ORIGINAL ARTICLE

Growth effects of systemic versus inhaled steroids in chronic lung disease

R M Nicholl, A Greenough, M King, P Cheeseman, H R Gamsu

Arch Dis Child Fetal Neonatal Ed 2002;**87**:F59–F61

See end of article for authors' affiliations

Correspondence to:
Dr R M Nicholl, Consultant
Paediatrician, Northwick
Park & St Mark's NHS
Trust, Harrow HA1 3UJ,
UK; drnicholl@aol.com

Accepted
19 February 2002

Aim: To compare the effects of inhaled and systemic steroids on growth in very low birthweight (VLBW) infants with chronic lung disease (CLD).

Methods: Sixteen babies with CLD randomly received inhaled budesonide (100 µg four times daily for 10 days via Aerochamber) or systemic steroids (dexamethasone 0.5 mg/kg/day, reducing over nine days). Linear growth (lower leg length, LLL) was measured by knemometry twice weekly.

Results: The gestational age, birth weight, postnatal age, and LLL velocity (LLLvel) were similar between the two groups at the start of treatment. At the end of the treatment period, LLLvel was reduced in the dexamethasone group (mean -0.01 mm/day) but had increased in the budesonide group (mean 0.48 mm/day). Mean weight gain was non-significantly lower in the dexamethasone group (5.8 g/kg/day) compared to the budesonide group (mean 12.7 g/kg/day).

Conclusion: Inhaled budesonide has less short term effects on growth than systemically administered dexamethasone.

The management of chronic lung disease (CLD) remains a major problem in neonatal intensive care. In many units, intubated babies with chronic oxygen dependency receive systemically administered dexamethasone. Meta-analysis of randomised trials has shown dexamethasone given systemically facilitates earlier extubation¹; it does, however, have important side effects. These include short term adverse effects on linear growth, shown using the technique of neonatal knemometry.² In an attempt to avoid such problems, corticosteroids are now also given by the inhaled route. The aim of this study was to assess whether administration by inhalation compared to systemically had less impact on short term growth of infants with CLD.

METHODS AND PATIENTS

Patients

As part of a trial investigating the effects of fortification of breast milk on growth,³ 52 very low birthweight (VLBW) infants had lower leg length (LLL) measurements using a neonatal knemometer twice weekly from birth to discharge over a 14 month period. Sixteen of the 52 infants (table 1) were entered into an unrelated randomised trial comparing the effects of inhaled and systemic steroids on lung function.⁴ Both studies were approved by the Research Ethics Committee of the King's College Hospital National Health Service Trust and written informed parental consent was obtained.

Methods

Infants were eligible for entry into the steroid trial if they were born at less than 32 weeks of gestation, ventilator dependent for at least five days, or oxygen dependent for at least 14 days, and either were failing to improve or deteriorating on the ventilator. Infants were randomised to receive either dexamethasone (0.5 mg/kg/day for three days; 0.3 mg/kg/day for three

days; followed by 0.1 mg/kg/day for four days) or inhaled budesonide (100 µg four times daily for 10 days) via an Aerochamber, into the ventilator circuit of those who were ventilator dependent.⁵ During the study period—the 10 days of steroid administration—the infants' LLLs were measured twice weekly. LLL was measured using a hand held neonatal knemometer (FORCE Institute, Copenhagen, Denmark).⁶ Three measurements were made and the results discarded, to allow for soft tissue compression. Five consecutive measurements were then taken and the average reading recorded. One investigator (RMN) made all the measurements. The standard deviation of the mean of the five readings was less than 0.8 mm for each measurement in all babies. LLL velocity (LLLvel, mm/day) was calculated as the change in LLL (mm), divided by the number of days between measurements, after the infant's discharge in order to avoid bias. The infants were weighed at least twice weekly using electronic scales. The weight gains from birth to study entry and during the study period were calculated for each infant retrospectively after discharge. The nurses recorded hourly all enteral and intravenous fluid intake. From those records the energy intakes for the 10 days prior to and during the study period were calculated retrospectively for each infant. Each infant's inspired oxygen requirement at the beginning and the end of the study was recorded.

