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Invited review

Maternal analgosedation and breastfeeding: guidance for the pediatrician

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Abstract

As part of analgosedative treatment modalities after delivery (e.g. caesarean related pain, birth related trauma, pre-existing pain syndromes), mothers are treated with different analgosedatives that may also affect the nursing infant. This review aims to summarize the available knowledge on commonly prescribed analgosedatives (opioids, intravenous and inhalational anesthetics, benzodiazepines, non-opioid analgesics, and local anesthetics) during breastfeeding.

We propose that the use of systemic non-opioid analgesics, local anesthetics, inhalational or intravenous anesthetics is safe when mothers are nursing. When systemic opioids are used, we recommend pediatricians to consider clinical monitoring of the infant for sedation. The duration of maternal exposure (> 4 days) and the presence of maternal signs of somnolence are hereby of additional relevance. We encourage research groups to report on their specific observations and expertise in order to further validate the current practices and guidance.

Keywords

Breastfeeding, analgosedation, safety, opioids, neonatal abstinence syndrome.

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Introduction

Most drugs are not extensively evaluated during pregnancy or postpartum, including the setting of breastfeeding [1-3]. This is to a large extent similar to the off-label and unlicensed pharmacotherapy in neonates and children. Consequently, the label commonly mentions a default setting that "*the drug has not been studied during pregnancy or breastfeeding*". Despite this, nursing women often need pharmacological treatment for a range of conditions. The ultimate goals of maternal drug use during breastfeeding are dual. First, this should provide effective and safe therapy for the maternal condition(s) (e.g. postpartum maternal analgesia, maternal co-morbidities, pregnancy related diseases). Simultaneously, we also aim to assure the safety for the nursing infant from (relevant) adverse events related to the maternal treatment [1-3]. Only very rarely, these goals overlap (e.g. maternal galactagogues intake to induce milk production, like metoclopramide or domperidone) [4].

In essence, exposure of a nursing mother to any dose of drug (maternal dose, D_m) will result in – be it very limited – transfer of the drug into the human milk (estimated infant dose, D_i). However, concentrations reached in the human milk are usually quite low and oral bioavailability in the infant should also be considered before any relevant pharmacological exposure (relative infant dose, RID = D_m/D_i * absorption) and effect in the infant needs to be anticipated (**Fig. 1**). The difference in drug concentration in the infant's plasma (**a** vs **b**) can be explained by the presence (**a**) or absence (**b**) of "initial loading related to fetal exposure to the same compound before delivery" [5, 6]. Age also matters, since the newborn seems to be more vulnerable to adverse effects when compared to infants and refers to the age-related changes in pharmacokinetics or -dynamics [7]. In essence, most drugs appear in mother's milk, but the final concentration time profiles in the infant depend on the concentration in the milk, the bio-availability, clearance capacity and the initial concentration (fetal + neonatal or only neonatal exposure). Finally, accumulation relates to the duration of exposure and the initial concentration in the newborn. In the setting of continuation of treatment of the mother from pregnancy to postpartum, the fetus will likely already be exposed to the maternal drugs, and the newborn will already

