



Neonatal Abstinence Syndrome due to In-utero Exposure to Gabapentin: A Case Report

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Authors' contributions

This work was carried out in collaboration between both authors. Author MG provided the case and helped write the draft of the manuscript. Author AB managed the literature searches, designed the figures, and helped write the draft of the manuscript. Both authors read and approved the final manuscript.

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Case Study

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ABSTRACT

We report the case of a neonate who likely developed symptoms of Neonatal Abstinence Syndrome after in-utero exposure to gabapentin for treatment of maternal chronic pain. The neonate developed symptoms of hypertonicity, tremor, and poor feeding twelve hours after delivery. Although the neonate was briefly exposed to the benzodiazepine alprazolam and the opioid oxycodone, the withdrawal symptoms were not characteristic of opioid or benzodiazepine withdrawal, such as hyperphagia, vomiting and loose stools. Due to a high suspicion of gabapentin withdrawal, the neonate was successfully treated with gabapentin and clonidine. Neonatal abstinence syndrome from gabapentin has been reported in the past [1] but in each of the reports the diagnosis has been questioned due to the prolonged maternal use of multiple other agents. We present a case with distinctly different symptoms of NAS after maternal exposure to gabapentin with discussion of the diagnosis, treatment and management of these neonates.

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1. INTRODUCTION

Neonatal abstinence syndrome (NAS) can occur after delivery in newborn babies who are exposed to opioids and other substances in-utero. Use of pain medications, such as methadone, for chronic pain is a common reason for NAS. Maternal use of non-opioid medications, such as gabapentin and anti-depressants, for the treatment of chronic pain is on the rise. Gabapentin is a gamma-aminobutyric acid (GABA)-mimetic compound that is used as an anti-epileptic medication, as well as, in the treatment of chronic [2-4] and nociceptive pain [5]. Fetal exposure to gabapentin can lead to NAS after delivery [1]. Yet, the withdrawal symptoms following in-utero gabapentin exposure may be different from that of withdrawal from opioid exposure and are poorly understood. We present the case of a newborn baby who likely developed NAS after in-utero exposure to gabapentin.

2. PRESENTATION OF CASE

A 1.8-kilogram male infant was born at 34 weeks post-conceptual age, for fetal decelerations to a 41-year-old female who presented to the obstetrics department with no prenatal care. The mother reported taking gabapentin 800 mg every eight hours for chronic pain throughout pregnancy. She also had a distant history of taking a variety of medications during pregnancy including methamphetamines, alprazolam, lisinopril, oxycodone and acetaminophen. She reported stopping all of the medications except gabapentin early in the pregnancy. However, when the maternal toxicology screen was positive for opioids and benzodiazepines, the mother reported also having taken oxycodone and alprazolam shortly before arriving at the labor and delivery unit, but adamantly denied using these medications at other points in the second and third trimester of pregnancy. Gabapentin is not tested on routine drug screen at our institution, but her ingestion of the drug was confirmed as being taken throughout pregnancy since conception. The baby was born via Cesarean section due to prolonged fetal decelerations and was taken to the neonatal intensive care unit for observation and monitoring. The neonate had a grade I intraventricular hemorrhage, but no other

congenital problems. Within 12 hours after delivery the baby developed symptoms of NAS with hypertonicity, tremor, and poor feeding. The baby remained symptomatic for 10 days and required gavage feedings with an orogastric tube. Initially the medical team felt the symptoms would be self-limiting, but the anorexia and tremor continued unabated. On day of life 11 the neonatal pain service was consulted and determined that the infant was clearly withdrawing from an intra-uterine exposure, but the withdrawal symptoms were atypical for opioids and unresponsive to opioid replacement. A trial of gabapentin was initiated at a dose of 10 mg/kg/day divided every 12 hours (fig. 1). Within 24 hours the infant's tone had normalized and the tremor stopped. Finnegan abstinence scores fell to zero and his appetite improved. Within 72 hours the infant was taking all feeds orally. A gabapentin blood level was sent on 10 mg/kg/day (mid dosing interval), which was 9.8 mcg/ml (range 2-20 mcg/ml). He developed some mild irritability and loose stools, which was thought possibly due to oxycodone exposure and was successfully treated with low dose clonidine (5 mcg/kg/day given every eight hours). He was slowly first weaned off gabapentin and then clonidine over the next 3 weeks without any return of symptoms. He was discharged home without any further problems and remained symptom free at follow-up.

3. DISCUSSION

NAS was originally described for infants following prolonged in-utero exposure to maternal opioids. In the last two decades NAS has been described for in-utero fetal exposure to multiple other drugs, including barbiturates, benzodiazepines, cocaine, methamphetamine, nicotine and antidepressants. Gabapentin is a GABA-mimetic medication originally used to treat spasticity and seizures. The use of Gabapentin has expanded to include treatment for nociceptive pain, such as peripheral neuropathy and diabetic neuropathy, as well as in chronic pain states such as trigeminal neuralgia, chronic headaches, and complex regional pain syndrome in adult and pediatric patients [6-14]. Due to the effectiveness of gabapentin as a non-opioid treatment for chronic pain there are an increasing number of parturient that are maintained on gabapentin for various pain syndromes.

