phenomenon of infectious diseases or limited to certain infections such as measles.[1]

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Short term linear growth in asthmatic children during treatment with prednisolone

Ole D Wolthers, Søren Pedersen

Abstract

***Objective*—To see whether small daily doses of prednisolone have any adverse effect on short term linear growth in children with mild asthma.**

***Design*—Double blind, random order crossover trial of two dosages of prednisolone. During run in and washout periods patients were given placebo. All treatment periods were of two weeks' duration.**

***Setting*—Outpatient clinic referrals in a secondary referral centre.**

***Patients*—14 Children (10 boys) aged 7-11 years with normal growth velocity during the previous year, no signs of puberty, and no history of receiving systemic or topical steroids during the two months before the study. One child was excluded because his pulmonary function deteriorated and another was withdrawn because of varicella.**

***Interventions*—2·5 And 5·0 mg prednisolone daily given in divided dosage in the morning and evening.**

***Main outcome measure*—Growth of the lower leg as measured twice a week by knemometry.**

***Results*—A significant reduction in mean growth velocity of the lower leg occurred in both prednisolone treatment periods. The mean difference between the run in period and the treatment period with 2·5 mg prednisolone daily was 0·63 mm/week (95% confidence interval 0·47 to 0·80 mm/week) and between the run in period and the treatment period with 5·0 mg prednisolone daily 0·57 mm/week (0·38 to 0·77 mm/week).**

***Conclusion*—Small daily doses of prednisolone suppress short term linear growth in children with mild asthma. The clinical relevance of this finding needs further study.**

Introduction

Growth suppression is a well known risk of long term treatment of children with oral steroids.[1,2] For many reasons it has not been possible to study this side effect under controlled conditions, so little is known about the actual doses that cause growth suppression. During recent years, however, knemometry has become established as a powerful tool for monitoring short term linear growth. The knemometer measures changes in the length of the lower leg with a high reproducibility and an accuracy of 0·09-0·16 mm.[3-6] The method has been shown to be useful in evaluating the response to treatment with growth promoting substances,[7-10] but only recently has it been suggested that it may also be used to detect growth suppression.[11,12] We decided to carry out a study under controlled conditions and with the use of knemometry to see whether 2·5 and 5·0 mg prednisolone daily had any adverse effect on short term linear growth in children with mild asthma.

Patients and methods

When planning the study we estimated the standard deviation of the mean growth rate of the lower leg to be 0·20 mm/week.[9,13] Given this assumption, we calculated that 12 patients would be enough to achieve a power of >0·90 in detecting a 50% reduction in growth rate, which was considered clinically relevant.[14] A 15% rate of withdrawal was estimated, so necessitating increasing the study population required by two patients.

Ten boys and four girls aged 7-11 years (mean 9·1) entered the study. All had mild asthma, needing only treatment as required with inhaled β_2 stimulants. None had received inhaled or oral corticosteroids within two months before the study, and no other drugs were taken during the study period. All children were preadolescent without any signs of puberty. Their growth velocities during the previous year ranged from 3·0 to 9·0 cm (mean 5·1 cm/year). Height at the beginning of the trial varied from −1·19 to 2·72 standard deviation scores (mean 0·34) and weight from 23·0 to 35·6 kg (mean 31·1 kg). The body surface area of the children ranged from 0·97 to 1·20 m^2 (mean 1·11 m^2). The study was approved by the local ethical committee and informed consent given by all children and their parents.

STUDY DESIGN

The study was a randomised double blind crossover trial with five periods of two weeks. In period 1 (run in) and periods 3 and 5 (washout) placebo was given, and in periods 2 and 4 the children took 2·5 and 5·0 mg prednisolone daily. Treatment order was allocated by means of a computerised randomisation scheme prepared in balanced blocks. All medicine was divided into two daily doses and taken in the morning and evening. The tablets, identical in size and appearance, were delivered in identical glasses labelled with case number, period number, and prescription. Tablets were counted before and after each treatment period.

