Is It Safe to Use Opioids for Obstetric Pain while Breastfeeding?

The report by Lam et al in this issue of The Journal examines central nervous system (CNS) depression of neonates who were breastfed by their mothers receiving oxycodone for postpartum analgesia.\(^1\) Approximately half of all infants born in North America are either delivered via cesarean delivery or with the use of an episiotomy to facilitate vaginal delivery. Until recently, combination products containing acetaminophen and codeine or, alternatively, codeine have been used to treat pain associated with these procedures. Although generally safe for the mother, it has recently been recognized that this practice can adversely affect newborn infants.\(^2\) Specifically, according to national survey data, more than half (55%) of infants in the United States were exclusively breastfed, and 8% received formula in addition to human milk. These statistics with those on postpartum codeine use and new guidelines\(^7\) about the use of codeine during breastfeeding in North America. As a result, there is now an overall “risk-averse” attitude toward the use of codeine by breastfeeding mothers.

On the basis of this recent publicity on neonatal death and neonatal CNS depression after codeine and breastfeeding, some clinicians are now prescribing oxycodone in place of codeine during the postpartum period. However, like codeine, oxycodone is also a substrate for CYP2D6. CYP2D6 catalyzes 14% of the circulating oxycodone metabolites and is 14 times more potent than oxycodone because of its 40-fold higher affinity for the mu-opioid receptor compared with

References

oxycodeone. Before the report of Lam et al., the neonatal safety of maternal oxycodeone use during breastfeeding had not been systematically evaluated. In their report, these authors clearly show that there was a 20.1% rate of CNS depression in the infants of breastfeeding mothers taking oxycodeone, as compared with 0.5% and 16.7% in groups of mothers ingesting only acetaminophen and codeine, respectively. Consequently, oxycodeone is not a safer alternative than codeine for the treatment of obstetric pain in mothers who are breastfeeding their infants.

Paradoxically, although codeine is indicated for the treatment of mild-to-moderate pain and constitutes the second step on the World Health Organization analgesic ladder for progressive treatment of increasing pain, the therapeutic usefulness of this second analgesic step (ie, “addition of a weak opioid when pain is inadequately treated by a non-opioid analgesic alone”) has been questioned because some studies suggest that weak opioids alone or with non-opioid analgesics do not produce greater analgesia than non-steroidal anti-inflammatory drugs. If these findings are supportive of the absence of analgesic evidence for opiate and non-opiate combination therapy, it is apparent that alternative solutions for pain control during the postpartum period in women who are breastfeeding are needed so as to minimize the risk of adverse effects in the neonate.

In theory, the best solution would be not to use codeine or oxycodeone during breastfeeding at all because of a lack of appropriate studies showing its efficacy and safety in breastfeeding mothers and their infants. However, despite the lack of proven therapeutic efficacy and with the potential for fatal toxicity in the neonate associated with maternal codeine use, the wide availability of this drug, its classification by the World Health Organization as an essential medicine, and more than a century of clinical experience with its use suggest that codeine will continue to be prescribed for the treatment of postpartum pain. Consequently, a more individualized approach to using this drug in this patient subpopulation must be embraced to minimize the chance for serious adverse events in the neonate. At the simplest end of this spectrum, prudent approaches might involve consideration of codeine pharmacokinetic properties (eg, time to peak concentration in plasma and breast milk, ratio of milk to plasma) and their extrapolation to the timing of drug administration and breastfeeding to lower potentially the milk-transmitted codeine dose with more intensive monitoring of the infant for expected code adverse events (eg, CNS depression, acute appearance of poor suck response, and/or feeding difficulty). The other end of the spectrum might involve prenatal CYP2D6 genotyping in mothers who plan to breastfeed. Through the use of established CYP2D6 activity scores, this would enable a priori prediction of mothers who are CYP2D6 ultrarapid metabolizers and, by inference, indicate a potentially greater risk profile for codeine in their infants. Finally, in mothers in whom an opiate represents the only potentially effective therapeutic option for postpartum pain control (ie, demonstrated non-response to appropriate doses of acetaminophen or ibuprofen), the least potent opiate (codeine) should be used at the lowest dose that provides pain relief; recognizing that this may represent either the absence or reduction of discomfort. Finally, as reflected by the current study and the general approach used by the Motherisk program in the last two decades, it is critical that drug use during and immediately after pregnancy be systematically evaluated not simply on the basis of historical context, but also by engaging relevant science and technology (eg, concentration monitoring, pharmacogenetics) to understand the association between drug exposure and response, both therapeutic and adverse. Only then can the most rational, necessary therapeutic decisions be made and, in the process, the risk to the newborn infant more effectively mitigated. In this way, we can provide the best care to mothers and their infants who often may depend on pharmacotherapy to improve their health and welfare.

