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Pediatrics 2004;114:e267-e269

DOI: 10.1542/peds.114.2.e267

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://www.pediatrics.org/cgi/content/full/114/2/e267>

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American Academy of Pediatrics

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Intrauterine Baclofen Exposure: A Multidisciplinary Approach

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ABSTRACT. Maternal use of the antispasmodic baclofen during pregnancy is an uncommon clinical scenario and leads to uncertainty regarding neonatal risks. We present a team-based, peripartum management plan designed for safe monitoring and minimizing the risk of neonatal withdrawal after unusual drug exposure. Incorporating the expertise of neonatology, nursing, pharmacy, neurology, and the lactation service, as well as parental input, this consensus approach was implemented in a case of maternal oral baclofen use with a successful outcome for the infant and family. *Pediatrics* 2004;114:e267–e269. URL: <http://www.pediatrics.org/cgi/content/full/114/2/e267>; baclofen, pregnancy, neonate, withdrawal, multidisciplinary.

ABBREVIATIONS. GABA, γ -aminobutyric acid; AAP, American Academy of Pediatrics.

Baclofen (Lioresal, Lioresal-Intrathecal, Medtronic, Minneapolis, MN) is a γ -aminobutyric acid (GABA) agonist administered orally or via intrathecal pump to control spasticity secondary to spinal cord disease or injury.¹ As a GABA agonist, baclofen binds to the GABA (B) receptor, inhibiting voltage-gated Ca^{2+} channels and leading to increased K^{+} conductance and decreased presynaptic release of excitatory neurotransmitters.² For both oral and intrathecal administration, abrupt baclofen discontinuation has been associated with significant withdrawal symptoms, including hyperthermia and seizures.^{3–7} These symptoms may occur over a period of several days and respond to reinitiation of baclofen therapy. Theoretical mechanisms for baclofen withdrawal seizures include suppression of endogenous GABA synthesis or GABA receptor expression.

A literature review identified 5 case reports representing a total of 6 pregnancies complicated by maternal baclofen use where neonatal outcomes were described.^{7–9} In the single case report involving oral administration, a woman was receiving baclofen 20 mg orally 4 times a day throughout pregnancy.¹⁰ On day of life 7, the newborn was admitted with gener-

alized convulsions unresponsive to all standard anticonvulsant therapies. Baclofen was initiated at 1 mg/kg/day enterally in 4 divided doses, and the convulsions were reported to have stopped 30 minutes after the first dose. The baclofen dose was tapered slowly over the next 2 weeks without recurrence of clinical seizure activity.¹⁰

This last report raises significant concerns over the appropriate treatment of newborns after oral baclofen use during pregnancy. In the case described below, we outline a team-based management plan designed to minimize the risk for abrupt drug withdrawal in a term infant who was exposed to oral baclofen in utero.

CASE REPORTS

Maternal History

The mother of our patient was a 38-year-old gravida 3 para 0 woman with reflex sympathetic dystrophy. Prenatal screens were negative, and both previous pregnancies resulted in first-trimester spontaneous losses. The reflex sympathetic dystrophy, diagnosed first during her teenage years, led to numerous back surgeries as well as to pharmacologic therapy. During this pregnancy, she received baclofen 10 mg orally twice a day, clonazepam (Klonopin) 1 mg orally twice a day, and controlled-release oxydone (OxyContin) 50 mg orally daily in divided doses.

Prenatal Consultation

In anticipation of neonatal withdrawal issues, a prenatal consultation was arranged in the last month of pregnancy. The family was educated regarding fetal narcotic exposure and neonatal withdrawal that was to be managed with a combination of phenobarbital and narcotics.¹¹ A discussion regarding baclofen exposure and withdrawal was limited because of the lack of reported cases. However, as the due date approached, the neonatal staff, in conjunction with the pediatric neurology and pharmacy services, prepared a postnatal management strategy related to baclofen withdrawal risks. The published report that seizures could present at 7 days of life and respond only to the administration of baclofen, a medication with which most neonatal services are unfamiliar, led to our decision to begin neonatal therapy immediately after delivery.

