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Pharmacokinetics of dexamethasone in premature neonates

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Abstract. *Objective*: Dexamethasone is frequently used in premature neonates with bronchopulmonary dysplasia, however little is known about its disposition in this population.
Methods: We evaluated the pharmacokinetics of dexamethasone in 9 premature neonates with a mean gestational age of 27.3 weeks and a postnatal age of 21.8 days.
Results: There was a strong relationship between clearance (4.96 $ml \cdot min^{-1} \cdot kg^{-1}$) and gestational age ($r = 0.884$). Pharmacokinetic parameters were grouped based on a gestational age of less than 27 weeks (Group I) and greater than 27 weeks (Group II). Mean clearance in group I and group II was 1.69 and 7.57 $ml \cdot min^{-1} \cdot kg^{-1}$, respectively. Mean distribution volume in group I and II was 1.26 and 2.19 $l \cdot kg^{-1}$, respectively. No significant relationships were noted between the disposition of dexamethasone and ventilator requirements or adverse effects.
Conclusion: The pharmacokinetics of dexamethasone in premature neonates was related to gestational age.

Key words Dexamethasone, Premature neonates; pharmacokinetics, bronchopulmonary dysplasia, infant: newborn

Introduction

Intravenous dexamethasone is commonly used in premature neonates to treat bronchopulmonary dysplasia (BPD). Controlled studies have documented that dexamethasone improves pulmonary function and reduces the need for mechanical ventilation [1–8]. Most investigators have reported a rapid therapeutic response after initial doses of 0.5 to 1 $mg \cdot kg^{-1} \cdot day^{-1}$ followed by a variable taper of 7 to 42 days. However, this high-dose regimen is empirical and there are no published studies evaluating the dosage requirement of dexamethasone in the neonatal population.

Dexamethasone may be associated with significant adverse effects. Dose-related side effects include elevations in systolic blood pressure [9], hypothalamic-pituitary-adrenal axis suppression [10–15], and increases in protein catabolism resulting in marked increases in blood urea nitrogen [16–18], elevated plasma amino acid concentrations [18], and poor weight gain during treatment [4–6,10,17,18]. Dose-related adverse effects may occur due to high plasma concentrations and excessive systemic drug exposure. Maturation of neonatal hepatic metabolism and renal function during development results in significant interpatient variability in drug disposition and may contribute to both therapeutic variability and adverse effects. The high potency and significant side effect profile of dexamethasone in neonates establishes the importance of defining its disposition.

This study evaluated the pharmacokinetics of dexamethasone in neonates. Several pharmacodynamic variables, including ventilator weaning, weight gain, and blood pressure were evaluated to identify potential relationships with dexamethasone pharmacokinetics.

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Methods and design

This open-label pharmacokinetic-pharmacodynamic study was approved by the Human Subjects Research Committee at Children's Hospital and The Ohio State University Hospital, Columbus, Ohio. Neonates were eligible for enrollment in the study after the attending physician's decision to treat with intravenous dexamethasone. Patients with the following conditions were excluded from

enrollment: a) congenital heart disease or multiple congenital anomalies; b) patent ductus arteriosus; and c) sepsis. Informed consent was obtained from parent(s) or authorized representative(s) of each patient before enrollment.

Blood samples were drawn immediately prior to dexamethasone administration (0 h), and at 0.5, 1, 3, 6, and 12 h after administration. The samples were collected from an umbilical artery catheter or a central venous line when possible. In patients with no central venous or arterial access, one blood sample was collected by capillary heelstick to determine the trough concentration of dexamethasone.

