

Puerperal seizures: not the usual suspects

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Abstract

We present a case of puerperal seizures and neonatal flaccidity due to abuse and abrupt withdrawal from zolpidem, following an elective Caesarean delivery at term.

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Introduction

Neurological manifestations may result from a variety of obstetric illnesses, including eclampsia, acute fatty liver of pregnancy and amniotic fluid embolism. Pre-existing medical conditions such as hypertension, rheumatological conditions or intracranial neoplasm may worsen during pregnancy or the puerperium, leading to seizures.¹

Case presentation

A 30-year-old nulliparous woman (G2/P0) underwent elective Caesarean delivery under spinal anaesthesia at 39 weeks' gestation, due to previous vaginal surgery. Her immediate postoperative course was uneventful. However, her 3.7 kg male infant had low Apgar scores of 7 at one minute and 8 at five minutes, and had flaccid tone. After initial resuscitation because of poor respiratory effort, the infant was transferred to the neonatal intensive care unit (NICU) for respiratory monitoring.

On the second post-delivery day, our patient had a short (lasting one to two minutes) witnessed, self-limiting, generalised tonic seizure in the postnatal ward. Immediate postictal examination revealed bilateral lower limb hypertonicity, sustained clonus and confusion. She was afebrile, normotensive and normoglycaemic. Laboratory investigations such as leukocyte count, uric acid and liver function tests were within normal limits and there were no features of meningism. The patient was electively transferred to the high-dependency unit (HDU) for close monitoring and observations. Six hours after transfer to HDU, she had a similar self-limiting seizure. She remained afebrile, normotensive and normoglycaemic.

We electively started her on phenytoin (15 mg/kg) as a loading dose while an urgent brain computed tomography (CT) scan was performed. The CT scan, chest X-ray and electrocardiogram were unremarkable.

Although the patient denied drug use in pregnancy initially, a subsequent detailed history revealed that she suffered from chronic insomnia and she admitted self-administration of zolpidem 100 mg per night for over two months prior to hospital admission. She reported stopping zolpidem a day before admission to hospital for the Caesarean delivery. She had been off the medication for about 30 hours at the first seizure event and 36 hours at the second seizure.

The patient was recommenced on zolpidem 20 mg, taken at night, and reviewed by an addiction specialist. She had no further seizure episodes and was discharged from hospital on the fifth day post-Caesarean section. The possibility of neonatal withdrawal was recognised once the mother admitted to zolpidem abuse, and although the baby was described as having a poor cry on the first day of life, he showed neither respiratory failure nor irritability during the initial 48 hours in NICU. The infant was discharged from NICU after a further uneventful 48 hours of observation.

Discussion

Sleep disturbances are not uncommon during pregnancy. About 95% of women without any psychiatric illness are estimated to experience some form of sleep disturbance during the course of their pregnancy.² Benign forms of sleep disturbance may respond to simple interventions, but more severe insomnia may have a significant impact on patients' quality of life and ability to function. Zolpidem, a sedative-

hypnotic agent, has been used in pregnancy for the short-term treatment of insomnia. However, literature regarding its reproductive safety profile has been sparse.³ In a Taiwanese study, the data from 2 497 mothers who received zolpidem treatment during pregnancy, and 12 485 randomly selected mothers who did not receive the drug, were included in the analysis. The results show that the adjusted odds ratios (ORs) for adverse pregnancy outcomes such as low birthweight of infants, preterm deliveries, infants being small for gestational age, and Caesarean delivery were all higher in mothers who received zolpidem treatment during pregnancy, relative to the randomly selected controls. The authors concluded that the risk of adverse pregnancy outcomes was higher among women who received zolpidem during pregnancy than among those who did not. However, no attempt was made to manage anxiety or depression, which are more likely to be present in those with sleep disturbance and are known to be independently associated with increases in the above-mentioned adverse outcomes.³

Zolpidem is a short-acting hypnotic with an imidazopyridine chemical structure which, like other benzodiazepines, acts on the γ -aminobutyric acid (GABA) A receptors. However, zolpidem possibly has selectivity for the GABA A α 1 subunit that produces the sedative, anxiolytic and anticonvulsant activities. Binding to the GABA A α 2 subunit produces anxiolysis, while other α subunits produce the muscle relaxant effects. The normal sedative dose of zolpidem is 10 mg and it is recommended that the drug should not be taken for more than seven to 10 consecutive days. Zolpidem has an anticonvulsant effect at 10 times the sedative dose and a muscle relaxant effect at 20 times the sedative dose.^{4,5}

Zolpidem is rapidly absorbed from the gastrointestinal tract and metabolised in the liver, mediated by human cytochrome P450 (CYP) enzymes, with a dominant role of CYP3A4. Its half-life is two hours with duration of action (for 10 mg) of four hours. Zolpidem is converted to inactive metabolites and excreted primarily by the kidneys.

Zolpidem was originally considered not to have the negative effects of benzodiazepines such as tolerance, abuse, dependence, rebound insomnia, and other withdrawal effects.⁴ However, there have been many reported cases of dependence and withdrawal symptoms, such as seizures, with abrupt withdrawal of high-dose zolpidem.⁴⁻¹⁰ It is not known if zolpidem crosses the human placenta, but its molecular weight (768 g/mol) is low enough that foetal exposure may be expected. In 2007, Askew presented a case report of zolpidem abuse in a 30-year-old parturient who had a spontaneous vaginal delivery at 38 weeks. Despite the finding of a significant amount of zolpidem in the cord blood sample of the baby, the neonate was active

and alert after normal delivery. The author did not record any withdrawal symptoms, and the mother and neonate were discharged after 48 hours of observation.⁶ The finding of a significant amount of zolpidem in the cord blood sample in this case report suggests that zolpidem may cross the human placenta and exposure to the foetus is not unlikely.⁴ In our case, obvious flaccidity and respiratory depression were noted in the neonate. Zolpidem is excreted in breast milk (less than 0.02% of administered dose), but the American Academy of Pediatrics considers it compatible with breastfeeding.¹¹

We managed our patient by recommencing zolpidem 20 mg *nocte*, and prescribing diazepam 5 mg every eight hours to raise the seizure threshold. There were no further seizures and the patient was discharged from hospital on the fifth postoperative day. The baby was discharged from NICU at four days of age and no subsequent drug withdrawal effects were detected.

Conclusion

Sleep disturbance in pregnancy is not uncommon and the use of zolpidem for its treatment is increasingly becoming routine. Maternal and neonatal morbidity from its abuse and subsequent abrupt withdrawal of zolpidem was significant in this case. A focused history and a higher index of clinical suspicion may help prevent similar cases.

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