Review Article

Estimation of drug pharmacokinetics from breastfeeding: a simple method based on meta-analysis

Abstract

Background

In resource-limited settings, breastfeeding is the healthiest source of nutrition for newborns. For economic/cultural reasons, breastfeeding is the preferred option for the majority of mothers, including HIV-positive mothers.

Objective: The objective of this review is to document parameters characterizing ARV diffusion into breast milk associated with the estimated ARV amount ingested by breastfed infant and clinical/biological abnormalities.

Data Source and Eligibility Criteria: 27 published articles on the aspects of Pharmacokinetic parameters on ARV diffusion into breast milk have shown a large variability without clear interpretation on drugs diffusion. Using PubMed and Embase, we conducted a search to identify all published studies at 2015 that characterized antiretroviral drug diffusion from mother to infant via breast milk. We identified 27 published studies that characterized antiretroviral drug passage from mother to infant (drug concentrations in mother's milk and breastfed plasma). Information was sufficiently complete for inclusion in the present analysis for only six antiretroviral drugs.

Results: Finally, only data for nevirapine and efavirenz were exploitable because some of the studies found null or non-detectable levels which were not suitable for simulations. Median (IQR) nevirapine CL/F were 0.022 (0.013-0.038) for newborns, 0.121 (0.116-0.125) for children and 0.056 (0.045-0.070) for mothers, all in L/h/kg. Efavirenz CL/F were 0.025 (0.016-0.039) for newborns, 0.273 (0.261-0.285) for children and 0.160 (0.153-0.167) for mothers, also in L/h/kg.

Conclusion: In this study, we tried to present a simple approach to estimate newborn's apparent clearance from paired mother's milk and breastfed newborn's plasma samples.

Key words: Breast milk, antiretroviral drugs, newborn exposure

1.INTRODUCTION

Exploring drug pharmacokinetics in newborns is only performed exceptionally because they represent a physiologically fragile population in which drug administration has to be limited. However, in some conditions, newborns can be indirectly exposed to drugs and consequently to the associated risk of adverse events, as is the case during breastfeeding. In this situation, the current practice consists in monitoring adverse effects in the newborn and in determining drug concentrations in the milk and sometimes in the newborn's plasma to have information on the newborn's drug exposure. Both types of information helps pediatricians in maintaining or not breastfeeding when mothers are treated. In a complementary way, milk and newborn's plasma concentrations can be used to estimate some pharmacokinetic (PK) parameters of the ingested drug, like the apparent clearance (Cl/F). Apparent clearance is a hybrid pharmacokinetic parameter combining information both on absorption and elimination. Estimation of Cl/F and comparison with values reported in infants and adults is

unfortunately not usually carried out while this comparison would bring information on the PK behavior of the drug at the beginning of the patient's life. PK behavior is essential information for some drugs, especially those with both a low therapeutic index, a large inter- but a low intra-individual PK variability and a pharmacokinetic-pharmacodynamic relationship. For these kind of drugs, the administered dose is determined taking into account the target exposure and the PK parameters of each patient.

Paired breast milk and newborn's plasma samples are necessary to estimate Cl/F and are mainly available for antiretroviral drugs in developing countries. Indeed, the benefits of breastfeeding (1-3) are particularly notable in developing countries, where no or suboptimal breastfeeding was the attributable cause of over 800,000 deaths, 11.6% of all deaths, among children under five years of age in 2011 (4) and where the increased risk of morbidity and mortality from diarrheal illness and pneumonia among non-breastfed infants has been clearly established (5, 6). As such, the World Health Organization (WHO) and UNICEF recommend exclusive breastfeeding for the first six months of life, with the introduction of complementary foods and continued breastfeeding up to 2 years of age or beyond (7). Similarly, for HIV-infected mothers, exclusive breastfeeding is recommended for the first six months of life, followed by the introduction of complementary foods and continued breastfeeding thereafter through 12 months of life, or until the child can be assured a nutritionally adequate and safe diet without breast milk (8). To prevent transmission of HIV from mother-to-child throughout the breastfeeding period, the WHO recommends maternal use of triple antiretroviral therapy (ART) during this period (9). Although it is a highly effective strategy to reduce HIV transmission from mother-to-child, it does increase an infant's exposure to antiretroviral drugs during breastfeeding via drug diffusion into the breast milk, which may expose them to the risk of adverse events (10-13). Therefore, the WHO has identified surveillance of infant antiretroviral-related toxicities during the breastfeeding period, as well as antiretroviral exposure effects on growth and development, as an area of critically needed focus (14).