Laboratory analysis

Blood was collected in pre-chilled EDTA Vacutainer® tubes (Becton Dickinson, Rutherford, N.J.) and centrifuged at 2000 × g at 4 °C for 15 min. Plasma was stored at −70 °C until analysed. Plasma dexamethasone concentrations were measured using a previously published radioimmunoassay method with minor modifications [19]. This radioimmunoassay is specific for dexamethasone with the following cross-reactivities: cortisol 0.04%, 11-deoxycortisol 0.07%, prednisolone 0.14%, triamcinolone acetonide 0.01%, betamethasone 10%, and aldosterone and corticosterone < 0.01% (product information, IgG Corp., Nashville, TN). Standards ranging in concentration from 0.1 to 20 $ng \cdot ml^{-1}$ were prepared in plasma. One hundred microliters of each standard was added to 100 µl of ^{3}H-dexamethasone (NET-467, NEN Research Products, Boston, MA) diluted to 20,000 $cpm \cdot ml^{-1}$, and 100 µl of reconstituted rabbit anti-dexamethasone serum (IgG-Dexamethasone-1, IgG Corp., Nashville, TN). The mixture was incubated at 4 °C for 24 h, followed by the addition of 200 µl of 1% activated charcoal suspension (C-5385 Sigma Chemical Co., St. Louis, MO). After 7 min of centrifugation at 2000 × g, aliquots of the supernatant were mixed with 10 ml of scintillation fluid (CytoScint ES®, #882453 scintillation solution, ICN Biomedicals, Inc., Irvine, CA) and radioactivity was measured with a Beckman LS 7000 Liquid Scintillation System (Beckman Instruments, Inc., Fullerton, CA). Percentage of bound ^{3}H-dexamethasone was plotted against log concentration and was analysed by least squares linear regression. All relationships were linear at concentrations ranging from 1.0 to 15 $ng \cdot ml^{-1}$, with correlation coefficients between 0.996 and 0.999. Accuracy, measured on 7 different days, was within 10.4% of theoretical for concentrations of 1, 10, and 15 $ng \cdot ml^{-1}$. Precision was calculated using 14 replicate samples analyzed on different days, yielding an interday coefficient of variation of less than 7.5%.

Pharmacokinetic analysis

The elimination rate constant was estimated from the slope of the terminal phase of the dexamethasone log plasma concentration versus-time curve. The area under the plasma concentration-time curve from time 0 to 12 h (AUC_{12}) was calculated using the linear trapezoidal rule. Following the first dose, the area under the plasma concentration versus-time curve from 0 to infinity ($AUC_{0-\infty}$) was calculated as the sum of AUC_{12} and the quotient of the plasma concentration at 12 h and elimination rate constant (C_{12}/k). Prior to steady state, $AUC_{0-\infty}$ was calculated as $(AUC_{12} + C_{12}/k) - C_{initial}/k$. At steady-state, $AUC_{0-\infty}$ equals AUC_{12}. Total clearance (CL), apparent volume of distribution (V) and elimination half-life ($t_{1/2}$) were calculated using the following equations: $CL = dose/AUC_{0-\infty}$, $V = CL/k$, and $t_{1/2} = 0.693 \cdot k^{-1}$.

Pharmacodynamic data

Pharmacodynamic data were collected before and during dexamethasone therapy. These data included the following: 1) Mechanical Ventilation: Ventilator settings (rate, peak inspiratory pressure, peak end expiratory pressure, and FiO_2) and blood gas data were obtained from respiratory care records. Weaning from the ventilator followed the standard of practice in the intensive care unit. The generally accepted target for pO_2 was 50 to 80 mmHg; pCO_2 40 to 60 mmHg; and a pH above 7.3. Weaning proceeded as rapidly as possible within these general guidelines, but was managed by the attending neonatologist independent of the study. Ventilator Index was calculated as the product of peak inspiratory pressure (PIP) (mmHg) and rate of ventilation. 2) Blood Pressure: A minimum of six determinations of blood pressures were recorded daily as obtained from nursing records. Baseline blood pressures were calculated by averaging blood pressures for the 5 days prior to initiating dexamethasone. 3) Laboratory Data: When ordered as part of the routine care, blood urea nitrogen and serum creatinine were recorded. 4) Weight, Nutrition and Fluid Balance: Fluid and nutrition requirements were determined by the standard of practice. The fluid intake, daily weights, daily caloric intake, and urine output were recorded. 5) Medications: Patients continued to receive bronchodilators and diuretics as ordered by the attending neonatologist independent of this study. All concurrent medications were noted.

Statistical analysis

Statistics were performed using SYSTAT (Systat, Inc., Evanston, IL). Relationships between variables were analyzed by Pearson's test for correlation. Step-wise multiple regression was used to determine significant linear relationships among variables. Differences in the means of normally distributed variables were compared by a two-sided Student *t*-test. Analysis of variance with repeated measures and Dunnett's post-hoc test were done to analyze differences in blood pressure and ventilator index over time. Statistical significance was achieved at $P < 0.05$.

