Disposition of betamethasone in parturient women after intramuscular administration

MARISA C. PETERSEN, J. J. ASHLEY, W. G. McBRIDE & *R.L. NATION
Perinatal Pharmacology Laboratory, Foundation 41 and Department of Pharmacy,
University of Sydney, Sydney, New South Wales, Australia

- 1 When betamethasone phosphate equivalent to 8 mg betamethasone was administered intramuscularly in solution (Celestone Injection) to pregnant women, a large proportion of this ester was absorbed unchanged. Bioavailability of betamethasone from the phosphate ester was as high as after intravenous injection.
- 2 When pregnant patients received the equivalent of either 6 or 12 mg betamethasone in a formulation containing 3.1 mg/ml betamethasone acetate suspended in a solution of 4 mg/ml betamethasone phosphate (Celestone Chronodose), much of the phosphate ester was absorbed intact but betamethasone acetate was not detected in plasma.
- 3 Availability of betamethasone from Celestone Chronodose was much lower than from Celestone Injection.
- 4 After administration of either formulation, maternal plasma cortisol concentrations fell towards a basal level but were rising again within 2 to 3 days of the last dose.
- 5 We conclude that Celestone Chronodose does not provide prolonged release of betamethasone and offers no advantage over Celestone Injection.

Keywords betamethasone bioavailability pregnancy prolonged release

Introduction

Neonatal respiratory distress syndrome (RDS) is still regarded, despite improved neonatal care facilities, as a major complication of premature births. Since the early clinical trials of Liggins & Howie (1972), antenatal administration of glucocorticoids to the mother has been used in an attempt to reduce the incidence of RDS. In a recent review, Ballard & Ballard (1979) reported that the many clinical studies which have now been completed have established that both the incidence and severity of RDS can be decreased by the use of glucocorticoids.

Despite growing evidence of the usefulness of glucocorticoids in preventing RDS, very little is

known of the disposition of these potent drugs in pregnant women. Several glucocorticoids have been used in this indication and for their use to be optimized, information must be gathered on the plasma levels of the various drugs, on their rates of elimination, and on their bioavailability after different routes of administration. Some work has been done by Tsuei *et al.* (1980) who examined the disposition and placental transfer of dexamethasone in pregnant women approaching delivery. Also, Ballard *et al.* (1975) measured betamethasone and cortisol levels in pregnant women after a 12 mg dose of betamethasone as a 'sustained release' formulation. In that study, cortisol levels were measured using a CBG-isotope assay and total glucocorticoid levels using a radioreceptor assay; the difference was attributed to betamethasone.

* Present address: School of Pharmacy, South Australian Institute of Technology, North Terrace, Adelaide, South Australia, 5000.

Betamethasone is the most commonly used glucocorticoid for the prevention of RDS in this hospital, and is administered either as Celestone Injection or as Celestone Chronodose. Celestone Injection consists of 5.3 mg/ml betamethasone disodium phosphate (BP), a soluble ester of betamethasone (BET), and may be administered intravenously (i.v.) or intramuscularly (i.m.); while Celestone Chronodose is a mixture of BP (4.0 mg/ml) in solution and betamethasone acetate (BA) (3.1 mg/ml) in suspension. The latter formulation is administered i.m.; the phosphate ester is expected to be rapidly released to the blood stream while the acetate ester is included to provide a repository for 'sustained release'. Both esters are expected to be hydrolysed *in vivo* to the active glucocorticoid BET. To study fully the disposition of BET and endogenous cortisol after administration of these formulations, we have developed sensitive and specific analytical techniques for BP (Petersen *et al.*, 1983b), BET, BA and cortisol (Petersen *et al.*, 1980a) in plasma.

We previously reported the placental transfer of BET (Petersen *et al.*, 1980b) and its disposition after i.v. administration to non-pregnant (Petersen *et al.*, 1983b) and pregnant (Petersen *et al.*, 1983a) subjects. The present report deals with the disposition of BET and cortisol in pregnant patients after the administration of Celestone Injection or Celestone Chronodose intramuscularly.