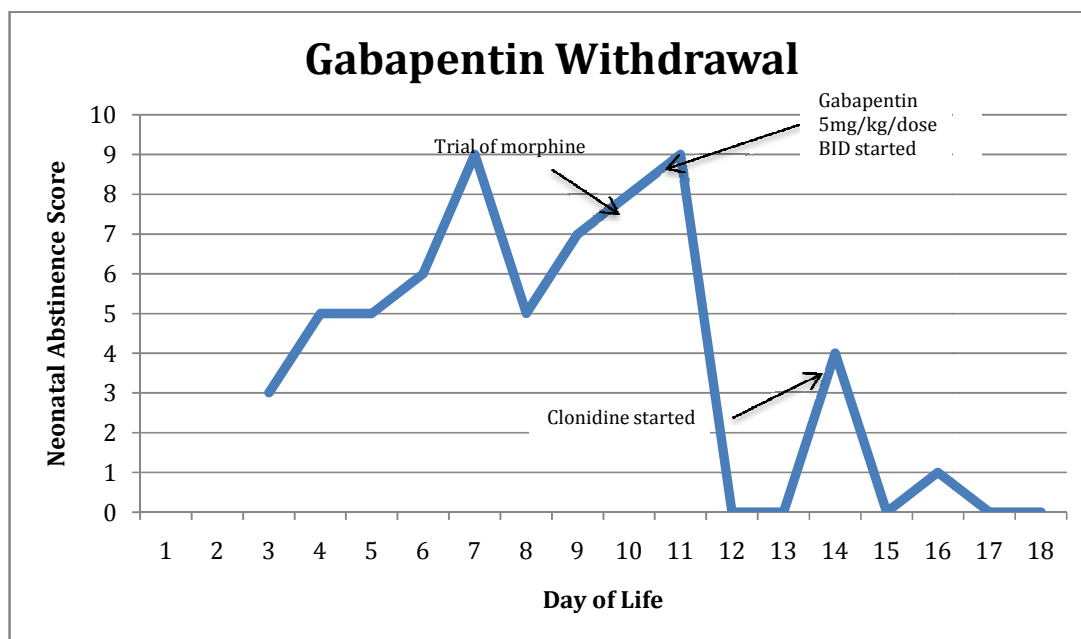


Fig. 1. Neonatal Abstinence Scores for this neonate with corresponding treatments.

Despite the increase use of gabapentin during pregnancy, there is very little literature on infants exposed to this substance in-utero. The current studies demonstrated no increased risk of congenital malformations [15-17]. However, the available literature is contradictory with respect to the effect gabapentin has on a preterm births. In a recent review of 51 patients, who were exposed to gabapentin because their mothers were taking the drug for a seizure disorder, there was no difference in the rates of cesarean section, miscarriage, low birth weight or congenital malformations compared to that of the general public [17]. However, another study looking at the effect of maternally administered gabapentin contradicted these results finding an increase in low birth weight and prematurity [18]. Even less literature exists on the potential withdrawal symptoms that neonates experience after in-utero exposure. In the study which found an increase in low birth weight and prematurity, 2 of the 61 births had symptoms of withdrawal but no details were given as to the exact symptoms or to the management. As in our case, the babies in this study were also exposed to other psychoactive agents making the diagnoses difficult to make. Since the mother's toxicology screen was positive for benzodiazepines, as a class, it was likely that this may have also affected the infant. However, withdrawal symptoms for benzodiazepines tend to be similar to the withdrawal symptoms of opioids, namely,

irritability and poor sleep. The baby in this case had symptoms, which were more similar to a fetus exposed to selective serotonin re-uptake inhibitor (SSRI) antidepressants, than opioids, such as tremor and poor feeding. Further, gabapentin has been utilized in adults experiencing opioid withdrawal as an adjuvant to methadone, but never as a sole agent to treat withdrawal. The combination of this neonate's symptoms and the successful treatment with gabapentin argues that gabapentin was the most likely agent causing the baby's NAS symptoms.

Diagnosis of gabapentin withdrawal remains challenging. The Finnegan withdrawal score is the most frequently used withdrawal scoring system [19,20] that allows healthcare providers to diagnose withdrawal, as well as follow the changes with treatment. The Finnegan score was originally designed to diagnose neonates who developed abstinence syndrome from opioids [21], has been validated for opioids, and has been used in assessing abstinence from neonatal exposure to other compounds, such as Selective Serotonin Reuptake Inhibitors, SSRIs [22]. For gabapentin, it is unclear if this scoring system is best to identify and track the response of a neonate to therapy. Given that it is our standard NAS scoring system it was used in this neonate.

The exact dosing of gabapentin in neonates remains unknown, as it is not frequently used in newborns. In pharmacokinetic studies, children less than 5 years of age had a reduced plasma concentration for a starting dose of 10 /mg/kg/day as well as an increased clearance of the medication [23,24]. Given that most treatment protocols for seizures recommend starting at a dose of 10 mg/kg/day and increasing the dose every 1-3 days, this baby was started at this initial dose. It was thought that the neonate might need larger doses and the plan was to increase the dose every 2 days until the symptoms were controlled and the abstinence scores decreased. However, in this newborn, all symptoms were controlled at the initial 10-mg/kg/day dose and the blood level was in the mid therapeutic range.

4. CONCLUSION

In summary we report the successful treatment of in-utero exposure to gabapentin, by re-introduction of the drug followed by a slow taper. Gabapentin, although usually self-limiting, withdrawal when present may require intervention with medical therapy when NAS symptoms are persistent. Infants born exposed to gabapentin should be observed closely for signs of withdrawal.

CONSENT

All authors declare that 'written informed consent was obtained from the patient's parents for publication of this case report and accompanying images.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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