MEASUREMENTS

Knemometry of the right lower leg was scheduled for twice a week, a knemometer manufactured by the inventor being used.[3] All measurements were performed by the same trained observer with no reference to previous days' recordings. The children were measured at roughly the same time (that is, within 30 minutes) in the afternoon (between 1 and 5 pm), as recommended for knemometry.[6] At each visit four estimations of length of the lower leg were made, the mean of the last three measurements being used for

Department of Paediatrics, Kolding Hospital, Denmark
Ole D Wolthers, MD, *research fellow*
Søren Pedersen, MD, *consultant paediatrician*

Correspondence to:
Dr O D Wolthers, Lervangen 62, Bredballe, DK-7120 Vejle, Denmark.

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analysis.[6] At each visit height (Harpenden stadiometer) and weight (electronic beam analyser) were also measured.

To avoid changes in diet and excessive weight gain during treatment with prednisolone dietary instructions were given to all children and their parents before the study. Once a week accurate dietary recordings were made with the aid of special diary cards. The recordings were evaluated by a dietitian, and if any indications of changes in dietary habits were noted new instructions were given.

Forced expiratory volume in one second was measured with a dry wedge spirometer (Vitalograph) at alternate visits, the best of three measurements being used for analysis. Peak expiratory flow was measured at home in the morning and evening (best out of three attempts) with a mini Wright peak flow meter. In addition, the use of inhaled β_2 stimulants (terbutaline 0·25 mg/puff) was recorded. To minimise the risk of a possible suppressive effect of reduced pulmonary function on growth only data from children showing less than 15% variation in pulmonary function between the various periods were analysed.

At each visit inquiries were made about the emotional wellbeing of the children and a thorough physical examination was carried out in order to detect any intercurrent illness or condition which might interfere with linear growth.[5,6] Any child who presented with a febrile illness at any time during the trial had all his or her data excluded from analysis.

ANALYSIS

Growth velocity of the lower leg was calculated for each period by linear regression analysis and expressed as mm/week. Growth velocities were analysed as described for crossover trial designs.[15] Neither period nor carryover effects were found. Analysis of variance was used to detect any overall difference in growth velocities. Significant changes were analysed by paired *t* test.

Results

One boy was withdrawn from analysis because of a 25% reduction in pulmonary function during the run in period. Another was excluded because he caught chickenpox during the first prednisolone period. Age and other characteristics were similar in the two children who were withdrawn and in the 12 who completed the study. Seven children were randomised to receive 5·0 mg prednisolone first and five to receive 2·5 mg prednisolone first. Compliance with the dosage regimen varied from 92% to 106% (mean 96%) during treatment with the lower dose and from 87% to 102% (mean 94%) during treatment with the higher dose. The mean interval between measurements with the knemometer was 3·9 days (range 2-7). The technical error with the knemometer (that is, the mean standard deviation of three successive estimations on the lower leg) was 0·09 mm.

There were no significant variations in pulmonary function, use of β_2 stimulants, or weight gain among the various treatment periods (table), and no changes in diet were recorded. Figure 1 shows the individual growth velocities and the table the mean growth velocities. The individual growth velocities were lower during treatment with prednisolone than during any of the placebo periods in all 12 children when receiving 5·0 mg and in 10 children when receiving 2·5 mg. Compared with the run in (first placebo) period the mean growth velocities during the second and third placebo periods were similar ($p=0·17$, $t=1·48$, df=11; $p=0·81$, $t=0·25$, df=11), but a significant reduction occurred during both prednisolone treatment periods, in which there was almost a complete halt in growth. The mean difference in growth velocity between the run in period and the treatment period with 2·5 mg prednisolone was 0·63 mm/week ($p<0·001$, $t=8·39$, df=11; 95% confidence interval 0·47 to 0·80 mm/week) and between the run in period and the treatment period with 5·0 mg prednisolone 0·57 mm/week ($p<0·001$, $t=6·51$, df=11; 95% confidence interval 0·38 to 0·77 mm/week). The growth suppressive effect of the two doses of prednisolone was the same ($p=0·56$, $t=0·61$, df=11).