Methods

Clinical protocol

Patients for whom an antenatal regimen of betamethasone had been prescribed were included in Groups I and II of this study. The protocol for blood sampling which had been approved by the Ethics Committee of the Women's Hospital, Crown Street, was fully explained to all patients, and their consent was obtained. Although no limitations were placed on their activity, the patients were generally in bed for the duration of blood sampling.

Group I Six patients (Nos 1–6) who were to receive the solution containing BP (10.6 mg) i.m. (Celestone Injection, Schering Corp, USA), equivalent to 8 mg BET, entered the study (Table 1). The dose was given into the upper, outer quadrant of a buttock using a 23G $\times$ 1½" needle, and the injection site was briefly massaged. Blood samples (8 ml) were drawn via a cannula in the forearm vein, using disposable plastic syringes, before dosing and at about 5, 15, 30, 45, 60, 90 min and 2, 3, 4, 5, 6, 7, 8, 10 h after dosing. The blood was transferred to plastic tubes containing ammonium heparin and sodium arsenate (Petersen *et al.*, 1980a), then centrifuged and the plasma frozen at -22°C until analysed. Additional blood samples were drawn at delivery from the mother and from the

Table 1 Patient characteristics

Patient	Pregnant weight (kg)	Height (cm)	Estimated gestation age (weeks)	Betamethasone* formulation and dose	Number of doses given	Prenatal medication
1	67	158	30	8 mg CI t.i.d.	3	diazepam
2	88	167	33	8 mg CI	1	diazepam
3	93	168	37	8 mg CI	1	–
4	68	150	32	8 mg CI t.i.d.	3	salbutamol
5	70	158	38	8 mg CI	1	hydrochlorthiazide
6	62	164	30	8 mg CI b.d.	2	ritodrine, propranolol
13	74	155	38	6 mg CC	1	–
14	71	166	36	12 mg CC	1	–
15	114	163	37	12 mg CC	1	hydrochlorthiazide, diazepam†
16	62	151	38	12 mg CC	1	atenolol, methyclothiazide, beclomethasone inhaler†
17	69	155	28	12 mg CC b.d.	2	–
18	63	163	31	6 mg CC q.i.d.	4	salbutamol
19	67	160	31	12 mg CC b.d.	2	–
20	67	170	30	6 mg CC t.i.d.	3	ritodrine, meperidine
21	64	173	33	12 mg CC b.d.	2	ritodrine, salbutamol

* Celestone Injection (CI) or Celestone Chronodose (CC) given every 12 h (b.d., 8 h (t.i.d.) or 6 h (q.i.d.)

† Medications continued post-delivery.

artery and vein of the clamped umbilical cord. In a total of 12 patients who received this betamethasone formulation, a blood sample was also drawn from the mother between 08.00 h and 11.00 h on the day after dosing and on alternate days for up to 10 days after the last dose was given. Plasma samples were analysed for BP, BET and cortisol (Petersen *et al.*, 1980a, 1983b).

Group II Nine patients (Nos 13–21), for whom the suspension formulation (Celestone Chronodose, Schering Corp, USA), had been prescribed were also included in the study (Table 1). They received the equivalent of either 6 mg or 12 mg BET. The method of injection and blood sampling schedule were as described for Group I patients; again blood samples were taken for up to 10 days after the last dose was given. The inclusion of sodium arsenate in the blood collection tubes stabilised BP but did not adequately prevent the breakdown of BA to BET. Therefore, immediately after collection into a tube containing sodium arsenate, each sample was placed in an ice bath, centrifuged within 5 min and the plasma transferred to a tube containing potassium fluoride (Petersen *et al.*, 1980a). No detectable breakdown of either ester occurred when blood samples were treated in this way. Plasma samples from this patient group were analysed for BP, BA, BET and cortisol (Petersen *et al.*, 1980a, 1983b).

Group III A group of patients (Nos 24–31) admitted to hospital the day before an elective caesarean section and for whom no glucocorticoids had been prescribed were included in this study to provide control plasma cortisol levels. Blood samples were collected on the day of admission, from the mother and umbilical cord vessels at delivery and from the mother between 08.00 h and 11.00 h on alternate mornings for up to 10 days post-partum. The plasma samples were analysed for cortisol (Petersen *et al.*, 1980a).

