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ARTICLE

Physiologically-based pharmacokinetic model to predict doxorubicin and paclitaxel exposure in infants through breast milk

David Damoiseaux[1] | **Frédéric Amant**[2,3] | **Jos H. Beijnen**[1,4] | **Shelby Barnett**[5] | **Gareth J. Veal**[5] | **Alwin D. R. Huitema**[1,6,7] | **Thomas P. C. Dorlo**[1,8]

[1]Department of Pharmacy and Pharmacology, The Netherlands Cancer Institute, Amsterdam, The Netherlands

[2]Department of Gynecology, The Netherlands Cancer Institute, Amsterdam, The Netherlands

[3]Gynecologic Oncology, UZ Leuven, Leuven, Belgium

[4]Utrecht Institute of Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands

[5]Newcastle University Centre for Cancer, Newcastle University, Newcastle upon Tyne, UK

[6]Department of Pharmacology, Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands

[7]Department of Clinical Pharmacy, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

[8]Department of Pharmacy, Uppsala University, Uppsala, Sweden

Correspondence
David Damoiseaux, Department of Pharmacy and Pharmacology, The Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX, Amsterdam, The Netherlands.
Email: d.damoiseaux@nki.nl

Abstract

Limited information is available concerning infant exposure and safety when breastfed by mothers receiving chemotherapy. Whereas defining distribution to breast milk is important to infer drug exposure, infant pharmacokinetics also determine to what extent the infant will be exposed to potential toxic effects. We aimed to assess the impact of chemotherapy containing breast milk on infants by predicting systemic and local (intestinal) exposure of paclitaxel and doxorubicin in infants through breast milk using a physiologically-based pharmacokinetic (PBPK) approach. Whole-body PBPK models of i.v. paclitaxel and doxorubicin were extended from the literature, with an oral absorption component to enable predictions in infants receiving paclitaxel or doxorubicin-containing breast milk. For safety considerations, worst-case scenarios were explored. Finally, paclitaxel and doxorubicin exposures in plasma and intestinal tissue of infants following feeding of breast milk from paclitaxel- or doxorubicin-treated mothers were simulated and breast milk discarding strategies were evaluated. The upper 95th percentile of the predicted peak concentrations in peripheral venous blood were 3.48 and 0.74 nM (0.4%–1.7% and 0.1%–1.8% of on-treatment) for paclitaxel and doxorubicin, respectively. Intestinal exposure reached peak concentrations of 1.0 and 140 μM for paclitaxel and doxorubicin, respectively. Discarding breast milk for the first 3 days after maternal chemotherapy administration reduced systemic and tissue exposures even further, to over 90% and 80% for paclitaxel and doxorubicin, respectively. PBPK simulations of chemotherapy exposure in infants after breastfeeding with chemotherapy containing breast milk suggest that particularly local gastrointestinal adverse events should be monitored, whereas systemic adverse events are not expected.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Limited information is available concerning infant exposure and safety when breastfed by mothers receiving chemotherapy.

WHAT QUESTION DID THIS STUDY ADDRESS?

What will the systemic and local (intestinal) exposure of paclitaxel and doxorubicin in infants be after ingesting chemotherapy containing breast milk?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

The chemotherapy exposure in infants while breastfed by a chemotherapy receiving mother.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

The insight we have provided here can inform and help clinicians in making informed decisions for women that want to breastfeed their infant during treatment for cancer in which this paper can be used as guidance.

INTRODUCTION

Treatment with chemotherapy is indicated in 40% of the women diagnosed with cancer during pregnancy. This can be continued during the postpartum period or chemotherapy may be started postpartum.[1] A lack of data on the subject, alongside the inherent cytotoxic nature of chemotherapy, have led to the general tendency to advise against breastfeeding during chemotherapy treatment. The long and tiring process of expressing milk during chemotherapy treatment, which is required to keep up milk production, results in a mere 10% of patients diagnosed with cancer during pregnancy successfully breastfeeding after treatment.[2,3] Deprivation of breastfeeding can have negative effects on both the infant and the mother, especially when considering the overwhelming benefits that breastfeeding offers to both parties. For mothers who received cancer treatment, breastfeeding provides strong maternal empowerment, contributing to psychological rehabilitation for survivors.[4,5] For infants, exclusive breastfeeding in the first 6 months of life is the single most effective preventive intervention for reducing infant mortality during the first year of life, along with many other physical and mental health benefits.[6–9]

The relative infant dosage (RID) is a commonly used metric representing the weight-adjusted percentage of the maternal dose. An RID below 5%–10% is generally considered to be an acceptable dose.[10] This arbitrary cutoff is probably too high for cytotoxic drugs with potentially mutagenic and carcinogenic properties, as well as potential neurotoxic effects of taxanes.[11] We previously demonstrated that paclitaxel and doxorubicin peak concentrations (C_{max}) in breast milk reached concentrations up to 20 and 300 ng/mL, respectively.[12] This corresponded to an estimated infant drug dose via breast milk, expressed as RID, of 0.13% for paclitaxel and 2.67% for doxorubicin. The cumulative sum of RIDs in a chemotherapy cycle were 0.06%–0.22% for paclitaxel and 3.3%–4.5% for doxorubicin. Discarding the first day of breast milk after administration of paclitaxel resulted in a cumulative RID less than 0.1%, whereas the first 3 days had to be discarded for doxorubicin to achieve a cumulative RID less than 1%. Although defining the RID in breast milk is an important first step to infer infant exposure, other factors, such as oral bioavailability and local exposure (intestines) from a breast milk matrix, also determine whether and to what extent the child will be exposed to the toxic effects of chemotherapy. In addition, immature absorption, metabolism, and other processes can result in uncharacterized differences in oral bioavailability compared to adults as well as pharmacodynamic differences.[13]

This is a serious shortcoming of previous case reports because there is no indication of what exposure can be expected in the infant when breast milk containing chemotherapy is fed to an infant. A suitable approach to obtain information regarding the exposure in infants would be the use of physiologically-based pharmacokinetic (PBPK) modeling, a method already commonly used for the prediction of adequate pediatric doses.[14] This bottom-up approach is especially useful because no observational data in the infant population is required. Predictions of chemotherapy exposure in all tissues can be acquired based on physiology of the infant population and physicochemical properties of the drug alone, and thereby without endangering the infants.