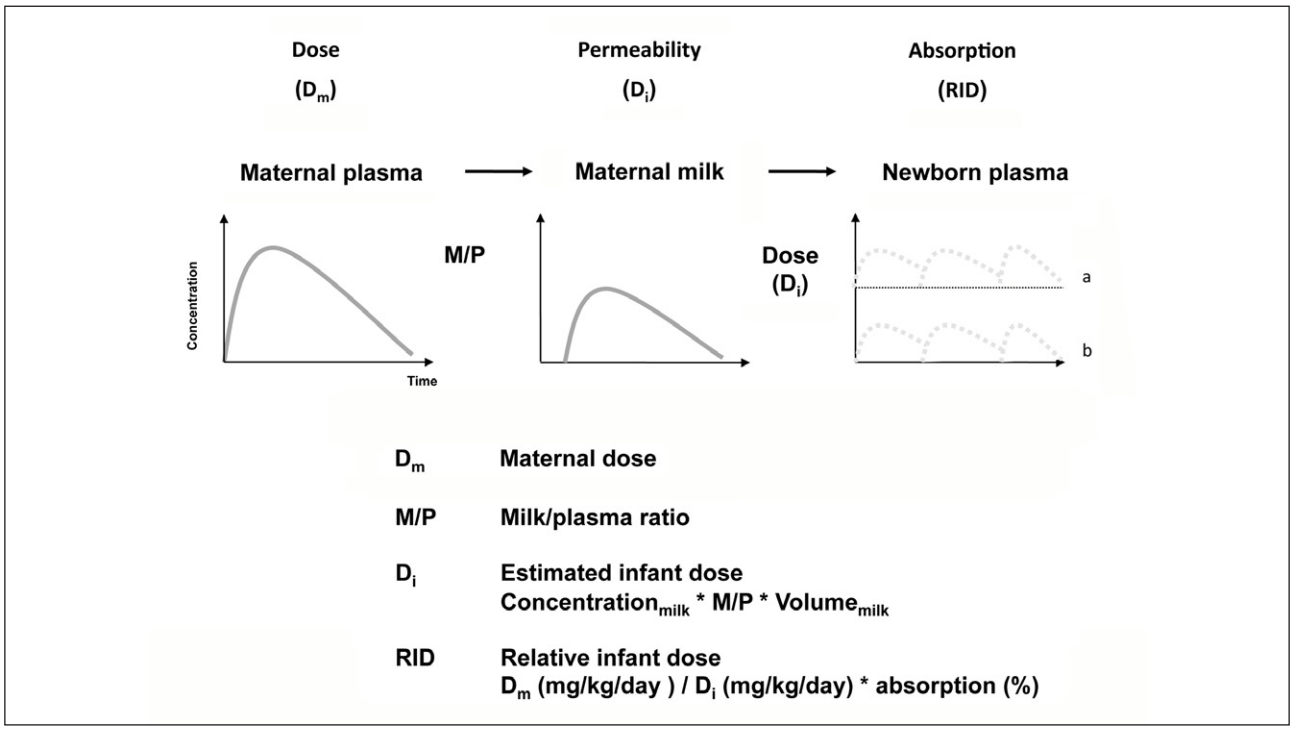

Figure 1. Maternal-infant pharmacokinetics in the setting of exposure through breastfeeding. The difference in drug concentration in the infant's plasma (**a** vs **b**) can be explained by the presence (**a**) or absence (**b**) of "initial loading related to fetal exposure to the same compound before delivery" [5, 6].

have an initial concentration of this compound at birth. The subsequent concentration will depend on the amount of exposure, the clearance capacity and the distribution volume characteristics (e.g. postnatal weight evolution) [5-7].

Despite the fact that lactating women are regular users of medications and that women are often advised to discontinue or stop nursing while taking the drug, there are only a limited number of drugs that have been identified as potentially harmful to the newborn [5, 6]. Using a prospective study design, Ito et al. documented in a cohort of 838 nursing infants with mothers taking medications that the incidence of adverse reactions was 11.2% (94/838) [8]. All these events were classified as minor reactions, not necessitating medical attention. Antibiotics (19.3%), antihistamines (9.4%), sedatives, antidepressants or anti-epileptics (7.1%), but also analgesics, including narcotics (11.2%) were most commonly associated with adverse reactions. The reported adverse reactions were diarrhea (antibiotics), drowsiness (analgesics, sedatives, antidepressants, antiepileptics) or irritability (antihistamines) [8]. The incidence, the type of reactions and compounds associated are in line with the systematic literature review performed by Anderson et al. [5]. Based on the evaluation of 100 published case reports, none were considered to be "definite" using a standard ranking scale, 47% were "probable", 53% were "possible". However, drugs with central nervous system activity accounted for about 50% of the events [5].

These data suggest that breastfeeding rarely needs to be discouraged or discontinued when a mother needs drug therapy, but some cautiousness about analgosedatives may be warranted [5, 6, 8]. As part of analgosedative treatment modalities after delivery (e.g. caesarean related pain, birth related trauma, pre-existing pain syndromes), mothers are exposed to different analgosedatives that may affect the nursing infant. This review aims to summarize the available knowledge on commonly prescribed analgosedatives (opioids, intravenous and inhalational anesthetics, benzodiazepines, non-opioid analgesics, and local anesthetics) during breastfeeding.

Compound specific observations

Opioids

The rate of breastfeeding has increased again steadily in the developed world [9, 10]. During this time, opioid use in the general population steadily increased as well. This means that the clinical experience with maternal opioids is still fairly limited with emerging data on (side)effects with codeine, oxycodone, methadone and tramadol during nursing [6, 11]. Opioid absorption after oral ingestion in neonates should be anticipated, while the extent of exposure through mother's milk will depend on maternal ingestion (dose) and metabolism. Neonatal clearance relates to the neonate's metabolic or renal elimination, and will be limited [7]. Such a setting has the potential to result in unanticipated side effects in individual cases.

