Beta Blockers and Lactation: An Update

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Abstract

Beta-adrenergic antagonists are one of the most commonly used class of agents in the treatment of hypertension. They have also demonstrated utility in the treatment of angina pectoris and certain arrhythmias and for the reduction in mortality following a myocardial infarction. The use of this class of agents creates the potential for beta-blocker exposure among lactating women. This review focuses on the most up-to-date data regarding the more common agents—metoprolol, atenolol, propranolol, carvedilol, nadolol, sotalol, and betaxolol—and their safety in lactating women. J Hum Lact 2000;16(3):240-245.

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Beta blockers are some of the most commonly used agents for the treatment of hypertension. Since the 1950s, numerous clinical trials have supported the use of selective beta blockers as first-line therapy for patients with chronic hypertension, angina pectoris, and certain arrhythmias and for the reduction of cardiovascular mortality in hemodynamically stable patients with definite or suspected acute myocardial infarction. The popularity of this class of agents creates a potential for beta-blocker exposure among women of childbearing age. Physicians are warned against prescribing certain beta blockers to women in their second or third trimester of pregnancy due to the potential risk of significant fetal harm, including low birth weight or size, cardiorespiratory depression, mild hypoglycemia, and growth retardation.1,3 Because only case reports or small observational studies for beta-blocker exposure during pregnancy are available, the degree of risk for beta-blocker fetopathy is unknown.

This article, the third of a three-part series, focuses on the most up-to-date information regarding beta blockers and lactation. Reviews of the current data on lactation with the group of antihypertensives, calcium channel antagonists (J Hum Lact. 2000;16:61-64), and angiotensin converting enzyme inhibitors/angiotensin receptor blockers (J Hum Lact. 2000;16:152-155) have been published previously.

Beta Blockers

The degree of excretion into breast milk of different beta-blockers (Figure 1) is dependent on their individual pharmacokinetic parameters and therefore cannot be characterized as a class. Although information is available on several different agents, most data focus on metoprolol, atenolol, and propranolol. Other agents, such as sotalol, nadolol, carvedilol, and betaxolol have been included in this review.

All beta blockers have the potential to cross into breast milk. The concern, as with all agents used by lactating women, is the risk of harm to the infant. Following initiation or dose increase of beta blockers, infants should be monitored for the signs and symptoms of adrenergic blockade, which manifests as respiratory depression, hypoglycemia, lethargy, and bradycardia.
**Metoprolol**

Metoprolol is a cardioselective beta adrenergic receptor blocker that has been extensively studied in lactating women. All reports and studies have demonstrated a substantial passage of drug into breast milk, with concentrations being greater than those found in plasma. In a case evaluation by Liedholm et al., accumulation of metoprolol was measured in three healthy, normotensive women who were given escalating metoprolol doses of 50 to 100 mg twice daily for a total of 4 days at cessation of nursing. The resulting AUC values were 2.6 to 3.7 times greater in milk than in serum. Another report by Kulas et al. of three hypertensive women who were taking 100 mg of metoprolol showed that the milk concentration was consistently greater than the plasma concentration and fluctuated based on the nursing interval. The AUC milk-plasma ratio ranged from 2.0 to 3.1. Despite these high milk concentrations, infant plasma concentrations were negligible. The authors of this study concluded that the infant’s exposure to metoprolol can be minimized if nursing is not initiated earlier than 3 to 4 hours after dosing.

These data are supported by Sandstrom et al., who evaluated metoprolol breast milk concentrations in three subsets of women. Each group demonstrated higher metoprolol concentrations in milk compared to plasma, yet the dose to the infants was negligible. The first group consisted of 10 hypertensive women who were treated with hydralazine and metoprolol (unknown dose). Despite the finding that the concentrations in breast milk were on average three times higher than those in maternal plasma, the amount of drug consumed by the neonate was negligible (less than 9 mcg/kg per feeding). The second group consisted of nine women who were treated with 100 to 200 mg daily...
of metoprolol. On average, the concentration of metoprolol in breast milk was 3.5 times higher than in plasma. Based on a 4 kg infant consuming one liter of breast milk per day, a daily dose of 0.07 mg/kg would be ingested by the infant, which is 20 to 40 times less than the normal dose for a hypertensive patient. The final group consisted of five women treated for high blood pressure with metoprolol alone or in combination with hydralazine. The concentration of metoprolol in milk was once again three times that found in plasma (1182 and 364 nmol/l, respectively). Despite the extensive degree of distribution seen with metoprolol, the American Academy of Pediatrics considers metoprolol to be compatible with breastfeeding.

Atenolol

The published data on the degree of atenolol passing into breast milk are conflicting. Some reports demonstrate equivalent concentrations in blood and milk, whereas others show significantly higher concentrations in breast milk.

