment of difficult asthma, is situated in the Swiss Alps at an altitude of 1690 M above sea level, and treats patients aged 8 years and older with unstable or uncontrolled asthma. The medical ethics committee of the Amsterdam Medical Center (AMC), Amsterdam, the Netherlands, approved the study. The children ≥ 12 years of age and the parents of all children provided written informed consent.

The diagnosis of asthma was made or dismissed on the basis of history, physical examination, confirmed bronchoconstriction with (partial) reversibility ($\geq 12\%$ FEV₁ predicted). Problematic severe asthma (PSA) was defined using criteria of the Dutch Pediatric Respiratory Society [11], which are based on task forces of the American Thoracic Society and European Respiratory Society, and ENFUMOSA study (Table 1) [2,12,13]. A positive score on PSA denotes persistent or severe asthma and lack of adequate control of asthma symptoms (such as exercise intolerance, two or more times per week in need of extra reliever therapy and night time symptoms) despite high doses of controller therapy, adequate use of spacers and devices, confirmed diagnosis and good compliance. Intake of medication was supervised during the stay in the clinic. Compliance was regarded as “poor” in cases of doubt or suspected lack of compliance on more than one day per week based on the history, and thus the criteria for problematic severe asthma were not met.

Design and treatment protocol

The prospective, uncontrolled design comprised pre- and post-treatment measurements. Two weeks before the start of clinical treatment in the high altitude clinic, all patients and parents received questionnaires at their homes. On the day of arrival, a medical history was taken in a structured interview including atopic symptoms, exercise intolerance, medication and reliever therapy. Pulmonary function testing was performed. The diagnosis of asthma and criteria of PSA

Table 1. Criteria problematic severe asthma.

1. Age ≥ 6 years.
2. ≥ 6 months treatment on the following treatment regime (doses are adapted to the Dutch situation):
 - Daily use of $\geq 800 \mu\text{g}$ budesonide/beclomethasone dipropionate or equivalent ($\geq 500 \mu\text{g}$ fluticasone or $\geq 400 \mu\text{g}$ beclomethasone dipropionate extra-fine or $\geq 320 \mu\text{g}$ ciclesonide),
 - Long acting β_2 -agonist,
 - A (history of) treatment on a leukotriene receptor antagonist
3. With respect to the medication mentioned above, at least one of the following criteria should apply:
 - Decreased exercise intolerance and/or symptoms at night and/or, use of reliever therapy ≥ 2 times weekly,
 - Frequent exacerbations with need for oral prednisolone (≥ 2 per year),
 - Exacerbation(s) requiring ICU treatment in history,
 - Persistent airway obstruction ($\text{FEV}_1 < 80\%$ post reliever).
4. At least 6 months treatment in pediatric practice.
5. History of good compliance.
6. Checked inhalation technique.
7. Confirmation of diagnosis asthma on pulmonary function testing defined as obstructive flow volume curve with (partial) reversibility of forced expiratory volume in 1 s (FEV_1) on β_2 -agonists.
8. Medication as mentioned above may be prescribed temporarily and build down due to the lack of effect.

FEV₁, forced expiratory volume in one second; LABA, long acting β_2 -agonist; LTRA, leukotriene receptor agonist; ICU, intensive care unit.

including (history of) compliance were approved or rejected by one selected pediatrician. A structured day program consisted of school, health education, physical exercise and multidisciplinary treatment. The treatment duration was scheduled for 10 weeks. Adherence to medication was assured before treatment in the clinic and reassured during the period of stay due to daily supervision of nurses while using medication. On the basis of weekly physical examination and the absence of exacerbations, the dosage of (oral prednisolone and) ICS was changed at intervals of 4 weeks. Dose reduction of ICS was based on pre-designed steps of 50% per time. Montelukast was not changed. At discharge, pulmonary function testing was repeated and the children completed questionnaires on asthma control and quality of life again.

