HORMONES 2002, 1(2):113-120

Research paper

The pituary - adrenal axis in very low birth weight preterm neonates after early systemic dexamethasone or inhaled budesonide treatment

Maria-Alexandra Magiakou[1], Costas Papagaroufalis[2], Maria Coumenidou[2], Maria Xanthou[2]

Endocrine Unit[1], First Pediatric Department, Athens University Medical School and the Second Neonatal Intensive Care Unit[2], "Agia Sophia" Children's Hospital, Athens, Greece.

ABSTRACT

Objective. The pituitary- adrenal function was evaluated in very low birth weight (VLBW) neonates (BW < 1500 gr) in order to elucidate whether or not early glucocorticoid treatment causes adrenal suppression, and whether infants who develop bronchopulmonary dysplasia (BPD) have low cortisol secretion. Subjects and methods. Thirty-two VLBW preterm infants of comparable gestational age and birth weight (all part of the multicenter OSECT trial, see below) were randomized into three groups: 9 infants received inhaled budesonide during the first 12 days of life (at the most), 6 infants received systemic dexamethasone during the same period, and 17 infants were not treated with glucocorticoids and served as controls. An ACTH stimulation test was performed in all infants on the 15th day of life and plasma cortisol values were determined at 0 and 60 min after intravenous infusion of cosyntropin. Results. No statistically significant differences were found in basal (0 min), stimulated (60 min) and delta (60-0 min) plasma cortisol values between the three groups studied, although the budesonide-treated group had lower basal cortisol values. Eleven infants of the control (untreated) group developed BPD, while 6 did not. Basal and stimulated plasma cortisol values were lower in infants who subsequently developed BPD, but the difference was not statistically significant. Conclusions. Our results indicate that in the dose, type and timing of glucocorticoid treatment used in our study, the adrenal reserve was not adversely affected when examined at the age of 2 weeks. Since the ACTH stimulation test provides only indirect information about the pituitary gland, these results may not fully ensure a normal HPA axis function at the hypothalamic -pituitary level. Furthermore, although the differences were not statistically significant, infants who developed BPD had lower basal and stimulated cortisol values compared to those who did not develop BPD.

Key words: hypothalamic-pituitary-adrenal axis, glucocorticoid treatment, broncho-pulmonary dysplasia, chronic lung disease, VLBW preterm neonates.

Address correspondence and requests for reprints to:
Maria Alexandra Magiakou, M.D., Clinical Associate, Second Department of Pediatrics, "P. & A. Kyriakou" Children's Hospital, 11527 Goudi, Athens, Greece

Received 16-11-01, Revised 03-01-02, Accepted 10-02-02

Abbreviations: HPA axis: hypothalamic-pituitary-adrenal axis, VLBW: very low birth weight, BPD: bronchopulmonary dysplasia, GA: gestational age, BW: birth weight.

INTRODUCTION

Both systemic dexamethasone and inhaled glucocorticoid treatment have beneficial effects on pulmonary function of ventilator-dependent preterm infants [1-6]. Early administration (within the first 3 days of life) of systemic or inhaled glucocorticoids reduces the severity of respiratory distress syndrome in very low birth weight (VLBW) preterm infants and facilitates the weaning from mechanical ventilation of infants with bronchopulmonary dysplasia (BPD)[2,3,6].

Controversies exist regarding the effect of glucocorticoid therapy on the function of the immature hypothalamic-pituitary adrenal (HPA) axis of VLBW preterm neonates. Systemic dexamethasone is mostly reported to cause suppression of the HPA axis[1,7-14], whereas the influence of inhaled glucocorticoids on the HPA axis remains unclear[5,15,16]. The reported differences in the degree and duration of glucocorticoid suppression could be attributed to sample variability and differences in the kind, the dose and length of glucocorticoid regimens, the timing of glucocorticoid initiation (late or early), as well as to the methodology and timing of adrenal function assessment[1,17].

Another issue is the evidence of "adrenal suppression" during the first weeks of life in infants who subsequently develop chronic lung disease, and the speculation that BPD might result from an inability to control the inflammatory response due to decreased cortisol secretion[18-20].

In the present study we evaluated the pituitary- adrenal function in VLBW neonates in order to answer the following questions: 1) Whether early glucocorticoid treatment causes adrenal suppression, and 2) whether infants who develop BPD have decreased cortisol secretion.

