



REVISTA BRASILEIRA DE ANESTESIOLOGIA

Publicação Oficial da Sociedade Brasileira de Anestesiologia
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REVIEW ARTICLE

Should maternal anesthesia delay breastfeeding? A systematic review of the literature



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Received 4 July 2018; accepted 6 November 2018

Available online 26 December 2018

KEYWORDS

Anesthetic drugs;
Anesthetic effect;
Exclusive breast
feeding

Abstract

Introduction: The importance and benefits of breastfeeding for the babies and mothers are well established and documented in the literature. However, it is frequent that lactating mothers need to undergo general or spinal anesthesia and, due to the lack of information, many of them interrupt breastfeeding after anesthesia. There are limited data available regarding anesthetics transfer to breast milk. This review aims to develop some considerations and recommendations based on available literature.

Methods: A systematic search of the literature was conducted by using the following health science databases: Embase, Lilacs, Pubmed, Scopus, and Web of Science. The latest literature search was performed on April 6th, 2018. Additional literature search was made via the World Health Organization's website. We used the following terms for the search strategy: "Anesthesia" and "Breastfeeding", and their derivatives.

Results: In this research, 599 registers were found, and 549 had been excluded by different reasons. Fifty manuscripts have been included, with different designs of studies: prospective trials, retrospective observational studies, reviews, case reports, randomized clinical trials, case-control, and website access. Small concentrations of the most anesthetic agents, are transferred to the breast milk; however, their administration seem to be safe for lactating mothers when administered as a single dose during anesthesia and this should not contraindicate the breastfeeding. On the other hand, high-doses, continuous or repeated administration of drugs increase the risk of adverse effects on neonates, and should be avoided. Few drugs, such as diazepam and meperidine, produce adverse effects on breastfed babies even in single doses. Dexmedetomidine seems to be safe if breastfeeding starts 24h after discontinuation of the drug.

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Conclusions: Most of the anesthetic drugs are safe for nursing mothers and offer low risk to the breastfed neonates when administered in single-dose. However, high-dose and repeated administration of drugs significantly increase the risk of adverse effects on neonates. Moreover, diazepam and meperidine should be avoided in nursing women. Finally, anesthesiologists and pediatricians should consider individual risk/benefit, with special attention to premature neonates or babies with concurrent diseases since they are more susceptible to adverse effects. © 2018 Published by Elsevier Editora Ltda. on behalf of Sociedade Brasileira de Anestesiologia. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

PALAVRAS-CHAVE

Anestésicos;
Efeito anestésico;
Aleitamento materno
exclusivo

A anestesia materna deve atrasar a amamentação? Revisão sistemática da literatura

Resumo

Introdução: A importância e os benefícios do aleitamento materno para os bebês e para as mães estão bem estabelecidos e documentados na literatura. No entanto, é frequente que mães lactantes precisem se submeter à anestesia geral ou raqui-anestesia e, devido à falta de informações, muitas delas interrompem a amamentação após a anestesia. Existem poucos dados disponíveis sobre a transferência de anestésicos para o leite materno. O objetivo desta revisão foi desenvolver algumas considerações e recomendações com base na literatura disponível.

Métodos: Uma busca sistemática da literatura foi realizada usando os seguintes bancos de dados em ciências da saúde: Embase, Lilacs, Pubmed, Scopus e Web of Science. A pesquisa bibliográfica mais recente foi realizada em 6 de abril de 2018. Uma pesquisa bibliográfica adicional foi realizada através do site da Organização Mundial da Saúde. Usamos os seguintes termos para a estratégia de busca: "Anestesia" e "Aleitamento materno", e seus derivados.

Resultados: Nesta pesquisa, 599 registros foram encontrados e 549 foram excluídos por diferentes razões. Foram incluídos 50 manuscritos, com diferentes modelos de estudos: estudos prospectivos, estudos observacionais retrospectivos, revisões, relatos de casos, ensaios clínicos randômicos, caso-controle e acesso a sites. Pequenas concentrações da maioria dos agentes anestésicos são transferidas para o leite materno; entretanto, sua administração parece ser segura para mães lactantes quando administrados em dose única durante a anestesia e isso não deve contraindicar o aleitamento materno. Por outro lado, altas doses, administração contínua ou repetida dos fármacos aumentam o risco de efeitos adversos em neonatos e devem ser evitados. Poucas drogas, como diazepam e meperidina, produzem efeitos adversos em bebês amamentados, mesmo quando administradas em doses únicas. Dexmedetomidina parece ser segura se a amamentação começar 24 horas após a interrupção do medicamento.

