Effects of Fetal Exposure to Diazoxide in Man

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Milner, R. D. G., and Chouksey, S. K. (1972). *Archives of Disease in Childhood*, 47, 537. **Effects of fetal exposure to diazoxide in man.** Four infants were born to women treated with oral diazoxide for the last 19 to 69 days of pregnancy. Maternal plasma levels of diazoxide in the 5 days before delivery were related to the intake of the drug and varied between 11 and 43 $\mu\text{g/ml}$. At delivery the umbilical plasma diazoxide level was lower than that in the mother and was 6.5 to 25 $\mu\text{g/ml}$. At the age of 24 hours the plasma diazoxide level in the infants had not altered appreciably. Diazoxide was present in the amniotic fluid and was excreted in the urine in the first week of life. Urinary diazoxide excretion was greatest on days 2 and 3 and had fallen to low or undetectable levels by days 6 and 7.

No effect of diazoxide was noted on the blood pressure or blood sugar levels of the infants in the first 24 hours. The glucose tolerance of 2 of the infants was normal at 24 hours, but that of the other 2, whose mothers had diabetes, was impaired. Each of the infants developed alopecia and one had hypertrichosis lanuginosa. Abnormal hair growth was first noted at the age of 1 week and persisted when the infants were last seen at the ages of 5 months to 1 year. The bone age of 3 was normal at a chronological age of 5 to 7 months but the fourth, when aged 1 year, had retarded ossification in the wrist. No abnormalities were detected in blood counts, immunoglobulin levels, or ocular development.

Diazoxide is a hypotensive benzothiadiazine that also causes hyperglycaemia due, in part, to inhibition of insulin secretion. Though the drug is little used in the conventional treatment of hypertension because of its side effects, recent reports indicate that it may play a useful role in hypertensive nephropathy and malignant hypertension (Pohl and Thurston, 1971; Mroczek *et al.*, 1971). Diazoxide has also been used, with good effect, in the treatment of hypoglycaemic syndromes in childhood (Drash *et al.*, 1968).

The present report concerns the outcome of 4 pregnancies in which women with severe pre-eclamptic toxæmia and hypertension were treated with oral diazoxide for periods ranging between 19 and 69 days up to the time of delivery. The successful treatment of the pregnant woman is the subject of a separate report (Pohl *et al.*, 1972). As nothing was known of the placental permeability to the drug or of its metabolism by the fetus, careful study of the newborn infant was essential for the well-being of the baby and offered a chance to answer some of the simpler questions on the perinatal pharmacology of diazoxide.

Boulos *et al.* (1971) recently reported that diazoxide given intravenously in high doses to pregnant sheep caused destruction of the islets of Langerhans of the fetal lamb and had possibly other secondary effects including cataract and muscle fibrosis. Diazoxide, given to children, commonly causes hypertrichosis lanuginosa (Koblenzer and Baker, 1968) and has been reported to cause rashes, nausea, and vomiting and an advanced bone age (Drash *et al.*, 1968; Green and Berger, 1968). In the adult, fluid retention, serum protein abnormalities, and alopecia have been described as further side effects of the drug. The 4 infants exposed to diazoxide *in utero* were studied intensively in the first hours of life to determine any possible effect of the drug on blood pressure or carbohydrate metabolism. Then, bearing in mind possible long-term side effects of the drug, the subsequent progress of the babies was followed carefully. The opportunity was also taken to measure maternal and neonatal plasma levels of diazoxide and the urinary excretion of the drug in the newborn.

Methods

Maternal venous blood was drawn daily for several days before delivery to determine maternal plasma

diazoxide levels. At delivery specimens of maternal blood, umbilical cord blood, and amniotic fluid were collected. An umbilical venous catheter was inserted shortly after birth and 0.2 ml blood samples were collected at the age of 15 min, 30 min, 1, 2, 3, 6, and 12 hours for blood sugar determinations. At 24 hours a 2 ml blood sample was collected for measurement of blood sugar and plasma diazoxide levels. At 24 or 30 hours an intravenous glucose tolerance test was performed 3 to 6 hours after the last feed. An injection of 50% glucose, 1 ml/kg was given via the umbilical catheter and 0.2 ml blood samples were collected, 3, 10, 20, 30, 40, and 60 minutes afterwards. An attempt was made to collect all urine passed for several days after birth. Each urine specimen collected was stored at 4 °C until a 24-hour specimen was complete, when the total volume was measured and an aliquot stored at -20 °C. Not all the specimens were collected in each case. Each infant was nursed in an incubator initially, and during the first 6 hours of life frequent observations of heart rate and blood pressure (by the flush method) were made. After the metabolic investigations were completed and when the infant was thriving normally, no further special precautions in management were taken.