SUBJECTS AND METHODS

Subjects

Thirty-two VLBW preterm infants were studied and were randomized into three groups: Group A: 9 infants [gestational age (GA) 27.3±1.5 wks, birth weight (BW) 1060±233 gr, mean ± SD] received inhaled budesonide, Group B: 6 infants (GA 28.3 ±2.0 wks, BW 1197±363 gr) received systemic dexamethasone, and Group C: 17 non- glucocorticoid treated infants (GA 28.0±1.5 wks, BW 1086±254 gr) served as controls. A Synachten stimulation test was carried out on the 15th day of life for evaluation of their pituitary-adrenal axis. Pertinent clinical data of the three groups are depicted in Tables 1-3.

All infants were admitted on the 1st-3rd day of life (enrollment day) to the Second Neonatal Intensive Care Unit of "Agia Sofia Children's Hospital", Athens, Greece, and were part of a "multicenter randomized open study of early corticosteroid treatment in preterm babies with respiratory illness (OSECT trial)". The OSECT trial was performed in order to define the effectiveness of early dexamethasone or inhaled budesonide treatment in reducing death and chronic lung disease in premature ba-

Table 1. Clinical data of Group A: neonates treated with ihnaled budesonide (n=9)

	GA (wks)	BW (gr)	Mother's* treatm/doses	Enrollment day	Dose** (μg/d)	Duration*** (days)	O_2 Discontinued (day)	BPD (±)
	30	1540	No	1	1200	10 (3-12)	17	-
	27	960	No	3	800	12 (3-14)	38	+
	28	1030	Yes/1	1	1200	10 (1-10)	15	-
	27	910	Yes/1	1	800	12 (1-12)	31	+
	27	1040	No	2	1200	12 (2-13)	33	+
	26	910	Yes/1	2	800	5 (2-6)	24	-
	29	1280	Yes/1	1	1200	12 (1-12)	42	+
	27	1120	Yes/2	1	1200	12 (1-12)	44	+
	25	750	Yes/2	2	800	12 (2-13)	36	+
mean±SD	27.3±1.5	1060±233				10.6±2.3		

* All treated mothers received 1 or 2 doses of betamethasone antenatally

** For infants of BW<1000 gr the dose of budesonide was 400 μgX2, for infants of BW>1000 gr the dose was 600μg X2

*** Duration of treatment with inhaled budesonide

GA: gestational age, wks: weeks, BW: birth weight, BPD: bronchopulmonary dysplasia

bies with respiratory failure[21].

Eligibility criteria were: 1) GA < 3O weeks with FiO2 requirements > 0.30 (babies of 30 and 31 wks were included if they needed FiO2 > 0.50), 2) Postnatal age < 72 h, 3) endotracheal intubation needed, 4) No contraindication to treatment such as severe congenital anomalies, severe intraventricular haemorrhage (grade III or IV), and proven systemic infection, and 5) Parental consent. Once these criteria had been fulfilled, the Randomization Centre determined whether the baby would be allocated to early treatment with dexamethasone or inhaled budesonide or delayed selective treatment with either drug (after the first 15 days of life). Thus, babies not treated during the first 15 days of life served as controls in the present study.

The diagnosis of BPD was based on an abnormal chest x-ray and dependence on supplemental oxygen at 28 days of life.

Therapeutic regimens

According to the protocol, budesonide was delivered by aerosol using a metered dose inhaler (200 μg/dose, Pulmicort, Astra Draco, Lund, Sweden) and an Aerochamber (MV 15, Trudell Medical, Canada) connected to the ventilator circuit. For babies of BW <1000 gr the dose was 2 puffs (400 μg) twice daily, whereas for BW >1000 gr the dose was 3 puffs (600 μg) twice daily. The duration of treatment for the budesonide-treated group is shown in Table 1. Dexamethasone sodium phosphate was administered I.V. in a dose of dexamethasone base 0.50 mg/kg/ day in two divided doses for 3 days, followed by 0.25 mg/kg/day in two divided doses for 3 days, then 0.10 mg/kg/day in two divided doses for 3 days, and finally 0.05 mg/kg/day in two divided doses for 3 days. The duration of treatment in the dexamethasone-treated group is shown in Table 2. Maximum treatment duration was 12 days for both budesonide and dexamethasone, but treatment was discontinued earlier than the 12th day if the babies were extubated.

