Risk to the Breast-Fed Neonate From Codeine Treatment to the Mother: A Quantitative Mechanistic Modeling Study

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Administering codeine to breast-feeding mothers had been considered safe until the recent death of a breast-fed neonate whose mother had been prescribed codeine. We investigated the risk of opioid poisoning to breast-fed neonates using coupled physiologically based pharmacokinetic models for the mother and child. Neonatal morphine plasma concentrations were simulated for various combinations of cytochrome P450 2D6 (CYP2D6) genotype and morphine clearance, assuming typical breast-feeding schedules and maternal codeine doses of ≤2.5 mg/kg/day. The simulations demonstrated that the mother's codeine and morphine clearances and the neonate's morphine clearance are the most critical determinants of morphine accumulation in the neonate. The cumulative doses ingested by the neonate over 14 days were 0.38 mg/kg codeine and 0.17 mg/kg morphine. Given the added effect of low neonatal elimination capacity for morphine, potentially toxic morphine plasma concentrations can be reached within 4 days in the neonate after repeated codeine dosing to the mother. Importantly, neonates of mothers with the ultrarapid CYP2D6 genotype and neonates of mothers who are extensive metabolizers have comparable risks of opioid poisoning.

For decades, it has been known that ingested morphine is excreted into breast milk.7,8 Although there have been investigations of morphine intake by neonates through breast milk after short periods (≤4 days) of administration of codeine to breast-feeding mothers2,9–16 (Tables 1 and 2), and case reports of opioid intoxication by direct administration of codeine to neonates have been reported17,18 (Table 3), there is still a lack of knowledge about the risk to the neonate posed by prolonged exposure to morphine through breast milk.

In this study, we explored the quantitative risk of opioid toxicity to a breast-fed neonate following repeated codeine administration to the mother. We used the method of whole-body physiology–based pharmacokinetic (PBPK) modeling. PBPK models have been developed to describe the action of pharmaceuticals in children, and these are used to mechanistically represent the age dependence of physiological factors that drive the absorption, distribution, and elimination of drugs.19–22

To simulate opioid uptake in nursing neonates, maternal and neonatal PBPK models for codeine and morphine were coupled. This coupled model was then used to identify critical parameter combinations that put the neonate at an increased risk for morphine accumulation and subsequent adverse reactions. These parameters were codeine dose administered to the mother, duration of intake of the drug by the mother, and CYP2D6 genotype as well as morphine plasma clearances.
(CL\textsubscript{MOR}) of the mother and neonate. Finally, the parameters relating to the Toronto case of neonatal death\textsuperscript{4,6} were simulated and analyzed with the help of the coupled model.

**PBPK model development**
In total, four whole-body PBPK models for codeine and morphine in mother and neonate were used (Figure 1). The morphine models were used as previously described,\textsuperscript{20} and the codeine models were developed in accordance with similar criteria. The following steps were considered to be relevant to morphine toxicity in the infant:

1. Codeine is repeatedly administered perorally and absorbed in the mother.
2. Codeine is biotransformed to morphine (and to other inactive metabolites) in the maternal liver through CYP2D6.
3. Codeine and morphine are excreted into the mother’s breast milk.

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<th>Table 1</th>
<th>Concentrations of codeine and morphine in plasma and breast milk after codeine or morphine administration to lactating women</th>
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<td>Toronto case (2006)</td>
<td>Codeine</td>
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<td>Findlay study (1981)</td>
<td>Codeine</td>
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<td>Meny study (1992)</td>
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<td>Guo study (2008)</td>
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<td>Baka study (2002)</td>
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<td>Robieux case (1990)</td>
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<td>Feilberg study (1989)</td>
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epi, epidurally; i.m. intramuscularly; i.v. intravenously; n.r., not reported; p.o., perorally; q6H, every 6 h.

