PAPERS AND ORIGINALS

Diazepam in Labour: Its Metabolism and Effect on the Clinical Condition and Thermogenesis of the Newborn

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Summary

Following the administration of diazepam to mothers in labour the clinical effects, changes in thermogenesis, and metabolism of the drug in the newborn were observed under carefully controlled conditions. A total maternal dose of 30 mg or less in the 15 hours before delivery had little effect on the infants' state. Larger doses, however, were accompanied by low Apgar scores at birth, apnoeic spells, hypotonia, reluctance to feed, and an impaired metabolic response to a cold stress. Measurement of plasma levels of diazepam and its active metabolite showed that both products were detectable in significant concentrations in some infants for up to eight days. We conclude that greater care should be taken in the use of this otherwise effective drug for the treatment of pre-eclampsia.

Introduction

In the past five years there has been an increasing use of diazepam in pregnancy and labour (Toulouse and Maffel 1965; Lean *et al.*, 1968; de Alvarez and Zighelboim, 1969). It is used in small doses as a tranquillizer (Flowers *et al.*, 1969) and in much larger doses, often with hydrallazine, in the management of pre-eclampsia and eclampsia (Leinzinger 1969, 1970; Joyce and Kenyon, 1972). Obstetric reports indicate successful control of blood pressure and prevention of convulsions, with little evidence of harm to the newborn (Leinzinger 1969, 1970; Joyce and Kenyon, 1972). There have, however, been reports of hypotonia (Flowers *et al.*, 1969; Rosanelli, 1970; Shannon *et al.*, 1972), low Apgar scores (Flowers *et al.*, 1969), and hypothermia (Owen *et al.*, 1972). Hyperbilirubinaemia was found to be due to the vehicle, sodium benzoate, with which the parenteral preparation was prepared (Schiff *et al.*, 1971).

We have observed that infants become hypothermic and manifest symptoms of central nervous system depression after the maternal administration of diazepam during labour. The rapid, active transplacental passage of diazepam is well documented (Scher *et al.*, 1972; Shannon *et al.*, 1972). Its subsequent fate is less predictable, some studies showing that it is rapidly eliminated (Shannon *et al.*, 1972), while others have shown that it is detectable for long periods in the newborn circulation (Hailey *et al.*, 1973).

An investigation was therefore undertaken (*a*) to assess the clinical status of infants after maternal diazepam, (*b*) to measure their metabolic response to a physiological cold stress, and (*c*) to measure maternal, cord, and neonatal plasma levels of diazepam and its metabolite desmethyldiazepam.

Patients and Methods

All infants studied were born either at the Royal Sussex County Hospital, Brighton, or at King's College Hospital, London. In each case parental consent was obtained for taking samples of venous blood from the infants. The procedures caused no harm to the infants.

Group 1 (table I) consisted of 18 infants (cases 1 to 18) whose mothers had been given 30 mg or less of diazepam (either intramuscularly or intravenously) in the 15 hours before delivery. Twelve of these mothers had mild pre-eclampsia; six had been given diazepam as a tranquillizer.

Group 2 (table II) consisted of 14 infants (cases 19 to 32) whose mothers had received more than 30 mg of diazepam parenterally in the 15 hours before delivery. Thirteen mothers had pre-eclampsia and one had had eclamptic fits.

All the infants were of 36 weeks' or more gestation and weighed more than 2,400 g. None had any evidence of congenital abnormality, birth injury, or infection. Six infants (table III) whose mothers had received anaesthetics or analgesic drugs

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TABLE I—*Clinical Details, Maternal Dose, and Effects of Diazepam on Neonates in Group 1 (Low Dose)*