Synachten test

The Synachten stimulation test (cosyntropin, a synthetic analog of corticotropin) was conducted in all children on the 15th day of life at 12.00 noon by using 3.5 μg/kg cosyntropin, based on work by Watterberg and Scott [19]. Plasma samples for cortisol determination were collected before and 60 minutes after intravenous infusion of cosyntropin (on the three first babies studied, we collected plasma at 0, 30, and 60 min, and proved that the peak response was achieved at 60 min. Thus, for reasons of blood withdrawal limitations, we skipped the 30 min plasma sample). Since there is published evidence that the evolving circadian rhythm of adrenocortical function is not well established in infants until 2 to 3 months of age, it was our own decision to standardize and perform the test at 12.00 noon in all infants[22,23] because this timing was technically most appropriate. Since Group A neonates received inhaled budesonide up to the 12th day of life (Table 1) and Group B neonates received systemic dexamethasone up to about the 7th day of life (Table 2), the performance of Synachten test on the 15th day of life corresponded to about 3 days and 1 week after discontinuation of inhaled budesonide and dexamethasone, respectively.

Plasma cortisol assay

Plasma cortisol values were assayed in duplicate with a commercially available radioimmunoassay kit (Gamma Coat TM [^{125}I] Cortisol Radioimmunoassay Kit, Inc-

Table 2. Clinical data of Group B: neonates treated with dexamethasone IV (n=6)

	GA (wks)	BW (gr)	Mother's* treatm/doses	Enrollment day	Dose** (mg/d)/days	Duration*** (days)	O_2 Discontinued (day)	BPD (±)
	27	950	No	2	0.48/3, 0.24/1	4 (2-5)	32	+
	26	850	Yes/1	2	0.48/3, 0.24/3	6 (2-7)	69	+
	27	1020	Yes/1	2	0.48/3, 0.24/3, 0.08/1	7 (2-8)	38	+
	30	1500	Yes/1	2	0.72/3, 0.32/3	6 (2-7)	18	-
	31	1780	No	1	0.88/3, 0.40/2	5 (1-5)	4	-
	29	1080	Yes/2	1	0.48/3, 0.24/3, 0.08/3	9 (1-9)	34	+
mean±SD	28.3±2.0	1197±363				6.2±1.7		

* All treated mothers received 1 or 2 doses of betamethasone antenatally

** dose of dexamethasone

*** duration of treatment with dexamethasone

GA: gestational age, wks: weeks, BW: birth weight, BPD: bronchopulmonary dysplasia

star Corporation, Stillwater, MN, USA) in the Laboratory of the Endocrine Unit of "Agia Sofia Children's Hospital". The intra-assay coefficient of variation ranged from 5.5-6.6%[24].

Statistical analysis

Results are presented as means ± SD. For the statistical analysis we used the Statistica'99, Statsoft, USA. A between groups analysis of variance (ANOVA) was used to statistically compare the overall results of the three groups in respect to cortisol at time 0 and cortisol at time 60, followed by Tukey's test for unequal sample sizes. Statistical significance was set at $p < 0.05$.

RESULTS

Cortisol values of the 3 groups of VLBW neonates

The three groups studied were comparable regarding GA and BW, and no statistically significant differences were found in basal (0 min), stimulated (60 min) and delta (60-0 min) plasma cortisol values between them (Table 4, Figure 1). None of the 9 budesonide-treated infants developed hypertension during treatment, whereas in 1/6 dexamethasone-treated and in 1/17 infants of the control group hypertension was observed.

Cortisol values of infants with and without BPD development in the non-glucocorticoid-treated group (control)

Eleven infants of the control group developed BPD and 6 did not. The two groups did not differ in GA and BW and no statistically significant differences were found in basal, stimulated and delta cortisol values between them (Table 5, Figure 2).

DISCUSSION

Although early systemic or inhaled glucocorticoid treatment has been widely used in VLBW preterm neonates to reduce the severity of respiratory distress syndrome and to facilitate the weaning from mechanical ventilation of infants with BPD, its influence on the HPA axis function of these neonates remains unclear[2,3,6,15,16,25].