All blood samples collected for plasma diazoxide determinations were heparinized. Plasma was separated by centrifugation within 1 hour of collection and stored at -20 °C. Amniotic fluid and urine were stored similarly. Blood sugar was measured on an 'Auto-analyser' by the method of Hoffman (1937). Diazoxide concentrations in plasma, urine, and amniotic fluid were measured by the method of Symchowicz *et al.* (1967) using the appropriate biological fluid as a reference blank. The rate of disappearance of an intravenous glucose load (K_t) was calculated as described by Greville (1943).

Case Reports

Case 1. The mother was a 34-year-old primigravida who was admitted to hospital on 12 March 1971 at 32 weeks for rest because of hypertension, oedema, and albuminuria. When conservative measures, frusemide and methyl dopa, failed to control the pre-eclamptic toxæmia, diazoxide 200 mg/day was substituted for methyl dopa on 18 March. The dose of diazoxide was increased to 300 mg/day and 400 mg/day on the 4th and 13th days of treatment, respectively, and then continued at this dose until delivery after 19 days treatment on 6 April. During the period of hospitalization fetal growth remained normal as judged clinically, by maternal oestriol excretion and by ultrasonic skull scans. The osseous development of the fetus was compatible with a gestational age of 34 weeks on 24 March.

A male infant weighing 2280 g was born by caesarean section at 36 weeks. No resuscitation was required. Frequent blood pressure recordings made during the first 24 hours of life varied between 75 and 90 mmHg. No clinical abnormalities were noted at this time and Dextrostix determinations of blood glucose levels performed 3-hourly were consistently 45 mg/100 ml or

above, whereas the blood sugar levels varied between 10 and 43 mg/100 ml (Table III). The rate of disappearance of the intravenous glucose load at 24 hours was 1.69% per minute which was the greatest of the 4 infants studied, but still within normal limits for the newborn (Bowie, Mulligan, and Schwartz, 1963). Five full blood counts performed in the first month of life were within normal limits. Alopecia of the vertex was first noted on the 6th day of life and has persisted. The infant was slow to thrive initially and the body weight dropped to a minimum of 1660 g at the age of 1 week. Apart from a sticky eye no other specific clinical abnormality was detected and from the age of 2 weeks progress was uneventful. When last seen at the age of 7 months on 2 November 1971 he was developing normally and the bone age was commensurate with the chronological age.

Case 2. The 23-year-old mother had one living child from three previous pregnancies each of which had been complicated by pre-eclamptic toxæmia. When first seen in the present pregnancy at 29 weeks by dates she had a blood pressure of 140/100 mmHg and oedema. She was admitted to hospital on 26 April 1971 for rest and inpatient management. Treatment with oral diazoxide 200 mg/day and frusemide 40 mg/day began the next day. Diazoxide dosage was increased to 400 mg/day, 600 mg/day, and 800 mg/day on the 3rd, 12th, and 22nd day of treatment. After 41 days' treatment she gave birth to a daughter weighing 3600 g by a normal vertex delivery on 8 June 1971 at 35 weeks. During the period of hospitalization fetal growth had been good as judged clinically, by urinary oestriol excretion and by fetal skull scans. Radiology on 27 May suggested that the gestational age was 4 weeks in advance of that calculated from the last menstrual period.

At birth no resuscitation was needed and the infant appeared normal on examination except for a ring of alopecia around the scalp (Fig. 1A) which became more obvious in the next 2 days. Blood pressure readings were not made in the first hours of life, but the heart rate remained steady 140-150/minute, and no clinical signs of hypotensive shock were observed. In the second week of life hypertrichosis lanuginosa was noted (Fig. 1B). This progressed and when most florid involved the forehead, cheeks, sacrum, buttocks, and dorsal surfaces of the arms and legs. Full blood counts on the 2nd and 6th days of life were within normal limits and serum immunoglobulin levels on the 3rd day were IgG 895 mg/100 ml and IgM <34 mg/100 ml.