Pulmonary function testing

Pulmonary function testing (PFT) was performed using the Masterscreen PFT (Jaeger Viasys, Germany). A standardized protocol was used and at least three technically correct maneuvers were performed. Short or long acting β_2 -agonists were stopped 12 h before PFT. Lung function parameters that were obtained and evaluated were forced expiratory volume in 1 s (FEV_1), vital capacity (VC) and Tiffeneau-index (FEV_1/VC). Airway inflammation was measured using the fractional concentration of exhaled nitric oxide (FeNO) according to the ATS and ERS guidelines [14]. The NIOX Flex (Aerocrine, Sweden) was used according to the manufacturer's instructions.

Instruments

Asthma control test

The childhood asthma control test (ACT) is a seven-item checklist. This questionnaire assesses the control of asthma at

the time of measurement, as reported by the child (four questions) and their caregivers. The childhood ACT has been validated in children from the age of 4 with relatively mild, controlled asthma [10]. A cut-off point of ≤ 19 indicates uncontrolled asthma with a sensitivity of 74% and a specificity of 68%. An association has been observed between ACT scores and specialist-assessed change in child's therapy ($F = 20.07$, $p < 0.001$) and specialist assessment of asthma control ($F = 36.89$, $p < 0.001$). Validation and cut-off points for children with more severe disease or less control have been described [15]. Since parents were absent during treatment, raw scores of the four child questions (self report; range 0–12) at the start of treatment and at discharge were compared.

Children's self-report: quality of life

The pediatric asthma quality of life questionnaire, PAQLQ(S), is a widely used disease-specific health-related quality of life self-report measure for children and adolescents aged 7–17 years [16]. It has three domains: symptoms (10 items), activity limitations (5 items) and emotional function (8 items). The item range 1–7 is reported per domain and for the whole instrument. Higher scores indicate better quality of life. The Dutch PAQLQ has adequate psychometric properties and excellent responsiveness [17].

Statistical analysis

Statistical analyses were done with SPSS 18.0. p Values < 0.05 (two-sided) were considered statistically significant. Pre- to post-treatment differences were examined with paired-samples t -tests and with a non-parametric test for lung function (Mann–Whitney U test). Hierarchical linear regression analysis was used to predict the budesonide dose at discharge while controlling for the baseline dose, age and gender. In the first block, the baseline dose of budesonide was entered; consequently in the next blocks, the pre- to post-therapy change of budesonide was predicted. In block 2, age and gender were entered as control variables. In block 3, lung function (FEV_1 and FeNO), ACT and PAQLQ were entered.

Results

Forty-four patients were eligible for inclusion. One was excluded due to a different diagnosis (dysfunctional breathing). Thus, 43 patients with a diagnosis of asthma were asked to participate in the study and all gave informed consent. Patient characteristics and baseline features are shown in Table 2; all had moderate persistent to severe asthma, and kept having symptoms despite a higher (step 3–4) of highest (step 5) dose of ICS and a (trial) of montelukast. Moreover, 74% of the patients fulfilled PSA criteria, whereas 26% did not due to either lack of (trial of) treatment with LTRA or suspected lack of compliance. The mean dose of inhaled controller medication was high: daily 1315 μg (SD 666) budesonide equivalent. Three patients were on a continuous administration of oral corticosteroids (dose 5–20 mg daily). Mean ACT on admission was 14.3 (range 5–24), four patients (10%) had a score higher than 19 (denoting “good control”). Nine (23%) had a score of 12 or less (“very poorly

Table 2. Characteristics of the 43 patients.

	Statistics
Female, number (%)	24 (58)
Problematic severe asthma, number (%)	32 (74)
Age, mean (SD) yrs	13.0 (2.4)
Length of stay, mean (SD) days	72 (30)
Daily inhaled Budesonide, mean (SD) μg	1315 (666)
Used medication: LTRAs, number (%)	24 (59)
LTRAs ^a in the recent past, number	8
Oral corticosteroids daily, number	3
FEV_1 ^b , mean (SD)	105.3 (14.5)
FEV_1/VC ^b , mean (SD)	114.8 (16.1)
FeNO, ppb, mean (SD)	39.8 (26.0)

^aLTRAs: leukotriene receptor agonists.

^b% pred = percentage predicted.

FEV_1 , forced expiratory volume in 1 s; FeNO, fractional concentration of exhaled nitric oxide; ppb, parts per billion.

