Neonatal barbiturate withdrawal

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Summary

An infant with neonatal barbiturate withdrawal syndrome is reported. The clinical features, diagnosis and treatment of this condition are discussed. A retrospective review of fifty-three infants of barbiturate-treated epileptic mothers indicated a high incidence of 'jitteriness' (17%) and feeding problems (36%) in the immediate neonatal period.

Introduction

Barbiturates were first introduced into medicine by Fisher and Von Mering in 1903, and they have been widely available for over half a century. With an epileptic population of 300,000, and an incidence of epilepsy in pregnancy of about 0.15%, it is surprising that neonatal barbiturate withdrawal has not received more attention in the U.K.

Case report

The mother, a 21-year-old primigravida with a 9-year history of epilepsy, had convulsions during the early part of her pregnancy, and was admitted at 30 weeks' gestation for assessment of therapy. During the rest of her pregnancy the drugs were phenobarbital 120 mg daily; primidone 1 g daily; phenytoin 450 mg daily and nitrazepam 5 mg nightly. No further convulsions occurred.

Labour was induced at 41 weeks. Pain relief before epidural anaesthesia was provided by pethidine 200 mg, promethazine 25 mg and entenox (nitrous oxide and oxygen). As a sedative for pre-eclampsia 1 litre of chlormethiazole 0.8% was given throughout labour.

A 3810 g male was born by forceps delivery. The Apgar score was 8 at 1 min. During the first 48 hr he was hypotonic and unable to suck, thereafter the tone increased and was accompanied by excessive high-pitched crying and 'jitteriness' (irritability and tremors). He was overactive and sweated profusely. Mouthing movements, sneezing and yawning were frequent. Despite a voracious appetite, feeding was accompanied by gagging, vomiting, and consequent weight-loss. The birth weight was regained only after 2 months. Electroencephalograms on the ninth and eleventh days were normal.

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As no real improvement was noted by the twelfth day, phenobarbital 7.5 mg/kg/day was commenced, and continued for 1 month, when the dose was gradually tapered. With the onset of treatment symptoms gradually abated, and by 6 weeks his behaviour and development were within normal limits.

Review of case notes

At the Aberdeen Maternity Hospital a retrospective review of the case notes of fifty-three infants of barbiturate-treated epileptic mothers did not reveal a single case fitting the full description of the barbiturate withdrawal syndrome. However, nine infants (17%) were noted to be jittery and nineteen infants (36%) had feeding difficulties. Both feeding difficulties and jitteriness were present in eight (15%). There were no associated biochemical abnormalities.

Of the fifty-three infants reviewed, three were less than 37 weeks' gestation, and a further four were small for gestational age. Thus, of this relatively well nourished mature group of infants, as many as twenty (38%) had an abnormality of neonatal behaviour.

Discussion

Transfer of barbiturates from mother to fetus is rapid, equilibrium being established within minutes. During fetal distribution there is preferential storage in the midbrain (Ploman and Persson, 1957). Neonatal behaviour is primarily midbrain in origin (Brazelton, 1970), thus abnormal behaviour following antepartum exposure to barbiturates is probably attributable to the effect of the barbiturate on the midbrain.

The first documented description of neonatal barbiturate withdrawal was by Desmond *et al.* in 1972. They indicated that the symptoms were similar to those characteristically seen in neonatal narcotic withdrawal, but intrauterine growth retardation was not a feature and symptom onset was later (range 30 min to 14 days, median 6 days). Unlike the infants of narcotic addicts, these infants had better Apgar scores and were less frequently jaundiced. Other features included jitteriness, excessive crying and alteration of the sleep pattern. Although not noted, convulsions have subsequently been reported (Bleyer and Marshall, 1972). Symptoms were milder and of

shorter duration when barbiturates were taken with other anticonvulsants.

Neonatal withdrawal is unrelated to the dose or type of barbiturate, but is probably dependent on the duration of exposure. Withdrawal is unlikely if barbiturates are taken only in the latter part of pregnancy for the prevention of hyperbilirubinaemia of the newborn. There is no apparent residual damage following withdrawal.

The diagnosis is facilitated by a history of barbiturate use in pregnancy, and such a history should be sought when neonatal behaviour is suggestive of withdrawal. In one recorded case (Bleyer and Marshall, 1972) the electroencephalogram demonstrated diffuse paroxysms of high voltage, slow-wave bursts, phenomena typical of adult barbiturate withdrawal, but in this infant it did not confirm the diagnosis.

Frequent feeds, adequate warmth and diminished environmental stimuli suffice in controlling symptoms in some infants, while others require sedation. Phenobarbital is effective, although the slow improvement noted by the present authors and others (Bleyer and Marshall, 1972) after initiation of therapy, suggests an elevated barbiturate tolerance. A dose in excess of the recommended anticonvulsant dose would probably be most effective. This should be reduced over a few months. The inability of chlorpromazine to prevent seizures in adult barbiturate withdrawal would seem to limit its use as the drug of first choice. Paregoric (camphorated tincture of opium) might be advantageous in the presence of diarrhoea. One of the first signs of improvement is the infant's ability to sleep for longer periods.

Other than failure of recognition, the rarity of this syndrome remains unexplained. In the adult, the onset and severity of withdrawal is to a certain extent dependent on the rate of excretion and degradation of the barbiturate. The rarity in the newborn may be partially explained by the prolonged half-life of barbiturate in many babies, consequent

upon immature hepatic and renal function (Jalling *et al.*, 1973).

This retrospective survey suggests that antenatal exposure to barbiturates contributed to the high incidence of jitteriness and feeding difficulties. Not surprisingly, jitteriness (Hill *et al.* 1974), vomiting (Erith, 1975) and deficient sucking (Kron, Stein and Goddard, 1966) have previously been reported following antenatal exposure to barbiturates.

It would appear that, while the complete withdrawal syndrome is uncommon, prolonged antenatal exposure to barbiturates may have a profound influence on neonatal behaviour.

Acknowledgments

The authors thank Professor A. G. M. Campbell, Dr G. Russell and Dr B. Dawson for helpful advice.

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