Most studies report that the HPA axis of preterm neonates is markedly suppressed after a prolonged late course of dexamethasone[7,8,12,13]. Scott et al report that even a brief period of exposure (5-7 days) to dexamethasone, administered late in life, may result in severe suppression[9]. On the other hand, Wilson et al and Kazzi et al

Table 3. Clinical data of Group C (control): neonates untreated with glucocorticoids (n=17)

	GA (wks)	BW (gr)	Mother's treatment	No of doses*	Enrollment day	Discontinuation of O_2 (day)	BPD (±)
	30	1050	betamethasone	1	2	38	+
	27	900	No	0	2	44	+
	28	1090	betamethasone	1	1	15	-
	27	1090	No	0	3	37	+
	27	820	No	0	3	27	-
	26	800	betamethasone	1	2	39	+
	29	1080	No	0	1	34	+
	27	1050	No	0	2	31	+
	28	1000	No	0	1	41	+
	31	1760	No	0	1	5	-
	31	1600	betamethasone	2	1	17	-
	27	920	No	0	1	101	+
	28	1100	betamethasone	2	1	8	-
	26	840	No	0	1	45	+
	28	1260	betamethasone	1	1	43	+
	28	1040	No	0	2	38	+
	28	1060	No	0	2	9	-
mean±SD	28.0±1.5	1086±254					

* doses of antenatal betamethasone, GA: gestational age, BW: birth weight, BPD: bronchopulmonary dysplasia

reported preservation of the HPA axis of preterm infants who received one week of dexamethasone late in life[26,27]. There are only two studies, in which the HPA axis was assessed after early systemic dexamethasone treatment[3,25]; Karlsson et al reported decreased basal cortisol values on days 3 and 5 of life in infants receiving dexamethasone for the first three days of life[25], whereas Tapia et al found normal basal and stimulated serum cortisol levels after a high-dose (36 μg/ kg) ACTH-test in VLBW preterm infants treated early with systemic dexamethasone

Table 4. Cortisol values of the three groups of VLBW neonates studied on the 15th day of life.

	GROUP A Budesonide-treated (n=9) (mean ± SD)	**GROUP B** Dexamethasone-treated (n=6) (mean ± SD)	**GROUP C** Controls (n=17) (mean ± SD)
GA (weeks)	27.3 ± 1.5	28.3 ± 2.0	28.0 ± 1.5
BW (gr)	1060 ± 233	1197 ± 363	1086 ± 254
Cortisol nmol/L (μg/dl)			
Basal (0 min)	151±102 (5.47 ± 3.7)	233±105 (8.43 ± 3.8)	275±163 (9.96 ± 5.9)
Stimulated (60 min)	557±199 (20.18 ± 7.2)	561±110(20.32 ± 4.0)	712±234 (25.82 ± 8.5)
Delta (60-0 min)	406±146 (14.71 ± 5.3)	328±135 (11.88 ± 4.9)	437±182 (15.85 ± 6.6)

budesonide vs dexamethasone	0 min p=0.57	60 min p=0.99
budesonide vs controls	0 min p=0.16	60 min p=0.27
dexamethasone vs controls	0 min p=0.86	60 min p=0.43