Results

Fifteen patients were enrolled in the study. The demographic and pharmacokinetic data are summarized in Table 1. The diagnoses in all but one patient included prematurity, respiratory distress syndrome and bronchopulmonary dysplasia. Patient 11 received dexamethasone to facilitate extubation following surgical omphalocele closure. Dexamethasone plasma concentrations were measured within the first 4 days of initiating treatment in all patients. Nine patients had a sufficient number of plasma concentrations to estimate all pharmacokinetic parameters. Patients 10 and 11 had only 3 blood samples collected, therefore only half-life was calculated in these patients. Patients 12 and 13 were switched to oral dexamethasone due to the loss of venous and arterial access after enrollment; thus, only trough concentrations measured. Patient 14 died of a fatal haemorrhage unrelated to the study. This patient's reported C_{min} preceded the C_{max} at non-steady state, thereby precluding calculation of kinetic parameters. The study was discontinued in patient 15 after the first blood sample at 12 h.

The mean (SD) gestational age (determined by the Ballard method) and birthweight of the nine evaluable patients were 27.3 (1.7) weeks and 885 (272) g (range 480–1330 g), respectively. At the time of enrollment,

Table 1 Demographic and pharmacokinetic data. All patients received dexamethasone q12 h except patient 11 (q6 h) GA = gestation age, PA = postnatal age, BW = birthweight, C_{max}/C_{min} = maximum/minimum observed plasma concentrations. Blank spaces appear when a parameter was not determined

Pt	GA (wks)	PA (days)	BW (grams)	Dose (mg/kg) (Dose number)	C_{max} ($ng \cdot ml^{-1}$)	C_{min} ($ng \cdot ml^{-1}$)	CL ($ml \cdot min^{-1} \cdot kg^{-1}$)	V ($l \cdot kg^{-1}$)	$t_{1/2}$ (hrs)
1	25	37	760	0.503 (1)	469.5	213.1	1.03	1.41	15.8
2	29	37	930	0.258 (5)	139.5	5.5	8.44	1.98	2.7
3	28	12	970	0.258 (5)	154.6	15.9	6.66	2.08	3.6
4	30	26	1018	0.249 (5)	111.6	3.4	12.2	2.32	2.2
5	28	10	1155	0.220 (2)	168.8	103.4	1.98	2.36	13.8
6	26	27	570	0.208 (1)	174.3	68.8	1.45	1.24	9.8
7	26	11	756	0.240 (3)	216.3	37.8	2.84	1.00	4.1
8	28	17	1330	0.275 (1)	130.7	8.5	8.60	2.22	3.0
9	26	19	480	0.213 (2)	270.9	132.2	1.44	1.39	11.1
10	30	14	1606	0.278 (2)	198	37.1			4.8
11	35	26	4770	0.500 (5)	461.7	182.5			4.0
12	28	71	1140	0.251 po (2)		8.1			
13	27	28	680	0.503 po (3)		7.4			
14	28	4	980	0.276[a] (3)	406.9	222.9			
15	26	85	680	0.229 (4)		27.1			

[a]Patient received 3 doses 10 hours apart

the mean postnatal age was 21.8 (10.5) days. Figure 1 illustrates the plasma dexamethasone concentration versus time curves. Significant variability was observed in the pharmacokinetic parameters (Table 2). There was a strong correlation between clearance (4.96 (4.09) $ml \cdot min^{-1} \cdot kg^{-1}$) and both gestational age ($r = 0.884$ $P = 0.002$) (Fig. 2) and postconceptional age ($r = 0.741$ $P = 0.022$). A step-wise multiple regression analysis

