Growth retardation after dexamethasone administration: assessment by knemometry

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Abstract

Knemometry has been used to measure lower leg growth during 32 nine day courses of dexamethasone in 26 babies ranging from 24 to 32 weeks' gestation at birth. Mean leg length velocity was 0.37 mm/day in the 10 days before steroids. Administration of dexamethasone was associated with a decrease in velocity in all babies, and in 15 leg shortening was documented. Mean leg length velocity during steroid treatment was -0.003 mm/day. After the course of dexamethasone was completed there was an immediate increase in leg length velocity to a mean of 0.52 mm/day over the first 10 days then falling to a value similar to the growth velocity observed before treatment. Leg length had reached the value predicted by growth before steroids about 30 days after dexamethasone. The reduction in leg length velocity occurred despite a significant increase in energy intake and decrease in oxygen requirements.

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Knemometry is a method of linear growth assessment that utilises precise measurement of knee-heel length with a purpose built measuring device. The technique was first described in young children,¹ and the device has been well validated in this age group.^{2,3} A neonatal knemometer was first described in 1988,⁴ and detailed evaluation has been published.⁵ The neonatal device allows frequent measurements of leg length, while causing minimal disturbance in even the sickest and smallest of premature babies, and is ideal for the assessment of factors that may influence growth in this age group.

Bronchopulmonary dysplasia is an important and frequent complication of neonatal care that has been associated with impairment of normal growth. Sauve and Singhal,⁶ in a follow up study of 179 babies with bronchopulmonary dysplasia, showed weight, height, head circumference, and arm muscle area measured at 4, 8, and 12 months and yearly until 8 years, to be significantly lower than in gestational age and year of birth matched controls. Lindroth and Mortenson found that, although length and weight were significantly lower at 2 years, complete catch up had occurred by 6 years of age.⁷ A different view has been expressed by Sell and Vaucher⁸ and Bozynski *et al*,⁹ who have suggested that the difference in growth attributed to bronchopulmonary dysplasia is no longer apparent if the growth rates are corrected for birth weight.

The interaction of growth and bronchopulmonary dysplasia remains uncertain, as does the means by which bronchopulmonary dysplasia might influence growth. Yeh *et al* found a significantly lower energy intake (405.5 v 526.7 kJ (97 v 126 kcal)/kg/day) and increased energy expenditure (330.2 v 244.5 kJ (79 v 58.5 kcal)/kg/day) in babies with bronchopulmonary dysplasia.¹⁰ In contrast, Kurzner *et al* found no difference in energy intake, but suggested that increased oxygen consumption (determined by indirect calorimetry) identified those babies with bronchopulmonary dysplasia who failed to grow.¹¹ Improvement in respiratory status, however, while reducing the work of breathing, is not associated with a decrease in oxygen consumption or energy expenditure.¹²

One other possible contribution to growth impairment, which has not been considered, is the impact of steroids administered for treatment of the bronchopulmonary dysplasia. Steroids have been shown to impair normal growth in children,¹³ and there is evidence that long term dexamethasone may impair growth in babies.^{14,15} Yeh *et al*, using dexamethasone within 12 hours of birth and continuing for a total of 15 days, showed significant reduction in weight gain in treated babies compared with controls over the first four weeks after birth, becoming similar by six weeks.¹⁶ Cummings *et al* showed that more babies receiving steroids had lengths below the 5th centile at 6 and 15 months than did untreated controls.¹⁷ The differences were not statistically significant, but numbers were small.

Knemometry allows the evaluation of short term changes in growth, and we have therefore assessed the acute effect of dexamethasone on growth using this technique.

Methods

Knemometry is performed routinely on all babies admitted to our neonatal unit. Both legs are measured within 24 hours of birth where possible and at two to three day intervals thereafter. Measurements are made with the observer blind to previous measurements that have been made on any individual baby and are stored unexamined until after the baby has been discharged. At this point, measurements are retrieved and the neonatal notes obtained. A detailed record of the baby's admission to the neonatal unit is compiled, and all information including a drug history is entered onto a computer database.