Complementarily to the clinical survey, the exploration of the pharmacokinetic behavior of antiretrovirals in breastfed newborns is essential as this special population can not be considered as "small adults" from a physiological and consequently from a pharmacokinetic point of view. The first aim of this paper was to estimate the apparent clearance in newborns for two antiretrovirals (efavirenz and nevirapine) commonly prescribed to HIV-infected breastfeeding mothers in developing countries. Secondly, the CL/F of these two drugs was compared with the values reported in children and adults.

2.MATERIALS AND METHODS

Using PubMed and Embase, we conducted a search to identify all published studies at 2015 that characterized antiretroviral drug diffusion from mother to infant via breast milk. To comply with study inclusion criteria, published findings had to provide information on antiretroviral drug concentration in paired breast milk and infant plasma, with values described as either mean and standard deviation (SD) or median and interquartile range (IQR) (Figure 1).

Monte Carlo simulations (20 000) were performed for milk and newborn's plasma concentrations using the Excel program (15, 16), applying a normal distribution. Volumes of breast milk ingested by the

breastfed infant were also simulated (20 000 simulations), using an average volume of 150 ± 20 mL/kg/day (Figure 1).

The newborn ingested dose (NID) was calculated applying the following formula: $NID = C_{milk} \times V_i$, where C_{milk} is the drug milk concentration and V_i is the milk volume ingested by the newborn. Newborn exposure (AUC_{24h}) was calculated by multiplying the newborn's plasma drug concentration for 24 hours ($AUC_{24h} = C_p \times 24h$) (Figure 1).

The CL/F (L/kg) was calculated by the following formula: $CL/F = \frac{NID}{AUC_{24h}}$. For adults and children, 20 000 Monte Carlo simulations were applied to CL/F values from the literature (17-21) (Figure 1). RStudio freeware (version 0.99.489, RStudio Inc.) was used to compare the density distributions of the simulations.

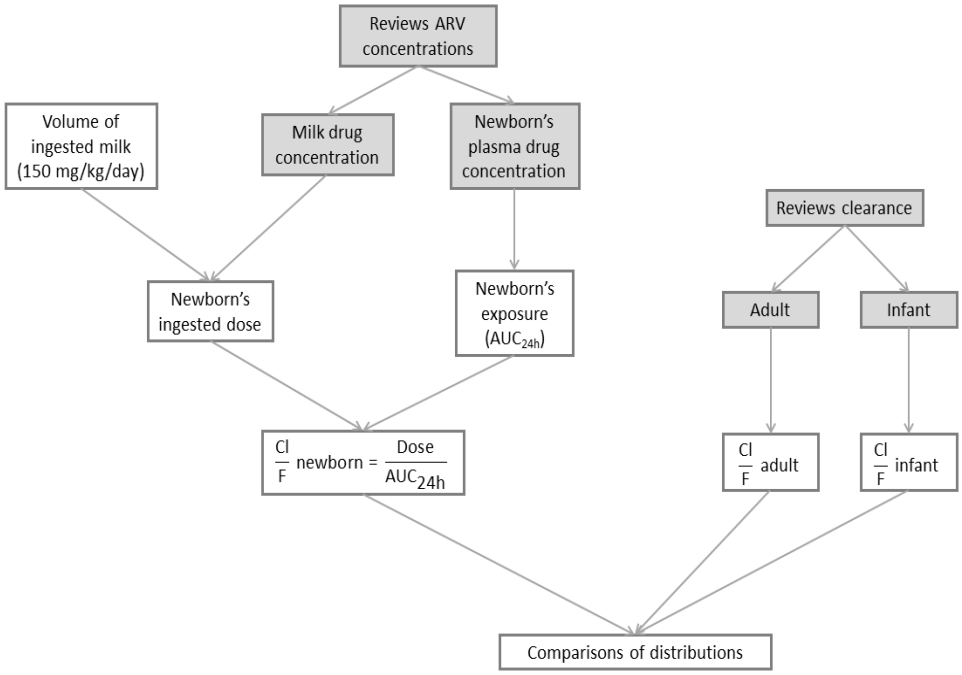

Figure 1: Estimation of newborn's and mother's apparent clearance

3.RESULTS

We identified 27 published studies that characterized antiretroviral drug passage from mother to infant (drug concentrations in mother's milk and breastfed plasma). Information was sufficiently complete for inclusion in the present analysis for only six antiretroviral drugs (flow diagram of studies selected is represented in Figure 2).