Conclusões: A maioria dos anestésicos é segura para mães que amamentam e oferecem baixo risco para os recém-nascidos amamentados quando a administração é em dose única. No entanto, altas doses e repetidas administrações de drogas aumentam significativamente o risco de efeitos adversos em recém-nascidos. Além disso, diazepam e meperidina devem ser evitados em mulheres que amamentam. Finalmente, anesthesiologists e pediatras devem considerar o risco-benefício individual, com atenção especial para os recém-nascidos prematuros ou bebês com doenças concomitantes, pois são mais suscetíveis a efeitos adversos.

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Background

The importance and benefits of breastfeeding are well established and documented in the literature. Human milk protects the infant against a variety of illnesses and infectious complications, reduces children mortality, and improves neurological development.¹ It also benefits the mother, by reducing risks of breast and ovarian cancer, Type II diabetes, and postpartum depression.¹ That is why the World Health Organization (WHO) and the American

Academy of Pediatrics (AAP) so strongly support breastfeeding, especially in the first six months of life.^{1,2}

It is frequent that lactating mothers need to undergo general or spinal anesthesia and, due to the lack of information, many of them interrupt breastfeeding because of the theoretical exposition of the breastfed baby to the administered anesthetic drugs.³ Most of the times, drug transfer to milk is negligible and the risks to the newborn are minimal. Hence, the interruption of breastfeeding can be more harmful to the child than the ingestion of small amounts of anesthetics.

Moreover, the use of labor pain relief medications is a controversial issue that has been raising concerns about safety, interference with labor, and birthing.⁴ As an example, many authors believe that use of labor analgesia causes neonates to exhibit disorganized, ineffective suckling at the breast, and mothers to proceed to early unintended weaning due to breastfeeding difficulties.⁵

There are limited data available; accordingly, research regarding anesthetics transfer to breast milk in humans is rare because of ethical implications of studies with mothers and babies. This review aims to develop some considerations based on available literature. Also, we aim to encourage further research to expand current knowledge (Table 1).

Methods

A systematic search of the available literature was conducted by using the following health science databases: Embase, Lilacs, Pubmed, Scopus, and Web of Science. The search terms used were (Anesthesia or Anesthetics or Anesthetic Drugs or Drugs, Anesthetic or Anesthetic Agents or Agents, Anesthetic or Anesthetic Effect or Effect, Anesthetic or Anesthetic Effects or Effects, Anesthetic) and (Breast Feeding or Feeding, Breast or Breastfeeding or Breast Feeding, Exclusive or Exclusive Breast Feeding or Breastfeeding, Exclusive or Exclusive Breastfeeding). There was no restriction regarding language or date of the article publication. The latest literature search was performed on April 6th, 2018. Moreover, an additional literature search was made via the WHO website: <http://www.who.int> on April 15th, 2018.

Two authors (MRO and MGS) independently screened the trials identified by the literature search. The authors examined each title and abstract to exclude clearly irrelevant studies and duplicates, and identified potentially relevant articles to be retrieved as a full-text article. The disagreements were resolved by consulting with another author (LHNL), who was also responsible for the quality assurance of the processes. The remaining authors (RML, NSPM, and DAA) independently determined the eligibility of full-text articles retrieved. The names of the author, institution, journal of publication, and results were unknown to the three investigators at this time. For the data extraction and management, two authors (MRO and MGS) independently evaluated the full-text articles. Any discrepancies were resolved by discussion with a third author (LHNL) (Table 2).

Results

From the search of the referred health science databases, 599 registers were found. After the analysis of manuscripts' titles, 549 registers were excluded because of the duplicity of titles (46 registers) and offtopic manuscripts (503 registers). Fifty articles were eligible. Fig. 1 depicted the summary of the literature search, based on PRISMA 2009 flow diagram.⁶

The 50 studies included in this systematic review consisted of 16 reviews, 13 prospective trials, 4 retrospective observational studies, 6 case reports, 9 randomized clinical trials, 1 case-control study, and 1 website access (Table 3).

