CASE REPORT

Serotonin syndrome in a breast-fed neonate

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SUMMARY

A late preterm presented with tachypnoea, jitteriness, irritability and low grade fever. Blood gas showed a compensated metabolic acidosis. His mother was taking the selective serotonin reuptake inhibitor (SSRI) fluoxetine, 60 mg/day, and he was exclusively breast-fed. The baby's serum level of fluoxetine on day 8 was within the adult therapeutic range and his symptoms were ascribed to fluoxetine toxicity. On changing to formula feeds, his symptoms resolved. SSRIs are commonly administered during pregnancy, but SSRI toxicity in infants is rarely reported. It is possible that this condition is under diagnosed or, alternatively, misdiagnosed as SSRI withdrawal in breast fed infants whose mothers are on SSRIs. There is limited research looking at serotonin excess in neonates, making case reports such as this important in our learning. Increased awareness may prompt more frequent measurements of blood levels in breast-fed infants whose mothers are on SSRIs.

BACKGROUND

Depressive and anxiety disorders occur in approximately 10%–15% of women during the perinatal period.[1] With many women requiring psychotropic medication, it is important for clinicians and mothers to be aware of the possible side effects to the unborn child, and, later, nursing infant.

The benefits of breast feeding are well known and is generally encouraged. However, during breast feeding, maternal medications may be excreted in the breast milk, carrying potential risks to the infant, such as neonatal toxicity and possible long-term effects on neurodevelopment.[1]

The selective serotonin-reuptake inhibitor (SSRI) fluoxetine is an antidepressant characterised by a long half-life, which ranges from 1 to 3 days after a single dose, and 4 to 6 days after long-term use. Its active metabolite, norfluoxetine has a half-life as long as 16 days. Owing to its pharmacokinetic properties, fluoxetine is more likely than other SSRIs to result in quantifiable levels in breast milk and infant serum. In utero exposure to fluoxetine will also contribute to postnatal infant serum levels.[2]

Our current guidance is that fluoxetine be kept in the lactation risk category L2—"a drug that has been studied in a limited number of breastfeeding women without an increase in adverse effects to the infant, and/or the evidence of a demonstrated risk that is likely to follow use of this medication in a breastfeeding woman is remote."[3] Therefore, mothers are usually advised that breastfeeding is not contraindicated if they are taking fluoxetine.

CASE PRESENTATION

A 36+4-week gestation infant of birth weight 2720 g was delivered by emergency caesarean section due to a prolonged second stage of labour. The baby developed regular respirations by 2 min of life. Apgar scores were 6 and 7 at 1 and 5 min, respectively. Cord gases were within the acceptable range with venous cord gas of pH 7.37, pCO2 5.4 kPa and base excess −2.2 mmol/L. He was taken to the neonatal unit on nasal CPAP in 35% oxygen. CPAP was discontinued at 7 h of age and thereafter the baby breathed spontaneously in room air.

On day 2 he was intermittently jittery. Electrolytes, calcium and blood glucose were checked and were within normal limits. He was discharged home on day 3. He continued to have 'jittery' movements, which progressively worsened. On day 7, his mother was admitted with a wound infection and the baby was reviewed. On examination, he was having jerking movements of all four limbs when awake and asleep. He was admitted to the neonatal unit for closer monitoring. It was noted that his mother was taking 60 mg of fluoxetine, the only medication that she had taken throughout her pregnancy, and that the baby was exclusively breast-fed.

On examination, the infant was extremely hypertonic and hyper-reflexic. Primitive reflexes were present. Handling and examination was very difficult due to the patient's constant jitteriness. He was tachypnoeic, with a compensated metabolic acidosis. Capillary blood gas showed a pH level of 7.42, pCO2 of 3.2 kPa, bicarbonate of 15.6 mmol/L and base excess of −6.7, lactate was 1.3 mmol/L. Low-grade fever of 37.8°C was noted.

Finnegan (4) scoring (a system routinely used to monitor physiological signs of drug withdrawal in neonates[4]) was started, with initial scores in the moderate range between 7 and 10.

INVESTIGATIONS

No seizures were noted on cerebral function monitoring or serial EEGs. Cranial US and brain MRI showed no abnormalities.

A full septic screen was negative, including viral studies on cerebrospinal fluid. A metabolic screen was also negative. Liver and renal function tests were normal throughout admission.

Urine drug screen was negative for amphetamines, opiates, methadone, benzodiazepines, cannabinoids, cocaine metabolites and barbiturates.