Finally, the present study and other reports have shown that there is a high concordance between CNS depression in the mother and that in the baby. As a consequence, when the mother exhibits CNS depression, the baby should be examined by a pediatrician. Also, in these cases and other literature cases, the severe CNS depression emerged after 4 days of use, when milk output increases. Therefore, any maternal need for these opioids >4 days after delivery should be monitored carefully, and the mother’s need for adequate pain control should not be neglected.

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Sickle Cell Disease does not Decrease Pulmonary Nitric Oxide

In this issue of *The Journal*, Radhakrishnan et al show that airway levels of nitric oxide (NO) are high in patients with sickle cell disease (SCD). This observation is precisely the opposite of what would be predicted according to the hypothesis that NO scavenging by free hemoglobin accounts for pulmonary hypertension in SCD. This paradox highlights misconceptions about endogenous NO levels measured in the lungs.

It has been nearly 15 years since it was first reported in *The Journal* that the fraction of exhaled NO (FE\(\text{NO}\)) is high in many pediatric patients with asthma. Since then, FE\(\text{NO}\) measurement has become an important biomarker in a subset of patients with asthma and in other diseases. NO in exhaled air is conventionally thought to represent a physiologically relevant concentration of an important biological mediator, levels of which are increased in the inflamed lung because of increased inducible NO synthase (NOS) expression. However, this interpretation does not explain several contradictions. First, even during inflammation, NO levels measured in exhaled air are 1000-fold too low to relax human airway smooth muscle and 100-fold too low to relax pulmonary vascular smooth muscle. Levels are 1000-fold lower than those used therapeutically in the newborn intensive care unit. Second, NO levels are low in many conditions associated with robust airway inflammation. These diseases include cystic fibrosis and primary ciliary dyskinesia (PCD). Third, FE\(\text{NO}\) levels are actually quite low in many patients with severe asthma. Fourth, NO should be beneficial for pulmonary hypertension by sequestering bioactive NO radical in the lung; yet this is the opposite of what was found.

With regard to the hyperhemolysis issue, this paradigm has recently been criticized extensively on scientific grounds and on the basis of common sense. For example, patients with paroxysmal nocturnal hemoglobinemia (PNH) have intravascular hemolysis. This contrasts with patients with SCD in whom hemolysis is primarily extravascular (splenic). Patients with PNH have plasma hemoglobin levels at least 10-fold higher than those encountered in patients with SCD. Yet patients with PNH do not have pulmonary hypertension. In a more common pediatric example, neonates who have hemolysis from ABO incompatibility typically have high plasma hemoglobin levels. Yet pulmonary hypertension fails to develop in these babies, although they are at term and at risk for persistent pulmonary hypertension. The entire hyperhemolysis paradigm lacks biological plausibility: intravascular levels of endogenous NO are virtually undetectable—even in the absence of cell free hemoglobin.

The second issue raised by the data of Radhakrishnan et al is why do some patients with high levels of airway inflammation—like those with PCD—have normal or low levels of pulmonary NO? In chronic obstructive pulmonary disease and cystic fibrosis, bronchial NO flux and alveolar NO concentration are normal or low. Even in severe asthma, a major subpopulation has very low levels of FE\(\text{NO}\). Radhakrishnan et al go on to show that arterial NO levels are not determinants of airflow obstruction, in PCD or SCD. Thus, contrary to popular belief, endogenous NO is: (1) not a general biomarker of inflammation; and (2) neither a positive (through bronchodilatation) nor a negative (through inflammation) determinant of airflow obstruction.

These contradictions are resolved by appreciating that NO radical is over-rated as a mediator. NOS products other than NO carry out most effects downstream of NOS activation—radical is over-rated as a mediator. NOS products other than NO carry out most effects downstream of NOS activation.