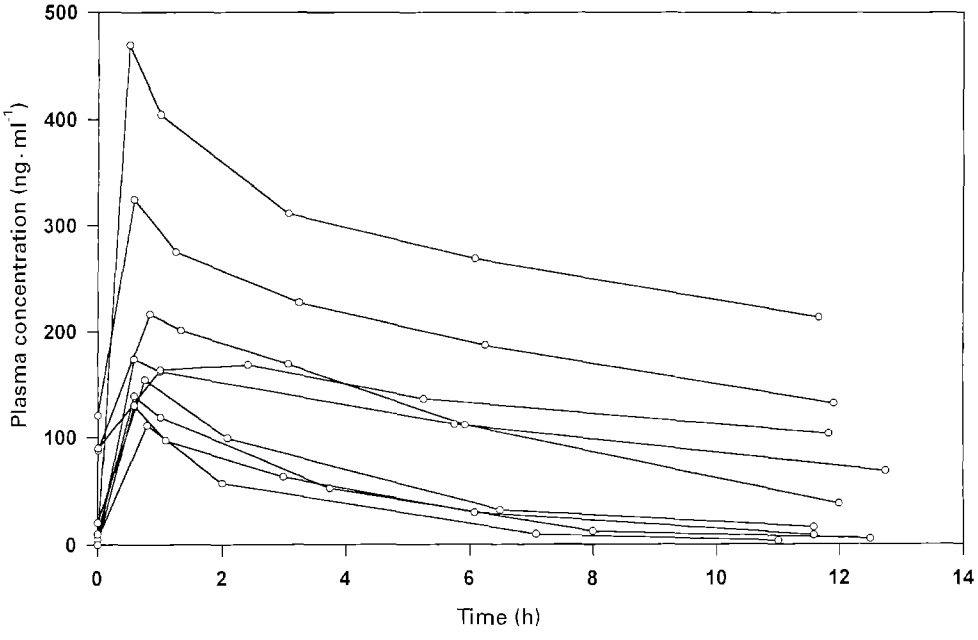

Fig. 1 Dexamethasone plasma concentration versus time

Table 2 Pharmacokinetic parameters of dexamethasone in premature neonates

Parameter	Mean (SD)	Range
CL ($ml \cdot min^{-1} \cdot kg^{-1}$)	4.96 (4.09)	1.03–12.2
V ($l \cdot kg^{-1}$)	1.78 (0.52)	1.00–2.36
$t_{1/2}$ (h)[a]	6.8 (4.9)	2.2–15.8

[a]Includes data from patients 10 and 11

using gestational age, postnatal age and postconceptional age demonstrated that gestational age significantly affected clearance, with the model explaining 77.8% of the variance in data ($P = 0.002$). After accounting for the effect of gestational age, neither postconceptional age nor postnatal age significantly improved the fit to the multiple regression model. Since the distribution of gestational ages appeared to be bimodal, the data were analysed to determine the likelihood of two discrete subpopulations. Group I included patients less than 27 weeks gestation ($n = 4$), and group II included those greater than 27 weeks gestation ($n = 5$). The more premature infants in group I (GA 25.8 (0.5) weeks) had a significantly lower mean clearance than those in group II (GA 28.5 (0.8) weeks), 1.69 (0.79) vs 7.57 (3.71) $ml \cdot min^{-1} \cdot kg^{-1}$, respectively ($P = 0.018$).

Mean apparent volume of distribution was 1.78 (0.52) $l \cdot kg^{-1}$ and was highly correlated with gestational age (r = 0.847 $P = 0.004$), birthweight (r = 0.830 $P = 0.006$) and the weight at the time of enrollment (r = 0.871 $P = 0.002$). In testing these variables, step-wise regression showed that weight at the time of enrollment was the most significant variable in predicting apparent volume of distribution, explaining 75.8% of the variance in data. When neonates were stratified based on gestational age, group I had a significantly lower volume of distribution, 1.26 (0.19) $l \cdot kg^{-1}$, as compared with group II, 2.19 (0.16) $l \cdot kg^{-1}$ ($P < 0.001$).

The effect of concomitant drugs on dexamethasone pharmacokinetics was analysed. Four patients received daily phenobarbital prior to and during treatment with dexamethasone. Due to the potential for induction of hepatic enzymes by phenobarbital, a stratified analysis of dexamethasone clearance was performed based on the administration of phenobarbital. There was no significant difference in clearance between patients receiving phenobarbital (mean gestational age 27.0 ± 1.2 weeks) and those not receiving phenobarbital (mean gestational age 27.6 (2.2) weeks), 4.9 (3.3) vs 5.0 (5.0) $ml \cdot min^{-1} \cdot kg^{-1}$, respectively ($P = 0.966$).