On day 8 of life, a serum fluoxetine level was requested. The result was 120 μg/L, a therapeutic adult level, likely to be toxic in a neonate.

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TREATMENT

Initially the patient was given intravenous antibiotic therapy for 48 h until a negative blood culture result was received. No other medications were prescribed.

When the fluoxetine level was known, the decision was made to stop breast-feeding and implement formula feeds.

OUTCOME AND FOLLOW-UP

After 5 days of exclusive formula feeding, Finnegan scores markedly improved, ranging between 3 and 6.

The baby was then discharged home at 1 month of age after being formula fed for 10 days. There was significant overall clinical improvement. He was only very mildly hypertonic with no associated jitteriness.

The baby was reviewed at 3 months of life and appeared to be developing normally, with a normal clinical examination.

DISCUSSION

It is well recognised that babies exposed to SSRIs and other psychotropic drugs in utero may develop symptoms of drug withdrawal following birth. Such symptoms include agitation, restlessness, irritability, insomnia, poor feeding, vomiting, diarrhoea, hypoglycaemia, hypothermia, respiratory distress, altered muscle tone, hyper-reflexia, tremors and seizures. A urine toxicology screen when taken shortly after birth in symptomatic babies can be used to exclude exposure to certain specified drugs.

Alehan *et al*[5] describe a case of a term infant born to a mother taking fluoxetine during pregnancy who presented shortly after birth with jitteriness and hypertonia. The infant was fully breast-fed and discharged at 6 weeks with slightly increased tone and intermittent eye deviations. At 3 years of age, the infant had mild mental retardation and microcephaly. Fluoxetine levels were not known and a diagnosis of fluoxetine withdrawal, rather than toxicity, was suggested.

In adults, features of SSRI withdrawal are very similar to those of serotonin excess, making it difficult to differentiate between the two conditions on clinical examination alone.[6]

Serotonin syndrome is a potentially life-threatening condition secondary to increased serotonergic activity in the central nervous system. It is well known in adult medicine, but has also been described in all age groups, including neonates, who have been exposed to SSRIs in utero. There are limited studies of serotonin syndrome in neonates but there is one prospective, controlled study that looked specifically at serotonergic symptoms in neonates whose mother's had taken an SSRI during pregnancy. The study found a timely relationship between declining serum drug concentrations and resolution of adverse symptoms in the neonates, suggesting that the mechanism behind the symptoms was central nervous system serotonergic overstimulation rather than an SSRI withdrawal syndrome.[7]

Our patient's persistent hyper-reflexia, rigidity, compensated metabolic acidosis and fever, on a background of a high serum fluoxetine, are consistent with Hunter's diagnostic criteria of serotonin syndrome.[8] The mechanism of the metabolic acidosis is unknown but described as a non-specific, common finding in serotonin toxicity.

In 2001, Isbister raised concerns regarding the use of the term 'neonatal withdrawal syndrome' in symptomatic neonates being born to mothers on SSRIs, as misdiagnosis could prompt the use of SSRIs to treat the condition with potential to increase toxicity.[9] Treatment of serotonin syndrome involves removal of the serotonin source and supportive care to normalise vital signs. In severe cases, serotonin antagonists such as cyproheptadine may be required alongside sedation with benzodiazepines while simultaneously discontinuing the source of the SSRI.[10] In our patient, symptoms resolved with discontinuation of breast feeding and implementation of formula feeds.

Measuring drug levels in our patient was extremely useful in finally making the diagnosis, as we compared the level to that which is known to be therapeutic in an adult. However, the problem does exist that there is no published data on what is an acceptable level of drug in a breastfeeding neonate and at what point the level becomes high enough to require cessation of breastfeeding. We can only suggest that the level be interpreted alongside clinical signs in the neonate.

Learning points

- Selective serotonin reuptake inhibitor (SSRI) toxicity does occur in the neonate.
- Toxicity may occur if a baby is breast-fed by a mother on a high dose of an SSRI. Signs and symptoms include tachypnoea, jitteriness, irritability, hypertonia, fever and compensated metabolic acidosis.
- To make the diagnosis, a drug level needs to be measured.
- Treatment options include changing or reducing the mother's medication (as directed by her physician or psychiatrist) or changing the infant's feed. Other options in severe cases, not required in our case, are a serotonin antagonist such as cyproheptadine alongside sedation with benzodiazepines.

Competing interests None declared.

Patient consent Obtained.

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