Further clinical progress was normal and when last seen on 2 November 1971 at the age of 5 months she was developing normally. The hypertrichosis lanuginosa was less; a few hairs remained over the sacrum and in the occipital region, but the alopecia had become more marked. The hair over the vertex and frontal region was short and thin (Fig. 1C). The bone age was 5 months.

Case 3. The mother was a 24-year-old insulin-dependent diabetic who had one previous successful

FIG. 1.—Case 2, (A) at 20 days, annular ring of alopecia which was present from birth; (B) at 20 days, excessive growth of hair on the forehead and face; (C) at 5 months, hair growth scanty.

FIG. 2.—Radiograph of wrist of Case 3 when aged 50 weeks showing bone age of 1 month.

pregnancy. She was admitted to hospital when 19 weeks pregnant on 27 July 1970 because of pre-eclamptic toxæmia complicating diabetic nephropathy, and she remained an inpatient until delivery on 18 November. Because of poor control of hypertension and oedema by frusemide and conservative measures, treatment with oral diazoxide began on 10 September and continued for 69 days until delivery. The daily dose varied between 300 and 400 mg. Fetal development was difficult to judge clinically because of severe hydramnios, but maternal oestriol excretion and repeated ultrasonic skull scans indicated good growth. On 6 October the radiological maturity of the fetus was 27 weeks when the gestational age was 29 weeks.

At 35 weeks' gestation a male infant weighing 2280 g was delivered by caesarean section. The condition of the infant was satisfactory at birth and thereafter. During the first 6 hours of life the heart rate remained within normal limits, 126–150/min, and 2-hourly blood pressure readings were between 70 and 85 mmHg. Blood counts on the 5th and 12th day were within normal limits. The baby had a good head of dark hair at birth, but lost it completely in the first few weeks of life. Subsequent growth of blonde hair has been sparse. The motor and mental development of the baby has remained normal up to the age of 1 year. The body weight developed along the 10th centile. On 2 November 1971 at a postnatal age of 50 weeks a radiograph of the wrist revealed one ossification centre only, corresponding to a bone age of 1 month (Fig. 2). Further radiographs revealed normal ossification centres at the head of the humerus, coracoid, head of the femur, distal femoral epiphysis, proximal and distal tibial epiphysis, talis, calcaneus, cuboid, and one cuneiform, while the capitellum of the humerus was barely visible.

Case 4. The mother was a 28-year-old insulin-dependent diabetic who had two previous normal pregnancies. She was admitted to hospital on 19 April 1971 when 32 weeks' pregnant because of pre-

eclamptic toxæmia. Treatment with frusemide and diazoxide began on 28 April and continued for 29 days until delivery on 26 May. The daily dose of diazoxide was 400 mg. Fetal growth remained normal throughout pregnancy as judged clinically and by repeated ultrasonic skull scans. The gestational age of the fetus on 24 May, judged radiologically, was 34 weeks.

A female infant, weighing 2260 g, was delivered by elective caesarean section at 38 weeks. Apart from the birthweight being below the 10th centile for the gestational age, no other abnormality was noted at birth. During the first 6 hours of life the heart rate varied between 104 and 134/min and hourly blood pressure readings were 70–80 mmHg. Full blood counts on the 13th and 26th days were normal and serum immunoglobulin levels on the 32nd day were IgG 688 mg/100 ml and IgM 89 mg/100 ml. Bilateral temporal alopecia was noted first on the 6th day of life and has persisted since. When last seen on 2 November 1971 at age 5 months the baby was clinically normal and the bone age was 3 to 4 months.

Clinical Investigations. All radiological estimates of fetal age were by the criteria of Russell (1969), and postnatal osseous development of the hand and wrist was judged according to Gruelich and Pyle (1959). The eyes of each infant were examined by an ophthalmic surgeon on 2 November 1971 and no abnormality was detected.