The magnitude of the risk of neonatal exposure to drugs in maternal plasma can be expressed by various indices, such as the milk-to-maternal plasma ratio (M/P ratio) and the infant-exposure index.⁷ The M/P ratio is obtained by dividing the drug concentration in breast milk to its concentration in maternal plasma. This ratio may vary according to the time after drug administration in which milk sample is collected.^{3,8} If the M/P ratio is <1 (less drug in milk than in plasma), it is considered usually safe to proceed with breastfeeding.⁹ The infant-exposure index is the ratio of the weight-adjusted dose of the infant to the weight-adjusted dose of the mother, and indicates the cumulative drug exposure.³ This index is calculated by the assumption of infants' milk ingestion of approximately 150 mL.kg⁻¹.day⁻¹.^{3,8} It has been suggested that indices <10% are unlikely to be of pharmacologic significance.^{3,9}

Effect of the individual class of drugs

Benzodiazepines

Diazepam should be avoided even in single doses in breastfeeding mothers due to its adverse effects in the neonate. Midazolam, on the other hand, seems to be safe when administered as a single dose.

Hypnotics

The main induction agents (propofol, thiopental, and etomidate) seem to be safe for lactating mothers when administered as a single dose at the induction of anesthesia.

Inhalational anesthetics

We have found little or no data regarding the exposure of nursing mothers to inhalation anesthetics. Halothane and xenon gas seem to be safe because their concentration in milk were considered negligible. As for isoflurane, enflurane, sevoflurane, and desflurane, the theoretical risk for the suckling infant is considered low because of their pharmacokinetic profile. Also, regarding nitrous oxide, we have not found clinical trials of its intrapartum use with breastfeeding as the primary outcome. But there is some evidence that it has the potential to cause positive effects on both women's psychoemotional experience of labor and breastfeeding success.¹⁰

Alfa₂-agonists

Dexmedetomidine seems to be safe if the breastfeeding starts 24 h after the discontinuation of the drug (Table 4).

Reversing agents

Neostigmine is safe for lactating mothers when used in high doses for myasthenia gravis treatment. Hence, we can infer that the small doses of this drug used in anesthesia offer no risk for the breastfed infants.

Opioids

Meperidine should be avoided even in single doses in breastfeeding mothers due to its adverse effects in the neonate. The other opioids seem to be safe when administered as a single dose.

Table 1 Summary of results from studies regarding Benzodiazepines.

Identification of the study	Type of study	<i>n</i>	Inclusion criteria	Anesthetics drug evaluated	Dose of drug	Evaluated outcomes	Recommendation of the study
Patrick MJ et al., 1972	Case report	1	1 week-old baby whose mother was taking Diazepam.	Diazepam	30 mg.day ⁻¹ per 3 days	Neonate with lethargy, weight loss and EEG consistent with sedative medication.	Best to avoid.
Cole et al., 1975	Retrospective observational study	9	Breastfeeding mothers receiving Diazepam for post-partum tranquilization due to persistent hypertension.	Diazepam	Not mentioned	High amounts of the active substance in one infant 10 days after a single dose.	Best to avoid.
Wesson et al., 1985	Retrospective observational study	1	Lactating woman with anxiety and tachycardia.	Diazepam	6–10 mg.day ⁻¹	Infant sedation (especially if within 8 h after dose).	Best to avoid.
Borgatta et al., 1997	Prospective trial	9	Lactating woman undergoing tube sterilization.	Diazepam	2.5–10 mg	Infant-exposure index = 3%.	Safe as a single dose.
Nitsun et al., 2006.	Prospective trial	5	Lactating women undergoing operative procedures with general anesthesia.	Midazolam	2 mg	Infant-exposure index <1.25%.	Safe as a single dose.
Matheson et al., 1990	Randomized study	2	Lactating women who needed sleeping pills after giving birth (5 day-period).	Midazolam	15 mg VO	M/P ratio = 0.15.	Safe as a single dose.

Table 2 Summary of results from studies regarding hypnotic drugs.