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<th>Table 2</th>
<th>Concentrations of codeine and morphine in plasma of breast-fed neonates after codeine or morphine administration to the mother</th>
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<tr>
<td>Administered drug</td>
<td>Maternal dose</td>
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<td>Toronto case (2006)</td>
<td>Codeine</td>
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<td>Meny study (1993)</td>
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n.r., not reported; p.o., perorally; q6H, every 6 h.
Elimination occurs through the renal route, primarily in the form of the glucuronidated metabolites with half-lives of 1.5–4 h in adults. Only a small amount of the dose (~10%) is excreted as unchanged morphine. In newborns and young infants, morphine elimination is much slower because of immature liver and kidney functions. The ontogeny of UGT2B7 is comparatively slow, and adult activity levels are attained between 2 months and 3 years of age. In neonates, the reported morphine clearance values range from 0.8 to 6.5 ml/min/kg (gestational age 24–41 weeks, median postnatal age 10 h); for older full-term neonates 1 to 7 days after birth, the corresponding clearance values are 6.3 to 10.4 ml/min/kg, and for infants 1 to 18 days after birth, the values are 1.8 to 6.6 ml/min/kg. Besides undergoing O-demethylation to morphine, codeine also undergoes N-demethylation mediated by CYP3A4 and glucuronidation into inactive metabolites norcodeine and codeine-6-glucuronide. These pathways are not explicitly modeled in this study.

In order to quantitatively describe the amounts of codeine and morphine that are ingested by the neonate, the amounts of codeine and morphine that are excreted into breast milk were estimated. Several studies have reported milk:plasma partition ratios for codeine and/or morphine (Table 1). On the basis of findings in the literature, we assumed a range of milk:plasma partition ratios of 2.20–2.31 for codeine and 1.1–4.1 for morphine.

The simulated concentration–time profiles of codeine and morphine in breast milk formed the basis for the calculation of neonatal opioid intake. The metabolites morphine-3-glucuronide and M6G are neglected in our model as potential opioid sources for the neonate because of insufficient information about their excretion into breast milk and oral absorption in neonates. The amount of breast milk that is ingested by a neonate was also taken from the literature: according to Casey et al., the total milk intake in the first 24 h after birth amounts to 13 g/kg (mean data), increasing on days 2 and 3 to 40 g/kg and 98 g/kg, respectively. On days 4 and 5, the daily milk intake increases further to 140 g/kg and 155 g/kg, respectively. The total daily milk intake is divided into eight meals, representing an average of one breast-feed every 3 h. The amounts of codeine and morphine that are ingested per breast-feed are calculated from the milk volume and the simulated breast milk concentrations.

In the neonatal model, the absorption of codeine and morphine was assumed to be rapid and complete. The metabolism of codeine to morphine in the neonate was also modeled: CYP2D6 activity in neonates is also related to genotype; it reaches ~3–5% of the adult level of activity during the first week of life and increases significantly thereafter. The CYP2D6 activity was set
to 10% of the level of activity of the same genotype in an adult and was assumed to be constant over the first 2 weeks of life.

The elimination rates for codeine and morphine in the mother and child are closely related to the accumulation potential of the opioids following repeated administration. Therefore, different values for maternal and neonatal morphine clearances were tested in the simulations by means of a sensitivity analysis as discussed below.

Establishment of a codeine nomogram

The cumulative effects of morphine and codeine doses in the neonate and the resulting plasma concentrations were simulated under various conditions. Maternal codeine doses of ≤2.5 mg/kg/day, assuming twice-daily administration to a virtual female weighing 60 kg, were simulated over the first 14 postpartum days. The results of this study can also be carried forward to other dosing regimens with the same daily dose because the distribution of the eight breast-feeds over 24 h effectively averages out the peak–trough fluctuations of codeine and morphine, making the model insensitive to changes in the codeine administration schedules (such as codeine intake every 4 or 6 h). The influence of maternal and neonatal CYP2D6 genotypes was investigated by simulating all combinations of CYP2D6, namely, PM, EM, and UM. The upper limit of the CYP2D6 clearance, obtained from the fit procedure based on in vivo data,24 was used throughout.

The role of the mother’s morphine elimination capacity was investigated within the reported range of morphine plasma clearances in healthy adults.37,38 Three different virtual mothers were defined with respect to morphine clearance characteristics: low (11 ml/min/kg, indicated as ↓), medium (21 ml/min/kg, ↔), and high (33 ml/min/kg, ↑). In neonates, four different clearance scenarios were simulated, including the most extreme scenario, in which the neonate is assumed to

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**Figure 2** Comparison of experimental pharmacokinetics parameters for codeine and morphine with corresponding simulated values. Boxes for experimental data present the minimum, median, and maximum of C<sub>max</sub> and AUC<sub>infinity</sub> for the CYP2D6 genotypes, PMs, EMs, and UM, following a single oral codeine dose of 30 mg. Lines and symbols (diamonds) represent the simulated minimum (highest clearance), median, and maximum (lowest clearance) C<sub>max</sub> and AUC<sub>infinity</sub> for the three genotypes. The experimental data are from the study by Kirchheiner et al.24 AUC<sub>infinity</sub>, area under the plasma concentration time curve interpolated to infinity; C<sub>max</sub>, peak plasma concentration; EM, extensive metabolizer; PM, poor metabolizer; UM, ultrarapid metabolizer.