Results

Plasma and urinary diazoxide. Measurements of maternal plasma diazoxide levels in the 5 days before delivery showed that there was a stable plasma concentration of the drug which was related to the oral intake of diazoxide (Table I). Three mothers (Cases 1, 3, and 4) received 400 mg diazoxide/24 hr and had plasma levels ranging from 10 to 16 µg/ml. The fourth (Case 2) received 800 mg diazoxide/24 hr and had plasma levels ranging between 34 and 43 µg/ml. At birth the

umbilical cord plasma concentration of diazoxide was lower than that in the mother but was related to the maternal level. One day later the plasma concentration in the infants had not changed significantly. Diazoxide was present in the amniotic fluid of all four fetuses, at a lower concentration than that found in the cord blood.

Little diazoxide was excreted in the urine in the first 24 hours of life in Cases 1, 2, and 3. This was probably due to the low volume, for Case 4, who passed 94 ml urine in the first 24 hours, excreted 1.17 mg diazoxide in that time (Table II). Diazoxide continued to be excreted in the urine during the first 5 days but the levels became much less or were undetectable on days 6 and 7.

Blood sugar levels and intravenous glucose tolerance. Blood sugar levels were measured frequently in the first 24 hours of life (Table III). The umbilical cord levels were high in Cases 3 and 4 whose mothers were diabetic, but the subsequent levels in these two and Case 2 were within normal limits. The levels in Case 1 were lower than in the other three and this infant also had the fastest disappearance rate of intravenous glucose at 24 hours (Table IV). The rate of disappearance of glucose after intravenous injection varied from 0.41 to 1.69% per minute, all falling within the range for normal infants of 3 to 6 hours of age (Bowie *et al.*, 1963). It is noteworthy that the two infants born of diabetic mothers had glucose disappearance

TABLE I
Diazoxide Levels in Plasma and Amniotic Fluid of Mothers and Infants

Case No.	Diazoxide Level in Plasma or Amniotic Fluid ($\mu\text{g/ml}$)								
	Maternal Plasma—Days Before Delivery						Neonatal Plasma		Amniotic Fluid At Delivery
	5	4	3	2	1	At Delivery	Umbilical Cord	24 hr	
1	—	—	—	—	14.0	10.0	—	5.0	4.5
2	—	34.0	34.0	43.0	—	34.0	25.0	26.0	8.0
3	11.5	14.5	16.0	15.5	16.0	14.0	6.5	8.0	3.0
4	—	—	—	12.0	11.0	11.0	12.0	8.0	3.0

TABLE II
Urinary Excretion of Diazoxide in 4 Newborn Infants

Case No.		Day of Life						
		1	2	3	4	5	6	7
1	Urine volume (ml)	18	144	132	—	—	130	100
	Diazoxide excretion (mg)	0.23	1.96	1.12	—	—	0.78	0.25
2	Urine volume (ml)	20	116	102	—	—	99	—
	Diazoxide excretion (mg)	0.3	1.74	1.53	—	—	0.19	—
3	Urine volume (ml)	24	103	103	97	123	153	—
	Diazoxide excretion (mg)	0.20	1.13	0.77	0.29	0.25	<0.15	—
4	Urine volume (ml)	94	70	—	—	—	—	110
	Diazoxide excretion (mg)	1.17	1.05	—	—	—	—	<0.11

TABLE III
Blood Sugar Levels in First 24 Hours of Life of 4 Infants Exposed to Diazoxide in utero

Case No.	Blood Sugar (mg/100 ml) at Different Times (hr) After Birth								
	0	$\frac{1}{4}$	$\frac{1}{2}$	1	2	3	6	12	24
1	30	40	35	26	18	43	10	40	40
2	—	90	76	64	70	124	34	40	92
3	300	165	75	105	45	25	120	57	97
4	230	90	80	40	50	55	80	50	70

TABLE IV
Intravenous Glucose Tolerance of 4 Newborn Infants Exposed to Diazoxide in utero

Case No.	Age (hr)	Blood Sugar Level (mg/100 ml) at Different Times (min) After Injection of 0.5 g Glucose/kg Body Weight						Kt
		3	10	20	30	40	60	
1	24	250	150	130	115	85	65	1.69
2	30	308	206	200	188	152	176	0.41
3	24	265	252	—	140	127	102	1.17*
	30	212	150	137	152	105	105	1.12
4	24	215	180†	150	165	135	135	0.60

*Glucose tolerance at 24 hr in Case 3 was performed 50 min after last feed.

†At 6 min.

constants much below the normal range described for such infants (Baird and Farquhar, 1962).