Pharmacokinetics and statistical analyses

Linear regression analysis was carried out on the terminal log-linear phase of the plasma concentration-time (C-t) curves to provide an estimate of the terminal-phase rate constant from which the plasma half-life ($t_{1/2}$) was calculated. Areas under the C-t curves (AUC) were calculated using the trapezoid rule with the appropriate extrapolation to infinite time

(Gibaldi & Perrier, 1975). When a patient was studied after a dose other than the first, the contribution from previous doses to AUC and peak plasma level was subtracted using the principle of superposition (Gibaldi & Perrier, 1975).

Differences between groups were tested using the Mann-Whitney U-Test (Goldstein, 1964); a two-sided test was applied and differences were considered significant when $P < 0.05$.

Results

After administration of the solution (Group I) into the gluteus maximus muscle, plasma concentrations of BP were measured in four patients. Peak concentrations were seen within 18–30 min, and ranged over 92–370 ng/ml (Figure 1a). After peaking the BP concentrations fell with a mean $t_{1/2}$ of 23.3 ± 7.6 min ($\pm$ s.d.); AUC was highly variable ranging over 3.7–15.4 $\mu\text{g/ml min}$ (mean 9.0 ± 5.5 $\mu\text{g/ml min}$). After dosing with BP, BET was not detected before 15 min and peak concentrations occurred at 60–130 min (Table 2). Peak BET concentrations of 33–75 ng/ml were observed before the levels dropped exponentially with a mean $t_{1/2}$ of 306 ± 93 min (Figure 2). The AUC for BET had a mean value of 29.0 ± 5.8 $\mu\text{g/ml min}$.

Patients who were studied after the first dose of the solution showed a steady drop in plasma cortisol concentrations over the 8–10 h sampling period (Figure 3). The mean half-life of decline was 267 ± 43 min and levels fell from predose concentrations between 150 ng/ml and 270 ng/ml to 20–30% of those levels after 8–10 h. Analysis of the samples drawn the morning after dosing showed the plasma concentrations of cortisol had dropped further to basal levels of 23–38 ng/ml (Table 3). Patients studied after subsequent doses of BP showed little variation in their plasma cortisol levels over the 8–10 h sampling period (Figure 3).

After the i.m. administration of the suspension to patients (Group II), plasma samples were analysed for BP, BET and cortisol as before, and for BA. BP concentrations were measured in plasma samples from four patients who received the equivalent of 12 mg BET. Plasma BP concentrations did not simply peak and then decline as in the Group I subjects but were found to be erratic (Figure 1b). Peak concentrations of BP ranged from 80–115 ng/ml, appearing within 30 min of dosing, but secondary peaks often occurred approximately 40–50 min after the dose was given. Terminal-phase $t_{1/2}$ (15–20 min) could only be estimated

Figure 1 Plasma BP concentrations after i.m. Injection of (a) Celestone injection containing 10.6 mg BP, and (b) Celestone Chronodose containing 8 mg BP.

from the last two samples from each patient, but were similar to those observed in the Group I subjects. Mean AUC for BP was 5.7 ± 1.0 $\mu\text{g/ml min}$. BET was not observed in plasma before 15 min after dosing, and peak concentrations were seen between 45 min and 102 min (Table 4). When the equivalent of 6 mg BET

was given, peak concentrations were 23–25 ng/ml ($n = 3$) and after the equivalent of 12 mg BET, a range of 35–63 ng/ml was observed. In all patients the plasma BET concentrations subsequently declined in a single exponential phase with a mean $t_{1/2}$ of 317 ± 74 min (Figure 2). AUC for BET was normalised by dividing

Table 2 Characteristics of betamethasone absorption after intramuscular Celestone Injection

Patient	Peak concentration (ng/ml)	Time to peak (min)	$t_{1/2}^{\dagger}$ (min)	AUC ‡ ($\mu\text{g ml}^{-1} \text{ min}$)	Normalised AUC* (min/ml)
1	66	60	283	34.8	4.4
2	46	60	465	32.0	4.0
3	33	90	241	18.3	2.3
4	75	90	269	31.9	4.0
5	45	125	363	29.5	3.7
6	65	130	215	27.6	3.5
Mean	55	93	306	29.0	3.7