A pivotal case report in 2006 of Koren et al. on codeine related poisoning in a newborn through breastfeeding reactivated the clinical research on maternal-infant opioid pharmacokinetics [12]. A pharmacogenetic link between maternal ultrafast metabolizer status for cytochrome p450 (CYP) 2D6 was documented, since this results in higher and faster conversion of codeine to morphine [12]. More recently, the same group documented that a combination of different maternal genetic polymorphisms (i.e. CYP 2D6 and P-glycoprotein polymorphisms) predicted 87% of the infant and maternal central nervous system depression cases with a sensitivity of 80% and a specificity of 87% in a cohort of 111 breastfeeding mother-infant pairs [13].

The incidence of central nervous system depression in breastfed neonates following maternal exposure to oxycodone, codeine or paracetamol was retrospectively compared in 533 mother-infant pairs. Lam et al. hereby clearly showed that there was a 20.1% rate of depression in infants of nursing mothers on oxycodone, as compared with 16.7% and 0.5% when treated with codeine or paracetamol [14]. Methadone is somewhat an outlier, since commonly used in a setting of maternal opioid addiction. Consequently, these neonates are already exposed to methadone in fetal life. Methadone is excreted into human milk (2-3% of weight-adjusted maternal dose), and there are data that suggest that these infants benefit from breastfeeding (blunted opioid withdrawal syndrome), hereby confirming an exposure/effect relation. Breastfed babies less commonly display neonatal abstinence syndrome and, if needed, the cumulative dose of methadone is lower and the length of hospital stay is shorter [6]. Finally, using a sparse sampling study design to assess transfer of tramadol and O-desmethyl tramadol into transitional breast milk, the relative

infant dose of 2-3% remained very limited. Based on these observations, the authors concluded that short-term maternal use of tramadol is compatible with breastfeeding [15].

There are also some additional clinical useful observations on maternal codeine and oxycodone exposure for the pediatrician. First, there is high concordance between maternal and neonatal somnolence. When the mother exhibits somnolence, the baby should be examined by a pediatrician. Secondly, severe somnolence commonly emerged after 4 days of use, when milk output increases, exposure increases and is prolonged. Therefore, any maternal need for opioids for more than 4 days after delivery warrants additional evaluation [16-18].

Obviously, there are major differences when opioids are administered by either systemic (oral, intravenous, transcutaneous) routes compared to loco-regional anesthesia. To illustrate this, we refer to the estimations of infant exposure in a setting of patient (maternal) controlled epidural pethidine administration [19]. The combined absolute infant dose of pethidine and norpethidine received via milk was 1.8% of the neonatal therapeutic dose and the combined relative infant dose was below the 10% recommended safety level. Based on these data, the authors concluded that breastfed infants are at low risk of relevant drug exposure in the setting of patient-controlled epidural pethidine [19]. The interaction between locoregional analgesia and breastfeeding outcome goes beyond drug exposure through breastfeeding, and we refer the interested reader to some reviews on this topic [20, 21].

Intravenous and inhalational anesthetics

Although the number of observations is limited, excretion of propofol in human milk does not equal infant exposure (**Fig. 1**) [22, 23]. This is because enteral absorption is the rate limiting factor. The same holds true for inhalational agents in postpartum, but buccal etomidate resorption has been observed. Obviously, this rationale only applies when these compounds are administered *after delivery*, since when administered during labor or before delivery, placental passage may result in fetal accumulation and subsequent effects [22].

Benzodiazepines

Lorazepam, midazolam or diazepam are commonly administered as anxiolytic. These compounds and some of their metabolites can be retrieved in human milk but concentrations remain very limited [22-24]. In 24 hours of human milk collection after a single dose, only 0.005% of the maternal midazolam dose was retrieved. Taking the subsequent oral bio-availability (50-60%) into account, it is very reasonable to assume that the exposure will be limited when administered after delivery. In contrast, plasma diazepam and its active metabolite (desmethyldiazepam) could be measured up to 7-10 days of postnatal age in neonatal plasma samples after administration to the mother *before delivery* [24].