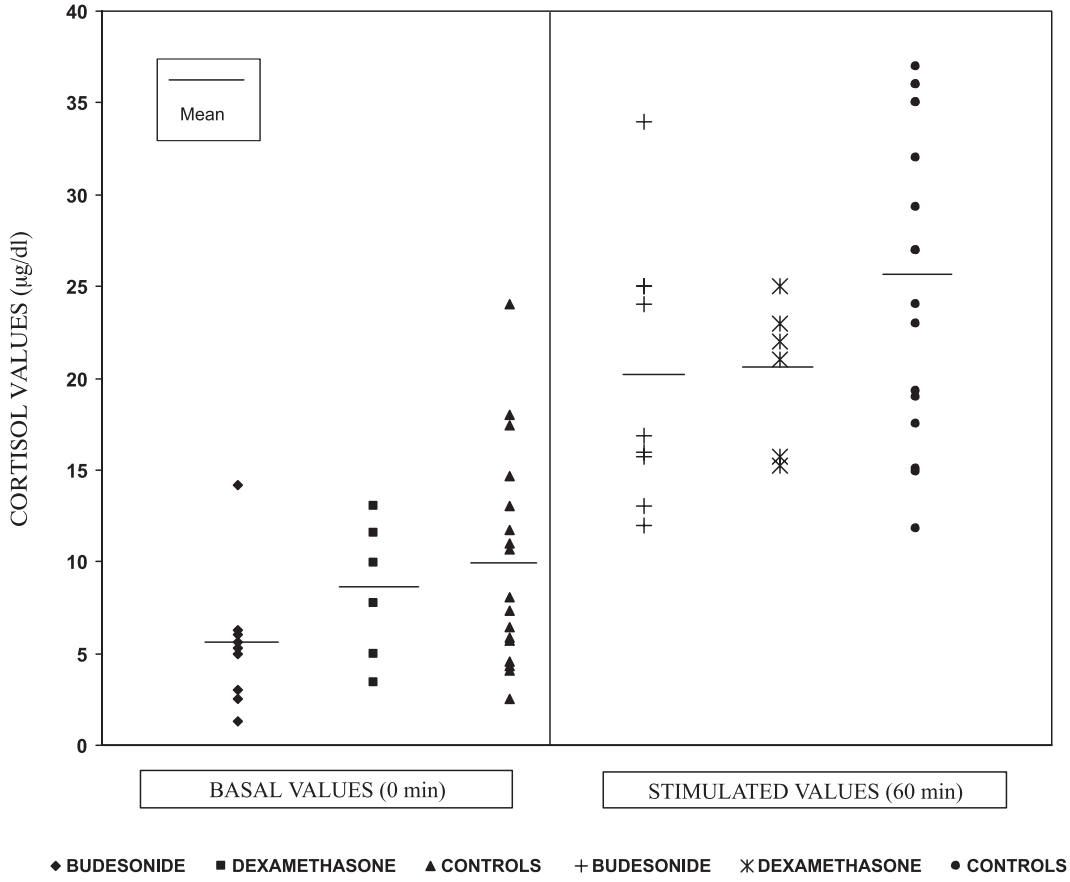


Figure 1. Basal (left panel) and stimulated (right pannel) cortisol values of the three groups of VLBW neonates studied. The horizontal lines represent the mean values. To convert metric values (μg/dl) to SI units (nmol/l) multiply by 27.59.

in a dose similar to the one used in our study [3].

Regarding inhaled glucocorticoids, Ng et al reported suppressed basal and stimulated ACTH and cortisol values after a CRH-test in VLBW infants treated early with inhaled fluticasone for a period of 2 weeks[15]. On the other hand, Cole et al reported slightly lower basal but normal stimulated cortisol levels after a low dose ACTH-test (3.5 μg/kg) in VLBW infants treated early with inhaled beclomethasone[16]. Two interpretations can be offered for this discrepancy: a) In these two studies a different level of the HPA axis was examined (CRH vs ACTH), and b) The ratio for systemic effects on the HPA

Table 5. Cortisol values of neonates with and without BPD development in the untreated group (control)

	BPD (n=11) (mean ± SD)	no BPD (n=6) (mean ± SD)	p value
GA (weeks)	27.5 ± 1.2	28.8 ± 1.7	0.09
BW (gr)	1003 ± 130	1238 ± 361	0.07
Cortisol nmol/l (μg/dl)			
Basal (0 min)	240±127 (8.7 ± 4.6)	339±212 (12.3 ± 7.7)	0.24
Stimulated (60 min)	643±229 (23.3 ± 8.3)	839±204 (30.4 ± 7.4)	0.10
Delta (60-0 min)	403±212 (14.6 ± 7.7)	499±105 (18.1 ± 3.8)	0.32

