Nadolol in pregnancy: A medical student's reflection on her pregnancy

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Abstract

Hypertension is a common concern during pregnancy. Beta-blockers are one potential treatment, but third trimester exposure has correlated with an increased risk of perinatal events. Nadolol, a nonselective beta blocker, has properties that differ from those of its selective counterparts, including longer half-life, decreased protein binding, and renal excretion in the unchanged form. There is very limited data on the use of nadolol during pregnancy, and its safety has not been completely evaluated. This case study documents the perinatal outcomes of nadolol use throughout a medical student's pregnancy and explores the experience in obtaining and undergoing medical care.

Keywords

Nalolol, Beta Blockers, Chronic Hypertension, Pregnancy, Medical Student Care, Neonatal Complications

Introduction

Hypertension in pregnancy is common with a prevalence of 5-10%.[1] All antihypertensives have been shown to cross the placenta with substantial evidence advising against the use of angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers due to potential harm to the fetus.[1,2] Multiple options for treatment exist but there is currently no consensus as to which agents are safest. Beta-blockers can be used, but their safety is controversial due to reports of fetal and neonatal adverse effects, including intrauterine growth restriction (IUGR) and neonatal hypoglycemia, bradycardia, and hypothermia. Nadolol, a nonselective beta blocker with a long half-life, is rarely used because of the potential detriment to the neonate.[3]

This case involves the use of nadolol during the pregnancy of a medical student and the resultant aftermath for the infant. Studies show that over 90% of medical students feel the need to seek medical care and, despite 95% having insurance, only half actually seek that care.[4,5] This patient's experience demonstrates the benefits and burdens a student has in obtaining medical care in an academic medical center; these include difficulties with access, confidentiality, financial strain and intrapersonal strain.[4-6]

Case Report

A 24-year-old primigravida in her third year of medical school had been treated with nadolol since 18 years of age for hypertension and migraine headaches. Aware of the dangers of beta blockers during pregnancy, she stopped her medication upon becoming pregnant. Cessation caused headaches, palpitations, tachycardia and dizziness. After failing other beta blockers (atenolol and propranolol), the medication was restarted, despite little published evidence. During the pregnancy, the dose was adjusted based upon her cardiac output, as measured by maternal impedance cardiography, which allowed tailoring the dose of her medication to her cardiac output. The dose ranged from 40 mg daily initially to a maximum of 120 mg at 12 weeks

gestation, before settling on 100 mg daily. Blood pressures remained satisfactory throughout her pregnancy and symptomatology improved with dose adjustments.

A two-vessel cord was diagnosed by ultrasound at 18 weeks. Nine weeks later, fetal premature atrial contractions were suspected from irregular heartbeats on fetal monitoring and confirmed with fetal echocardiogram. By 33 weeks, her son's estimated size, which had been normal, decreased to near growth restricted levels (15th percentile). Over the next five weeks, she continued weekly viability testing and periodic growth monitoring. An induction was planned at 38 weeks due to the chronic hypertension and decreasing growth parameters. She delivered a son via vaginal delivery. He weighed 2,675 grams (7th percentile) and APGAR scores were 8 and 9 at one and five minutes, respectively. A two-vessel cord was the only noted anomaly. Her last dose of nadolol had been 30 hours before delivery.

Two hours following delivery, her son was placed in a warmer after being found with a temperature of 96.6 degrees. Additionally, despite effective breastfeeding immediately after delivery, he required formula supplementation after being found to be hypoglycemic with a glucose of 36 mg/dl. He was returned to his mother four hours later, and he appeared flawless. Soon afterward however, while nursing he appeared dusky and lethargic. She immediately called for the nurses. Upon their assessment, an irregular bradycardic heart rate, hypoglycemia (glucose 31 mg/DL) and hypothermia (temperature 96.9 degrees) were seen before he was transferred to the neonatal intensive care unit (NICU).

In the NICU, he was placed in an incubator. Ampicillin and gentamycin were started until blood cultures were negative at 48 hours. Intravenous dextrose and water was required for his hypoglycemia despite intermittent feeding. The electrocardiogram (ECG) showed prolonged corrected QT interval and an irregular heart rhythm through seventeen hours of life and did not normalize until day two of life. He continued to have hypoglycemia, hypothermia, and apneic episodes until the next day. All follow-up outpatient visits since have been normal since his discharge on day five of life.

Discussion

Chronic hypertension, defined as systolic pressures of >140 mmHg and/or diastolic pressures >90 mmHg, either precedes pregnancy, is present before the twentieth week of gestation, or persists for longer than 12 weeks postpartum.[2] Mild to moderate hypertension in pregnancy is not usually treated.[1,2] Severe hypertension (systolic BP >160 mmHg and/or diastolic BP >110 mmHg) requires treatment to reduce the incidence of maternal stroke. Multiple options for treatment exist and all should be assumed to cross placenta, including methyldopa, calcium channel blockers, hydralazine, thiazide diuretics, clonidine, and beta blockers.[1]

Beta blockers are inexpensive, readily available and do not appear to be teratogenic.[1] Conversely, they are associated with fetal growth restriction, premature labor, neonatal bradycardia, hypoglycemia, and apnea.[3] Nadolol, a nonselective beta-blocker, acts at both β1 receptors, decreasing cardiac and renal sympathetic output, and β2 receptors, causing increased systemic vascular resistance but carry the side effects of constriction of airway smooth muscle.[1] It is a category C medication in pregnancy and generally considered safe after the first trimester.