Statistical analysis

The data were normally distributed (Shapiro Francia W test) and thus differences were assessed for statistical significance using paired or unpaired *t* tests, using Stata for Windows 5.0 (Stata Corporation, 702 University Drive East, College Station, Texas 77840, USA).

RESULTS

There were no statistically significant differences in the patient characteristics at study entry (table 1). The mean LLLvel prior to treatment was similar in the two groups, but the

Key message

- Systemic steroids have immediate adverse effects on growth
- Inhaled steroids appear to have less acute effects on growth

Abbreviations: BMF, breast milk fortifier; CLD, chronic lung disease; LLL, lower leg length; LLLvel, LLL velocity; VLBW, very low birthweight

Table 1 Patient demographics

	Dexamethasone	Budesonide	Difference in the means (95% CI)	p value
n	8	8		
Gestational age (weeks)	27 (1.7)	26.6 (1.2)	0.8 [−0.8 to 2.4]	ns
Birth weight (g)	919 (200)	845 (158)	74 [−126 to 274]	ns
At study entry:				
Postconceptional age (weeks)	33 (4)	33 (4)	0 [−4.6 to 3.9]	ns
Weight (g)	1263 (490)	1274 (413)	−11 [−498 to 476]	ns
Inspired oxygen concentration (%)	37.5 (10.4)	29.4 (5.0)	8.1 [−0.6 to 16.8]	ns
Prior to the study:				
Weight gain (g/kg/day)	6 (3.7)	5.1 (7.6)	0.9 [−5.5 to 7.2]	ns
LLlvel (mm/day)	0.32 (0.12)	0.30 (0.15)	0.02 [−0.12 to 0.16]	ns
Energy intake (kcal/kg/day)	104 (29)	124 (41)	−20 [−52 to 11]	ns
At the end of the study period:				
Postconceptional age (weeks)	34 (4.5)	34 (4)	0 [−4.5 to 4.5]	ns
Weight (g)	1340 (471)	1407 (390)	−67 [−530 to 396]	ns
Weight gain (g/kg/day)	5.8 (6.4)	12.7 (9.2)	−7.0 [−15.5 to 1.5]	ns
LLlvel (mm/day)	−0.01 (0.13)	0.48 (0.30)	−0.48 [−0.73 to −0.24]	0.0009
Inspired oxygen concentration (%)	23.4 (3.0)	29.5 (10.7)	−6.1 [−14.6 to 2.3]	ns
Energy intake (kcal/kg/day) during the study period	118 (26)	122 (18)	−4 [−28 to 19]	ns

Data are presented as mean (SD).

Table 2 Changes during the study period

	Dexamethasone (n=8)	Budesonide (n=8)	Difference (budesonide – dexamethasone)
LLlvel (mm/day)	−0.33 (0.22)	0.18 (0.31)	0.5 (0.27)*
Weight (g)	77 (70)	133 (85)	56 (78)
Weight gain (g/kg/day)	−0.3 (8.0)	7.6 (13.2)	7.9 (10.9)
Energy intake (kcal/kg/day)	14 (25.2)	−2.0 (21.3)	−16.3 (23.4)
Inspired oxygen concentration (%)	−14.1 (8.8)	0.13 (13.0)	14.3 (11.1)*

Data are presented as mean (SD).

*Indicates a significant difference.

mean LLlvel at the end of the study was −0.01 mm/day in the dexamethasone group and 0.48 mm/day in the budesonide group ($p < 0.001$; table 1). Five of the eight infants in the dexamethasone group had a negative LLlvel at the end of the study period, indicating shortening of the lower leg. No infants in the budesonide group had a negative LLlvel after treatment.