**Figure 3** Calculated steady-state plasma and breast milk peak morphine concentrations following twice-daily oral codeine administration, as a function of CYP2D6 genotype (shaded) and morphine clearance (striped). The range of breast milk concentrations for a given genotype/clearance combination is represented by error bars and is based on the range of reported milk:plasma concentration ratios. The left y axis shows concentrations after a daily codeine dose of 1 mg/kg, the right y axis after a daily codeine dose of 2 mg/kg. CYP2D6, cytochrome P450 2D6; EM, extensive metabolizer; GT, genotype; PM, poor metabolizer; UM, ultrarapid metabolizer.
After repeated twice-daily dosing, the simulated maternal plasma and breast milk steady-state morphine peak concentrations were reached after 4 days. The peak plasma concentration varied within a 60-fold range, depending on CYP2D6 genotype and morphine clearance (Figure 3). As expected, the CYP2D6 PM mother with a high morphine clearance defined the lower bound ($C_{\text{max}} = 0.5 \mu g/l$ at 1 mg/kg/day codeine), and the UM mother with low morphine clearance defined the upper bound ($C_{\text{max}} = 21 \mu g/l$). Regardless of morphine clearance, all PMs were at the lower end of the spectrum. Interestingly, within the EM and UM genotypes, morphine clearance, not CYP2D6 genotype, was the dominating factor for $C_{\text{max}}$. These results are mirrored in the values of breast milk concentrations.

**Codeine nomogram**

The cumulative morphine doses in the neonate for all maternal CYP2D6 genotypes and morphine clearance phenotype combinations, as a function of maternal codeine dose, are presented in Figure 4. The cumulative amount of morphine ingested by the neonate increases linearly with maternal codeine dose. The maximum cumulative dose to the breast-fed neonate over 14 days, as obtained in this study, was 0.17 mg/kg. The horizontal gray bars in Figure 4 indicate the neonate dose that leads to potentially toxic morphine levels of 10 to 20 $\mu g/l$ in the neonate.40 Apparently, the primary driver of $C_{\text{max}}$ in the neonate is the morphine clearance of the child. In the extreme case of a complete lack of morphine elimination capacity, morphine $C_{\text{max}}$ values of 10 $\mu g/l$ can be reached even in PM mothers with repeated administration of codeine doses of 1.5–2.5 mg/kg/day. In EM or UM mothers, by comparison, the same peak levels can be expected at codeine doses between 0.2 and 0.9 mg/kg/day (depending on

**RESULTS**

The results of the genotype-specific optimization of intrinsic CYP2D6 clearance values are shown in Figure 2. The AUC$_{\text{infinity}}$ and $C_{\text{max}}$ of codeine and morphine as reported in ref. 24 can be simultaneously described by the coupled model, providing a good representation of codeine and morphine pharmacokinetics.

The Toronto case

Koren et al. and Madadi et al. reported that the mother in Toronto had initially been prescribed two tablets each containing 30 mg codeine and 500 mg acetaminophen (not included in the simulation) every 12 h beginning on the day of delivery.4,6,23 The dose was halved from day 2 onward because of somnolence and constipation in the mother. From day 7 onward, the male newborn (birth weight 3.880 kg) showed intermittent difficulties in breast-feeding and an increasing lethargy.4 This was accounted for in our simulation by reducing the simulated milk intake of the neonate to 75% of the average value (i.e., 105 ml/kg). The mother and the neonate were CYP2D6 UMs.4,6 Their morphine clearances were set to the lower bounds (11 and 0 ml/min/kg, respectively), representing the pharmacokinetic worst-case scenario. Simulated breast milk and plasma concentrations were compared with observed values.

**Figure 4** Nomogram of the calculated neonatal cumulative morphine doses after 14 days of repeated oral codeine treatment to the mother. The total amount of morphine ingested by the neonate through breast milk was calculated for all combinations of CYP2D6 GT and $C_{\text{MOR}}$ as a function of maternal codeine dose. Clearance of codeine by means of CYP2D6 was set to the maximum value derived for the three genotypes. Milk:plasma concentration ratios were set to the mean value of 2.46. The gray bars indicate the neonate doses that lead to neonatal plasma concentrations of 10 $\mu g/l$ and 20 $\mu g/l$ for the two most vulnerable neonate phenotypes, with no morphine clearance (Ø) and very low morphine clearance (0.6 ml/min/kg, ↓↓), respectively. The top and bottom of each gray bars indicate data from a CYP2D6 UM and a CYP2D6 PM neonate, respectively. $C_{\text{max}}$ peak plasma concentration; $C_{\text{MOR}}$ morphine clearance; EM, extensive metabolizer; GT, genotype; PM, poor metabolizer; UM, ultra rapid metabolizer.