When the mean growth velocities during the washout periods after treament with 2·5 and 5·0 mg prednisolone respectively (0·98 and 0·79 mm/week) were compared

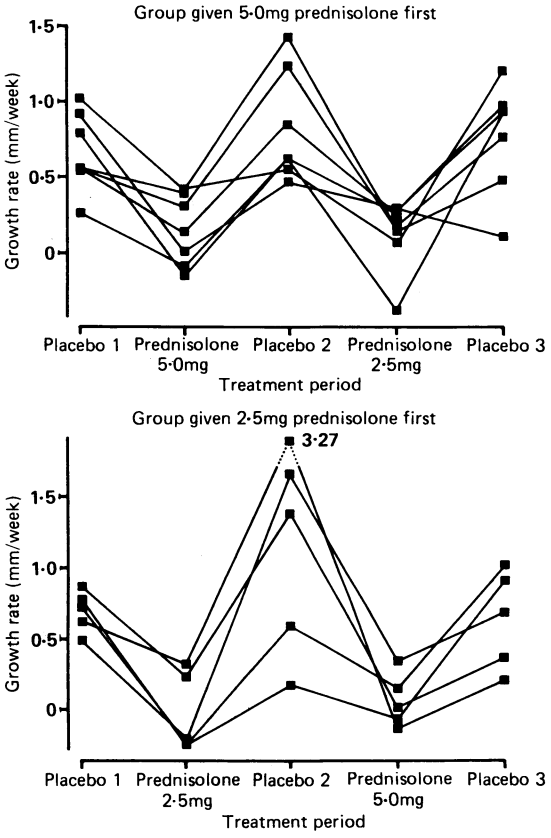

FIG 1—*Lower leg growth velocities in 12 children during placebo periods and during treatment with 2·5 and 5·0 mg prednisolone daily*

Mean short term growth velocity, height, weight, and pulmonary function at hospital and at home and use of β_2 agonists in 12 children with mild asthma during treatment with placebo and small doses of prednisolone

Treatment period	Growth velocity (mm/week) (1 SD)	Height (cm)	Weight (kg)	Forced expiratory volume in 1 s (l)	Peak expiratory flow (l/min)		Use of β_2 stimulants (puffs/day)
					Morning	Evening	
Placebo 1	0·68 (0·21)	138·8	31·3	1·80	274	306	0·9
Prednisolone 2·5 mg	0·04 (0·25)*	139·1	31·5	1·93	302	309	0·8
Placebo 2	1·06 (0·83)	139·2	31·6	1·88	302	314	2·0
Prednisolone 5·0 mg	0·10 (0·21)*	139·1	31·5	1·96	300	313	1·1
Placebo 3	0·71 (0·35)	139·3	31·9	1·90	301	315	1·0

*Growth velocity in each active treatment period differed significantly ($p<0·001$) from that in each placebo period but there were no other significant differences.

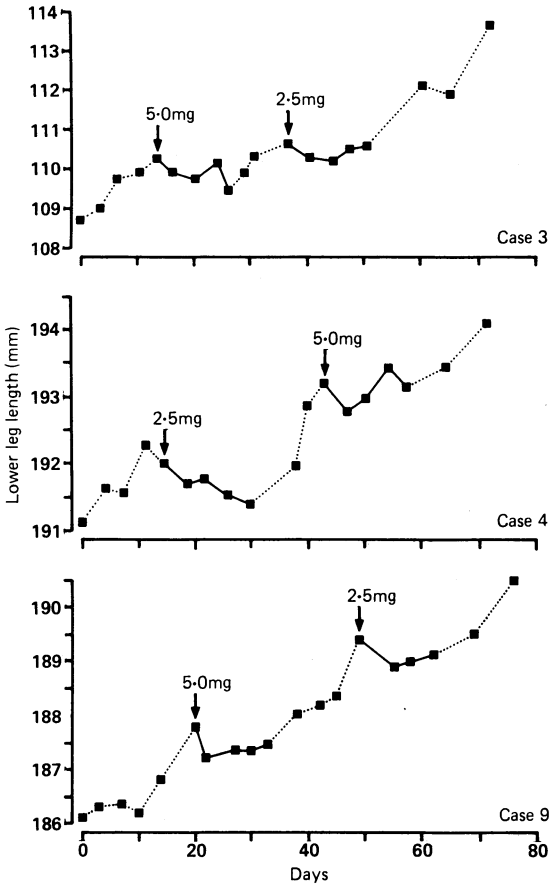

FIG 2—*Individual lower leg growth curves in three children during placebo periods (dotted lines) and during treatment with 2·5 and 5·0 mg prednisolone daily (solid lines)*