Identification of the study	Type of study	<i>n</i>	Inclusion criteria	Anesthetics drug evaluated	Dose of drug	Evaluated outcomes	Recommendation of the study
Esener et al., 1992	Randomized clinical trial	40	Women undergoing elective cesarean section under general anesthesia.	Thiopental and etomidate	20 women received 5 mg.kg ⁻¹ thiopental at the induction. 20 women received 0.3 mg.kg ⁻¹ etomidate at the induction.	Thiopental–colostrum: plasma ratios = 0.67–0.68. Etomidate–colostrum: plasma ratio = 1.2 at 30 min. No etomidate detected in the 2 h plasma samples.	Both drugs are safe as a single dose.
Andersen et al., 1987	Prospective trial	16	8 lactating women undergoing minor elective surgery and 8 women undergoing elective cesarean section.	Thiopental	Patients received 5 mg.kg ⁻¹ mean at induction time.	M/P ratio < 1 in both groups.	Safe as a single dose.
Nitsun et al., 2006.	Prospective trial	5	Lactating women undergoing operative procedures with general anesthesia.	Propofol	Patients received 2.5 mg.kg ⁻¹ at induction of anesthesia.	Infant-exposure index < 1.25%.	Safe as a single dose.
Dailand et al., 1989	Randomized clinical trial	21	Women undergoing elective cesarean section under general anesthesia.	Propofol	Group 1: 2.5 mg.kg ⁻¹ at induction. Group 2: induction (same dose of Group 1) + maintenance (5 mg.kg ⁻¹ .h ⁻¹ of propofol).	Insignificant exposure of the baby through breast milk compared to the placental transfer of the drug.	Propofol was considered safe as a single dose and after continuous infusion.

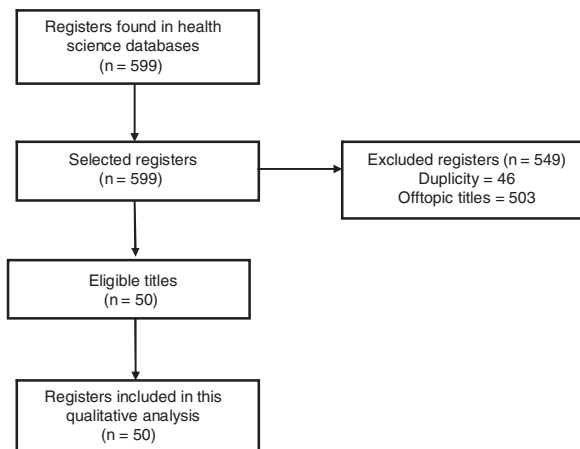


Figure 1 Flowchart regarding the literature search.

Local anesthetics

The main local anesthetics (lidocaine, bupivacaine, and levobupivacaine) seem to be safe for lactating mothers when administered as a single dose. As for ropivacaine, we have found limited data regarding its transfer to breast milk. But we found no reports of adverse effects on breastfed infants following maternal analgesia with epidural ropivacaine.

Discussion

Most of the anesthetic drugs are safe for nursing mothers and offer low risk to the breastfed neonates (Table 5).

The drugs administered to the mother usually pass from maternal plasma to the breast milk by passive diffusion.⁷ Several factors affect the excretion of medications into milk: maternal plasma concentration, protein binding, drug ionization, lipid and water solubility, drug molecular weight, and presence of active metabolites.^{7-9,11-34} The susceptibility of the neonate to the drug depends on the maternal dose and duration of therapy, frequency of feeding, volume of milk consumed, bioavailability, the half-life of the drug in the infant, and maturity of the baby. Accordingly, premature babies are more susceptible to the adverse effects caused by medications.^{7,9,14}

Benzodiazepines

Diazepam is a lipid-soluble drug, unionized in plasma, thus has the potential to easily cross biological barriers, and has long half-life elimination, such as 20–50 h in adults, which can be even longer in neonates.^{8,9,15} The M/P ratio of diazepam ranges from 0.1 to 0.58.⁸ Both diazepam and its main metabolite, desmethyl-diazepam, are metabolized by the enzyme group cytochrome P450 II C8–10, which is genetically determined.^{8,15} Therefore, the amount of diazepam, and its active metabolite, in serum and in breast milk will be

Table 3 Summary of results from studies regarding inhalational anesthetics.

Identification of the study	Type of study	n	Inclusion criteria	Anesthetics drug evaluated	Dose of drug	Evaluated outcomes	Recommendation of the study
Coté et al., 1976	Case report	1	Lactating practicing anesthetist exposed to halothane in the operating room.	Halothane	–	Halothane concentration in milk after 5 h of exposure = 2 ppm.	Theoretically safe.
Stuttman et al., 2010	Case reports	4	Mothers undergoing urgent surgeries with general anesthesia.	Xenon gas	Concentration 65%–69%	No traces of gas were found in milk at any time.	Safe after one exposition.