GA: gestational age, BW: birth weight, BPD: bronchopulmonary dysplasia

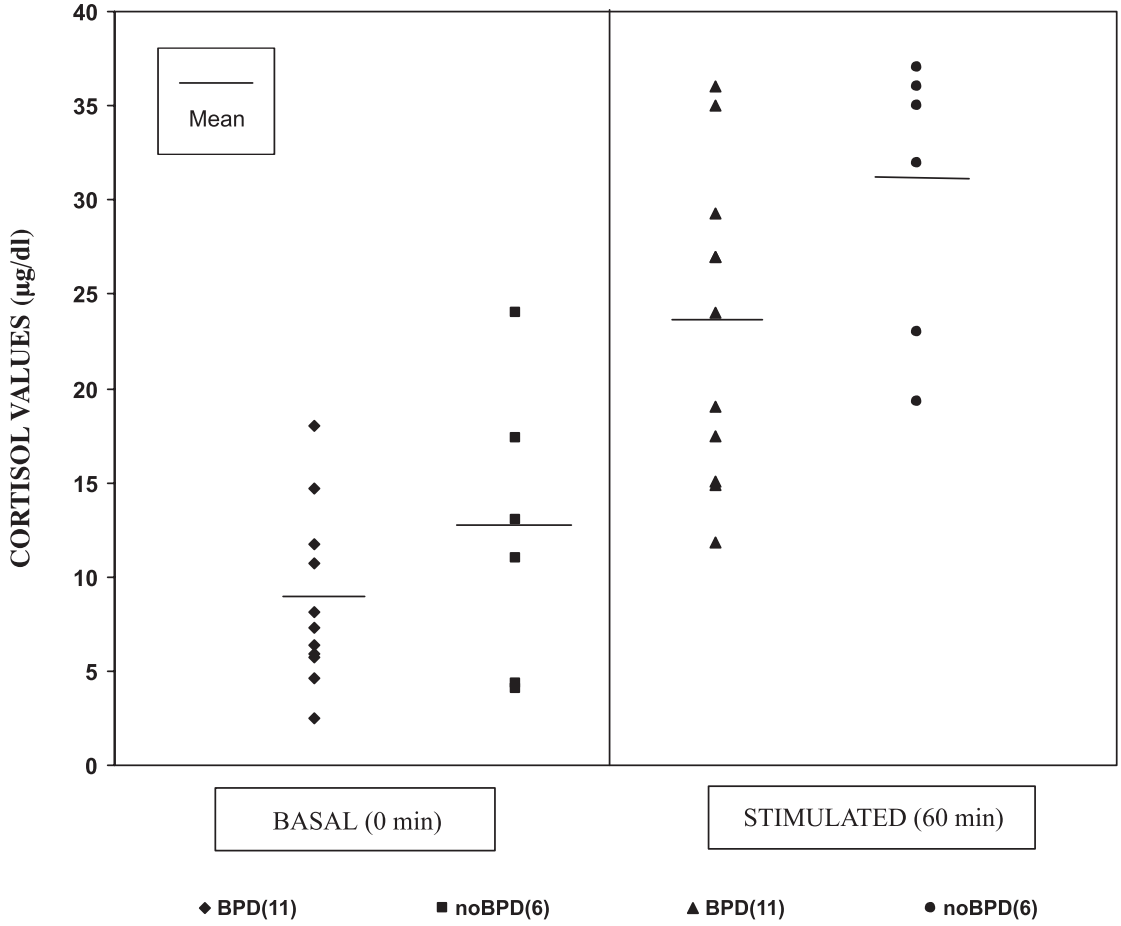


Figure 2. Basal (left panel) and stimulated (right pannel) cortisol values of infants with and without BPD in the non-glucocorticoid-treated group (control). The horizontal lines represent the mean values. To convert metric values (μg/dl) to SI units (nmol/l) multiply by 27.59.

axis of fluticasone and budesonide is approximately 3:1 on a μg per μg basis[28], whereas beclomethasone has a systemic effect comparable to budesonide on the HPA axis.

Among our study subjects, 6/9, 4/6, and 6/17 of budesonide-treated, dexamethasone-treated and untreated infants, respectively, had received 1-2 doses of antenatal betamethasone. Nevertheless, it has been shown that the HPA axis in preterm infants, whose mothers received 1-2 doses of antenatal glucocorticoids, had recovered by day 7 of life[29,30]. Hence the antenatal therapy should not have influenced our data since the study was carried out on the 15th day of life.

In our study the basal cortisol values did not differ significantly between the 3 groups studied (budesonide: 151±102 nmol/l (5.47±3.7 μg/dl), dexamethasone: 233±105 nmol/l (8.43±3.8 μg/dl) and controls: 275±163 nmol/l (9.96±5.9 μg/dl). The lower basal cortisol values of the budesonide-treated group might be due to the fact that budesonide treatment continued for several days longer than dexamethasone (mean duration of treatment with budesonide, and dexamethasone 10.6±2.3 days, and 6.2±1.7 days, respectively, see Tables 1 and 2). All 3 groups showed adequate response of the adrenals to exogenous ACTH stimulation (mean stimulated cortisol at 60 min±SD: 557±199 (20.18±7.2), 561±110 (20.32±4.0), 712±234 (25.82±8.5) in budesonide-treated, dexamethasone-treated, and controls, respectively).

A serum cortisol level > 359nmol/l (13 μg/dl) in the ACTH test of premature infants[26] represents a normal response. Variable doses of ACTH have been used for the evaluation of adrenal function in the VLBW infants ranging from 3,5 μg/kgr to 36μg/kgr[16,17,19,26]. In a most recent study an ACTH dose of 0,5 μg was used with adequate response in nonventilated infants[31]. We used the lowest ACTH dose used at the time of the study (3,5 μg/kgr). One may argue that by using even lower dose, namely 0,5 μg, a difference between the three groups would have become evident, but this is quite hypothetical and rather unlikely. The lower basal cortisol values of the budesonide-treated group with adequate response of the adrenals in conjunction with the inadequate response to CRH previously reported might indicate that the adrenal responsiveness recovers earlier than the CRH-ACTH axis.

