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Concentrations of Cis(Z)-flupentixol in Maternal Serum, Amniotic Fluid, Umbilical Cord Serum, and Milk

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Abstract. A venous blood sample and an umbilical cord blood sample were obtained from five young women treated with the neuroleptic drug, cis(Z)-flupentixol decanoate in Viscoleo (intramuscularly) or flupentixol (orally) at the time of giving birth. In two cases amniotic fluid was also obtained, and from three of the mothers milk and simultaneous blood samples were obtained in the lactation period. Concentrations of the active drug, cis(Z)-flupentixol were measured in serum, amniotic fluid, and milk by radioimmunoassay. It was found that the concentration of the active drug in umbilical cord serum (fetal serum) was lower than that in serum from the mother – the ratio being about 0.24. Thus the amounts of drug reaching the fetus are low, but they cannot be considered unimportant. The concentrations found in milk were about 30% higher than the serum concentrations. However, the amounts of drug administered to the neonate with the milk are very low and, unless the neonate differs considerably from the adult as to sensitivity to or metabolism of this particular drug, they are of no importance.

Key words: Pregnancy – Lactation – Serum and umbilical cord serum concentrations – Milk concentrations – Cis(Z)-flupentixol

Definitive data concerning the passage of neuroleptic drugs across the placenta have not yet been established although these drugs have been given to a number of women during pregnancy. Fidelma O'Donoghue (1971) studied body fluids from fetuses and mothers after administration of chlorpromazine given as a single intramuscular dose shortly before delivery and found transplacental passage of this drug, but quantitative data were not obtained. The excretion of neuroleptics with the milk has been hardly investigated. Wiles et al. (1978) have found that chlorpromazine is excreted with milk in concentrations which are roughly the same as those found in plasma.

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Materials and Methods

In 3 years we have collected five cases where women (aged 24–29 years) have received the neuroleptic drug, cis(Z)-flupentixol; four as depot injections (Fluanxol Depot, H. Lundbeck & Co. A/S, Copenhagen, Denmark; Depixol Inj, H. Lundbeck & Co. A/S, Copenhagen, Denmark), one as oral medication (Fluanxol, H. Lundbeck & Co. A/S, Copenhagen, Denmark; Depixol, H. Lundbeck & Co. A/S, Copenhagen, Denmark) during pregnancy and lactation. Blood samples were taken occasionally during the pregnancy and at birth where a sample of umbilical cord blood was also obtained. In two cases amniotic fluid was obtained by ultrasound-guided amniocentesis with the patients' informed consent. Milk samples were obtained in the lactation period from three of the patients. A blood sample was taken at the same time. The blood samples were centrifuged and serum removed and kept frozen (−20°C) until analysis. Amniotic fluid and milk were kept in the same way as serum. The concentration of cis(Z)-flupentixol, the active compound in the depot preparation as well as in the oral preparation, was estimated in serum, amniotic fluid, and milk by a specific radioimmunoassay with a limit of sensitivity of 0.3 ng/ml (Jørgensen 1978).

Results and Discussion

The concentrations of cis(Z)-flupentixol in serum from the mother (at birth), the fetus (umbilical cord serum), and in amniotic fluid, together with the administered doses, appear in Table 1. Figures in parentheses for patient SH are the concentrations originally measured in samples labelled serum from the mother and the umbilical cord. However, as the serum concentrations measured during the pregnancy were in the range 3.1–6.4 ng/ml and the concentration on the last-but-one injection day before birth (16 days before birth) was 3.6 ng/ml, a serum concentration of 0.9 ng/ml in the mother at the day of birth is unbelievable. The most probable explanation is that an interchange has occurred and that the concentrations should appear as given in Table 1. It can be seen that the concentrations

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Table 1. Concentrations of cis(Z)-flupentixol (ng/ml) in serum from the mother (at birth), umbilical cord serum and amniotic fluid from women administered flupentixol (F) or cis(Z)-flupentixol decanoate (F-D)

Patient	Dose	Mother's serum	Umbilical cord serum	Amniotic fluid
BA	40 mg F-D/2 weeks	1.7	0.6	0.4
VL	30 mg F-D/2 weeks	2.1	0.3	0.5
SH	60 mg F-D/2 weeks	3.9 (0.9)	0.9 (3.9)	–
JP	60 mg F-D/3 weeks	4.3	0.7	–
LJ	2 mg F/day	1.3	0.4	–

Table 2. Concentrations of cis(Z)-flupentixol (ng/ml) in serum and milk from women administered flupentixol (F) or cis(Z)-flupentixol decanoate (F-D)

Patient	Dose	Serum conc.	Milk conc.	Day after birth
BA	40 mg F-D/2 weeks	1.5	0.8	4
		1.3	1.8	41
JP	60 mg F-D/3 weeks	1.4	1.8	17
LJ	2 mg F/day	1.5	1.8	30

in umbilical cord serum are considerably lower than the corresponding concentrations in serum from the mother – the mean ratio of concentrations of fetal blood to maternal blood being 0.24 regardless of whether patient SH is included. The concentrations in amniotic fluid seem to be of the same order as those of umbilical cord serum. The data show that the amounts of psychoactive drug which reaches the fetus are low, but not unimportant. The five children appeared normal on routine clinical examinations and seem to be growing normally.

The concentrations of the active drug in milk and corresponding serum samples appear in Table 2. Apart from the sample from patient BA at 4 days after birth which may be atypical as the milk has not yet attained its final composition, the data show a consistent relationship between milk and serum drug concentration, with drug concentrations in milk being about 30% higher than in serum. From the drug concentrations in milk it appears that the intake of cis(Z)-flupentixol would be about 2 µg/day for the baby on a daily milk consumption of about one litre. Taking body weights into account this is the equivalent of a dose of about 40 µg for an adult. Thus unless the neonate differs considerably from the adult in sensitivity towards the drug or in metabolism, the amount of drug administered to the neonate with the milk is negligible when flupentixol or cis(Z)-flupentixol decanoate are given to the mother in conventional doses.

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