Case No.	Maturity (Weeks)	Birth Weight (g)	Method of Delivery	Total Dose of Diazepam During 15 Hours before Delivery	Apgar Score at 1 Minute	Symptoms Attributable to Diazepam
1	41	3,210	Spontaneous, vertex	15 mg	8	None
2	40	3,490	L.S.C.S.	30 mg	9	„
3	40	3,360	Spontaneous, vertex	20 mg	7	„
4	40	3,690	Forceps, vertex	25 mg	2	„
5	44	3,710	Forceps, vertex	20 mg	3	„
6	41	2,850	Spontaneous, vertex	30 mg	6	Hypotonia and reluctance to feed for 3 days
7	40	3,090	Spontaneous, vertex	30 mg	6	None
8	38	2,950	Spontaneous, vertex	20 mg	10	„
9	42	4,390	Forceps, vertex	20 mg	9	„
10	40	4,290	Spontaneous, vertex	10 mg	10	„
11	40	3,510	Spontaneous, vertex	10 mg	9	„
12	40	2,500	Spontaneous, vertex	12·5 mg	9	„
13	36	2,770	Spontaneous, vertex	30 mg (+5 mg t.d.s. for 14 weeks previously)	7	Lethargic and reluctant to feed for 48 hours
14	42	3,100	Spontaneous, vertex	20 mg	6	None
15	42	3,100	Spontaneous, vertex	30 mg	7	„
16	41	3,440	Spontaneous, vertex	20 mg	6	„
17	40	3,140	Spontaneous, vertex	10 mg (+30 mg between 40 and 15 hr before delivery)	5	Temp. 34·9°C at 30 min
18	40	3,080	Elective forceps for pre-eclamptic toxaemia	30 mg	5	None

L.S.C.S. = Lower segment caesarean section.

TABLE II—*Clinical Details, Maternal Dose, and Effects of Diazepam on Neonates in Group 2 (High Dose)*

Case No.	Maturity (Weeks)	Birth Weight (g)	Method of Delivery	Total Dose of Diazepam During 15 Hours before Delivery	Apgar Score at 1 Minute	Symptoms Attributable to Diazepam
19	40	3,520	Forceps, vertex	68 mg	5	Intubated. Spontaneous regular respiration at 8 min. Hypotonia, lethargy. Failure to suck for 48 hr
20	40	4,030	Forceps, vertex	160 mg	2	Intubated. Required I.P.P.R. for 30 min before shallow regular respiration established. Hypotonia, lethargy. Failure to suck for 48 hr
21	40	2,400	Spontaneous, vertex	60 mg	7	Hypothermia. Temp. 35°C at 11 hr
22	40	2,680	Forceps, vertex	40 mg	8	Lethargy. Feeble cry for 24 hr
23	41	3,100	Forceps, vertex	70 mg	1	Intubated. Spontaneous respiration at 7 min. Secondary apnoea at 15 min. Required I.P.P.R. for 2 hr 15 min. Hypotonia for 48 hr
24	41	3,400	Forceps, vertex	160 mg	2	Intubated. Spontaneous respiration at 5 min. Lethargy, hypotonia, areflexia, failure to suck for 48 hr. Apnoeic attack at 13 hr
25	38	3,050	Spontaneous, vertex	80 mg	9	Temp. 35°C and slow, shallow respiration at 5 hr. Hypotonia, areflexia, and failure to suck for 36 hr
26	39	3,780	Spontaneous, vertex	40 mg	3	Intubated. Temp. <35°C for 1 hr. Failure to suck for 3 days
27	37	2,410	Spontaneous, vertex	70 mg	6	Intubated. Poor suck. Temp. briefly <35°C
28	41	2,980	Forceps, vertex	60 mg	4	Intubated. Hypotonia. Failure to suck for 2 days. Temp. <35°C at 4 hr
29	36	2,880	Forceps, vertex	200 mg	3	Intubated. Temp. <35°C for ½ hr. Hypotonia Failure to suck for 3 days
30	40	2,930	L.S.C.S. Failed trial of labour	40 mg	2	Failure to suck for 24 hr. Temp. 35°C at 2 hr
31	41	3,780	Forceps, vertex	40 mg	2	Intubated. Hypotonia. Failure to suck for 24 hr
32	38	2,660	Forceps, vertex	45 mg	3	Intubated, Hypotonia. Failure to suck for 48 hr. Temp. 34·5°C at ½ hr

N.B. Most mothers were given pethidine 150 mg and promethazine hydrochloride 25 mg on one or two occasions during labour. Mothers with severe pre-eclamptic toxaemia were given hydrallazine hydrochloride.
L.S.C.S. = Lower segment caesarean section. I.P.P.R. = Intermittent positive-pressure respiration.