Completely lack morphine elimination capacity (i.e., morphine plasma clearance = 0 ml/min/kg indicated as Ø). The other three scenarios represented very low (0.6 ml/min/kg, ↓↓), low (3 ml/min/kg, ↓), and medium (8 ml/min/kg, ↔) morphine clearance.59 The outcome of this sensitivity analysis was translated into two nomograms.
the maternal morphine clearance). Neonates with low morphine clearance (0.6 ml/min/kg) who are breast-fed by UM or EM mothers who also have low morphine clearance (11 ml/min/kg) can be expected to have a morphine $C_{\text{max}}$ of 10 $\mu$g/l at maternal codeine doses of 1.25 and 1.75 mg/kg/day, respectively, after 14 consecutive days of treatment.

Figure 5 shows the neonatal morphine $C_{\text{max}}$ reached on days 4, 7, 10, and 14 after repeated administration of codeine to the mother. This information is presented for five maternal codeine doses between 0.5 and 2.5 mg/kg/day for all genotype and morphine clearance combinations (only parameter combinations leading to neonatal morphine peak plasma concentrations above 10 $\mu$g/l are considered). This figure highlights the importance of the daily codeine dose of the mother, as the number of combinations leading to excessive neonatal concentrations greatly increases with the maternal codeine dose. $C_{\text{max}}$ levels above 20 $\mu$g/l were reached only in neonates with no morphine elimination capacity. The CYP2D6 genotype of the neonate had only a minor impact on the $C_{\text{max}}$ (Figure 4, gray bars; Figure 5, horizontal error bars).

The Toronto case
In the light of the results of the sensitivity analysis, only the extreme combination of an upper-bound CYP2D6 UM codeine clearance, a low maternal morphine clearance, and a high milk:plasma ratio can explain the observed milk concentration.
of 87 µg/l on day 10, as was reported in the Toronto case. Figure 6 presents the simulated concentration–time profiles for plasma and milk relating to this extreme combination of parameters as compared with the experimental breast milk concentration. Although the simulated peak level in milk on day 10 matched the experimental value, the mean simulated concentration on day 10 is lower by a factor of approximately 2.

The cumulative amounts of morphine and codeine ingested by the breast-fed neonate are shown in Figure 6, along with the resulting time course of morphine in the neonate’s plasma. On day 14, a morphine plasma concentration of 54 µg/l was obtained per the simulation, which is ~20% lower than that reported (70 µg/l postmortem) in the Toronto case.4,6 We estimated that the contribution of ingested codeine to the overall morphine concentration amounts to 14.7%.

**DISCUSSION**

Codeine for the treatment of post-labor pain has been considered to be “usually compatible with breast-feeding,”11 and ~120,000 women receive codeine postpartum every year in Canada alone.41 After a recent fatal case of opioid toxicity in a breast-fed newborn, the presumed safety of prescribing codeine to breast-feeding mothers has been intensely scrutinized.4,6,23,41–46 This is despite the fact that breast milk and neonatal plasma concentrations in that case of fatality were unexpectedly high in comparison with other reports relating to such concentrations (Tables 1 and 2). The US Food and Drug Administration responded in the form of a warning that codeine administration to UM mothers can lead to higher-than-expected morphine concentrations in breast milk.5

Our study applied coupled PBPK models to more fully comprehend how the CYP2D6 genotype and codeine and morphine clearances are linked to neonatal morphine plasma concentrations in breast-fed newborns of mothers who have been prescribed codeine. The model parameterization of codeine formation from morphine via CYP2D6 was carried out using the data set of Kirchheiner et al.,24 who studied the kinetics of codeine, morphine, and their metabolites after a single codeine dose in CYP2D6-genotyped male individuals. Unfortunately, no such data are available for lactating mothers. Therefore, the model assumes that the intrinsic CYP2D6 clearance values derived from the data in ref. 24 can be applied in lactating mothers as well.