† terminal phase $t_{1/2}$

‡ area under the plasma concentration-time curve

* AUC/ μg betamethasone administered

Figure 2 Plasma BET concentrations after i.m. Injection of Celestone injection equivalent to 8 mg BET (○) (patient no. 4) and Celestone Chronodose equivalent to 12 mg BET (□) (patient no. 21).

by the dose of BET (in μg); this resulted in a mean normalised AUC of $2.4 \pm 0.6 \mu\text{g ml}^{-1} \text{ min}$. BA was not detected in any of the plasma samples assayed, including those taken for up to 10 days after dosing.

Plasma cortisol concentrations in patients administered the suspension followed a pattern

very similar to that observed in Group I patients. After the first dose of the suspension, cortisol levels fell smoothly over the next 8–10 h with a mean half-life of $258 \pm 55 \text{ min}$ (Figure 3) and the plasma sample collected the morning after dosing contained only 21–38 ng/ml (Table 3), representing the basal production level. In

Figure 3 Plasma cortisol levels in patient Nos 2 (■), 6 (□), 14 (○), 17 (▲) and 19 (●).

Table 3 Plasma cortisol levels (ng/ml) in all patient groups

Patient	Time of pre-dose sample	Dose studied	Pre-dose level (ng/ml)	8–10 h post-dose (ng/ml)	Days after last dose			
					1	2–3	5–6	8–10
(ng/ml)								
Group I								
1	1415 h	1	189	36	–	–	*	–
2	1130	1	269	61	–	*	344	207
3	1315	1	149	57	38	*	145	145
4	1530	3	16.5	11.4	62		89	89
5	1230	1	178	48	23	*	213	185
6	1430	2	47	34	30	*	201	127
7	1515	1	228	–	40	*	146	204
8	1430	1	111	–	35	*	121	154
9	–	1	–	–	–	*	207	156
10	1130	1	248	50	31	*	174	137
11	–	1	–	–	56	*	116	187
12	1600	1	334	–	–	*	279	285
Group II								
13	1317 h	1	186	69	33	*	–	–
14	1130	1	395	69	–	*	206	–
15	1530	1	221	68	21	*	26	45
16	1300	1	234	81	38	*	60	198
17	0900	2	47	37	48		102	
18	0530	4	24	21	19			
19	0830	1	190	48	32		167	183
20	1110	1	220	63	–	*	264	185
21	2030	1	158	70	35			
22	–	1	–	–	37	*	68	130
Group III								
24	–	–	386	*	173	275	110	
25	208	205	262	*	200	188	158	
26	275	131	211	*	189	148	142	
27	362	263	468	*	–	361	206	
28	–	–	–	*	480	206	147	
29	264	224	345	*	268	204	204	
30	–	–	–	*	211	220	–	
31	155	–	326	*	372	191	138	

* Indicates when delivery occurred

patients studied after subsequent doses of the suspension, the cortisol levels remained relatively constant over the 8–10 h sampling schedule, i.e. they were not further suppressed by extra doses of the suspension (Figure 3).

Duration of adrenal suppression

In patients from Groups I and II whose labour was successfully stopped and premature delivery was avoided (subjects 4, 17, 19), plasma cortisol

levels had begun to return to normal pregnancy levels with 2–3 days of the last dose of BET (Table 3). When delivery occurred within 22–26 h of the last dose of BET, cortisol levels in the mother and the umbilical vessels were generally lower than in Group III patients (Table 5) but maternal levels were often higher than those measured some hours previously (Table 3). A higher concentration of cortisol was always found in the umbilical artery than in the umbilical vein. After delivery, maternal cortisol levels in Group I and II patients increased

Table 4 Characteristics of betamethasone absorption after Celestone Chronodose

Patient	Peak concentration (ng/ml)	Time to peak (min)	$t_{1/2}^{\dagger}$ (min)	AUC ‡ ($\mu\text{g ml}^{-1} \text{ min}$)	Normalised AUC ** (min/ml)
13*	24	60	215	16.2	2.7
14	35	90	231	14.4	1.2
15	49	102	447	32.9	2.7
16	63	83	376	41.2	3.4
17	60	90	301	31.5	2.6
18*	25	45	334	13.4	2.2
19	55	102	376	32.6	2.7
20*	23	90	274	11.0	1.8
21	53	89	301	28.7	2.4
Mean	24 (6 mg dose) 53 (12 mg dose)	83	317	—	2.4

* Received equivalent of 6 mg betamethasone, while other patients received equivalent of 12 mg betamethasone.