Table 4 Summary of results from one study regarding dexmedetomidine.

Identification of the study	Type of study	n	Inclusion criteria	Anesthetics drug evaluated	Dose of drug	Evaluated outcomes	Recommendation of the study
Nakanishi et al., 2017	Prospective trial	4	Patients undergoing cesarean section with sedation.	Dexmedetomidine	Not mentioned.	M/P ratio: 0.76–0.88. Undetectable in all breast milk samples at 24 h after discontinuation.	Safe if reinitiated 24 h after exposure.

Table 5 Summary of results from one study regarding neostigmine.

Identification of the study	Type of study	n	Inclusion criteria	Anesthetics drug evaluated	Dose of drug	Evaluated outcomes	Recommendation of the study
Fraser et al., 1963	Retrospective observational study	6	Nursing mothers with myasthenia gravis.	Neostigmine	Not mentioned.	No side-effects on the neonates, except abdominal cramps in one of them.	Safe

higher if the mother and/or the baby are poor metabolizers. Although there is some evidence of the safety when a single dose of diazepam is administered in breastfeeding women,³ a number of case reports and studies have shown significant adverse effects on breastfed infants whose mothers were receiving diazepam.^{16–18}

On the other hand, midazolam has a short half-life (2–5 h in adults) and a low passage rate to breast milk.^{14,19} As the pieces of evidence suggest, it is unlikely that breastfeeding after a single dose of midazolam would cause harm to the neonate, especially if the baby is breastfed more than 4 h after administration. However, the effects of long-term intravenous or oral midazolam administration were not documented by the studies and may be of concern (Table 6).

Hypnotics

Although the half-life of thiopental is long (8–11 h in adults), the transfer of the drug to milk was considered negligible.²⁰ Moreover, thiopental plasma concentration decreases more slowly than etomidate concentration; however, its M/P ratio is <1.²¹ Thus, the use of typical doses of thiopental for anesthesia induction should not delay breastfeeding (Table 7).

Different from thiopental, propofol has a short half-life (4–7 h in adults), but it can circulate for a much longer time (maximum half-life 63 h), probably due to the redistribution from deep compartments.⁸ However, as it is rapidly cleared from maternal and neonatal circulation, it seems not to have adverse effects on infants.^{9,15} All the studies and reports analyzed agreed that propofol given as single dose is innocuous for the suckling newborn.^{22,23} More studies are needed, however, to evaluate the safety of propofol when it is used as a continuous infusion to maintain total intravenous anesthesia in lactating mothers.

As for etomidate, limited data are available. One study used either thiopental (5 mg.kg⁻¹) or etomidate (0.3 mg.kg⁻¹) for induction of general anesthesia during elective cesarean section.²¹ The analysis of colostrum samples showed a mean concentration of 16.2 ng.mL⁻¹ of etomidate 2 h after its use. The authors concluded that etomidate is rapidly cleared from colostrum and, therefore, may be used in lactating mothers.²¹

We have not found any published human studies regarding the breast milk transfer of ketamine. More studies are needed to guarantee the safety of its use.

Alfa₂-agonists

The use of dexmedetomidine for cesarean section is an analgesic alternative to opioids or benzodiazepines. However, the dexmedetomidine label states that caution should be exercised when the drug is administered to a breastfeeding mother. Recently, a new method (liquid chromatography–tandem mass spectrometry) for determination of dexmedetomidine concentration in human breast milk was developed and tested in four patients that underwent sedation with dexmedetomidine for cesarean section.²⁴ The study suggests that breastfeeding can be started safely at 24 h after discontinuation of the drug.²⁴

Inhalational agents

Traces of halothane have been found in breast milk of a lactating practicing anesthetist in a 1976 study.²⁵ The concentration of gas in milk was approximately 2 ppm after 5 h of working exposure, which was consistent with the concentration within the operating room. The authors concluded that the amount of drug transferred to the suckling neonate was too low to cause harm. However, we have not found any published data about the transfer of halothane to breast milk in women exposed to it during general anesthesia.