Table 3. Mean scores (SD) on admission and at discharge and t - and p -values: lung function measurements, control of asthma (ACT) and quality of life (PAQLQ(S)).

	N	Admission mean (SD)	Discharge mean (SD)	t	p^d
FEV_1 ^a	41	105.1 (14.7)	108.1 (13.9)	−1.5	0.14
FEV_1/VC ^a	39	115.3 (16.4)	111.5 (12.1)	1.7	0.10
FeNO ^b	42	39.8 (26.4)	15.2 (7.6)	6.3	< 0.001
Eq Budesonide ^c	41	1315 (666)	1132 (514)	2.5	0.02
ACT total child	32	6.5 (1.7)	9.7 (1.7)	−8.5	< 0.001
PAQLQ(S) total	37	4.8 (1.2)	6.2 (.76)	−7.3	< 0.001

FEV_1 , forced expiratory volume in 1 s; VC, vital capacity; FeNO, fractional concentration of exhaled nitric oxide; Eq, Equivalent; ACT, asthma control test; PAQLQ(S), pediatric asthma quality of life questionnaire (self-report).

^a% pred, percentage predicted.

^bppb = parts per billion.

^c μg .

^dPaired samples t -test.

controlled”). Data on ACT of four patients were missing due to reporting later than the first week of treatment.

Table 3 shows a detailed description of lung function parameters, inhaled steroid use and ACT and PAQLQ(S) on admission and discharge. Lung function (FEV_1 , FEV_1/VC) did not change significantly and still projected in the (higher) normal range. FeNO improved significantly ($p < 0.001$) as did asthma control and quality of life ($p < 0.001$).

The inhaled steroid dose could significantly be decreased ($p = 0.02$). The effect size (d) of the difference was 0.31. Daily ICS doses were stable in 29 patients, decreased (400–800 $\mu\text{g}/\text{day}$) in 12 patients, decreased (1200 $\mu\text{g}/\text{day}$) in 1 patient and increased in 1 patient. Oral steroids could be stopped completely in all three patients.

The results of multiple regression analysis are shown in Table 4. In the first block, baseline values of budesonide equivalents highly significantly correlated with budesonide values at discharge. Of the biographic variables, female sex was almost significantly associated with budesonide suggesting that after correction for baseline values, reducing ICS might be somewhat more likely in the boys than the girls. Separate regression analyses for boys and girls did not yield significant predictors other than budesonide at baseline. FEV_1 , FeNO, ACT or PAQLQ(S) at admission did not

Table 4. Results of regression analyses predicting budesonide at discharge from the baseline dose (Block 1), person characteristics (Block 2), and in separate regression analyses FEV₁, FeNO, ACT and PAQLQ (Block 3).

	FEV ₁ (n = 41)		FeNO (n = 41)		ACT (n = 34)		PAQLQ(S) (n = 35)	
	β	Adj R ²	β	Adj R ²	β	Adj R ²	β	Adj R ²
Block 1								
Baseline budesonide	0.71 ^a	0.49 ^a	0.71 ^a	0.49 ^a	0.85 ^a	0.72 ^a	0.86 ^a	0.72 ^a
Block 2								
Female sex	–0.20 ^b	0.51	–0.20 ^b	0.51	–0.08	0.71	–0.14	0.73
Age	0.01		0.01		0.04		0.02	
Block 3								
FEV ₁	–0.05	0.50		0.50		0.71		0.72
FeNO			–0.02					
c-ACT					0.08			
PAQLQ(S)							0.01	

FEV₁, forced expiratory volume in 1 s; FeNO, fractional concentration of exhaled nitric oxide; ACT, childhood asthma control test; PAQLQ(S), pediatric asthma quality of life questionnaire (self-report).

^a $p < 0.001$, ^b $p < 0.10$.

correlate with the possibility to reduce the dose of daily inhaled steroids.

Discussion

We described a referral population of children with asthma being treated in a high altitude clinic where the majority had PSA. At the end of treatment, we found a stable lung function that projected in the normal range, and we found an improvement in FeNO level, asthma control and quality of life while ICS levels were reduced. All oral steroids could be stopped. There were no associations found between the level of disease control at baseline and other clinical parameters measured at baseline and the likelihood of reducing steroids.