Besides free morphine itself, its primary glucuronide metabolite M6G formed by UGT2B7 also exhibits opioid activity and could potentially contribute to neonatal toxicity. In this model, we neglected the putative role of M6G because (i) information about the oral bioavailability of the metabolite in neonates is lacking and (ii) data about breast milk concentrations of morphine glucuronides are not clear. In a study carried out by Wittels et al.,15 the concentrations of morphine-3-glucuronide were found to be substantially lower—by an estimated factor of 20—than morphine concentrations in breast milk. In contrast, Baka et al.13 reported milk-plasma partition coefficients of between 0.76 and 2.73 for M6G in the colostrum of three lactating women. In absolute numbers, the M6G concentrations in breast milk were <1.1 mg/l at cumulative intravenous morphine doses from 0.33 to 0.92 mg/kg over 24 h. Three other subjects in that study had no detectable morphine or M6G levels.13 The oral bioavailability of M6G has thus far been studied only in adults and is reported to be small (11% (ref. 46)). It is reasonable to assume that only small amounts of morphine glucuronides can be directly taken up by the breast-fed neonate. On the other hand, it is well known that the capacity for deglucuronidation is greatly enhanced during fetal and neonatal stages.45 It is therefore possible that morphine is formed through deglucuronidation in the neonate’s intestine after ingestion of morphine-3-glucuronide or M6G and subsequently absorbed. This effect, among others, could explain the observed discrepancy between the simulated free-morphine concentration of 54 ng/ml in the neonatal plasma and the reported postmortem plasma concentration of 70 ng/ml found in the Toronto infant who died of
toxicity. It also highlights the need to assume extreme parameter combinations (UM mother with low morphine clearance, high milk:plasma ratio, and no neonatal morphine clearance). But any glucuronidation that might have occurred in the liver of the neonate would have led to a decrease in free morphine in plasma and would thereby have increased the gap between the simulation findings and the observed data. Another important reason for this discrepancy is the fact that the blood sample of the neonate was obtained postmortem. It is very likely that this value does not reflect the plasma level at the time of death, because redistribution of the drug from tissue compartments can occur postmortem, leading to findings of increased plasma concentrations. However, the fact that only the assumption of a combination of extreme parameter values can even approach a reasonable explanation of the experimental data reflects the rarity of the fatal Toronto event. The findings from our simulations, which demonstrate that it is possible for lethal levels of morphine to occur in neonates, support the conclusion that the neonate died from indirect morphine intoxication caused by codeine treatment to the mother. Even after a neonate’s intake of codeine and morphine with milk is reduced because of the onset of drowsiness (from day 7 onward), morphine plasma levels can continue to increase. Contrary to the suggestion of Bateman et al., it is indeed possible for breast-fed infants to ingest a lethal dose of codeine.44

Very recently, Madadi and co-workers, in a retrospective analysis of the characteristics of mothers who had been prescribed codeine and their breast-fed infants with and without symptoms of central nervous system depression, demonstrated an effect of the maternal codeine dose on observed neonatal opioid toxicity.23 Symptoms of central nervous system depression occurred at maternal codeine doses of 1.62 ± 0.79 mg/kg/day (mean ± SD), whereas in asymptomatic cases the maternal dose was significantly lower (1.02 ± 0.54 mg/kg/day). In line with this observation, our model predicted the onset of opioid activity in the neonate for maternal doses of 1–2 mg/kg/day (Figure 4).

There are three major findings from our nomogram that have not yet been adequately addressed so far. The first is that neonates of CYP2D6 EM mothers are at only a slightly lower risk for ingesting toxic amounts of morphine as compared with neonates of UM mothers. This is a consequence of the large overlap of morphine peak concentrations observed in CYP2D6 EMs and UMs24 (Figure 2). Although the experimental and simulated morphine pharmacokinetics parameters for PMs show no overlap with those of the other two genotypes, EMs and UMs have an almost identical Cmax range and exhibit a large overlap in AUCinfinity. Zanger et al. also demonstrated a substantial functional overlap in liver biopsies of individuals genotyped as CYP2D6 EMs and UMs.48 The second major finding is the dominating role of the maternal capacity to eliminate morphine. An EM mother with low morphine clearance (11 ml/min/kg) showed even higher plasma and breast milk morphine concentrations than did a UM mother with average morphine clearance (21 ml/min/kg. Figure 3). However, the factor that dominates the overall risk profile is the neonatal morphine clearance. The sensitivity analysis with respect to the neonatal morphine clearance showed that even a low morphine plasma clearance of 3 ml/min/kg prevents a breast-fed neonate from accumulating amounts of morphine that could cause adverse symptoms, when the mother takes codeine in doses ≤2.5 mg/kg/day for 2 weeks after delivery. According to the findings of the simulation, only very low (0.6 ml/min/kg) or negligible neonate morphine clearances lead to neonatal morphine plasma levels >10 µg/l.