TABLE III—*Clinical Details and Maternal Drugs in Control Series of Babies*

Case	Maturity (Weeks)	Birth Weight (g)	Method of Delivery	Drugs Administered during 15 Hours before Delivery	Apgar Score at 1 Minute	Neonatal Complications
A	38	3,500	Forceps, vertex	Pethidine, promethazine	10	None
B	40	3,010	Spontaneous, vertex	Pethidine	10	„
C	40	3,530	Forceps, vertex	Pethidine 450 mg, promethazine 50 mg	9	„
D	38	3,080	L.S.C.S. Breech with prolapsed cord	General anaesthetic only	8	„
E	39	3,270	Spontaneous, vertex	Pethidine 450 mg, promethazine 75 mg	6	„
F	40	3,140	Forceps, vertex	Pethidine 300 mg, promethazine 50 mg, morphine 15 mg	8	„

L.S.C.S. = Lower segment caesarean section.

other than diazepam were used as controls in the metabolic rate studies. They were of similar gestational age and birth weight.

CLINICAL ASSESSMENT

The infants were delivered in rooms where the temperature ranged from 23·0 to 24·5°C. They were dried and wrapped in either warm towels or silver swaddlers before resuscitation. The Apgar score was assessed at one minute and then at intervals until the infant was fit for transfer to a nursery with an environmental temperature of 23·5 to 24·5°C, or to a special care baby unit (temperature about 26°C), or to an incubator. The rectal temperature, respiratory effort, muscle tone, and sucking reflex were recorded four-hourly for at least 36 hours.

RESPONSE TO COLD

Seven high-dose infants, one low-dose infant, and the six controls were subjected to a cold stress when in a healthy state after delivery. Their mothers had recovered from labour and, with the father, gave consent to the test, which they were invited to witness. Most did so.

The infants were placed in a metabolic chamber set at a temperature in the middle of their thermoneutral range (the environmental temperature range in which the metabolic rate is minimal) (Hey and Katz, 1970). The relative humidity in the chamber was the same as that of the surrounding atmosphere. Oxygen consumption and carbon dioxide production and hence the respiratory quotient of each infant were measured at one-minute intervals for an hour using a Kipp diaferometer; activity was measured by a non-touch method using a modified Animex activity meter; rectal, skin, and environmental temperatures and humidity were monitored continuously.

After one hour the environmental temperature was lowered to that obtaining in the nursery where the infant would have been nursed had we not become aware of the importance of maintaining a warmer environment after the administration of maternal diazepam. The mean fall in ambient temperature was 6·4°C. The resultant changes in oxygen consumption, respiratory quotient, activity, and skin and rectal temperatures were recorded.

PLASMA ANALYSIS

Samples of maternal plasma at delivery, cord plasma, and infants' plasma at 24 hours were analysed for diazepam and desmethyldiazepam (Ro5-2180) by electron-capture gas chromatography (de Silva and Puglisi, 1970). Further samples were collected from 16 infants at varying intervals from 48 hours to the eighth day of life to determine the subsequent fate of diazepam in neonates. In six cases maternal blood was obtained before the administration of diazepam.

Results

CLINICAL ASSESSMENT

No infant in group 1 (low dose) had a low Apgar score attributable to diazepam (table I). Cases 4 and 5 had low scores after large doses of pethidine given within two hours of delivery and responded rapidly to endotracheal intubation and parenteral Lethidrone (nalorphine). None of these infants showed any late respiratory depression.

A rectal temperature below 35°C was recorded in case 17; however, the mother had received an additional 30 mg of diazepam in the 24 hours before the observation period.

Two infants (cases 6 and 13) were reluctant to feed, requiring tube feeds for three and two days respectively; the mother in case 13 had been given diazepam 15 mg daily for 14 weeks before delivery. The other infant (case 6) was hypotonic for 72 hours.

Of the 14 infants in group 2 (high dose) 10 had low Apgar scores and required endotracheal intubation (table II). One infant (case 23) developed prolonged secondary apnoea, and one (case 24) had apnoeic spells without hypoglycaemia, pulmonary aspiration, or other identifiable cause. Two further infants (cases 20 and 25) had shallow but adequate ventilation.

In spite of all precautions eight infants had a rectal temperature of 35°C or below within the first 12 hours of life.

Twelve infants had marked hypotonia with depressed reflexes for 36-48 hours. Ten infants failed to suck and required tube feeding for 36-72 hours.