Pharmacodynamics

All patients were given dexamethasone to facilitate weaning from mechanical ventilation. Only the first 9 patients with complete data sets were included in the pharmacodynamic analysis. During the 7 days after initiating treatment, one patient was extubated while 8 patients remained on mechanical ventilation. Figure 3 illustrates the effect of dexamethasone on ventilator index. Compared to the ventilator index on day 0, the mean index was significantly lower on days 2 through 7 after initiating dexamethasone ($P < 0.05$). No associations between dexamethasone plasma concentrations, clearance, AUC, cumulative dose, and improvements in ventilator index were noted.

Daily mean systolic and diastolic blood pressures increased after initiating dexamethasone. Diastolic blood pressure was significantly elevated by day 3 as compared with the baseline diastolic blood pressure, 41.3 (8.4) vs 30.5 (5.2) mmHg ($P = 0.04$), respectively.

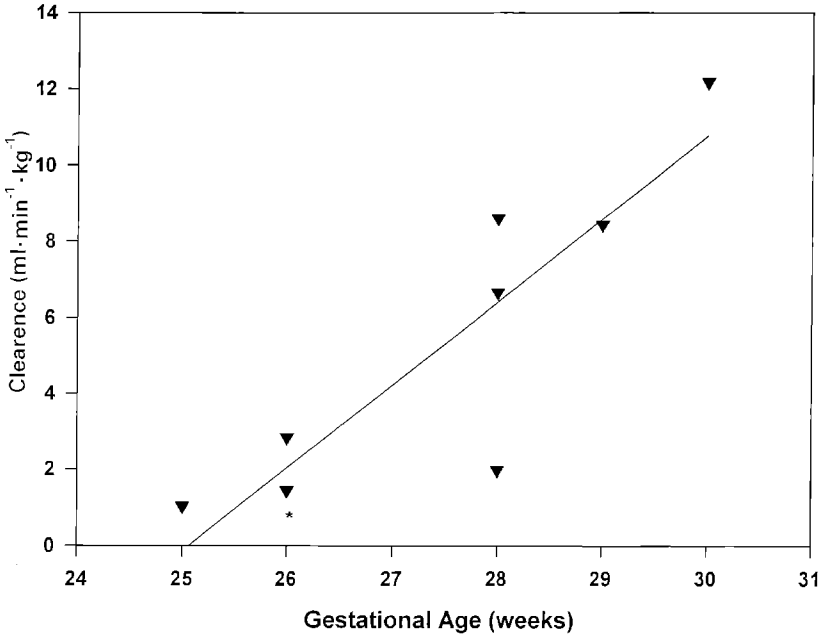

Fig. 2 Gestational age (GA) versus clearance (CL).
CL = −54.67 + 2.18(GA)
(r = 0.884, $P = 0.002$)
* represents 2 data points

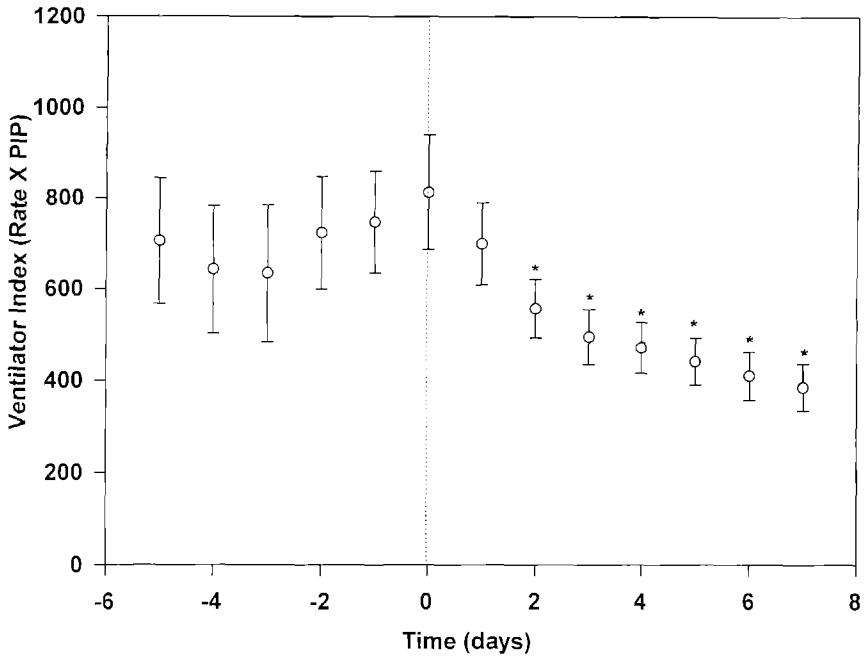

Fig. 3 Mean (± SEM) ventilator index versus time. * $P < 0.05$

However, no relationships were noted between blood pressure and either clearance, cumulative dose, or AUC.