† terminal phase $t_{1/2}$

‡ area under the plasma concentration-time curve

** AUC/ μg betamethasone administered

rapidly and had begun to approach their new nonpregnant levels within two or three days of the last dose of glucocorticoid (Table 3). Patient No. 15 whose cortisol levels remained low was receiving 20 mg diazepam per day for hypertension until the sixth postnatal day.

Plasma cortisol levels in Group III patients (Nos 24–31) who were studied in the post-partum period tended to drop gradually from the elevated levels seen at delivery to approach their new non-pregnant levels (Table 3). Cortisol levels in these patients 5–10 days post-

partum were similar to those observed in Group I and II patients 5–10 days after the last dose of BET, when delivery had intervened.

Discussion

After i.m. administration of the solution, the $t_{1/2}$ of decline of BP plasma concentrations was five times greater than that observed after i.v. administration of the solution (Petersen *et al.*, 1983a), and probably reflected the rate of

Table 5 Plasma cortisol levels (ng/ml) at delivery

Patient	D–D* interval (h)	Maternal vein	Umbilical artery	Umbilical vein
Group I				
5	25.5	90	15	7
7	24.3	59	19	12
8	26.5	132	Not detectable	
9	24.3	79	51	25
Group II				
13	24.0	149	50	25
15	22.0	28	12	6
16	25.0	68	43	31
23	—	91	25	18
Group III				
25	—	224	26	20
26	—	165	126	80
29	—	422	59	28
30	—	359	63	60
31	—	249	50	31

* Time interval from last dose to delivery.

absorption of BP from the muscle rather than the very rapid elimination process. The mean AUC for BP after i.m. administration was 65% of that observed after the same dose was given i.v., indicating that a large proportion of BP reaches the bloodstream before hydrolysis to BET occurs (Figure 4). Interindividual variability in the BP AUC was greater after i.m. administration and may have been due to variable extents of hydrolysis of BP to BET in the muscle. Importantly, wherever the hydrolysis of BP to BET occurred, the availability of BET to the systemic circulation was as high after i.m. injection as after i.v. administration, since the BET AUC after the two routes of administration were not significantly different (Petersen *et al.*, 1983a). The similarity in AUCs indicated that the relative bioavailability of BET both from the phosphate ester and from the i.m. injection site was excellent. However, peak concentrations of BET were lower ($P < 0.05$) and were reached later ($P < 0.01$) after an i.m. dose of BP than after the same dose of BP given i.v. (Petersen *et al.*, 1983a). In keeping with the comparable bioavailability and the lower, later peak concentrations observed after i.m. administration, BET concentrations in the terminal phase of the curve were higher than those observed after i.v. administration of the solution.

As may be expected, the administration of the solution by either route had a similar effect on plasma cortisol levels (Petersen *et al.*, 1983a). A slow decline in cortisol levels was observed over the 24 h following the first dose of BP. The minimum level reached (20–40 ng/

ml) was not further suppressed by subsequent doses of BP since this represented the basal production level that is generally thought not to be controlled by the negative feedback system (Ceresa *et al.*, 1970). After the completion of BET therapy, the return of normal cortisol production appeared to be rapid with increasing plasma levels observed in the mother 48 h after the last i.m. dose of the solution.