Regarding the use of isoflurane, enflurane, sevoflurane, and desflurane, we have not found any published studies regarding their transfer to human breast milk. But, given their pharmacokinetics characteristics (low solubility, rapid excretion, and poor oral bioavailability) and the brief maternal exposure period, the theoretical risk for the suckling infant is considered low according to authors.^{7,8,12–15}

As for nitrous oxide, there is a scarcity of clinical trials of its intrapartum use with breastfeeding as the primary outcome. Even if the effects vary from woman to woman, nitrous oxide affects hormones that are important during labor and birth, including endorphins and epinephrine/norepinephrine, while it does not reduce the release or effectiveness of endogenous oxytocin.²⁶ These data imply that nitrous oxide has the potential to cause positive effects on both women's psychoemotional experience of labor and breastfeeding success.¹⁰ Significant adverse effects on the neonate have not been reported.^{27–29} Although there is no evidence of adverse effects of the maternal use of nitrous oxide or the fetus, the strength of that evidence is far from conclusive.

Table 6 Summary of results from the studies regarding opioids.

Identification of the study	Type of study	<i>n</i>	Inclusion criteria	Anesthetics drug evaluated	Dose of drug	Evaluated outcomes	Recommendation of the study
Feilberg et al., 1989	Randomized clinical trial	5	Lactating women who underwent surgery.	Morphine	Epidural: 4 mg of morphine in the epidural catheter. General anesthesia: 5 mg IV and 5–10 mg of morphine IM.	M/P ratio: 1.1–3.6. Infant exposure index < 6%	Safe as a single dose.
Robieux et al., 1990	Case report	1	Nursing women with severe arthritic back pain from Lupus. She used high doses (200 mg.day ⁻¹) of morphine during pregnancy and after giving birth, tapered down the dose to 10–20 mg.day ⁻¹ .	Morphine	The morphine dosage was tapered down from 50 mg every 6 h to 5 mg every 6 h. The day before the study, the mother received 10 mg morphine orally every 6 h. During the day of the study, she received 10 mg.day ⁻¹ .	The concentration of the drug in neonate serum was 4 ng.mL ⁻¹ (potentially harmful), compatible with analgesic effects. However, no adverse symptoms were observed in the infant (probably due to tolerance to opioids after a chronic exposure intra-uterus and through breastfeeding).	Caution with chronic exposure.
Wittels et al., 1990	Randomized clinical trial	10	5 nursing women receiving epidural analgesia (PCA) with morphine after undergoing elective cesarean section.	Morphine	Not mentioned	The nursing neonates achieved neurobehavioral scores similar to those of normal neonates after spontaneous vaginal delivery.	Safe.
Wittels et al., 1990	Randomized clinical trial	10	5 Nursing women receiving epidural analgesia (PCA) with meperidine after undergoing elective cesarean section.	Meperidine	Not mentioned	Normeperidine accumulates in breast milk and is associated with neonatal neurobehavioral depression on the 3 rd day of life.	Best to avoid.

Table 6 (Continued)

Identification of the study	Type of study	<i>n</i>	Inclusion criteria	Anesthetics drug evaluated	Dose of drug	Evaluated outcomes	Recommendation of the study
Peiker et al., 1980	Prospective trial	9	Lactating mothers with pain.	Meperidine	50 mg IM	M/P ratio: 1.07–1.2. Normeperidine was not analyzed.	Safe as a single dose (the active metabolite was not analyzed).
Borgatta et al., 1997	Prospective trial	8	Lactating woman undergoing tube sterilization.	Meperidine	35 mg	M/P ratio = 2.3. Infant exposure-index: 1.2%–3.5%	Safe as a single dose.
Nitsun et al., 2006	Prospective trial	5	Lactating women undergoing operative procedures with general anesthesia.	Fentanyl	100 mcg	Infant-exposure index < 1.25%.	Safe as a single dose.
Leuschen et al., 1990	Prospective trial	10	Women undergoing labor analgesia.	Fentanyl	50–400 mcg IV	Infant-exposure index = 3%.	Safe as a single dose.
Madej et al., 1987	Randomized clinical trial	50	Women undergoing elective cesarean section.	Fentanyl	Single epidural dose for analgesia.	No detectable levels of fentanyl were found in breast milk.	Safe as a single dose.
Madej et al., 1987	Randomized clinical trial	50	Women undergoing elective cesarean section.	Sufentanil	Single epidural dose for analgesia.	No detectable levels of sufentanil were found in breast milk.	Safe as a single dose.

