Placental Transfer of Chlorpromazine

Case Report

A 33-year-old mother had a history of puerperal depression after the birth of her first child 6 years earlier. She presented with symptoms of a schizoaffective disorder, mainly depressive, at 36 weeks of her second pregnancy which was otherwise normal. She was sedated heavily with chlorpromazine, initially 350 mg. daily, rising to a maximum of 1800 mg. during the 5th day of treatment. She was also given occasional doses of sodium amytal, haloperidol, amitryptiline hydrochloride, diperodon hydrochloride (Akineton), and lithium carbonate. After one week of treatment, she developed albuminuria and hypertension and, after spontaneous onset of labour, delivered normally a boy weighing 3-8 kg. She had by then received a total dose of 8000 mg. chlorpromazine in 10 days, 6300 mg. having been given in the last 6 days.

The infant had an Apgar score of 7 at 1 minute and 9 at 5 minutes when cried well, but grunting respiration was noticed. This, with tachypnoea, persisted for 12 hours and he was abnormally apathetic. Chest x-ray and blood gases were normal. He was not breastfed. When examined at 24 hours he was persistently in State 2 (Prechtl and Beintema, 1964), only occasionally arousable to State 3–4. He was hypotonic with diminished spontaneous movements and depressed reflex responses. The Moro response showed a high arousal threshold. There was no asymmetry.

He remained in this state of apathy for the first 2 days and required intermittent tube feeding. By the third day, he was less sleepy and feeding well. He became jaundiced, serum bilirubin rising to a maximum of 13-5 mg. on the 4th day, and also lost 400 g, in weight, not beginning to gain weight until the 15th day.

At 6 days, he was still lethargic and slow with feeds, but examination (now in State 3–4) showed a marked improvement, particularly in tone. Responses were more easily elicited though still weaker than normal.

By the time of discharge at 3 weeks, he was lively and feeding well. He had normal tone and motility, with normal responses and reflexes.

He has since been assessed at 6 weeks, 3 months, and 6 months, and shows normal development.

Serial studies on the infant’s urine during the first few days of life showed high excretion rates of phenothiazines, initially correlating well with the clinical findings.

The phenothiazine excretion was measured directly in the urine by using the F.P.N. reaction of Forrest and Forrest (1960) and by extraction into ether (at pH 12), using the method of Lucas and Fabierkiewicz (1963).

Chromatography of the urine carried out by the method of Sunshine, Fike, and Landesman (1966), though at first considered abnormal in the amount of free phenothiazine, revealed a pattern similar to some adults taking high doses, i.e. greater than 400 mg. a day (I. Zingulas, 1968, personal communication).

Comment

In the absence of any other perinatal cause for the infant’s respiratory and central depression, it was postulated that this might be due to placental transfer of drugs, in this case chlorpromazine.

Chlorpromazine has both central and peripheral actions. The mechanism of the central effect is not fully understood but is mediated via the hypothalamus and brain-stem, and results in sleepiness, apathy, and indifference. The peripheral action is an adrenergic blockade causing postural hypotension and peripheral vasodilatation resulting in heat loss (Laurence, 1966). The drug is metabolized in the liver, and the effects last for 8 hours, but a beneficial effect on the behaviour disorders may persist for 2 weeks after the last dose (Laurence, 1966).

The administration of the drug in doses higher than 500 mg. daily in late pregnancy has been shown to be associated with an increased incidence of respiratory distress in the newborn (Sobel, 1960).

Urine studies on the infant show that he received
Short Reports

Case Report

The child, a male, was born spontaneously at term weighing 3900 g. The mother was a known heroin addict, who by her own account was taking heroin 20 mg. thrice daily and methadone 10 mg. 4-hourly intravenously. Her last dose of heroin 20 mg. was given 1 hour before delivery of the infant. Initially he gave no cause for anxiety, but at 45 hours he refused part of a feed and vomited once. One hour later he became very restless and had several clonic spasms. He passed one loose motion. Temperature was 37.4°C, respiration rate 80/minute, heart rate 180/minute.

He had a continual high-pitched cry, moderately dilated pupils, bilateral ankle clonus, and a peculiar musty odour. Hb, WBC, blood glucose, plasma calcium, and urine and stool culture were all normal. He was treated with phenobarbitone 5 mg. 8-hourly and also had morphine 3 mg. intramuscularly. This had no appreciable effect, and he was given a further 3 mg. morphine after 10 minutes and 4 hours. The second dose of morphine had little effect. The third dose rendered him stuporous. A fourth dose of morphine 3 mg. was given at 96 hours, and at 6 days chlorpromazine 2 mg. 8-hourly was substituted for the phenobarbitone. The child then became alert and was able to take feeds normally. He required no further narcotics and at 4½ months, when last seen, was developing normally.

Comment

The diagnosis of congenital morphinism is not difficult if the mother is known to be an addict. The clinical features are fever, tachycardia, tachypnoea, sweating, vomiting, diarrhoea, irritability, and fits. The cry is said to be peculiarly high-pitched and persistent. The vomiting and diarrhoea may lead to dehydration, electrolyte loss, and collapse. The mortality in untreated cases is as high as 90% (Goodfriend, Shey, and Klein, 1956).

The differential diagnosis includes the causes of fits, especially hypoglycaemia, hypocalcaemia, and meningitis, and the causes of diarrhoea and vomiting. The offspring of addicted mothers are usually small for dates and tend to suffer from the complications of dysmaturity (Perlmuter, 1967). Pneumonia seems to have been a frequent finding in those who have come to necropsy (Goodfriend et al., 1956). It is important to remember that symptoms of withdrawal are rarely present at birth and may begin as late as 96 hours (Sernoff, 1967).

Treatment consists essentially of maintenance of nutrition and fluid and electrolyte balance combined with small doses of morphine analogues. There has been much discussion regarding the relative merits of paregoric, methadone, and morphine, but no one seems to have exclusive

Congenital Narcotic Addiction

The occurrence of withdrawal symptoms in the newborn infants of mothers addicted to heroin or morphine is now well documented. The subject has been extensively reviewed by Hill and Desmond (1963) and by Cobrinik, Hood, and Chusid (1959). Nearly 300 cases have now been reported, all from the United States of America. The following is the first report of a case in the United Kingdom.

large amounts of chlorpromazine. Since he was not breast-fed, this must have been due to placental transfer. The slow clearing of the drug is explained by the immature liver of the newborn. The infant’s subsequently normal development suggests that the initial symptoms were due to a transient cause, rather than to any permanent perinatal cerebral damage.

Summary

A newborn infant, whose mother had received a high dose of chlorpromazine in late pregnancy, was found to be abnormally apathetic in the neonatal period. Drug excretion studies showed this to be associated with placental transfer of chlorpromazine.

We thank Dr. L. Stimmier for allowing us to give details of his patient.

REFERENCES


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