The absorption of BP from the muscle after administration of the suspension was more erratic than after i.m. solution, suggesting that the suspension formulation modifies this process. The AUC for BP after each of these formulations was similar when a correction for dose had been made, indicating that again a large proportion of BP reaches the systemic circulation before it is hydrolysed to BET. When the suspension was administered to patients, no BA was detected in any plasma sample, even those taken for up to 10 days after the last dose, so any release of BA from the muscle site to the bloodstream must have been extremely slow. Alternatively, BA may have slowly dissolved and been hydrolysed to BET in the muscle and released into the bloodstream as the active glucocorticoid (Figure 4). If this was the case, a prolongation of the terminal-phase $t_{1/2}$ of BET might have been expected but was not observed; the half-life of BET in Group II patients was not different from that observed in Group I patients. Additionally, no BET was detected between the second and tenth days after the last dose of the suspension. The relative bioavailability of BET after i.m. (and i.v.) administration of the

Figure 4 Schematic representation of the possible fates of BP and BA after i.m. injection.

solution was approximately 65%. Very slow release of BA, over several days may have occurred, resulting in BA and BET levels below the sensitivity limits of our assay (Petersen *et al.*, 1980a); however plasma cortisol levels did not remain suppressed for any longer after administration of the suspension than after the solution was given. It appeared, therefore, that the suspension formulation afforded poor bioavailability of BET and that BA imparted no marked 'sustained release' characteristic to the formulation. The equivalent of 12 mg BET when administered in this form yielded plasma concentrations and AUC of BET only equal to or less than those obtained after i.m. injection of solution equivalent to 8 mg BET (Figure 2). Plasma concentrations of BET in the foetus reflect the time-course of concentrations observed in the mother, but are approximately 30% of maternal values (Petersen *et al.*, 1980b). Therefore, if sustained glucocorticoid levels are required in the foetus, specifically at the lung, for efficacy, the use of the suspension in preference to the solution would appear to be warranted.

The time for which the adrenals are suppressed is important as a measure of both the duration of plasma concentrations of the exogenous glucocorticoid and possible undesirable effects due to prolonged suppression of the maternal and foetal/neonatal adrenals. We found that maternal plasma cortisol levels began to rise 2–3 days after the last dose of either 12 mg BET as Celestone Chronodose or 8 mg BET as Celestone Injection given i.m. In fact when delivery occurred approximately 24 h after a dose of glucocorticoid our data suggested that the maternal adrenal was capable of responding to this stress by slightly increasing its cortisol output. The effect of antenatal administration of BET on endogenous cortisol levels in the mother and in the umbilical cord has been studied previously. Ohrlander *et al.* (1975), Maltau *et al.* (1979) and Ballard *et al.* (1975) found, as we did, that maternal cortisol levels fell to about 10–30% of predose levels in the 24 h after the first 12 mg dose of the suspension, and began to increase again 2–4 days after the last dose had been given. The

number of doses used in these studies varied from one dose to three doses given 24 h apart. After this last regimen, Gennser *et al.* (1976) found that plasma cortisol levels in the umbilical cord remained low, at about 25 ng/ml, for 3–4 days after the last dose of the glucocorticoid. There was no difference between treated and control groups with respect to cord cortisol levels if delivery occurred 4 days or more after the last dose of BET. Ohrlander *et al.* (1977), Sybulski (1977) and Ballard *et al.* (1980) have all found that neonates born with suppressed plasma cortisol levels have increasing adrenal function in their first neonatal day and are capable of responding normally to stress.

Our results indicated that the suspension provided no advantage over i.m. administration of the solution as regards duration of glucocorticoid activity. The relative bioavailability of BET from the former formulation was both low (65%) and variable making it considerably less reliable than the solution in terms of the plasma BET concentrations achieved. If sustained levels of glucocorticoid are required in the foetus for foetal lung maturation, the use of Celestone Injection in smaller doses and at shorter dosage intervals than are usually recommended for Celestone Chronodose would have the effect of decreasing plasma concentration fluctuations and maintaining sustained plasma concentrations of BET. Apart from the poor bioavailability of BET from the suspension, this formulation has the further disadvantage of being painful to the patient on injection, and it would appear from our data that at least part of the insoluble BA injected remains at the injection site for relatively long periods of time. In contrast, i.m. administration of the solution resulted in a bioavailability of BET similar to that seen after i.v. administration of the solution and so provided a formulation that was reliable and simpler to administer.

