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Inhaled versus systemic steroids in chronic oxygen dependency of preterm infants

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Abstract The speed of action and side-effects of systemic versus inhaled steroids was compared in infants with mild-moderate oxygen dependency. Forty infants (median gestational age 27 weeks) were randomized to receive either 10 days of dexamethasone (systemic group) or budesonide (100 μg qds) (inhaled group). At randomization, there was no significant difference in the gestational or postnatal age, inspired oxygen requirements or compliance of the respiratory system of the two groups. After 36 h of treatment, there were significant changes ($P < 0.01$) in both the inspired oxygen concentration and compliance of the respiratory system in the systemic but not the inhaled group. Only after 1 week of inhaled therapy were improvements in respiratory status noted but, even at that time, the inspired oxygen requirement was significantly lower in the systemic versus the inhaled group. In the systemic group only, however, were there significant increases in blood pressure.

Conclusion Systemically administered rather than inhaled steroids appear to have a faster onset of action.

Key words Chronic lung disease · Prematurity · Steroids

Abbreviations *BDP* beclomethasone dipropionate · *CRS* compliance of the respiratory system · *NICU* neonatal intensive care unit

Introduction

Numerous studies [1, 5, 6, 17] have demonstrated that corticosteroids, when administered systemically, either intravenously or orally, can improve the respiratory status of premature infants. Unfortunately, however, there are side-effects [12] of such treatment, particularly hypertension [9] which, can cause serious morbidity. In a pilot study, we were able to show that steroids, when administered by inhalation, that is via a metered dose inhaler and spacer device, had fewer side-effects, in particular no episodes of serious hypertension [7]. Those preliminary data [7] also suggested that inhaled steroids might improve lung function. The effect. however, appeared to occur more slowly than when steroids were administered systemically; a reduction in oxygen requirement being noted only at 1 week [7] rather than at 36 h as occurs with systemic treatment [10]. We have now performed a randomized trial to compare the timing of possible beneficial effects of the two methods of administration. In addition, we also wished to determine whether systemic compared to inhaled steroids had a greater effect on blood pressure.

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Methods

Consecutive infants in alternate months were entered into the study if they were born at less than 32 weeks of gestation and considered by the clinician in charge to merit steroid therapy. The criteria used were that the infant at least remained ventilator-dependent for 5 days or oxygen-dependent for 14 days and his or her respiratory status had failed to improve (i.e. there had been no reduction in requirement for respiratory support) or was deteriorating (i.e. there had been an increase in the requirements for respiratory support) over the preceding 48 h. Infants were considered for recruitment throughout their admission to the Neonatal Intensive Care Unit (NICU) providing they met the preceding criteria. Infants were only randomized, however, if the following problems were excluded: patent ductus arteriosus, systemic infection, gastro-oesophageal reflux and aspiration.

Infants were randomized using consecutive opaque envelopes to receive corticosteroids systemically or by inhalation. If randomized to the systemic group, they received dexamethasone intravenously or orally depending on the infant's clinical status, at a dosage of 0.5 mg/kg per day for 3 days; 0.3 mg/kg per day for a further 3 days and 0.1 mg/kg per day for 4 days. The daily medication was given in two divided doses. The "inhaled" group recieved budesonide 100 μg qds which was given via a Nebuhaler (Astra Pharmaceuticals Ltd) and face mask to non-ventilated infants [7] and via an Aerochamber (Trudell Medical, Ontario) directly into the ventilator circuit for infants who were ventilated or receiving nasal continuous positive airways pressure. The course

Table 1 Patient characteristics and inspired oxygen requirements related to method of administration

Median (range) or number (n)	Systemic	Inhaled
n	20	20
Gestational age (weeks)	27 (24–31)	27 (24–30)
Birth weight (g)	818 (425–1460)	849 (584–1270)
Postnatal age (days)	27 (8–118)	26 (5–97)
Antenatal dexamethasone *(n)*	11	12
Postnatal surfactant *(n)*	12	14
IPPV *(n)*	8	5
FiO_2 Baseline (–12 h)	0.32 (0.23–0.56)	0.31 (0.23–0.50)
After		
12 h	0.31 (0.21–0.53)	0.31 (0.25–0.57)
36 h	0.26 (0.21–0.41)	0.29 (0.25–0.57)
1 week	0.23 (0.21–0.41)	0.27 (0.21–0.44)

of budesonide was continued for 10 days regardless of whether the infant was extubated during the study.