Our results indicate that early and of relatively short duration systemic dexamethasone and inhaled budesonide treatment do not significantly suppress the HPA axis of these neonates. Obviously the ACTH stimulation test provides only indirect information about the functional capacity of the pituitary gland. Hence these results may not fully ensure normal HPA axis function at the hypothalamic-pituitary level.

Watterberg et al. reported that at the end of the first week of life, infants who subsequently developed BPD and prolonged oxygen dependence had significantly lower cortisol secretion in response to ACTH than infants who recovered without BPD[19]. The same group of investigators recently reported significantly lower cortisol secretion in response to ACTH in infants who developed BPD and were tested between 2 and 3 weeks of age[20]. A recent study, however, did not confirm these findings[32]. We did not find statistically significant differences in either basal or stimulated cortisol between infants who developed BPD and those who did not in the group of the 17 neonates untreated with glucocorticoids. We must say, however, that infants who developed BPD had lower basal and stimulated cortisol values compared to those who did not develop BPD, and we cannot exclude the possibility that, if the sample size were larger, the differences might acquire statistical significance.

In conclusion, in the dose, type and timing of glucocorticoid treatment used in our study, the adrenal reserve was not adversely affected when examined at the age of 2 weeks. Regarding the probable correlation of low cortisol levels with development of BPD, we consider that our findings are not enough to exclude or support the existing hypothesis that BPD might be a result of incapacity of the adrenals to secrete adequate amounts of cortisol in a setting of increased stress.

REFERENCES

1. Ng PC. The effectiveness and side effects of dexamethasone in preterm infants with bronchopulmonary dysplasia. Arch Dis Child 1993; 68: 330-336.
2. Rastogi A, Akintorin SM, Bez ML, Morales P, Pildes RS. A controlled trial of dexamethasone to prevent bronchopulmonary dysplasia in surfactant-treated infants. Pediatrics 1998; 98: 204-210.
3. Tapia JL, Ramirez R, Cifuentes J, et al. The effect of early dexamethasone administration on bronchopulmonary dysplasia in preterm infants with respiratory distress syndrome. J Pediatr 1998; 132: 48-52.
4. Arnon S, Grigg J, Silverman M. Effectiveness of budesonide aerosol in ventilator-dependent preterm babies: a preliminary report. Ped Pulmonol 1996; 21: 231-235.
5. Liu EA, Heldt GP. A trial of the safety of inhaled beclomethasone in ventilator - treated neonates. J Pediatr 1996; 129: 154-156.
6. Cole CH, Colton T, Shah BL, et al. Early inhaled gluco-