The authors wish to thank Dr C. Collier, the honorary and the resident medical staff of the Women's Hospital for their assistance in the implementation of the clinical protocol; and Mary Davidson for typing the manuscript.

References

- Ballard, P. L. & Ballard, R. A. (1979). Corticosteroids and respiratory distress syndrome. Status 1979. *Pediatrics*, **63**, 163–165.
- Ballard, P. L., Granberg, P. & Ballard, R. A. (1975). Glucocorticoid levels in maternal and cord serum after prenatal betamethasone therapy to prevent respiratory distress syndrome. *J. clin. Invest.*, **56**, 1548–1554.
- Ballard, P. L., Gluckman, P. D., Liggins, G. C., Kaplan, S. L. & Grumbach, M. M. (1980). Steroid and growth hormone levels in premature infants after prenatal betamethasone therapy to prevent respiratory distress syndrome. *Ped. Res.*, **14**, 122–127.
- Ceresa, F., Angeli, A., Bocuzzi, G. & Perotti, L. (1970). Impulsive and basal ACTH secretion

- phases in normal subjects, in obese subjects with signs of adrenocortical hyperfunction and in hyperthyroid patients. *J. clin. Endocrinol.*, **31**, 491–501.
- Gennser, G., Ohrlander, P. & Eneroth, P. (1976). Cortisol in amniotic fluid and cord blood in relation to prenatal betamethasone load and delivery. *Am. J. Obstet. Gynecol.*, **124**, 43–50.
- Gibaldi, M. & Perrier, D. (1975). *Pharmacokinetics*. New York: Marcel Dekker Inc.
- Goldstein, A. (1964). *Biostatistics, an introductory text*, pp 55–57. New York: Macmillan Publishing Co., Inc.
- Liggins, G. C. & Howie, R. N. (1972). A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. *Pediatrics*, **50**, 515–525.
- Maltau, J. M., Stokke, K. T. & Moe, N. (1979). Effects of betamethasone on plasma levels of estriol, cortisol and HCS in late pregnancy. *Acta Obstet. Gynecol. Scand.*, **58**, 235–238.
- Ohrlander, S. A. V., Gennser, G. M. & Grennert, L. (1975). Impact of betamethasone load given to pregnant women on endocrine balance of fetoplacental unit. *Am. J. Obstet. Gynecol.*, **123**, 228–236.
- Ohrlander, S., Gennser, G., Nilsson, K. O. & Eneroth, P. (1977). ACTH test to neonates after administration of corticosteroids during gestation. *Obstet. Gynecol.*, **46**, 691–694.
- Petersen, M. C., Collier, C. B., Ashley, J. J., McBride, W. G. & Nation, R. L. (1983a). Pharmacokinetics of betamethasone in parturient women after intravenous administration. *Eur. J. clin. Pharmacol.*, **25**, 803–810.
- Petersen, M. C., Nation, R. L. & Ashley, J. J. (1980a). Simultaneous determination of betamethasone, betamethasone acetate and hydrocortisone in biological fluids using high performance liquid chromatography. *J. Chromatogr.*, **183**, 131–139.
- Petersen, M. C., Nation, R. L., Ashley, J. J. & McBride, W. G. (1980b). The placental transfer of betamethasone. *Eur. J. clin. Pharmacol.*, **18**, 245–247.
- Petersen, M. C., Nation, R. L., McBride, W. G., Ashley, J. J. & Moore, R. G. (1983b). Pharmacokinetics of betamethasone in healthy adults after intravenous administration. *Eur. J. clin. Pharmacol.*, **25**, 643–650.
- Sybulski, S. (1977). Effect of antepartum betamethasone treatment on cortisol levels in plasma, amniotic fluid and the neonate. *Am. J. Obstet. Gynecol.*, **127**, 871–874.
- Tsuei, S. E., Petersen, M. C., Ashley, J. J., McBride, W. G. & Moore, R. G. (1980). Disposition of synthetic glucocorticoids II. Dexamethasone in parturient women. *Clin. Pharmac. Ther.*, **28**, 88–98.

(Received November 25, 1983,
accepted April 27, 1984)