Discussion

Each mother in this study had severe hypertension which had not responded to conventional therapy and which, if continued, might have endangered her life. Diazoxide was used as an alternative to premature delivery in the hope of improving the chances of fetal survival by prolonging pregnancy. The question raised by the use of diazoxide was whether the benefit conferred by the drug in prolonging pregnancy was offset to some extent by an effect of the drug on the fetus. While a study of four patients could not answer this question categorically, it seemed important to document the natural history of intrauterine exposure to the drug. Previous reports of the use of diazoxide in pregnancy have been confined to the effects of a single intravenous injection and no mention has been made of the fetal outcome (Finnerty, 1963; McCartney, 1967; Landesman *et al.*, 1969).

The plasma concentration of the drug in the fetus at delivery was similar to or less than that in the mother. The maternal plasma levels of diazoxide were stable in the 5 days before delivery (Table I) suggesting that the fetus had been exposed to similar levels of the drug throughout the period of treatment. Support for this interpretation comes from the observation that the plasma diazoxide level of fetal lambs whose mothers were treated with the drug was approximately half of the maternal level (Boulos *et al.*, 1971). The presence of diazoxide in the amniotic fluid suggested fetal renal excretion of the drug. The plasma diazoxide concentration changed little in the first 24 hours of life, despite some loss of the drug in the urine (Tables I and II). The urinary loss of diazoxide appeared to be related to the urine volume in the first 3 days of life, but became less thereafter,

falling to low or undetectable levels by days 6 and 7. It seems reasonable to conclude that the infant born to a mother treated with diazoxide continues to be exposed to the drug for the first week of extrauterine life.

The drug had little effect on blood sugar levels in the first 24 hours of life and the glucose tolerance of the two infants born to nondiabetic mothers was within normal limits. These findings could be taken as indirect evidence of the unimportant role played by insulin in glucose homeostasis at this time. The reduction of glucose tolerance in the two infants born to diabetic mothers was compatible with inhibition of insulin secretion in infants who are normally hyperinsulinaemic. Measurements of blood pressure in the immediate neonatal period were incomplete, but the clinical normality of each of the four infants ruled out the possibility of a serious effect of diazoxide on the cardiovascular system. Effects on the haematopoietic system or immune competence were not studied systematically, but no abnormality was noted in routine blood counts or immunoglobulin levels.

Alopecia and hypertrichosis were the only causes for concern before discharge from hospital. When the infants were seen on 2 November 1971 each still had abnormal hair growth which was most marked in Case 2 (Fig. 1C). The hair was thin and patchy over the vault of the skull. A further period of follow-up is necessary to determine the long-term effect on hair growth. The eyes were examined because of the report that one fetal lamb exposed to diazoxide *in utero* developed cataracts (Boulos *et al.*, 1971), but no abnormality was detected. The bone age was determined because of reports that some children on long-term treatment with diazoxide for hypoglycaemia had advanced bone age (Drash *et al.*, 1968; Green and Berger, 1968). In three cases the bone age judged by radiographs of the hand and wrist was in keeping with the chronological age. In the fourth

(Case 3) there was retardation of osseous development at the wrist, but further investigation showed that the overall pattern of ossification in the upper and lower limbs was within normal limits. Discrepancy between the bony development of the wrist and the rest of the limbs has been commented on before (Sontag, Snell, and Anderson, 1939). Though it is tempting to associate causally the abnormalities in the infants with intrauterine exposure to diazoxide, this was not the only drug given to the mothers. In each case diazoxide and frusemide were given together and in one of the four cases the mother had been treated with methyl-dopa before starting diazoxide treatment. The balance of evidence indicates that diazoxide probably did have a causative role in the abnormalities seen, since the drug is known to affect hair growth and bone development, whereas no such effect has been ascribed to the other drugs used.

The desirability of using oral diazoxide in pregnant women is a difficult question. The present study indicates that exposure to the drug *in utero* may affect hair growth in the infant and the permanence of the effects has yet to be assessed. On the other hand, if normal blood pressure had not been achieved by drug therapy, the women would have been delivered earlier, with greatly increased risk to the fetus and newborn infant.

We are grateful to Professor J. A. Davis for his encouragement, to the nursing staff of the Special Care Baby Unit for their help in collecting specimens, and to Mr. M. A. Ashworth who performed the diazoxide determinations.

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