In the previous case report, successful treatment with baclofen was initiated at 1 mg/kg/day divided into 4 doses. On the basis of the pharmacokinetic data in adults ($t_{1/2}$ 3.75 \pm 0.96 hours, 70%–85% renal clearance), this dosing interval seemed reasonable for a neonate.¹ In our case, the parents expressed a desire to expose their newborn infant to the lowest possible baclofen dose. Given that the pregnancy exposure was one quarter of the daily dose in the single case report (20 mg vs 80 mg/day), the team selected an initial dose of 0.5 mg/kg/day in 4 divided doses (one half of the reported dose to maintain a margin of safety). Realizing that the starting dose was somewhat arbitrary, the team agreed that in the absence of signs of baclofen withdrawal, we would wean the enteral dose by half every 3 days. Baclofen would be discontinued at day 10 of life, followed by a 3-day period of monitoring in the hospital before discharge.

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Received for publication Nov 11, 2003; accepted Mar 10, 2004.

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Breastfeeding

Before delivery, an additional consideration addressed was the safety and advisability of breastfeeding. Our neonatal intensive care unit lactation service was contacted to evaluate this unusual situation. Our institution currently evaluates medications using the American Academy of Pediatrics (AAP) guidelines in conjunction with *Medications and Mother's Milk* by Thomas Hale. The AAP classifies baclofen as "usually compatible with breastfeeding."¹² In the absence of AAP classification for clonazepam and oxycodone, our lactation service consulted Thomas Hale, who considers these 2 agents moderately safe for breastfeeding and recommends observing the nursing infant for sedation.¹³ In sum, the team concluded that the benefits of breastfeeding outweighed the potential risk to the infant.

Delivery

A infant girl was delivered at 39 2/7 weeks' gestation by uncomplicated cesarean section for breech presentation and maternal health considerations. Apgar scores were 7 and 8 at 1 and 5 minutes, respectively, and birth weight was 3.71 kg. The initial newborn physical examination demonstrated no apparent anomalies; however, shortly after delivery, the infant developed grunting, flaring, retracting, increased work of breathing, and course breath sounds bilaterally. The patient received continuous positive airway pressure in the delivery room and was transferred to the neonatal intensive care unit for treatment of respiratory distress.

Postnatal Course

The initial chest radiograph was consistent with retained fetal lung fluid, and within 4 hours the infant was weaned off of continuous positive airway pressure to room air with resolution of the respiratory distress. She began breast/bottle feedings on day of life 1 and tolerated them well. Additional work-up included urine and meconium toxicology and a cord blood sample sent for a baclofen level (see below). Baclofen 0.5 mg/kg/day was initiated within the first hours of life (0.5 mg/kg/day, 4 divided doses, orally or per gavage if necessary).

Neonatal Abstinence Scores over the first 24 hours of life ranged from 6 to 11, leading to the initiation of phenobarbital therapy. Opiate withdrawal signs resolved promptly without the need for concomitant oral narcotic therapy. The phenobarbital dose was weaned every 3 days as tolerated.

No signs of clinical seizure activity were detected during the hospitalization, and the baclofen wean proceeded according to plan. Baclofen was discontinued after 9 days of therapy, at the same time that the umbilical cord venous baclofen level was reported as below the limit of quantitation (0.08 $\mu\text{g}/\text{mL}$; Quest Diagnostics Nichols USA, Teterboro, NJ). After a period of observation off of baclofen but receiving low-dose phenobarbital, the patient was discharged from the hospital at day of life 16. Her neurologic examination was normal at discharge and at a 6-week follow-up visit.

DISCUSSION

Antenatal communication with our patient's family achieved 2 goals: we were able to prepare them for the possible side effects of baclofen and oxycodone withdrawal while also developing a comprehensive care plan for the postpartum period. Baclofen is a relatively small (molecular weight: 213.7), hydrophilic molecule with low protein binding (30%) and hence has the potential for both significant transplacental passage and a prolonged half-life in the neonate as a result of immature renal function and metabolic processes.^{14,15} To date, human data are insufficient to determine embryo/fetal risk after baclofen use during pregnancy.