A case report by Fowler et al. of a 26-year-old woman who was taking atenolol 100 mg daily for hypertension throughout her pregnancy documents similar concentrations of atenolol in maternal serum and breast milk. Although plasma atenolol was undetectable in the neonate, the neonatal urinary atenolol concentration was slightly above that in breast milk, exhibiting renal excretion of the small dose ingested via breast milk. Similarly, a case series by Thorley examined the pharmacokinetics of atenolol in five hypertensive females who were given atenolol 100 mg daily during the puerperim. Two hours after dosing, serum and milk samples were obtained. The mean milk concentration of atenolol was 630 ± 271 ng/ml, and the mean blood-milk ratio was 1.3. Atenolol seemed to be distributed between blood and milk in approximately the same proportions. No infants demonstrated symptoms of beta-adrenergic blockade. Assuming neonatal milk intake of 500 ml per day, the calculated maximum daily dose received by the infant would be 0.3 mg.

These reports conflict with that of White et al., who report on a 23-year-old woman evaluated after receiving daily doses ranging from 25 to 100 mg. The peak breast milk concentrations ranged from 2.9 to 3.6 times those found in plasma. The plasma atenolol concentration in the infant was undetectable, and the infant did not demonstrate any symptoms of adrenergic blockade. It was calculated that a maternal daily dose of 100 mg would expose the infant to 0.13 mg of atenolol per feeding. Similar results were seen in a case series by Liedholm, which looked at seven hypertensive women receiving atenolol (5 patients received 100 mg; 2 patients received 50 mg). Blood and milk concentrations were obtained before the final dose was administered and 3, 6, 9, and 12 hours later. For all patients, milk concentrations were significantly higher than those found in plasma. The mean AUC in milk was 4.5 times higher than that found in plasma. It was concluded that the calculated infant serum concentrations would be low, yet the infant should be monitored for symptoms of beta-adrenergic blockade.

Greater variations in plasma concentrations were seen in a case series by Kulas et al. of 4 hypertensive women who received a daily dose of 100 mg. The AUC milk-plasma ratios ranged from 1.1 to 3.1. Higher drug concentrations were found in the milk, yet they were negligible in the infant plasma. The authors concluded that avoidance of breastfeeding for 3 to 4 hours after dosing reduces the infant’s possible drug exposure.

Although measured concentrations in milk are low, as detailed by these studies, one case of a neonate experiencing toxic effects has been documented. Because of postpartum hypertension, the mother was prescribed atenolol 50 mg twice daily while breastfeeding. At 5 days of age, the baby girl became cyanotic and bradycardic. Breastfeeding was discontinued on day 8 of the baby’s life, and the infant was clinically normal 6 hours later. Breast milk obtained 1.5 hours after a 50 mg dose showed a concentration of 469 ng/ml. The infant serum concentration 48 hours after breastfeeding was 2010 ng/ml and 24 hours later was 140 ng/ml. Using an estimated volume of distribution of 0.55 L/kg, it was calculated that the infant must have absorbed a minimum daily dose of 8.97 mg of the 100 mg atenolol dose (50 mg twice daily) taken by the mother. The authors stressed the potential risk of breastfeeding during atenolol therapy.

The American Academy of Pediatrics has recommended that safer alternatives over atenolol should be used.

Propranolol

Propranolol is a nonselective beta-adrenergic blocker that has been shown to be secreted into breast milk. Bauer et al. evaluated both continuous dosing (40 mg 4 times daily) as well as single dosing of 40 mg in a 30-year-old postpartum woman who was treated for
premature ventricular beats. After the single dose, both milk and plasma concentrations peaked 2 to 3 hours after dosing. Breast milk concentrations were less than 40% of the peak plasma concentration. After continuous dosing, peak concentrations in the milk were 64% of those found in plasma 3 hours after the final dose. However, propranolol concentrations in plasma and milk were equal 8 hours after the final dose. Throughout dosing, no signs of adrenergic blockade were seen in the infant. Using the peak propranolol concentration (42 ng/ml propranolol in breast milk) after dosage of 160 mg/day, and assuming that the infant’s milk ingestion does not exceed 500 ml/day, the calculated maximum infant load would be 0.021 mg/day. The maximum safe neonatal dose is estimated to be 0.60 mg/kg/day. These authors conclude that the dosage ingested by the breast-fed infant would be considerably lower than the therapeutic dose. However, close observation for signs of adrenergic blockade should be carried out, especially in newborn infants, because an immature hepatic microsomal enzyme system places them at an increased risk for drug accumulation.

These findings are consistent with others’ findings. Thorley looked at five women who were receiving propranolol 40 mg twice daily. The mean blood-milk ratio 2 hours after dosing was found to be 2.0. Case reports by Taylor and Turner and Levitan and Manion involved doses ranging from 30 to 40 mg daily also demonstrated milk levels to be lower than those found in plasma. In both cases, the infant was devoid of any adrenergic symptoms, and the amount of drug to which the infant was exposed was found to be negligible.

A study of three lactating women by Livingstone et al. and Smith et al. evaluated the pharmacokinetics of propranolol and its metabolites, propranolol glucuronide and naphthoxylatic acid, in breast milk and plasma. The dose needed to achieve adequate blood pressure control was 30 to 160 mg/day. The mean peak levels of plasma propranolol and its metabolic products did not differ significantly. Although two infants developed hypoglycemia, regardless of causality, typical doses ingested by nursing infants were calculated to be approximately 0.1% of the maternal dose. In this study, propranolol was dosed during pregnancy, and it was stated that the infants would be subject to much higher doses in utero. From these data, the authors suggest that breastfeeding while receiving treatment with propranolol is safe. The American Academy of Pediatrics supports this recommendation.