Twelve hours prior to commencing therapy (–12, baseline) and then at 12 and 36 h and 1 week after randomization, the infants' requirement for respiratory support was noted, compliance measured and blood pressure recorded. The infants' respiratory support requirements were recorded hourly by the nurses on observation charts. Changes in respiratory support were made by the clinical team according to the results of regular blood gas measurement which was performed only on clinical grounds. Adjustments in the level of respiratory support were made to ensure a PaO_2 of between 60 and 80 mmHg or an oxygen saturation between 90% and 95% and to avoid a respiratory acidosis (pH < 7.25).

Compliance of the respiratory system (CRS) was measured using the occlusion technique [4]. A face mask (Laerdal size 01) was firmly applied over the infant's nose and mouth. The distal portion of a pneumotachograph (Mercury F10L), which fitted snugly into the face mask, could be occluded manually. In the ventilated infants, the pneumotachograph was inserted into the end of the endotracheal tube. The pneumotachograph recorded flow signals which were electronically integrated to give volume. Airway pressure was measured from the infant's side of the pneumotachograph (Validyne pressure transducer ± 50 cmH_2O). The infant's airway was temporarily occluded at end inspiration, in ventilated infants these occlusions were made during very temporary disconnections from the ventilator. The occlusion provoked the Hering Breuer reflex resulting in a temporary apnoea, as indicated by a plateau in the airway pressure tracing. CRS was calculated from the inspiratory volume prior to the occlusion, divided by the height of the airway pressure plateau during the occlusion. Ten occlusions were made on each occasion and their mean value taken as the infant's CRS, which was expressed in millilitre/cmH_2O per kilogram. The coefficient of variation of the CRS measurements was 14%. Two infants on two occasions were apnoeic during ventilation. As a consequence the occlusion technique could not be used and to estimate CRS the volume change from a positive pressure inflation maintained until there was no volume change was used. Ten separate measurements were made on each occasion and compliance calculated as the mean and again expressed in millilitre/cmH_2O per kilogram.

Throughout the 10-day study period the infants' blood pressure was measured 6-hourly by oscillometry. The mean BPs of the two groups at baseline, 12 and 36 h and 1 week after commencing treatment were compared. Episodes of severe hypertension (systolic BP > 100 mmHg [10], systemic sepsis (positive blood culture), hyperglycaemia (blood sugar > 7 mmol/l), and infants requiring insulin (blood sugar > 10 mmol/l for 12 h) throughout the study period were recorded.

Analysis

Differences were assessed for statistical significance using the Mann Whitney U-test or chi-square test as appropriate and ANOVA for repeated measurements; where an overall significant *P* value (< 0.01) was found then the Scheffe F-test was used to identify where the differences lay.

Trial size

Previous data [10] demonstrated that the standard deviation of the reduction (expressed as a percentage change from the baseline) in the inspired oxygen concentration at 36 h and 1 week after commencing systemic steroid therapy was 7%. Recruitment of 40 patients allowed us to detect, with 80% power at the 5% level, such a difference in the absolute inspired oxygen requirements at 1 week between regimes. In addition, that trial size enabled us to detect a reduction in the occurrence of severe hypertension from 30% [9] in the systemic group to 0% in the inhaled group.

Patients

Forty infants, median gestational age 27 weeks (range 24–31) were enrolled into the study (Table 1). During the 24-month study period 240 infants < 32 weeks were admitted to the NICU. All infants followed the NICU's routine policies regarding fluid administration, that is small amounts of enteral feeding were introduced at 48 h unless contraindicated and the volume of fluid increased if tolerated. Expressed breast milk was used preferentially if available, otherwise infants received a standard preterm formula. Infants who remained on parenteral nutrition received on average 10 g/kg per day of glucose unless they had evidence of hypoglycaemia or hyperglycaemia.

This study was approved by the King's College Hospital Ethics Committee.