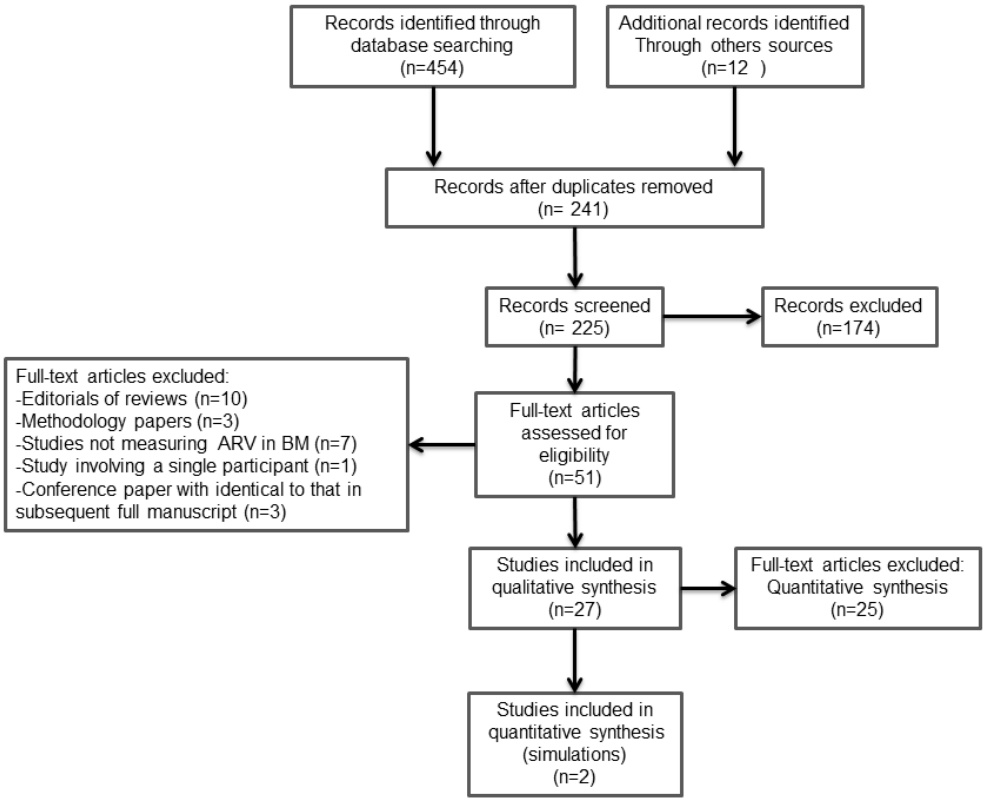

Figure 2: Flow diagram of article selection during review process

Selected molecules concerned two nucleoside reverse transcriptase inhibitors (NRTIs), stavudine and lamivudine; two non-nucleoside reverse transcriptase inhibitors (NNRTIs), nevirapine and efavirenz; and one pharmacokinetically-enhanced protease inhibitor, lopinavir/ritonavir. Finally, only data for nevirapine and efavirenz were exploitable because some of the studies (11, 22) found null or non-detectable levels which were not suitable for simulations. The data obtained from bibliography and used for simulations are collected in Table 1.

Table 1. Data used for simulations

		Efavirenz	***Nevirapine***
New born	**C_{milk} (mg/mL)**	3.51±1.72 [1]	2.901 (2.097-4.684) [2]
	C_p breastfed (mg/mL)	0.86±0.41 [1]	0.809 (0.535-1.061) [2]
	Reference	(23)	(11)
Infant	**CL/F (L/h)**	5.1 (6.1%) [3]	1.81 (5.7%) [3]
	Weight (kg)	18,7 *	15 *
	Reference	(17)	(21)
Adult	**CL/F (L/h)**	11.2 (6.8%) [3]	3.93 (2.76–4.32) [2]
	Weight (kg)	70 **	70 **
	Reference	(17)	(18)

[1]Average±SD; [2] Median (IQR); [3] Average (RSE%);* Median value; **Standard weight

Median (IQR) nevirapine CL/F were 0.022 (0.013-0.038) for newborns, 0.121 (0.116-0.125) for children and 0.056 (0.045-0.070) for mothers, all in L/h/kg. Efavirenz CL/F were 0.025 (0.016-0.039) for newborns, 0.273 (0.261-0.285) for children and 0.160 (0.153-0.167) for mothers, also in L/h/kg. The density distribution of the simulations results are shown in Figure 3.