Beneficial reduction in FeNO levels during high altitude treatment without intensifying the medication regime, have been shown before in allergic and non-allergic patients [18,19]. The most obvious mechanism is that reduction in allergen exposure and reduction in other environmental inflammatory triggers reduces the degree of inflammation and thus the level of FeNO, but the exact mechanism behind this is still to be elucidated. No randomized controlled trials comparing treatment modules at high altitude and sea-level have been performed yet. The possible importance of vitamin D has recently been suggested [20,21]. One parallel group study compared atopic adolescents with mild to moderate asthma in high altitude treatment and at sea level [8]. This small study of 18 adolescents showed better improvement in BHR and urinary levels of eosinophil protein X and leukotriene E4 in the group that was treated at high altitude I. Moreover, 6 weeks after renewed allergen exposure at sea level these improvements were maintained.

The lack of associations between self-reports of asthma control and quality of life with clinical parameters is in line with the results of a recent study in a group of adolescents with partly uncontrolled asthma showing no significant correlations between asthma control and lung function parameters or psychosocial problems [22]. The lack of an association between disease-specific factors like lung function, asthma control or QOL is not easy to understand. Perhaps the heterogeneity of the population of children with PSA plays a role [3]. Another explanation might be that the

study is done in adolescents, who commonly want to be as “normal” as possible and also want to be part of a peer group. When these patients are admitted together, their self-reported QOL and ACT can be exaggerated, which may explain the lack of correlation between lung function measures. The absence of correlations suggests that lung function parameters, disease-specific quality of life and asthma control are independent domains of health status. This supports the idea that a “total” approach or multidisciplinary treatment is needed in order to interact with all domains of PSA in children and adolescents.

There are several study limitations. The power of the study is low with this small sample size. As the selected children mainly classified for PSA, the sample is not representative for all childhood asthma in general. We did neither assess reversibility of FEV₁ in all children at entrance, nor atopy or smoking at home, so we were not able to examine the possible relevance of these variables in multiple regression analysis. This prospective study lacks a follow-up measurement due to geographical problems (the children went home) and differences in lung function measurement at high altitude and sea level. Follow-up of ACT and QOL of our study group and association with behavioral problems have been reported previously [7,23]. The current study was not designed as a randomized controlled trial which would have given better insight into possible causal relationships. Theoretically, randomization into a multidisciplinary treatment clinic at high altitude or sea-level is possible, but the referral system and insurance policy in the Netherlands hamper such a study design. Adherence to medication was already assured before treatment in the clinic and reassured during the period of stay due to daily supervision. However, it might have changed during the treatment period. We did not use a smart tracker or other device before and during the treatment period to elucidate this further. Finally, children were treated away from their systemic context, which might temporarily have altered their subjective scores on asthma control or quality of life. Despite these limitations, this study helps to characterize (scarcely reported) detailed aspects of PSA in children.

The importance of structural evaluation of all children with PSA has been emphasized [24]. Nurse-led home visits could elucidate a number of potentially modifiable factors in this

population at risk. In our population, we could at least stabilize the disease possibly by taking away home factors that might be harmful to the asthma and adding a structured, hypo allergenic environment.

In conclusion, our study shows improvement in FeNO, quality of life and asthma control in a group of mostly PSA patients which made the disease more treatable. Since correlations between these parameters were not found, we think that treatment of this selected group should focus on all possible determinants of the disease and functioning, preferably during one and the same admission. This means a comprehensive approach for the child with PSA. In future research on children with PSA, routine asthma measures should be combined with ACT, QOL and preferably psychosocial data. This will help us understand the nature of this complex disease and finally tailor the complex treatment of PSA in children.

This study provides detailed data on children with PSA before and after treatment at high altitude. The multidisciplinary treatment tailors treatment to several disease domains of the child with PSA. After treatment, improvement of control is observed while tapering the dose of inhaled steroids. This underlines that PSA is not synonymous to therapy resistant asthma. The results indicate that multidisciplinary treatment at high altitude might be considered a viable treatment option for children with PSA.

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Declaration of interest

The authors report no conflicts of interest.

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