For this study, information was extracted from the database on all babies who had

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received dexamethasone for the treatment of prolonged oxygen dependency. Our initial regimen for treatment with dexamethasone is to use a nine day course of 0.2 mg/kg three times a day. If there is a subsequent relapse, a second course is given with the same starting dose, but then reducing to a twice daily regimen after three days and once daily after six days. Some babies who show particular steroid sensitivity may continue to have a reducing course for several weeks, and in some babies alternate day steroids are used. This study includes data from babies who had received dexamethasone for nine days by either full dose or reducing course. Babies who had already received one course of steroids were included for a second period of analysis providing that the previous course had been a minimum of three weeks earlier.

For those babies who fulfilled these criteria, mean leg length was recorded for the duration of the admission and mean daily oxygen requirement was calculated from the intensive care records. In a small number of babies, low flow oxygen was given by nasal cannulae. As a predictable relationship between flow and inspired oxygen concentration does not seem to exist, oxygen data from these babies have not been included. All babies were monitored by pulse oximetry, and the inspired oxygen concentration modified to maintain oxygen saturation in the range of 94–98%. Data were also collected on all intravenous and oral fluids and any energy supplements used. From these values, the daily energy intake was calculated using the manufacturers' data for proprietary feeds, supplements and intravenous nutrition and, where breast milk was given, using the values for mature breast milk given by the Department of Health and Social Security.¹⁸

To allow analysis of the data, the study was divided into three 10 day periods – before, during, and after the course of dexamethasone – starting on day 0. Complete data were obtained for all babies for these three periods. In 19 babies data were also available for a further 20 days. Within each of these time periods, linear regression analysis of all the measurements of leg length was performed to gain an estimate of leg length velocity, and inspired oxygen and energy intake was calculated. Comparison of these periods was made by paired *t* tests and confidence interval analysis. Analysis was performed using the Statsview and CIA packages.

Results

Over an 18 month period, 26 babies fulfilling the inclusion criteria received a total of 32 courses of dexamethasone. Twenty babies received one nine day course and six babies two nine day courses at least three weeks apart. Details of the babies are given in table 1.

Each of the individual responses to administration of dexamethasone is shown in fig 1. In every baby there is a decrease in leg length velocity and, in 24 of 32, this decrease is more than 50% of the pretreatment velocity and in

Table 1 Details of babies receiving dexamethasone

	Mean	Range
Gestational age (weeks)	27.4	24–32
Birth weight (g)	996	625–1515
Age when dexamethasone commenced (days)	39	11–149
Weight when dexamethasone commenced (g)	1472	705–2950

Figure 1 Individual responses to administration of dexamethasone.

Figure 2 Apparent decrease in leg length during dexamethasone administration.

18 it is more than 75%. In 15 babies, leg length velocity attained a negative value, implying actual shortening of the limb.

Measurements of both legs in a 27 week gestation baby receiving dexamethasone are shown in fig 2, and clearly show the reduction in leg length in this individual. Over the same period of time, weight remained constant. As these observations were made with the observer blind to previous measurements and with no knowledge of the length of the opposite leg on the same day, there is no doubt that shortening is a real phenomenon.

In the period after dexamethasone, leg length velocity increases and in 24 of the babies is higher than in the period before dexamethasone was administered. Five of the babies were ventilated at the time that dexamethasone was given and six were receiving a reducing course. The response in these babies was no different from that seen in those receiving a full course of dexamethasone, and thus all results have been considered together.

Table 2 Average leg length velocities before, during, and 1–10 and 11–30 days after dexamethasone

	Study period			
	Before	During	After	Late
Days	–10 to –1	0 to 8	9 to 19	20 to 40
No	31	31	31	19
Mean leg length velocity (mm/day)	0.367	–0.003	0.518	0.345
95% Confidence intervals	0.292 to 0.442	–0.081 to 0.075	0.455 to 0.58	0.231 to 0.459

Table 3 Comparison of leg length velocity before, during, and 1–10 and 11–30 days after dexamethasone; comparison by paired *t* test and confidence interval analysis

Periods compared	Difference (mm/day)	95% Confidence intervals
Before <i>v</i> during	–0.37	–0.28 to –0.46
During <i>v</i> after	0.52	0.43 to 0.62
Before <i>v</i> after	0.15	0.06 to 0.24
After <i>v</i> late	–0.16	–0.02 to –0.29
Before <i>v</i> late	0.05	–0.05 to 0.15

Figure 3 Combined data: mean (SEM) increment in leg length from the 10th day before dexamethasone given (dotted line represents the continuation of the growth line before dexamethasone).