The 6 cases in the literature and our experience described above raise the question of which baclofen dose and route of exposure during pregnancy puts a neonate at risk for withdrawal. Intrathecal baclofen

administration has not been associated with adverse neonatal outcomes, likely related to the route of administration and that daily doses are 20 to 100 times lower than the oral doses with a similar reduction in plasma levels.^{16,17}

In our case, we had to address whether there was a threshold effect for oral baclofen dosage, ie, how equivalent was the risk from maternal baclofen 80 mg/day versus 20 mg/day? We believed that a single maternal plasma baclofen level obtained during the third trimester would not be a clear indicator of fetal exposure over the entire pregnancy. Our patient had a cord blood baclofen level below detection, possibly related to maternal, placental, or fetal baclofen pharmacokinetics, and one could argue in hindsight that the neonate may not have been at significant risk for baclofen withdrawal. In the absence of definitive data on a safe level of intrauterine baclofen exposure and pending documentation of a neonatal blood level, we conclude that each neonate who is exposed to baclofen through maternal oral dosing should be a candidate for monitoring and prophylactic therapy. The dosing of prophylactic baclofen should be based on maternal dosing and titrated to effect (prevention of seizures).

The multidisciplinary team's approach was influenced strongly by the limited literature available regarding the treatment of infants who are exposed prenatally to baclofen, the report of seizures presenting at 7 days when the patient might be home, and the long-term side effects that irretractable seizures may cause. This report is designed to assist others in developing a treatment plan before the delivery of the infant to provide safe, comprehensive, and cost-effective management. The implementation of this treatment plan was aided greatly by parental involvement in its design.

ACKNOWLEDGMENT

We appreciate the efforts of Wendy Calderon in preparation of the manuscript.

REFERENCES

1. Standaert DG, Young AB. Treatment of central nervous system degenerative disorders. In: Hardman JG, Limbird LE, Gilman AG, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 10th ed. New York, NY: McGraw-Hill; 2001:549–568
2. Treiman DM. GABAergic mechanisms in epilepsy. *Epilepsia*. 2001;42:8–12
3. Terrence CF, Fromm GH. Complications of baclofen withdrawal. *Arch Neurol*. 1981;38:588–589
4. Barker I, Grant IS. Convulsions after abrupt withdrawal of baclofen. *Lancet*. 1982;556–557
5. Hyser CL, Drake ME. Status epilepticus after baclofen withdrawal. *JAMA*. 1984;76:533–538
6. Kofler M, Leis AA. Prolonged seizure activity after baclofen withdrawal. *Neurology*. 1992;42:687–698
7. Roberts AG, Graves CR, Konrad PE, et al. Intrathecal baclofen pump implantation during pregnancy. *Neurology*. 2003;8:1156–1157
8. Munoz FC, Marco DG, Perez AV, Camacho MM. Pregnancy outcome in a woman exposed to continuous intrathecal baclofen infusion. *Ann Pharmacother*. 2000;34:956
9. Delhaas EM, Verhagen J. Pregnancy in a quadriplegic patient treated with continuous intrathecal baclofen infusion to manage her severe spasticity. Case report. *Paraplegia*. 1992;30:527–528

10. Ratnayaka BDM, Dhaliwal H, Watkin S. Neonatal convulsions after withdrawal of baclofen. *BMJ*. 2001;323:85
11. Coyle MJ, Ferguson A, Lagasse L, Oh W, Lester B. Diluted tincture of opium (DTO) and phenobarbital versus phenobarbital alone for neonatal opiate withdrawal in term infants. *Pediatrics*. 2002;140:561–564
12. Ward RM, Bates BA, Benitz WE, et al. The transfer of drugs and other chemicals into human milk. *Pediatrics*. 2001;108:776–789
13. Hale TW. *Medications and Mother's Milk*. 10th ed. Amarillo, TX: Pharmasoft Publishing; 2002
14. Chasnoff IJ. Prenatal substance exposure: maternal screening and neonatal identification and management. *Neoreviews*. 2003;4:e228–e235
15. Sweetman S, ed. Martindale: The Complete Drug Reference. London, UK: Pharmaceutical Press. Electronic version, MICROMEDEX, Greenwood Village, Colorado (Edition expires 12/2003).
16. Lewis KS, Mueller WM. Intrathecal baclofen for severe spasticity secondary to spinal cord injury. *Ann Pharmacother*. 1993;27:767–774
17. Kroin JS. Intrathecal drug administration. Present use and future trends. *Clin Pharmacokinet*. 1992;22:319–326

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