RESPONSE TO COLD

The change in the metabolic rate of the infants studied, shown by a change in oxygen consumption in response to cold, varied from a rise of 51% to a fall of 9% (mean 12% rise) (table IV). All the controls increased their metabolic rate by 20-65% (mean 35% rise). This difference is highly significant ($P < 0.01$). A statistically significant fall in respiratory quotient ($P < 0.05$), indicating a shift towards fat catabolism, was found in the controls, whereas no such change was noted in the study infants. The mean five-minute activity scores in the warm environment were compared with scores in the cold and the increase in activity was noted. The mean rise in the diazepam group was 22 units and in the control group 70 units. This difference just fails to reach significance at the 0·05 level. The deep rectal temperature fell by a mean of 0·35°C (range 0 to 1·1°C) in the diazepam group and by a mean of 0·1°C (range 0 to 0·4°C) in the controls. The skin temperature fell by a mean of 0·8°C (range 0·4 to 1·4°C) in the diazepam group and by a mean of 0·4°C (—1·2 to + 0·4°C) in the controls. All these temperature changes were just below the 0·05 level of significance.

TABLE IV—*Summary of Changes in Temperature, Metabolic Rate, and Activity on Cold Stress*

Case	% Rise in O_2 Consumption	Change in Respiratory Quotient	Change in Core Temp. (°C)	Change in Skin Temp. (°C)	Change in Activity Score
18	9	+0·02	−1·1	−1·3	35 — 70
26	− 4	+0·03	−0·1	−1·0	25 — 35
27	51	−0·05	−0·6	−0·6	30 — 70
28	9	−0·02	−0·2	−0·7	5 — 25
29	20	−0·04	−0·2	−0·4	5 — 5
30	18	−0·01	−0·4	−0·5	5 — 70
31	0	−0·06	−0·6	−1·4	30 — 20
32	− 9	+0·09	−0·2	−0·6	5 — 5
A	26	−0·02	0	−0·7	20 —205
B	20	−0·15	+0·1	+0·4	10 — 30
C	65	−0·06	0	0	0 — 60
D	40	−0·11	−0·1	+0·2	5 — 50
E	20	−0·04	−0·2	−0·9	30 —110
F	42	−0·08	−0·1	−0·2	50 — 70
Study *v.* control babies	$P < 0.01$	$P < 0.05$	$P > 0.05$	$P > 0.05$	$P > 0.05$

PLASMA LEVEL ANALYSIS

Plasma levels of diazepan and desmethyldiazepam are given in table V, and table VI shows the mean values and standard errors for low-dose and high-dose cases. There was clearly a significant difference in levels between the two groups. It should, however, be realized that the numbers of samples at two days and after four days were small, so that the standard errors of the means (S.E. of mean) have less significance than for maternal, cord, and day 1 samples. The higher plasma levels found in the high-dose group were consistent with the higher incidence of adverse effects in that group.

No benzodiazepine was detected in six control specimens taken from the mothers before administration of diazepam.

Discussion

CLINICAL EFFECTS

A total dose of 30 mg of diazepam in the 15 hours before delivery seems to have little adverse effect on the infant. The adverse effect noted in case 13 was most likely due to the administration of diazepam for 14 weeks before delivery, resulting in increased tissue storage of the drug, and this seems to be borne out by the high plasma levels and the great excess of cord over maternal diazepam.

When a total dose of 30 mg of diazepam is exceeded the incidence of neonatal complications rises. Primary or secondary apnoea may occur; poor sucking, hypotonia, and hyporeflexia make feeding difficult, and inhalation of feeds is a constant hazard. There is a high incidence of hypothermia.

RESPONSE TO COLD

The cold stress suffered by the study and control infants was of small magnitude and brief duration. In spite of this all the con-