The velocities for these three periods and for a further 20 day period are given in table 2 and statistical comparisons in table 3.

Figure 3 shows the changes in leg length for all babies, expressed as the increment in mm from the length 10 days before dexamethasone was started. The effect of dexamethasone on leg growth is clearly seen. After dexamethasone is stopped, there is an initial increase in velocity that is not sustained. The dotted line superimposed on this graph is the linear regression line of the points before the administration of dexamethasone. Comparison of the actual measurements made against this line suggests that the leg length will have reached the value predicted from growth velocity before steroids by around 30 days after the steroids were given. The data do not extend sufficiently far beyond this point to comment on longer term progress.

Figure 4 shows the daily increase in weight over the same time period. After dexamethasone is commenced there is an immediate reduction in lower leg growth, but weight gain continues at the same rate for three days before starting to decrease. As soon as dexamethasone is stopped, there is a rapid increase in weight so

that it rises above the pretreatment prediction line within six days of stopping dexamethasone and continues to rise above the line throughout the study period.

These changes in length and weight occurred despite an apparent improvement in respiratory status, as indicated by a reduction in the inspired oxygen, and despite an increase in the energy intake. Mean inspired oxygen was 39.8% in the 10 days before dexamethasone, falling to 33.1% during dexamethasone, and 31.2% in the 10 days thereafter. Average daily energy intake rose from 468.2 kJ (112 kcal) kg/day before dexamethasone to 551.8 kJ (132 kcal) kg/day during, and remained at 543.4 kJ (130 kcal) kg/day thereafter.

Discussion

The data presented here clearly show that administration of dexamethasone is associated with an immediate disturbance of lower leg growth, which may be manifest as a reduction or cessation of normal growth or even as actual limb shrinkage. This persists throughout a nine day course of dexamethasone and occurs whether the baby is ventilated or breathing spontaneously, and whether the baby is receiving a full or reducing course. There may be a difference in the response to the different regimens, but there were insufficient babies in this study to attempt comparison. After dexamethasone is stopped, there is an immediate increase in leg length velocity to a value higher than that seen before steroids. This catch up persists for about 10 days, after which the velocity returns to that seen before steroids. Data from the period after dexamethasone suggest that the leg length will have returned to the level predicted from pretreatment velocity by around 30 days. The immediate decrease in leg length velocity occurs despite a significant increase in energy input and a significant reduction in oxygen requirements, while the increase in velocity after treatment occurs while oxygen requirements and energy input remain unchanged. It would thus appear that dexamethasone causes a highly significant disturbance of normal growth that cannot be explained by changes in energy input or oxygen requirements.

Figure 4 Combined data: mean (SEM) weight increase from the 10th day before dexamethasone given (dotted line represents the continuation of the growth line before dexamethasone).

The reduction in oxygen requirements during treatment is as would be expected from the controlled trials of dexamethasone in bronchopulmonary dysplasia.¹⁹⁻²¹ The increase in energy input during and after dexamethasone treatment was an interesting finding, as we do not have an active policy of fluid restriction in babies with bronchopulmonary dysplasia or of energy supplementation during treatment with steroids. Review of the charts suggested that the increased energy input was partially due to an increase in energy supplements for poor weight gain and partially due to the babies receiving larger volumes of feed, although total volume prescribed was not deliberately changed. Nursing staff who care for these babies have suggested that this may be due to the babies becoming more irritable while receiving dexamethasone and being offered extra feed to try to pacify them.

Assuming that growth before dexamethasone would have continued at the same velocity had steroids not been administered, a short course does not seem to influence growth potential, as a growth spurt after the course has finished eventually restores the leg length to the value that would have been predicted from presteroid growth. Similar changes in weight and fibula length have been reported in infants receiving corticotrophin (ACTH) for treatment of retinopathy,²² but there are no other comparable short term measurements of linear growth. Measurements of weight change have shown an initial decrease in weight gain followed by catch up to bring the weight to levels measured in controls within a relatively short period of time.^{14 16 20} At one year follow up eight infants who received a three week course of dexamethasone had similar bone ages, weight, height, and head circumference to control babies.²³ The data that we have presented here suggest that there may be a disproportionate alteration in weight gain and linear growth after dexamethasone, and care should be taken in interpretation of claims of adequate growth based solely on weight measurements.