In the context of this model, a total absence of morphine clearance must be interpreted as either a lack of glucuronidation capacity in neonates or a result of an efficient deglucuronidation that is more rapid than renal excretion of the glucuronide.37 In addition, this assumption implies impaired kidney function, because morphine in its free or conjugated form is excreted renally. Both interpretations are difficult to justify, because it is widely accepted that both UGT2B7 activity and glomerular filtration are already sufficiently mature during the fetal stage itself. On the other hand, in a neonate that can efficiently eliminate morphine, it is impossible to observe such an extreme accumulation of morphine in plasma as was seen in the case of the Toronto newborn over a time span of 13 days. One possible explanation for this discrepancy is that neonatal morphine clearance values that are reported in the literature could be erroneously high. Typically, such values are derived from “steady-state” concentrations, but in the event of very low elimination rates, the times to reach steady state are quite long—estimated to be >5 days for clearance of 0.6 ml/min/kg—often longer than the administration period of morphine.

A clinically relevant question arises as to whether exposure windows can be identified, i.e., ranges in which morphine concentrations are below the toxicity threshold for the mother but above it for the neonate. Although a general answer cannot be given because of interindividual differences in the susceptibility to opioids, this study provides an indication that such an exposure window indeed exists. Our simulation results for the Toronto case suggest that the mother may have experienced adverse effects at the beginning of the therapy (peak plasma concentration of 37 µg/l) with the initial codeine dose of 120 mg/day. This is in agreement with the reported somnolence and constipation on day 2. After reduction of the codeine dose to 60 mg/day, peak plasma levels of 22 µg/l were obtained in the simulation; some individuals may tolerate such levels without adverse reactions. Further evidence for the existence of an exposure window is given in the case–control study carried out by Madadi et al., who reported that in their study cohort there was a 29% probability that the mother would be asymptomatic while the child showed symptoms of central nervous system depression (5 of 17 mother–child pairs).

Another factor of clinical relevance is potential coadministration of CYP3A4 inhibitors. Inhibition of the N-demethylation pathway that converts codeine into inactive norcodeine increases the probability of high morphine concentrations. In at least one reported case, opioid intoxication after codeine treatment was attributed partly to the coadministration of CYP3A4 inhibitors.49 This is of particular importance for lactating women who receive CYP3A4-inhibiting antibacterial agents for the treatment of postpartum infections.

Finally, it should be noted that the virtual neonate that was simulated in this study represented a full-term baby and might
therefore not reflect special physiological characteristics of pre-term neonates that might be of relevance for the pharmacokinetics of opioids (altered protein binding, for example). The results of this study are thus limited to full-term babies.

In summary, our model is capable of simulating the accumulation of morphine in the plasma of full-term neonates during repeated maternal codeine intake and to identify high-risk parameter combinations for neonatal opioid intoxication. The results support the validity of the questions that have recently been raised regarding the unmonitored use of codeine in breast-feeding mothers. In addition to the recent warning, we explicitly suggest that mothers with CYP2D6 EM genotype be included in the warning, given that the differences between EMs and UMbs with respect to the rate and extent of morphine formation from codeine are small. Of even greater importance, however, is the need to assess maternal and neonatal morphine clearances. These have emerged as the most important predictors of neonatal morphine accumulation. Unmonitored use of codeine for post-labor pain in breast-feeding mothers should not be considered a safe practice.

METHODS

All models were built in the PK-Sim generic whole-body PBPK modeling software (version 4.0; Bayer Technology Services, Leverkusen, Germany). PK-Sim-generated PBPK models were exported and coupled in the MoBi software (version 2.0; Bayer Technology Services). All optimizations and batch mode simulations were carried out using Matlab (version 7; MathWorks, Natick, MA) and the MoBi Toolbox for Matlab (version 2.0; Bayer Technology Services).

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CONFLICT OF INTEREST

S.W., K.C., and J.L. are employees of Bayer Technology Services GmbH, the company that owns and commercializes the software platform used for the simulations (PK-Sim and MoBi). A.N.E. and G.A. declared no conflict of interest. No particular funding was provided for this study.

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