**Carvedilol**

It has been documented in animal studies that carvedilol is excreted into milk; however, the degree of passage in humans is unknown. Therefore, the manufacturers recommended that the possible risks to the infant be weighed against the benefits to the mother.

**Nadolol**

Nadolol is a long-acting beta blocker that exhibits a small degree of protein binding. There is little information about the safety of nadolol to the infant when used by lactating mothers. The most extensive data have been reported by Devlin et al., who studied 12 normotensive lactating females who took 80 mg daily for 5 consecutive days. Milk and serum levels were obtained before, during, and after dosing. Twenty hours after dosing, drug levels in milk were considerably higher than those found in the serum, 442.9 ± 47.1 ng/ml and 161.9 ± 16.7 ng/ml, respectively. Based on daily milk production of 1 liter and a mean steady-state milk level of 356.9 ng/ml, it was calculated that the total amount of nadolol in maternal milk would be 0.356 mcg/kg/day. Assuming equivalent dosing on a weight basis for adults and children, a 5 kg infant would receive 2% to 7% of the therapeutic infant dose (0.5 to 2.5 mg/kg/day). It was concluded that nadolol should be used with caution in lactating women.

Another case report by Fox et al. of a 37-year-old hypertensive woman who was taking 20 mg daily also demonstrates passage into breast milk. Milk levels 36 hours after dosing were 146 ng/ml. Based on the above findings, the American Academy of Pediatrics finds nadolol compatible with breastfeeding, but due to limited data, it is recommended that infants be monitored for symptoms of beta blockade.

**Sotalol**

Sotalol is a beta blocker used most often for the treatment of ventricular arrhythmias. O’Hare et al. studied the effects of sotalol in five hypertensive women. Each received an initial daily dose of 200 mg, with dose escalation in 200 mg/day increments to achieve a blood pressure of less than 140/90 mm Hg. Mean drug concentrations were 10.5 ug/ml in milk and 2.3 ug/ml in maternal plasma, resulting in a milk-plasma ratio of 4.6. No adverse events were seen in the breastfed infants. O’Hare et al. concluded that due to the high sotalol levels obtained, a possible risk to the infant may be evident and therefore use should be avoided during lactation.
The extensive passage of sotalol into breast milk is further supported by two case reports.\(^{26,27}\) In a 22-year-old woman with palpitations from cardiomyopathy who was taking 240 mg of sotalol daily, the milk-serum ratios varied depending on the time since feeding and the maternal dose but ranged from 2.43 to 5.64.\(^{26}\) Based on an average milk intake of 0.15 kg/day, it was calculated that the infant would receive 20% to 23% of the maternal dose (0.41 to 0.58 mg/kg). The dose recommended for an infant is 2 to 4 mg/kg/day. From this information, the author recommended breastfeeding only if close monitoring of the infant could be provided. In another case report, a 23-year-old woman was taking sotalol 80 mg twice daily and flecainide for ventricular tachycardia and premature ventricular complexes.\(^{27}\) Milk and serum levels were obtained on days 5 and 7 postpartum, resulting in a milk-plasma ratio of 3.57 and 2.75, respectively. Based on the above reports, the American Academy of Pediatrics finds sotalol to be compatible with breastfeeding.\(^{9}\)

**Betaxolol**

Betaxolol is a cardioselective beta-adrenoreceptor antagonist that exhibits extensive bioavailability, low protein binding, and high lipid solubility. The effects of betaxolol were studied in three hypertensive women who were taking 10 mg daily for 24 to 72 hours after delivery.\(^{28}\) Milk-to-serum concentrations ranged from 2.0 to 11.6, suggesting accumulation of betaxolol in breast milk. It was determined that with ingestion of 300 to 500 ml of milk per day, the dose given to the infant would be 0.006 to 0.03 mg/kg/day. Reference doses in adults are 0.15 to 0.30 mg/kg/day. The use of betaxolol has not been studied in infants and children. The American Academy of Pediatrics\(^{9}\) and the manufacturer of betaxolol\(^{29}\) recommend that infants whose mothers are taking betaxolol be monitored for symptoms of beta blockade.

**Conclusion**

The choice of antihypertensive therapy in lactating women, when pharmacological intervention is needed, is dependent on the patient’s response to medication and the amount of drug excreted in the milk. Based on the literature reviewed, metoprolol, propranolol, and nadolol may be considered compatible with lactation. Due to the limited or conflicting data available on atenolol, carvediolol, sotalol, and betaxolol, similar conclusions cannot be drawn. Although many of these agents have been deemed safe, the infant should be carefully monitored for symptoms of beta blockade on initiation of therapy or dose increase. Both the clinician and the mother have to consider the risk-benefit ratio when maternal medication is prescribed.

**References**