There was a significant decline in the rate of weight gain during the treatment with dexamethasone. During the 7 days prior to treatment, the rate of weight increase was 14.0 $g \cdot day^{-1}$ (95% CI, 8.3 to 19.8 g/day) as compared with a weight loss of 4.1 $g \cdot day^{-1}$ (95% CI, −10.1 to 2.0 $g \cdot day^{-1}$) during the 10 days after initiating treatment. This weight loss could not be explained by a reduction in caloric intake nor a change in fluid status (data not shown). The clearance and AUC of dexamethasone were not related to changes in weight after initiating dexamethasone. Blood urea nitrogen (BUN) increased in 8 of the 9 evaluable patients. This is consistent with the probability of increased protein catabolism and the lack of weight gain. The mean BUN for the seven days before therapy was 2.9 (1.6) $mmol \cdot l^{-1}$ (8.1 (4.5) $mg \cdot dl^{-1}$), which increased to a peak of 8.8 (3.7) $mmol \cdot l^{-1}$ (24.5 (10.4) $mg \cdot dl^{-1}$) in an average 3.6 days ($P = 0.001$). BUN remained elevated during dexamethasone treatment for a mean 10.3 days before returning to baseline. The increased BUN was not explained by decreased renal function or increased protein intake, nor did it correlate with weight loss or dexamethasone pharmacokinetics.

Discussion

Intravenous dexamethasone is commonly used in premature neonates with chronic lung disease to hasten weaning from mechanical ventilation. Little is known about dexamethasone pharmacokinetics nor its optimal dosage regimen in premature neonates. As with many drugs used in neonates [20], we observed wide interindividual variability in dexamethasone pharmacokinetics. Dexamethasone clearance was best predicted by gestational age. Neonates less than 27 weeks gestation had almost a five-fold lower clearance than those greater than 27 weeks gestation.

The mean clearance of dexamethasone noted in this study is similar to data reported in adults. Tsuei et al. reported a clearance of 3.31–4.17 $ml \cdot min^{-1} \cdot kg^{-1}$ in 12 healthy adults [21] and Eadie et al. observed a mean clearance of 7.35 $ml \cdot min^{-1} \cdot kg^{-1}$ in ten adults with neurological disorders [22]. In a recent study by Charles et al., the mean dexamethasone clearance in 7 extremely low birth weight infants was 2.4 $ml \cdot min^{-1} \cdot kg^{-1}$, approximately half the clearance observed in our patients [23]. However, the mean gestational age of the 7 patients in their study (25.6 (0.5) weeks) was lower than the gestational age of patients in our study (27.3 (1.7) weeks). Notably, when we analyzed only those with gestational ages less than or equal to 27 weeks (mean gestational age 25.8 (0.5) weeks), the mean clearance observed in this study was comparable to the mean clearance reported by Charles et al, 1.7 $ml \cdot min^{-1} \cdot kg^{-1}$ and 2.4 $ml \cdot min^{-1} \cdot kg^{-1}$, respectively. While it is not known to what degree dexamethasone is metabolized or renally eliminated in premature neonates, it is reasonable to conclude that the elimination pathway(s) for dexamethasone may be poorly developed in many very low birth weight infants and maturation may occur with increased gestational age.

The mean apparent volume of distribution in our neonatal population was similar to that reported by Charles et al (1.91 (0.48) $l \cdot kg^{-1}$) [23], however it was significantly higher than the distribution volume reported in healthy adults (0.765 (0.249) $l \cdot kg^{-1}$) [21]. When analysing the data based on gestational age,

neonates less than 27 weeks gestation had a lower V than those born greater than 27 weeks gestation. Furthermore, weight-normalized V was related to birthweight and the actual weight at the time of enrollment. Weight at enrollment explained the most variability in data, although weight is indirectly related to gestational age. A possible explanation for this phenomenon may include increased tissue binding as a result of developmental changes in the tissue compartment as a percent of total body weight.