Third trimester exposure however, has correlated with an increased risk of perinatal events and functional, rather than anatomic, neonatal disorders.[7]

Growth restriction is a well-known gestational effect of beta-blockers.[2] The risk of IUGR, seizures, sepsis, and respiratory distress syndrome are higher in infants born to mothers treated with beta-blockers. Decreased fetal circulation may contribute to development of small for gestational age infants.[8] Oakes et al demonstrated that propranolol, another non-selective beta blocker, can cause an 18% decrease in umbilical cord blood flow. It is reasonable that decreased nutrition from decreased umbilical cord blood flow could contribute to growth restrictions.[9]

Postnatal complications can also occur. Hypoglycemia is a well-established effect in infants born to mothers treated with beta-blockers. Low glucose can be attributed to the infant's low birth weight and fetal distress during birth,[3] but beta-blockade is known to interfere with metabolic and autonomic responses to hypoglycemia by reducing insulin sensitivity and release. Blocking catecholaminergic promotion of glycogenolysis may also increase the risk of hypoglycemia in instances when glycogen stores are already limited, as in low birth weight infants.[10,11]

Nadolol itself has different characteristics compared to other beta-blockers. Serum concentrations have been shown to be higher at 12 and 38 hours after delivery than in cord blood. Nadolol's increased effects can be explained in three ways. Primarily, neonatal hemoconcentration and redistribution of the tissue-sequestered drug levels increase postnatally. Secondarily, it is more active as it has a longer half-life and is only 30% protein bound (compared to 90% for propranolol). Finally, nadolol is excreted unchanged in the kidneys. Retention can occur by a decreased glomerular filtration in the first days of life.[3] All these factors can cause the natural effects of beta blockade to persist. This case demonstrates that the use of nadolol during pregnancy carries risk and that adverse effects will become more prevalent hours after, rather than immediately after, birth.

Like that of many parents of infants in the NICU, this birth story was drastically different than expected. As the patient, however, her experience was further altered from her accustomed role of a medical student participating in rounds. Studies show that medical students' stress in obtaining medical care exceeds that of the general population in several areas.[4] The primary cited deterrents are access to care and financial strain.[4,5] These specific concerns were perceived to be true in this case as routine obstetric office hours conflicted with required rotations. Despite regulations that allowed for time to obtain medical care, fear of missing educational rotations and the accompanying stigma from supervising residents and attendings were perceived. Financial burdens also were felt. Even with a short stay in the NICU, and despite being on her parents insurance, the hospital bill was in the thousands of dollars, placing financial strain on their family. An option to navigate these barriers of accessibility and cost is informal consultation. 46.7% of fourth year medical students have been shown to obtain informal medical advice through colleagues for easier access.[4,5] In a highly proceduralized field, this was not an option.

Student-patients also cite strain on interpersonal relationships as an impediment to seeking medical care.[4-6] For her, this was multifactorial and presented challenges as well as benefits. Confidentiality was non-existent. Every visit brought her face to face with multiple classmates

privy to many private details of her case. Also the burden of knowledge weighed heavily upon her. Overhearing nurses discuss the strangeness of the heart tracings, not knowing she was a medical student who understood all they said, increased her anxiety. Information was explained in technical terms by those who knew her training and left her with the responsibility of translating the medical jargon to an anxious husband. Feeling the need to censor some information caused her to carry an unequal portion of the knowledge burden. To compound that stress, the specter of believing that she should have prevented the entire situation haunted her and questions were left unasked as she worried that her physicians would think less of her knowledge base. Together, all of these factors create an unmet need for care of medical students that rivals the rates of at-risk patient populations.[4] While adjusting to these barriers, she recognized some benefits to being a student during her patient experience. Through it all, two close classmates were rotating through the NICU, who were able to spend extra time relaying the NICU team's concerns and plans to the family.

When reflecting on her birth story, this student remains optimistic that her future patients will benefit from the experience. Playing the role of medical student-patient presented transformative and poignant moments. These contributed to her growth and development, both personally and professionally. When medical student–patients embrace the power of these moments, they are presented with unique opportunities to become permeated with empathy, ensuring their future patients will be better treated and respected.

Conclusion

Resources for detecting and correcting the predictable metabolic and hemodynamic abnormalities associated with beta-blockade in the newborn should be immediately available, and nadolol should be avoided in pregnancy when safer options are available. Additionally, medical educators and teaching institutions should develop inexpensive and confidential health services that fit with students' demanding schedules. With the correct experiences, student-patients can embrace and integrate their personal health experiences and provide more compassionate care to their patients.

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