Table 7 Summary of results from the studies regarding local anesthetics.

Identification of the study	Type of study	<i>n</i>	Inclusion criteria	Anesthetics drug evaluated	Dose of drug	Evaluated outcomes	Recommendation of the study
Zeisler et al., 1986	Case report	1	Lactating woman receiving IV lidocaine for ventricular dysrhythmia.	Lidocaine	Antiarrhythmic doses (much higher doses than the ones with anesthetic effects.)	M/P ratio = 0.4.	Safe even in high antiarrhythmic doses
Ortega et al., 1999	Prospective trial	27	Women undergoing cesarean section.	Lidocaine and Bupivacaine	Lidocaine 183 ± 104 mg AND Bupivacaine 82 ± 29.4 mg (epidural anesthesia)	Low concentrations of lidocaine and bupivacaine in breast milk. Most of the newborns had a maximal APGAR score and no adverse reactions were reported.	Both are safe.
Giuliani et al., 2001	Prospective trial.	7	Nursing women undergoing dental treatment with a local anesthetic.	Lidocaine without adrenaline	72–144 mg	The amount of lidocaine and its main metabolite in breast milk was considered very small.	Safe.
Naulty et al., 1983	Prospective trial	<i>n?</i>	Women undergoing vaginal delivery with epidural anesthesia.	Bupivacaine	Not mentioned	No concentration of the drug was detectable in all milk samples at the sensitivity limit of 0.02 mcg.ml ⁻¹ .	Safe.
Bolat et al., 2014	Randomized clinical trial.	20	Women undergoing elective cesarean section.	Bupivacaine/ levobupivacaine	Bupi: 82.5 ± 12.1 mg. Levobupi: 80.0 ± 10.5 mg	M/P ratio Bupi = 0.37 ± 0.14. M/P ratio lev-obupi = 0.34 ± 0.13.	Both are safe.

A recent report described the use of general anesthesia in four lactating women using propofol for induction and remifentanyl associated with xenon gas for maintenance. Immediately after extubation, there was no trace of xenon gas in maternal milk.³⁰ These results seem promising for lactating women in the future.

Muscle relaxants

Even though we have not found any published studies about milk transfer of muscle relaxants, some conclusions can be achieved based on the pharmacokinetic profile of these drugs.

Succinylcholine is rapidly metabolized in maternal plasma and has a very short elimination half-life (3–5 min).^{7,8,12–15} Hence, its excretion in breast milk can be considered negligible. Similarly, the nondepolarizing agents, including rocuronium, pancuronium, vecuronium, atracurium, and cisatracurium, have poor lipid solubility, do not cross biological membranes easily, and are fully ionized in normal pH. Even if small amounts of the drugs are excreted into breast milk, they have very poor absorption from the neonatal gastrointestinal tract.^{7,8,12–15} Therefore, these drugs are theoretically safe for breastfed babies. An interesting historical fact that confirms the safety of muscle relaxants is that the South American Indians, without any harm to their babies, ate the meat from animals killed with curare-poisoned arrows.^{8,12–15}

Reversing agents

Neostigmine has a half-life of 15–30 min and is quickly cleared from plasma after being administered.¹⁴ In a study published in 1963, neostigmine could not be detected in breast milk of a woman treated for myasthenia gravis.³¹

As for Sugammadex, we have not found any published studies regarding its transfer to human breast milk, probably because it is a new drug. Further research is needed regarding its safety.

Opioids

There are contradictory reports regarding the impact of the use of opioids on breastfeeding.³² Highly lipophilic drugs, such as fentanyl, can easily cross the placenta, leading to neonatal depression and negatively affect breastfeeding.^{33,34} The risk of nursing problems seems to be dose- and type of opioid-dependent.^{35,36} On the other hand, there are a series of published reports about the safety of epidural, intrathecal, or single dose systemic opioids.^{37–39}

Morphine's half-life is 2–3 h in adults and 12–16 h in newborns.¹⁵ It is transferred to breast milk in small amounts and has an oral bioavailability of only 30%.⁷ Its main metabolite, morphine-6-glucuronide, is more potent than morphine and has a oral bioavailability of 4%.⁷ Most authors agreed that the use of a single dose of morphine is considered safe for breastfeeding,⁴⁰ while multiple doses⁴¹ and PCA morphine³⁵ should be avoided.