The most interesting observation made in this study is the leg shortening seen in almost half of the babies studied. We believe this to be a genuine observation, as it arises from multiple measurements on a number of different babies recorded by an observer blind to the previous measurements. This is unlikely to be due to a loss of soft tissue fluid, as, in studies on other babies, we have observed loss of very substantial amounts of weight (as much as 30% of body weight in one baby with hydrops) without a significant change in leg length. Measurements made on individual babies have shown that marked limb shrinkage may occur without any concomitant decrease in weight. Furthermore, comparison of the overall trends in leg length and weight show that a simple relation between leg length and weight does not occur. Steroids are well known to reduce growth in older children, and decreases in leg length have been observed in association with periods of ill health and steroid treatment in older children,³ and

have been postulated to be due to postural compression of non-growing cartilage. This cannot, however, explain the phenomenon demonstrated in these babies who are nursed horizontally.

The effect that dexamethasone has on linear growth is probably multifactorial. Administration of dexamethasone has been shown to increase protein catabolism from nitrogen balance studies²⁴ and by measurement of amino acid profiles.²⁵ This may be compounded by a state of relative protein malnutrition in babies with bronchopulmonary dysplasia and growth failure.²⁶ An increase in catabolism in our study would to some extent be offset by the increased energy intake measured.

An alteration of energy expenditure as a result of steroid administration could have some part in the observed effect, as increased work of breathing, increased oxygen consumption, and increased energy expenditure are features of infants with bronchopulmonary dysplasia.^{10 26 27} Treatment with dexamethasone has been shown to result in improved respiratory mechanics and decreased work of breathing,²⁸ but improving respiratory mechanics may not necessarily decrease oxygen consumption.¹² An improvement in respiratory mechanics is unlikely to account for much of our observation, as growth decreased as respiratory function improved, then increased while respiratory function was stable.

Dexamethasone may have an additional effect by influencing the endocrine control of perinatal growth. It has been hypothesised that fetal and infantile growth is predominantly determined by insulin and insulin-like growth factors,²⁹ and the importance of growth hormone has been clearly demonstrated.³⁰ Dexamethasone enhances insulin-like growth factor-1 (IGF-1, somatomedin C) activity in human fibroblast culture,³¹ but in children has been shown to decrease IGF-1 activity without an associated change in concentration.³² In addition, dexamethasone has been shown to modulate the activity of epidermal growth factor.³³ Growth hormone concentrations were suppressed in babies born to mothers who had received antenatal steroids, but the initial low values were followed by a rise to concentrations higher than those seen in controls whose mothers did not receive steroids.³⁴ Whether any of these endocrine changes contribute to the observed effect of dexamethasone is unclear, but these studies show that hormonal effects are possible.

The shrinkage of the limb that we have observed may be explained by a potent effect of dexamethasone on the growth plate. In vitro studies on condylar cartilage from mice have shown that dexamethasone causes a very rapid decrease in DNA and protein content and protein synthesis. Control condyles showed a steady growth, whereas those exposed to steroids exhibited pronounced shrinkage and degeneration of existing cells.³⁵ The human growth plate has been shown to be an extremely active area in intrauterine life with rapidly changing structure and size in the latter

half of pregnancy. In this period, the upper tibial growth plate alone has been shown to turn over at a rate of 176 $\mu\text{m}/\text{day}$.³⁶ When the observed changes in leg length are considered in the context of the dynamics of growth plate formation, it is not surprising that dramatic changes and even limb shrinkage may occur.

Dexamethasone may exert an effect on growth through endocrine or metabolic pathways, by modification of collagen and bone deposition, or by a combination of all of these. These effects are probably superimposed on an intrinsic growth rate that is genetically determined for each individual.³⁷ From our data, it would seem that the disruptive effect of steroids on normal growth may be severe. Silverman *et al* first described the effect of ACTH on weight gain and linear growth in 1951,²² and emphasised that the long term effects of this treatment were unclear. This is still the case today and while there is increasing evidence to suggest minimal long term respiratory benefit from dexamethasone,^{38 39} we feel that our study should be added to the growing list of data that advocates caution in the use of this potent drug.

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