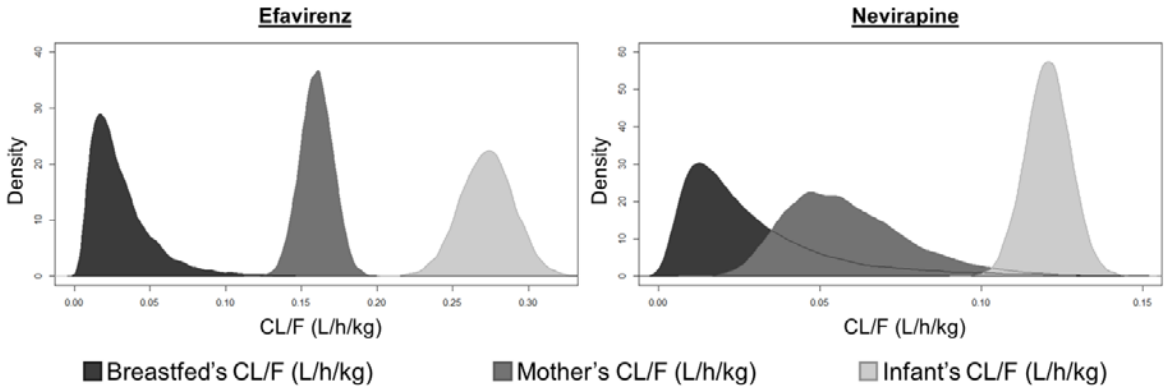

Figure 3: Distribution of simulated breastfed newborns', mothers' and infants' apparent clearances

4.DISCUSSION

In this study, we tried to present a simple approach to estimate newborn's apparent clearance from paired mother's milk and breastfed newborn's plasma samples. Apparent clearances *per* kilogram were largely superior for infants than for breastfed newborns (5-fold greater for nevirapine and 10-fold greater for efavirenz). Mothers' apparent clearances were also superior to those of breastfed newborns for nevirapine (2.5-fold) and efavirenz (more than 5-fold).

In the case of efavirenz, we used children' and adults' clearances estimated by the model published by Salem et al. (17). These authors validated a base model using children' samples, for children aged from 2 months to 16 years old. Later, this base model was allometrically scaled to a weight of 70 kg leading to a final model used for the prediction of efavirenz pharmacokinetics in adults. In the same study, the authors established that 90% of efavirenz metabolism maturity was not reached until 9 months. This is coherent with the low apparent clearances that we estimated for breastfed newborns. Moreover, higher CL/F *per* kg in children (0.19 L/h/kg; 0.21-0.26 L/h/kg) than in adults (0.15 L/h/kg) were also reported by other authors (24, 25). These results seem to be explained by the fact that efavirenz is mainly metabolized by the enzyme CYP450 2B6, the expression of which increases with age (26). However, CYP2B6 expression does not completely explain the fact that adults present lower

apparent clearances compared with children. Consequently, modifications of efavirenz diffusion through the intestinal wall between childhood and adulthood cannot be excluded.

With nevirapine, Nikanjam et al. (27) reported that apparent clearance was lower during the first year of life while the values increase after the first year and remain stable from 1 to more than 12 years old. In a previous review published by Hoody and Fletcher (25), CL/F was found to be the same for adults and children older than 8 years (0.060 L/h/kg), but it was 2-fold higher for infants from 9 months to 8 years (0.120 L/h/kg). For newborns from 48 to 72 hours of life, CL/F was 0.0361 L/h/kg. All these values are consistent with our results. Nevirapine is mainly metabolized by CYP3A5 in African populations (28, 29). However, as de Wildt et al. (30) did not show any change in CYP3A5 enzymatic activity related to age, the mechanisms implicated in the age-based changes in apparent clearance are still unclear.

While our results underline the difference between newborns' and children' apparent clearance for antiretrovirals, we are aware of the limitations of our study. Firstly, quantifying the volume of ingested milk is challenging. Thus, we used the standard assumption of 150 mL/kg/day breast milk intake. Because we do not have any information on the actual distribution of consumption, we proposed a range of 20 mL/kg/day among and below 150 mL/kg/day for this distribution. Secondly, the mothers' and children' apparent clearances, used to compare with newborns' apparent clearances, were obtained from different populations. For efavirenz, the selected population (adults and children) came from the United States with a 50% Afro-American population. For nevirapine, the adult population was Dutch while the children were from Kenya. We cannot exclude a possible inter-population pharmacokinetic variability. To improve our approach, it will be necessary to use children and adult data from the same population as that of newborns. Finally, breastfed newborn's ingested dose and plasma AUC were estimated from a single time point during the dosing interval. Our computation assumes a constant concentration of drug in ingested breast milk as well as in breastfed infant plasma throughout the dosing interval. This assumption seems reasonable for two reasons: (i) drug concentration in both matrices (breast milk and breastfed infant plasma) is supposed to be at steady state due to the repeated drug ingestion by the mother; (31) (31) low variation of drug concentration is expected in ingested milk due to the short duration of breastfeeding (+/- 20 minutes of suckling) as well as in breastfed infant plasma due to repeated sucklings throughout the dosing interval (6-8 sucklings/day) mimicking a perfusion.

5.CONCLUSION

Our approach enabled us to estimate the apparent clearance in newborns and to obtain some information on the pharmacokinetic behavior of drugs in this special population who cannot be considered as "small adults".

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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