TABLE V—*Blood Levels of Diazepam (D) and Desmethyldiazepam (DD) in g/ml*

Case No.	Drug	Maternal	Cord	24 hr	48 hr	Subsequent Levels	Cord/ Maternal Ratio of D and of DD
1	D	0·36	0·40	0·14			1·11
	DD	0·32	0·59	0·15			1·84
2	D	0·23	0·30	0·05			1·30
	DD	0·43	0·48	0·40			1·11
3	D	0·32	0·68	0·38			2·12
	DD	0·09	0·19	0·24			2·11
4	D	0·30	0·36	0·30			1·20
	DD	0·30	0·36	0·07			1·20
5	D	0·31	0·07	0·22			0·22
	DD	0·83	<0·002	0·59			—
6	D	0·19	0·23	0·16			1·20
	DD	0·42	0·48	0·24			1·14
7	D	0·15	0·23	0·29			1·53
	DD	0·16	0·17	0·24			1·06
8	D	<0·002	<0·002		<0·002	<0·002 (Day 6)	—
	DD	<0·002	<0·002		<0·002	<0·002 (Day 6)	—
9	D	0·140	0·110	0·120	0·037	<0·001 (Day 5)	0·79
	DD	<0·002	0·008	0·014	0·012	<0·002 (Day 5)	—
10	D	0·036	0·135	0·05	0·001		3·75
	DD	0	0				—
11	D	0·30	0·09		0·08	0·009 (Day 4)	0·30
	DD	0	0		0	0 (Day 4)	—
12	D	0·13	0·19		0·01	0·004 (Day 6)	1·46
	DD	0	0		0	0 (Day 6)	—
13	D	0·165	0·55		0·69	0·39 (Day 4)	3·33
	DD	0·187	0·49		0·53	0·49 (Day 4)	2·62
14	D	0·04	0·09		0·05	0·06 (Day 4)	2·22
	DD	0·04	0·08		0·08	0 (Day 4)	2·00
15	D	0·11	0·24		0·11	0 (Day 4)	2·18
	DD	0·10	0·15		0·08	0 (Day 4)	1·50
16	D	0·10	0·18		0·08	0·0 (Day 8)	1·80
	DD	0·02	0		0	0 (Day 8)	—
17	D	Not measured					
	DD						
18	D	0·62	0·62		0·47		1·00
	DD	1·11	0·71		0·91		0·64
19	D	Not measured					
	DD						
20	D	Not measured					
	DD						
21	D	0·36	0·40	0·14			1·11
	DD	0·19	0·39	0·14			2·05
22	D	0·400	0·39	0·27			0·98
	DD	0·005	0·07	0·14			14·00
23	D	0·81	0·90	0·57			1·11
	DD	0·24	0·82	0·29			3·42
24	D		0·395		0·687	0·134 (Day 5)	
	DD		0·362		2·106	0·579 (Day 5)	
25	D	0·086		0·234	0·064		
	DD	0·103		0·547	0·100		
26	D	0·38	0·22	0·07	0·15	0·09 (Day 8)	0·58
	DD	0·30	0·19	0·06	0·14	0·15 (Day 8)	0·63
27	D	0·32	0·24	0·39	0·27	0·40 (Day 6)	0·75
	DD	0·08	0·84	0·13	0·12	0·16 (Day 6)	10·5
28	D	0·37	1·00	0·36	0·31	0·21 (Day 6)	2·70
	DD	0·05	0·11	0·12	0·17	0·23 (Day 6)	2·20
29	D	1·71	1·58	1·60	0·73	0·07 (Day 7)	0·92
	DD	1·52	1·27	1·28	1·79	0·06 (Day 7)	0·84
30	D	0·73	1·09	0·85	0·79	0·03 (Day 7)	1·49
	DD	0·20	0·36	0·42	0·43	0·46 (Day 7)	1·80
31	D	0·390	0·490				1·26
	DD	<0·002	<0·002				—
32	D	0·44	0·640	0·310	0·060	0·040 (Day 7)	1·45
	DD	0·05	0·255	0·133	0·169	0·059 (Day 7)	5·10

TABLE VI—*Diazepam and Desmethyldiazepam Levels in Neonates (µg/ml)*

		Group 1		Group 2	
		Mean	S.E. of Mean	Mean	S.E. of Mean
Diazepam	Maternal	0·180	0·025	0·540	0·110
	Cord	0·241	0·045	0·664	0·117
	1 Day	0·171	0·039	0·480	0·143
	2 Days	0·132	0·081	0·350	0·097
	≥4 Days	0·058	0·048	0·240	0·093
Desmethyldiazepam	Maternal	0·181	0·057	0·321	0·139
	Cord	0·188	0·054	0·448	0·110
	1 Day	0·194	0·060	0·326	0·117
	2 Days	0·078	0·057	0·631	0·245
	≥4 Days	0·054	0·050	0·575	0·241