individually with those during the run in period no significant differences emerged ($p=0·29$, $t=1·12$, df=11; $p=0·90$, $t=0·58$, df=11) and the growth velocities were similar ($p=0·58$, $t=0·58$, df=11). Hence no catch up growth was detected during the washout periods. The apparently higher growth velocity in the washout period after treatment with 2·5 mg prednisolone was due to an extremely large increment of lower leg length in a child who was measured only twice during that period, roughly three hours earlier than usual.

Figure 2 shows the individual lower leg growth curves in three representative cases. In 21 of the 24 prednisolone treatment periods a shortening of the lower leg was found during the first week. In 14 of these periods this was followed by small increments of leg length during the second week.

Two children presented with non-febrile exanthemas of two days' duration during the first prednisolone treatment period. Three children had a mild cold during the run in period and one had a cold during the second prednisolone treatment period. In no case did these incidents seem to affect growth. Three children suffered mild side effects that might be ascribed to prednisolone—namely, headache, acne, and emotional lability.

Discussion

Several factors have been suggested as influencing growth in children with asthma, such as severity of the disease, acute exacerbations, respiratory insufficiency, infections, inadequate nutrition, psychological distress, suppression of normal physical activity, and treatment with corticosteroids.[16-20] Furthermore, short term growth velocity may change periodically at intervals between 30 and 55 days and lower leg length may show diurnal and day to day variations.[4 6 21] The influence of the last three factors on measurements of the lower leg can be reduced by doing frequent measurements at short intervals at the same time in the afternoon in a group of children. We tried to keep all the other variables constant throughout the study, and our finding of an almost identical growth rate during the three placebo periods, which were separated by several weeks, indicates that we succeeded. We therefore conclude that the pronounced reduction in growth velocity of the lower leg during the treatment periods must have been due to the prednisolone.

The initial shortening of the lower leg during virtually all prednisolone treatment periods was similar to the shortening found in children suffering from acute febrile illness and other forms of catabolic stress.[5 22 23] Shortening was also reported in a child receiving alternate day prednisolone on the days when prednisolone was taken.[12] This phenomenon has been suggested as due to postural compression of non-growing cartilage and bone and may represent true changes in bone length.[5 6 12 22] When short treatment periods are studied the reduction in length of the lower leg may influence the overall result to a larger extent than if longer periods are used. Nevertheless, even after adjustment for this initial effect the suppressive influence of prednisolone on lower leg growth was highly significant.

Many factors may influence the growth suppressive effect of corticosteroids, including individual variations in absorption, metabolism, and sensitivity; potency of the drug; mode of administration; dose; and frequency of dosing.[24 25] Twice daily prednisolone is usually avoided in favour of once daily or alternate day dosing because divided daily doses seem to be more potent in inhibiting growth.[25] Our trial, however, was designed to test whether knemometry could be used to detect changes in growth velocity caused by the pharmacological influence of corticosteroids during short term treatment. We were therefore interested in a potent systemic activity and hence for our trial a twice daily regimen was appropriate. Secondly, we intended that our findings should serve as a reference for future knemometry studies of the influence of inhaled corticosteroids on linear growth. As these drugs are mostly given twice daily we used the divided dose regimen in order to create comparable study conditions.

Uncontrolled studies measuring height in children with asthma during long term treatment with prednisolone suggest that growth impairment may occur with daily doses of around 5 mg.[2 26] We therefore investigated this dose and a dose of 2·5 mg prednisolone, assuming that the lower dose would influence growth to a less extent.