Results

There were no statistically significant differences between the two groups at trial entry (Table 1). In the systemic group there was a significant reduction in the oxygen requirements throughout the 1st week (–12 to 12 h, $P < 0.05$, –12 to 36 h, $P < 0.01$; –12 to 7 days, $P < 0.01$) (Table 1). No such significant changes were noted in the inhaled group. At 1 week, the inspired oxygen concentra-

Table 2 CRS (ml/cmH_2O/kg) results related to method of administration median (range)

	Systemic	Inhaled
Prior to	0.64 (0.38–1.55)	0.71 (0.26–1.16)
After		
12 h	0.73 (0.45–1.67)	0.72 (0.23–1.15)
36 h	0.86 (0.53–2.31)	0.74 (0.26–1.39)
1 week	0.96 (0.38–1.82)	0.88 (0.53–1.40)

tion was significantly lower in the systemic versus the inhaled group, $P < 0.02$, (Table 1). In addition, the mean reduction in the inspired oxygen requirements from the pretreatment values was significantly greater at 36 h, but not at 1 week, in the systemic compared to the inhaled group ($P < 0.01$) (Fig. 1). CRS significantly improved throughout the 1st week in the systemic group (–12 to 12 hours $P < 0.05$, –12 to 36 h, $P < 0.01$, –12 h to 7 days, $P < 0.01$), but in the inhaled group the change from baseline was only significant at 1 week ($P < 0.01$) (Table 2). The improvement in CRS from baseline was significantly greater at 36 h, but not 1 week, in the systemic compared to the inhaled group ($P < 0.01$), (Fig. 2).

The mean blood pressure increased significantly from –12 to 12 h only in the systemic group ($P < 0.01$) and was significantly higher in that group compared to the inhaled group at 12, 36 h and 1 week ($P < 0.01$) (Table 3). In the systemic group there was a trend towards more complications regarding infection and hyperglycaemia (Table 4). In all cases of systemic infection, *Staphylococcus epidermidis* was isolated from blood cultures. One infant in the inhaled group developed truncal skin sepsis, both a *Candida* species and *S. epidermidis* were isolated from culture of the skin swabs. There were no significant differences

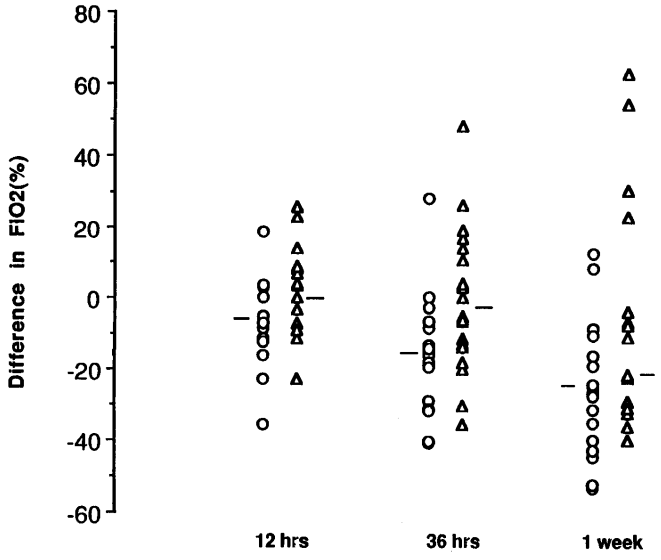

Fig. 1 The difference in the inspired oxygen requirement from baseline to 12 and 36 h and 1 week. Individual data and the medians of the groups (–) demonstrated. ○ systemic, △ inhaled

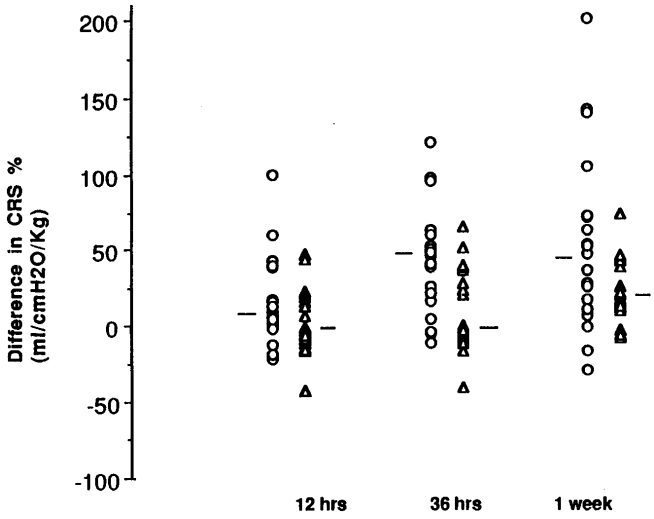

Fig. 2 The difference in the CRS from baseline to 12 and 36 h and 1 week. Individual data and the medians of the groups (–) demonstrated. ○ systemic, △ inhaled

Table 3 Mean blood pressure (mmHg) related to method of administration median (range)