As for fentanyl, breastfeeding can be considered safe following the administration of a single-dose to the mother.^{22,42}

However, we have not found information regarding multiple intravenous doses or continuous infusion. No adverse effects were observed on newborns after epidural administration of fentanyl.⁴³

Alfentanil and sufentanil have rapid clearance from the plasma, which makes it unlikely that low maternal doses would cause significant harm to the suckling infant.^{8,14,15,19} In one study with 50 patients, no detectable levels of fentanyl or sufentanil were found in breast milk after epidural anesthesia for cesarean section.⁴³

Regarding remifentanyl, we have found no published data about its maternal administration and its influence on the breastfed newborn. However, considering its short context-sensitive half-life (less than 10 min), it may be considered safe for lactating mothers.⁷

On the other hand, meperidine, and its main active metabolite, normeperidine, have long half-lives in adults and in neonates (13 h and 63 h, respectively), different from the other opioids.^{7,9} Although no side effects in neonates are demonstrated after maternal treatment with single doses of meperidine,^{3,44} there are reports of neonatal respiratory depression and neurobehavioral depression with multiple doses.³⁵ Hence, most authors agreed that this drug should be avoided in long-term treatment.

Local anesthetics

Lidocaine has short half-life both in adults (1–2.2 h) and in neonates (2.9–3.3 h).⁸ It also has poor oral bioavailability (less than 30%).^{12–14} Most authors demonstrate that lidocaine is excreted into breast milk in low concentrations,^{45–47} even when administered with maximal antiarrhythmic maternal doses.⁴⁵ Thus, it seems to be safe in nursing women.

Bupivacaine was also considered safe in parturients undergoing epidural analgesia. No concentration of the drug was detectable in all milk samples at the sensitivity limit of 0.02 mcg.mL⁻¹.⁴⁸ The safety was also demonstrated for levobupivacaine,¹¹ which has similar M/P ratio profile as the racemic bupivacaine.

Regarding ropivacaine, limited data are available. But there are no reports of adverse effects on breastfed infants following maternal analgesia with epidural ropivacaine.^{13,49}

Regarding epidural analgesia for labor, the main concern is that epidural drugs, especially opioids, cross the placenta and decrease neonatal neurobehavioral scores, which may negatively affect breastfeeding. However, it is important to bear in mind that the exposure of the baby to the anesthetic drugs through breast milk is insignificant compared to the placental transfer of the drug. Several studies have been published regarding this matter, with conflicting results. A systematic review, regarding the outcomes in breastfeeding following labor epidural analgesia, showed 12 studies demonstrating negative associations between epidurals and breastfeeding success, 10 studies demonstrating no effects, and 1 study with a positive association.⁴⁹ The authors agreed with the publications' deficiencies mentioned by previous authors, as following⁵⁰: inadequate randomization, variation of type and dosage of analgesia, different methods to evaluate breastfeeding success, and failure to control confounding variables. All these limitations make the current literature insufficient to make evidence-based

recommendations based on the neonatal neurobehavioral scores. Therefore, further studies are needed.

Conclusion

Breastfeeding is extremely important for the child's development and, hence, must be encouraged. Its success depends on several factors. One of the most important factors is the support from the family and the institution where the birth occurs. Epidural analgesia may possibly have a negative influence on breastfeeding's quality, but the studies have failed to demonstrate causation, and, for the moment, this form of analgesia is the one with the least side-effects for the neonate.

According to current literature, the transfer of the most common anesthetic agents to breast milk is very small when they are used on a single-dose treatment. Therefore, the risks for the healthy suckling infant are almost negligible and breastfeeding should not be interrupted. However, high-dose and repeated administration of drugs significantly increase the risk of adverse effects on neonates. In these situations, the anesthetist, together with the pediatrician, should perform an individual risk/benefit analysis. Another important consideration is that premature neonates, or babies with a concurrent disease, are more susceptible to develop side-effects. In all these situations, mothers must be well informed about the risks and benefits of the chosen therapy, as well as its impact on breastfeeding.

Different from the other anesthetic drugs, diazepam and meperidine should be avoided in nursing women. Although some studies suggest that they are safe in single doses, the adverse effects in neonates reported by other authors are very important not to be taken into account.

Conflicts of interest

The authors declare no conflicts of interest.

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