trol infants, including three whose mothers received 300 mg of pethidine or more in nine hours before delivery and one who was born by caesarean section under general anaesthesia, responded with an increase in activity, a rise in metabolic rate, and a fall in respiratory quotient. The study infants failed to respond, and had the cold stress continued for longer than 30 minutes the difference in skin and core temperatures would have shown greater degrees of significance. In one infant in the low-dose group (case 18) and one in the high-dose group (case 31) the duration of cold stress was reduced by 10 minutes because the skin temperatures had fallen by more than 1°C. Case 32 (high dose) was severely affected, though the mother had been given only 45 mg of diazepam in the 15 hours before delivery. She had, however, been given 5 mg three times a day for two weeks before this, and the cord and 24-hour plasma levels of the drug were high. Presumably during prolonged administration the fetal fat stores became saturated and after delivery the infant was unable to handle the subsequent larger dose.

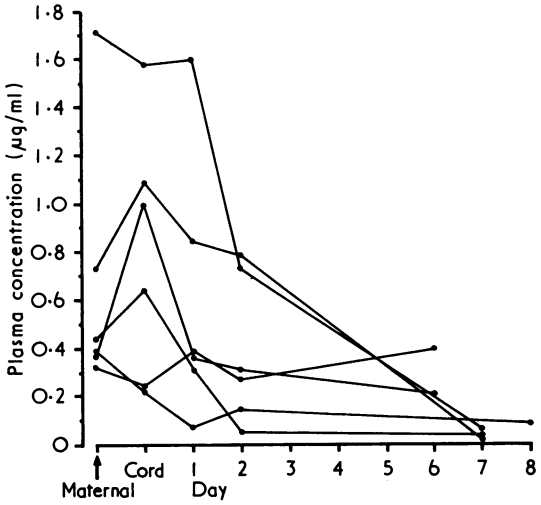

FIG. 1—Plasma concentrations of diazepam in six high-dose cases where samples were obtained beyond fifth day.

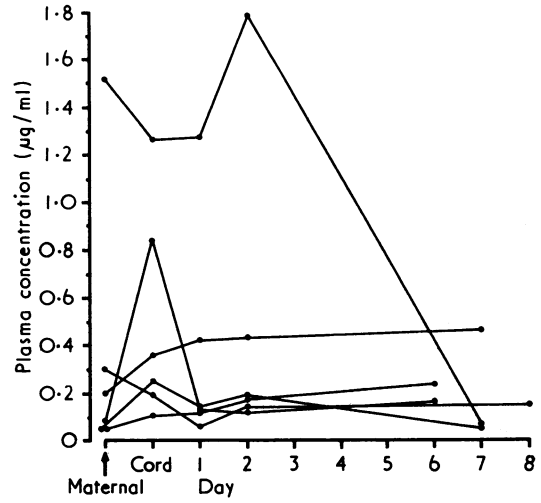

FIG. 2—Plasma concentrations of desmethyldiazepam in six high-dose cases where samples were obtained beyond fifth day.

DIAZEPAM METABOLISM

Several trends are apparent from analysis of the plasma levels. Firstly, with three exceptions the combined cord levels of diazepam and desmethyldiazepam were higher than the corresponding maternal levels. Secondly, diazepam levels fell steadily after birth in most cases (fig. 1), but in two high-dose cases there was a subsequent rise in diazepam concentration, probably indicating release of the drug from tissue stores. Thirdly, it was found that in the low-dose series desmethyldiazepam was either rapidly removed or not detected at all in the infant, whereas in the high-dose series the levels of this

metabolite fell much less sharply than diazepam, and in five cases was higher on the second day than on the first (fig. 2). Fourthly, many cases produced a plateau with virtually no fall in desmethyldiazepam over seven days (fig. 2). Desmethyldiazepam has been shown in animals to have a pharmacological activity of 70% of the parent compound (Randall *et al.*, 1965), and its persistence is therefore important. Fifthly, it was noted that a cross-over in degradation curves occurs at about two days (fig. 3), indicating conversion of diazepam to desmethyldiazepam. Lastly, in five cases appreciable levels of diazepam were found in the infant even though the mother had been given the drug intramuscularly within three hours of delivery. Thus the absorption and transfer from mother to fetus is rapid, while the metabolism in the newborn baby may be greatly impaired.