	Systemic	Inhaled
Prior to	38 (31–72)	41 (32–55)
After		
12 h	48 (39–80)	41 (32–52)
36 h	53 (39–77)	43 (30–54)
1 week	56 (38–81)	43 (34–60)

Table 4 Adverse effects related to method of administration (number)

	Systemic	Inhaled
Systolic blood pressure > 100 mmHg	2	0
Sepsis (blood culture positive)	6	2
Oral candidiasis	0	0
Hyperglycaemia		
> 7 mmol/l	6	1
requiring insulin	1	0

Table 5 Outcome related to method of administration data expressed as median (range) or *n* (%)

	Systemic	Inhaled
Duration (days) of:		
mechanical ventilation	19 (3–57)	10 (1–35)
supplementary oxygen	60 (28–120)	47 (28–120)
Day 28:		
ventilated	3 (15)	2 (11)
oxygen dependent	20 (100)	20 (100)
36 weeks postconceptional age:		
ventilated	0	0
oxygen dependent	8 (40)	8 (40)
Survival until discharge	18 (90)	19 (95)

regarding duration of respiratory support related to administration method (Table 5).

Discussion

These results suggest that systemically administered versus inhaled steroids are associated with a faster onset of action. One possible explanation for those findings was that our method of administering the inhaled steroids was ineffective. We do not, however, feel that is the case, as we have used similar systems to deliver both bronchodilator [18] and prophylactic [19] medication in premature infants with positive effects on both symptom status and lung function. The results are unlikely to be explained by employment of an ineffective regimen of administration, as 100 μg qds of beclomethasone dipropionate (BDP) and as 200 μg bd resulted in similar control of mild stable childhood asthma [16] and no clinically important difference between BDP and budesonide was found in a randomized crossover study involving asthmatic children [14]. The total daily dosage of 400 μg was chosen as this has been effective in treating young asthmatic children [8, 15]. It may be, however, that this was too small to impact on the chronic oxygen dependency of prematurely born infants. Standard doses of up to 800 μg of both BDP and budesonide have been given without either notable effects on the hypothalamic pituitary adrenal axis function or resulting in other systemic side-effects [2, 11], thus it would seem reasonable in future randomized studies to assess the efficacy of a higher inhaled steroid dose, up to 800 μg.

None of the patients studied required more than 0.6 inspired oxygen concentration at randomization and only a minority required ventilation. They thus can be considered to have only mild-moderate chronic oxygen dependency. This was by chance, as we recruited consecutive babies in alternate months, the latter restriction being due to the availability of researchers to measure lung function. Of the infants, 65% received postnatal surfactant and 58% of their mothers antenatal dexamethasone and this may have influenced the severity of chronic oxygen dependency. Although none of our infants had severe chronic lung disease, there was no significant difference in the level of inspired oxygen concentration of the two groups at randomization (Table 1). We do feel, therefore, that we could fairly compare inhaled versus systemic steroids, while appreciating that this comparison was made in a population with mild-moderate disease.

At 1 week, as has been noted previously [7], administration of inhaled steroids was associated with an improvement in CRS. Neither this nor the previous study [7], however, incorporated a placebo arm. Thus, it is not possible to exclude that this apparent beneficial effect of inhaled steroids was simply due to improvement with increasing postnatal age.

Oropharyngeal infection and colonization with *Candida albicans* has been recognized as a complication of inhaled corticosteroids, but the incidence of symptomatic candidiasis in both adults [3] and children [13] has been reported as low. Thus, the lack of positive findings in this study was not surprising, particularly as a spacer device was used with the metered dose inhaler. One infant, however, did develop topical candidiasis, but as this was not on the face it may have been unrelated to the treatment. In the systemically treated group, there was a higher incidence of positive blood cultures and a greater number of infants developed hyperglycaemia. In addition, there was a significant elevation of the mean blood pressure after only 12 h of treatment with systemic but not inhaled steroids. Only two infants had a systolic blood pressure greater than 100 mmHg, a level we have previously used as criteria to indicate the need for antihypertensive treatment [9]. It is possible, however, that rather than a specific level of blood pressure, it is the rate or magnitude of change in blood pressure which can cause morbidity and thus we should not be complacent about these findings.

Our results suggest that systemically administered rather than inhaled steroids have a faster onset of action. Elevation of blood pressure, hyperglycaemia and systemic infection, however, were more common in the systemic group. It is therefore important to pursue identification of an alternative efficacious method of administration of steroids to avoid such adverse effects.

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