The mean weight gain, prior to randomisation did not differ significantly between the two groups (table 1). Prior to enrolment in the study, two infants in the dexamethasone group had received breast milk fortifier (BMF) for five and seven days respectively, and two in the budesonide group had received BMF for six and 10 days respectively. During the study no infants in the dexamethasone group receive BMF; three in the budesonide group received BMF for four, five, and 10 days respectively. There was no statistically significant difference in inspired oxygen concentration at the start of the study between the two groups. The energy intake of the two groups did not differ significantly either prior to or during the study (table 1). Over the study period weight gain was higher in the budesonide compared to the dexamethasone group, but this trend did not reach statistical significance (table 1). In the dexamethasone, but not the budesonide, group there was a significant reduction in mean inspired oxygen requirement ($p = 0.0027$; table 1). During the study period, changes in LLlvel and inspired oxygen concentration were significantly different between the two groups ($p = 0.0011$, $p = 0.0132$ respectively; table 2).

DISCUSSION

We have shown that inhaled steroids did not have an adverse effect on short term growth as indicated by LLlvel. The mean LLlvel of the infants in the budesonide group (0.48 mm/day) was similar to that reported by Gibson and colleagues⁶ in 324

infants of 23–42 weeks gestation. The dexamethasone treated infants tended to have a lower weight gain than those who received budesonide. This was despite similar energy intakes in the two groups before and during the study. The similar weight gain of the two groups prior to randomisation does suggest that the difference seen during treatment reflects a further adverse effect of systemically administered corticosteroids in VLBW infants with CLD. It was not possible to blind staff or researchers to which treatment individuals received. To minimise any bias, however, both LLlvel and weight gain were calculated only after the infant had been discharged. The lack of effect of inhaled rather than systemically administered steroids on LLlvel is also seen in young children with asthma. Although the number of infants included in our study was small, we did see a significant impact of dexamethasone on growth. That, and the highly significant difference between the two groups we highlight, further suggests our findings are genuine. Studies comparing systemic to inhaled steroids have shown that the latter route is less efficacious.^{4,7} A greater amount of steroids, however, has usually been given systemically. Increasing the inhaled dose may then improve efficacy, but could increase side effects. On the basis of the present findings, we suggest that measuring LLlvel by knemometry would be a useful method to indicate whether higher doses of inhaled steroids would have more adverse effects, as shown by impairment of short term growth.

Authors' affiliations

R M Nicholl, A Greenough, M King, P Cheeseman, H R Gamsu, Children Nationwide Regional Neonatal Intensive Care Centre, King's College Hospital, London, UK

REFERENCES

- 1 **Halliday HL**, Ehrenkranz RA. Delayed (>3 weeks) postnatal corticosteroids for chronic lung disease in preterm infants (Cochrane Review). In: *The Cochrane Library, Issue 1*. Oxford: Update Software, 2000.
- 2 **Gibson AT**, Pearce RG, Wales JKH. Growth retardation after dexamethasone administration: assessment by knemometry. *Arch Dis Child* 1993;**69**:505–9.
- 3 **Nicholl RM**, Gamsu HR. Changes in growth and metabolism in very low birthweight infants fed with fortified breast milk. *Acta Paediatr* 1999;**88**:1056–61.
- 4 **Dimitriou G**, Greenough A, Giffin FJ, *et al*. Inhaled versus systemic steroids in chronic oxygen dependency in preterm infants. *Eur J Pediatr* 1997;**156**:51–5.
- 5 **Giep T**, Raibb P, Zuerlein T, *et al*. Trial of beclomethasone dipropionate by metered-dose inhaler in ventilator-dependent neonates less than 1500 grams. *Am J Perinatol* 1996;**13**:5–9.
- 6 **Gibson AT**, Pearce RG, Wales JKH. Knemometry and the assessment of growth in premature infants. *Arch Dis Child* 1993;**69**:498–504.
- 7 **Groneck P**, Goetze-Speer B, Speer CP. Effects of inhaled beclomethasone compared to systemic dexamethasone on lung inflammation in preterm infants at risk of chronic lung disease. *Pediatr Pulmonol* 1999;**27**:383–7.

Find out what's in the latest issue
the moment it's published

Email Alerts

Sign up to receive the table of contents by email every month. You can select from three alerts:
Table of Contents (full), TOC Awareness (notice only); *Archives of Disease in Childhood* related announcements.

www.archdischild.com