corticoid therapy to prevent bronchopulmonary dysplasia. N Engl J Med 1999; 340: 1005-1010.
7. Ng PC, Wong GWK, Lam CWK, et al. Pituitary-adrenal suppression and recovery in preterm very low birth weight infants after dexamethasone treatment for bronchopulmonary dysplasia. J Clin Endocrinol Metab 1997; 82: 2429-2432.
8. Ford LR, Willi SM, Hollis BW, Wright NM. Suppression and revovery of the neonatal hypothalamic-pituitary-adrenal axis after prolonged dexamethasone therapy. J Pediatr 1997; 131: 722-726.
9. Scott SM, Backstrom C, Bessman S. Effect of 5 days dexamethasone therapy on ventilator dependence and adrenocorticotropic hormone-stimulated cortisol concentrations. J Perinatol 1997; 17: 24-28.
10. Bloomfield D, Knight DB, Harding JE. Side effects of 2 different dexamethasone courses for preterm infants at risk of chronic lung disease : a randomized trial. J Pediatr 1998; 133: 395-400.
11. Kari MA, Raivio KO, Stenman UH, Voutilainen R. Serum cortisol, dehydroepiandrosterone sulfate, and steroid-binding globulins in preterm neonates: Effect of gestational age and dexamethasone therapy. Pediatr Res 1996; 40: 319-324.
12. Rizvi ZB, Aniol HS, Myers TF, Zeller WP, Fisher SG, Anderson CL. Effects of dexamethasone on the hypothalamic-pituitary-adrenal axis in preterm infants. J Pediatr 1992; 120: 961-965.
13. Alkalay Al, Pomerance JJ, Puri AR, et al. Hypothalamic-pituitary-adrenal axis function in very low birth weight infants with dexamethasone. Pediatrics 1990; 86: 204-210.
14. Ng PC, Blackburn ME, Brownlee KG, Buckler JMH, Dear PRF. Adrenal response in very low birth weight babies after dexamethasone treatment for bronchopulmonary dysplasia. Arch Dis Child 1989; 64: 1721-1726.
15. Ng PC, Fok TF, Wong GWK, et al. Pituitary-adrenal suppression in preterm, very low birth weight infants after inhaled fluticasone propionate treatment. J Clin Endocrinol Metab 1998; 83: 2390-2393.
16. Cole CH, Shah B, Abbasi S, et al. Adrenal function in premature infants during inhaled beclomethasone therapy. J Pediatr 1999; 135: 65-70.
17. Alkalay AL, Klein AH, Nagel RA, Pomerance JJ. Evaluation of hypothalamic-pituitary-adrenal axis in premature infants treated with dexamethasone. Am J Perinatol 1996; 13: 473-477.
18. Korte C, Styne D, Merritt TA, Mayes D, Wertz A, Helbock HJ. Adrenocortical function in the very low birth weight infant: improved testing sensitivity and association with neonatal outcome. J Pediatr 1996; 128: 257-263.
19. Watterberg KL, Scott SM. Evidence of early adrenal insufficiency in babies who develop bronchopulmonary dysplasia. Pediatrics 1995; 95: 120-125.
20. Watterberg KL, Gerdes JS, Gifford KL, Lin H. Prophylaxis against early adrenal insufficiency to prevent chronic lung disease in premature infants. Pediatrics 1999; 104: 1258-1263.
21. Halliday HL, Patterson CC, Halahakoon CW. A multicenter, randomized open study of early corticosteroid treatment (OSECT) in preterm infants with respiratory illness: comparison of early and late treatment and of dexamethasone and inhaled budesonide. Pediatrics 2001; 107: 232-240.
22. Vermes I, Dohanics J, Toth G, Pongracz J. Maturation of the circadian rhythm of the adrenocortical functions in human neonates and infants. Horm Res 1980; 12: 237-244.
23. Metzger DL, Wright NM, Veldhuis JD, Rogol AD, Kerrigan JR. Characterization of pulsatile secretion and clearance of plasma cortisol in premature and term neonates using deconvolution analysis. J Clin Endocrinol Metab 1993; 77: 458-463.
24. Chard T. An introduction to Radioimmunoassay and Related Techniques, in Burdon RH, Van Klippenberg PH (eds): Laboratory Techniques in Biochemistry and Molecular Biology, 4th revised edition, New York: Elsevier, 1990; Volume 6, Part II: p. 139-142.
25. Karlsson R, Kallio J, Toppari J, Scheinin M, Kero P. Antenatal and early postnatal dexamethasone treatment decreases cortisol secretion in preterm infants. Horm Res 2000; 53: 170-176.
26. Wilson DM, Baldwin RB, Ariagno RL. A randomized, placebo-controlled trial of the effects of dexamethasone on the hypothalamic-pituitary-adrenal axis in preterm infants. J Pediatr 1988; 113: 764-768.
27. Kazzi NJ, Brans YW, Poland LR. Dexamethasone effects on the hospital course of infants with bronchopulmonary dysplasia who are dependent on artificial ventilation. Pediatrics 1990; 86: 722-727.
28. Pedersen S, O' Byrne P. A comparison of the efficacy and safety of inhaled corticosteroids in asthma. Allergy 1997; 52 (Suppl 39): 1-34.
29. Terrone DA, Smith LG Jr, Wolf EJ, Uzbay LA, Sun S, Miller RC. Neonatal effects and serum cortisol levels after multiple courses of maternal corticosteroids. Obstet Gynecol 1997; 90: 819-823.
30. Ng PC, Wong GWK, Lam CWK, et al. Pituitary-adrenal response in preterm very low birth weight infants after treatment with antenatal corticosteroids. J Clin Endocrinol Metab 1997; 82: 3548-3552.
31. Huysman MWA, Hokken-Koelega ACS, de Ridder MAJ, Sauer PJJ. Adrenal function in sick very preterm infants. Ped Research 2000; 48:629-633.
32. Merz U, Pfaffle R, Peschgens T, Hornchen H. The hypothalamic-pituitary-adrenal axis in preterm infants weighing σ 1250 g: association with perinatal data and chronic lung disease. Acta Paediatr 1998; 87: 313-317.