Non-opioid analgesics

Human milk and plasma paracetamol levels were monitored in 3 lactating women after ingestion of 500 mg dose of paracetamol in the postpartum period. Paracetamol concentrations remained lower in human milk (milk/plasma ratio of 0.76). Since less than 0.1% of the maternal dose would be present in 100 ml milk, nursing should not be discontinued following maternal paracetamol exposure [25]. Similarly, ibuprofen in human milk and serum was quantified in 12 patients who had ingested one 400 mg tablet of ibuprofen every 6 hours over a 24 hour period immediately following delivery (relief post-caesarean pain). Ibuprofen could not be quantified in human milk [26]. Based on the lower limit of quantification (1 μg/ml), less than 1 mg of ibuprofen per day is excreted in breast milk. Similar findings have been described for ketorolac [27]. Even if these compounds result in exposure, the extent will remain limited and much lower than that clinical registered dosing for analgesia or temperature reduction [28].

Local anesthetics

Local anesthetics (including lidocaine, ropivacaine, and bupivacaine) are commonly administered as part of regional anesthetic techniques (e.g. regional pain block, epidural) and data are mainly available in mothers during labor or for anesthesia [29]. Data on excretion of lidocaine and bupivacaine in human milk have been reported. To illustrate this, we refer to a paper of Giuliani et al. [30]. The authors quantified lidocaine and its metabolite (monoethyl-glycinexylidide, MEGX) disposition in 7 nursing mothers (23-39 years, 3.6 to 7.2 ml 2% lidocaine without adrenaline, dental care). Based on these observations, the daily infant exposure to lidocaine and MEGX were 73.41 ± 38.94 μg/L/day

and 66.1 ± 28.5 μg/L/day. Moreover, absorption following oral ingestion is limited. Based on the available evidence, the exposure is limited with minor statistical significant, but clinical irrelevant effects.

Discussion

There is an increase in breastfeeding, supported by – among others – the Baby Friendly Hospital initiative. Consequently, women also want to breastfeed shortly following analgosedation [9, 10, 23]. In general, the short-term use of these drugs already limits the risks of these effects, while prolonged exposure should increase our vigilance.

Based on the observations retrieved in literature, the use of systemic non-opioid analgesics, local anesthetics, and inhalational or intravenous anesthetics seems safe for nursing mothers. When systemic opioids are used, we recommend pediatricians to consider some clinical monitoring with specific emphasis on the duration of exposure (4 days pivotal) and the presence of any maternal sign (somnolence) [16]. Finally, the use of benzodiazepines should be limited with preference to those with shorter half-life. Under these circumstances, the most appropriate advice to a nursing mother undergoing anesthesia is that she may reinitiate breastfeeding when she feels sufficiently alert to do so.

Obviously, the knowledge on clinical pharmacology during breastfeeding evolves rapidly and has become a field of active clinical research. This means that updated, reliable information should be easy accessible. Besides textbooks, LactMed is a free online database with information on drugs and lactation as one of the newest additions to the National Library of Medicine's TOXNET system [31]. Similarly, the Motherisk program also has an updated and useful website that can be searched, and is open for advice [32]. We encourage research groups to report on their specific observations and expertise in order to further validate the current practices.

Neonatal abstinence syndrome (NAS) following prolonged maternal exposure to opioids is a separate setting that warrants a tailored, specific approach [33]. As part of such a tailored approach, there are data that suggest that breastfeeding reduces the incidence and duration of NAS [33-36]. Based on a pooled dataset of 400 neonates (218 breastfed, 54.5%), there is a significant reduction in NAS (54% vs 77%, number needed to treat 5-6). The same trends are observed when the duration of opioid treatment (18 to 23 days) or the length of hospital stay (4 to 10 days) are considered [34-36]. Another benefit with this approach is that administering methadone to the neonate and young infant through breastfeeding results in much more gradual exposure to this drug and prevent inadvertent dosing. The major limitation of the above mentioned observational studies is bias. All studies reported that breastfed neonates required less pharmacological interventions and had shorter hospital stays. However, these effects may be due to confounding (i.e. breastfeeding is just a "marker") factors. Among others, these could be better adherence, less psychological co-morbidity, or differences in staff attitudes towards nursing women [37].

Conclusions

In conclusion, the use of systemic non-opioid analgesics, local anesthetics, inhalational or intravenous anesthetics seems safe when mothers are nursing. When systemic opioids are used, we recommend pediatricians to consider some clinical monitoring with specific emphasis on the duration of exposure and the presence of any maternal sign (somnolence). We encourage research groups to report on their specific observations and expertise in order to further validate the current practices and guidance.

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Declaration of interest

The Authors declare that there is no conflict of interest.

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