Elimination half-life depends on both clearance and distribution volume. The half-life of dexamethasone in healthy adults has ranged from 2.4 to 3.4 hours [21]. Richter et al. reported half-life ranging from 2.3 to 9.5 h in 12 infants and children of ages 0.25 to 16.8 y [24]. The longer half-life in infants and children may be a result of lower clearance and/or larger distribution volume. We found that half-life ranged from 2.2 to 15.8 h (mean 6.8 (4.9) h). In neonates less than 27 weeks gestation, the mean half life was 10.2 (4.8) h as compared with 4.9 (4.0) h in those greater than 27 weeks. The half-life of the more premature group is similar to the 9.3 (3.3) h half-life reported by Charles et al. in a similar patient population [23]. Thus, premature neonates less than 27 weeks gestation may have a longer dexamethasone half-life and may therefore require longer dosage intervals to minimize dexamethasone accumulation than infants born closer to term.

There is evidence of a dexamethasone dose-response relationship in the treatment of BPD [25, 26]. Mammel et al. reported greater therapeutic response at 0.5 $mg \cdot kg^{-1} \cdot day^{-1}$ than at 0.1 $mg \cdot kg^{-1} \cdot day^{-1}$ [25]. We found no relationships between plasma concentrations, pharmacokinetic parameters, and therapeutic endpoints or adverse effects. As previously reported [1,2,5,25], we observed a rapid reduction in peak inspiratory pressure and ventilator rate within the first several days of therapy. However, no correlation was noted between the rate or extent of improvement and dexamethasone's clearance or AUC. This may be explained, in part, by 1) the large weight-normalized doses which may already elicit near maximal responses; and 2) the high potency of dexamethasone and its extended biologic half-life, which may result in responses less dependent on plasma concentrations. Similar observations have been reported in the treatment of asthma, where massive doses of parenteral corticosteroids did not produce a more rapid improvement or a better outcome than lower conventional doses [27].

Adverse effects may have unique plasma concentration-response curves, thus making it important to understand these relationships in order to optimize therapy. The adverse effects of dexamethasone in this study were similar to those previously reported [28]. We attempted to determine whether the adverse effects were related to the disposition of dexamethasone. Both systolic and diastolic blood pressure were significantly elevated early in the course of therapy. Previous investigators reported a correlation between dexamethasone-induced hypertension and cumulative dose [9]. In addition, others found an attenuation of hypertension with dose reductions [4]. These data would suggest a correlation between plasma concentrations or AUC and blood pressure, however we found no such relationships. Dexamethasone also causes significant tissue catabolism in neonates [4–6,8,10,17,18]. Previous investigators have reported weight loss or poor weight gain [4–6,10,17,18], increases in plasma amino acid concentrations [18], and increases in blood urea nitrogen [16–18] during dexamethasone therapy. Furthermore, these effects have been reported to be dose-dependent [4–8,16]. We noted a decrease in weight gain after initiating dexamethasone and consistent with previous studies, there was a marked coincident increase in BUN, unexplained by a change in renal function, urine output, or protein intake. Overall, however, there was no relationship between dexamethasone pharmacokinetics and these physiologic data.

While the number of enrolled patients was sufficient to characterize the pharmacokinetics, a larger population is needed to determine possible relationships between the kinetics and therapeutic endpoints or adverse effects. As with other drugs used in the neonatal population, we observed variability in the disposition of dexamethasone. With smaller volumes of distribution and lower clearances in those born most prematurely, there is the potential for markedly higher plasma concentrations over the course of therapy. The potential for increased risk of adverse effects as a result of treating all premature neonates with a uniform dosage regimen must be considered. This is not without precedent since investigators have reported increased adverse effects in adults with low corticosteroid clearances [29,30]. Based on the findings of this study, premature neonates less than 27 weeks gestation had a significantly lower clearance than neonates born greater than 27 weeks gestation. We speculate that doses may need to be individualized based on gestational age and that extremely premature infants may therefore require lower doses of dexamethasone. This consideration for dose individualization is based on pharmacokinetic principles only and larger clinical studies are needed to determine the optimal dosage regimen.

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