When evaluating the suppression of growth during both treatment periods with respect to long term growth compliance with treatment should be considered. Compliance is likely to be less during long term treatment than during a short term study. It seems unlikely, however, that the growth suppressive effects of the small doses of prednisolone used in our study would be so pronounced during long term treatment. Possibly the growth suppressive effect might be reduced with time as a result of adjustment of the body to exogenous corticosteroids. This, however, can be tested only in a controlled long term study, which is ruled out ethically. Elucidating the possibility from the results of other knemometry studies is difficult. Several have shown that short term growth kinetics are not good predictors of long term growth velocity in normal children and children with growth disorders, probably owing to the non-linearity of short term growth and to the day to day variation of lower leg length mentioned above.[5 27 28] On the other hand, a significant correlation between lower leg and statural growth velocities has been found in a group of normal children.[13] These findings therefore

indicate that even the small doses of prednisolone used in our short term study may adversely affect long term growth in children with mild asthma. The exact extent of the growth inhibition and its clinical relevance, however, need further study.

Despite the short study periods the variations in lower leg length during prednisolone treatment were much larger than the technical error of the knemometer. Hence in measuring changes in a physiological parameter knemometry may have the potential of being the first non-invasive method of assessing the systemic effects of exogenous steroids and may be an important alternative or adjunct to biochemical measures of the systemic effects of topical steroids.

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The epidemiology of infertility in Aberdeen

Allan Templeton, Cynthia Fraser, Barbara Thompson

Abstract

***Objective*—To study the prevalence of infertility, both primary and secondary, outcome of pregnancy, occupation, and uptake of medical services in a total population of women from a geographically defined area.**

***Design*—A postal questionnaire survey of an age cohort of women who had completed their fertility, and who were randomly selected from the Grampian Health Board's primary care register.**

***Setting*—Aberdeen city district.**

***Subjects*—1024 Women in the age group 46-50, of whom 130 had to be excluded. Of the remaining 894 women, 766 (86%) responded to the questionnaire.**

***Main outcome measures*—Response to questionnaire on pregnancy history, the length of time taken to become pregnant each time, and whether medical advice had been sought.**

***Results*—Among the 766 women contacted, 602 (79%) reported no difficulties in having children, 56 (7%) had chosen not to have children, and the remaining 108 (14%) had experienced infertility, defined as having difficulty in becoming pregnant for more than two years. In total 68 (9%) women had primary infertility, of whom 41 (5%) eventually conceived. Of the 40 (5%) with secondary infertility, 23 (3%) conceived. Overall, 52 (7%) of the population were left with an unresolved problem of infertility. Only 67 (62%) infertile women had made use of hospital services, and a further 8 (7%) had consulted their general practitioners. Among those who conceived there was no difference in the proportion who sought advice compared with those who did not.**

***Conclusion*—The overall prevalence of infertility was 14%, although half of these women eventually conceived. Primary infertility was more common than secondary infertility. Only 62% of infertile women attended a hospital clinic for treatment of their infertility.**

Department of Obstetrics and Gynaecology, University of Aberdeen, Foresterhill, Aberdeen AB9 2ZD
Allan Templeton, MD, *professor*
Cynthia Fraser, MA, *research assistant*

Medical Research Council, Medical Sociology Unit, Aberdeen
Barbara Thompson, PHD, *honorary research fellow*

Correspondence to:
Professor Templeton.

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Introduction

"Even today there is very little factual information about the prevalence of infertility."[1] As the Warnock committee observed, accurate statistics about this common and distressing condition are not available. Yet many would consider this information to be essential to our understanding of the problem and to the planning of effective services. There is no population based survey of the prevalence of infertility in the United Kingdom, although preliminary results from a small feasibility study and from a survey of general practitioner records have been reported.[2,3] Hitherto, estimates have been derived from census data, the general household survey,[4] and longitudinal studies of subsections of the population—such as women stopping contraception, presumably with the intention of becoming pregnant.[5-7]

Almost all of what is known about the characteristics of infertile women has been derived from clinic based