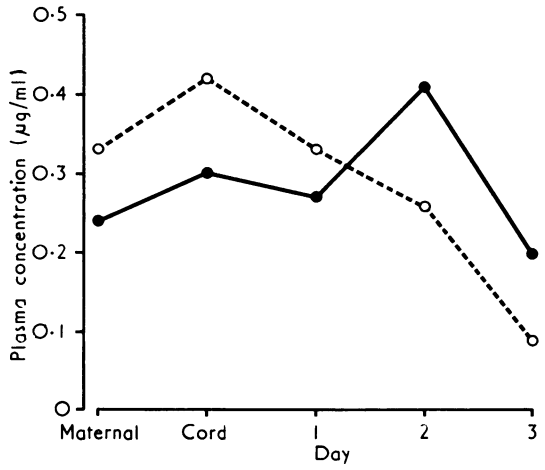

FIG. 3—Mean plasma concentrations of diazepam and desmethyldiazepam showing cross-over in degradation curves. O—O Diazepam. ●—● Desmethyldiazepam.

Conclusion

Our data show that a total dose of 30 mg of diazepam in the 15 hours before delivery has little adverse effect on the infant. When a total dose in excess of 30 mg is given over the same period there is an increased incidence of low Apgar score. The infant may become apnoeic several hours after initiation of spontaneous respiration. Hypotonia, drowsiness, and reluctance to feed occur in a high proportion. All the cases studied had an impaired metabolic response to cold, which was more profound than in those infants who had not received diazepam.

In most cases the neonate is capable of metabolizing diazepam in small doses, but the drug and its active metabolite persist for at least a week in pharmacologically active concentrations after high doses to the mother. We wish to alert all obstetricians and those caring for neonates to the effects of maternal diazepam on the newborn infant. While we recognize the value of this drug in the treatment of pre-eclampsia and eclampsia we recommend caution in the doses used and careful observation of all infants born to these mothers for at least 36 hours after delivery. This is especially important when the infant is, by virtue of its size, maturity, or underlying disease, already susceptible to hypothermia, respiratory depression, or feeding difficulty.

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References

de Alvarez, R. R., and Zighelboim, I. (1969). *Pennsylvania Medicine*, **72**, 3.
de Silva, J. A. F., and Puglisi, C. V. (1970). *Analytical Chemistry*, **42**, 1725.
Flowers, C. E., Rudolph, A. J., and Desmond, M. M. (1969). *Obstetrics and Gynecology*, **34**, 68.
Hailey, D. M., Dunn, P. M., and Thearle, M. J. (1973). *Proceedings of the Royal Society of Medicine*. In press.
Hey, E. N., and Katz, M. (1970). *Archives of Disease in Childhood*, **45**, 328.
Joyce, D. N., and Kenyon, V. G. (1972). *Journal of Obstetrics and Gynaecology of the British Commonwealth*, **79**, 250.
Lean, T. H., Ratnam, S. S., and Sivasamboom, R. (1968). *Journal of Obstetrics and Gynaecology of the British Commonwealth*, **75**, 856.
Leinzinger, E. (1969). *Die Spätgestose (EPH-Gestose)*, ed. E. T. Rippmann, p. 189. Basel, Schwabe.
Leinzinger, E. (1970). *Wiener klinische Wochenschrift*, **82**, 584.
Owen, J. R., Irani, S. F., and Blair, A. W. (1972). *Archives of Disease in Childhood*, **47**, 107.
Randall, R. O., Schechel, C. L., and Benziger, R. F. (1965). *Current Therapeutic Research*, **7**, 590.
Rosanelli, K. (1970). *Geburtshilfe und Frauenheilkunde*, **30**, 713.
Scher, J., Hailey, D. M., and Beard, R. W. (1972). *Journal of Obstetrics and Gynaecology of the British Commonwealth*, **79**, 635.
Schiff, D., Chan, G., and Stern, L. (1971). *Pediatrics*, **48**, 139.
Shannon, R. W., Fraser, G. P., Aitken, R. G., and Harper, J. R. (1972). *British Journal of Clinical Practice*, **26**, 271.
Toulouse, R., and Maffel, J. L. (1965). *Revue Française de Gynécologie et d'Obstétrique*, **60**, 263.