In the current study, we assessed the impact of breastfeeding during chemotherapy on infants by predicting the worst-case scenario systemic and local (intestinal)

exposure of paclitaxel and doxorubicin in infants using a PBPK approach. Hereby, we aim to generate data to support clinicians in making informed decisions about possible risks of exposure to the infant, for women who want to breastfeed during treatment for cancer.

METHODS

Data

A previously developed population pharmacokinetic (PK) model was used to predict concentrations of paclitaxel and doxorubicin in breast milk at timepoints of 1.7, 3.4, 5.1, 6.9, 8.6, 10.3, 12, 15, 18, 21, and 24 h each day,[15] seven feeding times during the day and four feeding times during the night based on Kent et al.,[16] starting from the maternal administration of chemotherapy. The maternal doses in the simulation were 80 mg/m^2 (every 2 weeks) and 60 mg/m^2 (weekly) with an infusion time of 3 and 2 h for paclitaxel and doxorubicin, respectively. An infant was assumed to have a standard daily milk volume intake of 150 mL/kg/day,[17] with an assumed 11 feeds a day this corresponds to an average milk volume of 13.64 mL/kg/feed. Cumulative doses ingested by the infant were 0.039 (over 7 days) and 0.271 (over 14 days) mg/kg for paclitaxel and doxorubicin, respectively, if no breast milk was discarded after maternal administration. The complete dosing schedule for each feed can be found in Tables S1 and S2.

Model development for paclitaxel started from the whole-body PBPK model of i.v. paclitaxel, which was obtained from the Open Systems Pharmacology (OSP) GitHub repository,[18] the model was developed using clinical studies in adults and evaluated for its predictive performance of CYP2C8 mediated clearance after i.v. administration in children. Model development for doxorubicin started from the whole-body PBPK model of i.v. doxorubicin published and kindly provided by Hanke et al.,[19] the model was developed using clinical data of a doxorubicin study arm in adults.

PBPK model development

The i.v. PBPK models were extended with oral absorption-related parameters to enable predictions in infants drinking paclitaxel or doxorubicin-containing breast milk. Due to the lack of observed data in infants, we were unable to evaluate what parameter values resulted in accurate predictions of paclitaxel exposure in infants. For safety considerations, we chose to use parameter values derived from a sensitivity analysis associated with the worst-case scenario for the infant, maximizing the predicted area under the concentration-time curve from zero until infinite time ($AUC_{0\text{-inf}}$) in plasma. Absorption-related parameters, including administration with and without co-administration of food (breast milk), different methods for the calculation of the partition coefficient, specific intestinal permeability, and gastrointestinal tract (GIT) pH and transit time were evaluated. In addition, we considered base model parameters error-prone for our extrapolation. Maturation of several parameters, such as renal function and metabolic enzymes CYP2C8 and CYP3A4 were incorporated in the model using predefined maturation curves in PK-Sim.[20] In addition, GIT expression of CYP enzymes was used from a predefined Gene Human expression database available in PK-Sim to define CYP enzyme metabolism in the GIT. However, hepatic clearance in the base model of doxorubicin was not specified to specific enzymes and therefore no maturation effect and GIT metabolism could be applied and this was, therefore, included in the sensitivity analysis. Finally, simulations in an infant population were performed with worst case-scenario parameter values.

Introduced parameters and co-administration of food

The co-administration with or without food (breast milk) was evaluated by the introduction of an event at the moment of administration. A meal event can be defined by the amount of energy, volume, and solid fraction. Breast milk contains 69 kilocalories per 100 mL breast milk, has a volume of 150 mL/kg/day divided by the number of daily doses, and has no solid fraction. Two different approaches for calculation of the partition coefficient were evaluated, the PK-Sim standard method, which uses lipophilicity measure, and the Rodgers and Rowland method, which uses electrostatic interaction. In PK-Sim, the specific intestinal permeability is calculated from drug lipophilicity and effective molecular weight. This resulted in a calculated specific intestinal permeability of 3.84×10^{-6} cm/min and 1.46×10^{-7} cm/min for paclitaxel and doxorubicin, respectively (equation in Supplementary Materials).[21]

Sensitivity analysis

A sensitivity analysis was performed to find reasonable parameter values resulting in the highest systemic exposure (worst-case scenario). Parameter values were either increased or decreased in steps of 25% or both (in case it was not obvious if either increase or decrease would result in higher exposure) except for categorical parameters, specific intestinal permeability, which was increased by 50% and 100%, and GIT pH for doxorubicin was not evaluated because of

its already high solubility in the model (with a minimal solubility of 1800 mg/L at a pH of 9). $AUC_{0\text{-inf}}$ in plasma was calculated for each situation with the trapezoidal rule. The parameter values resulting in the highest $AUC_{0\text{-inf}}$ in plasma were then included for the final simulations if greater than 2% increase in $AUC_{0\text{-inf}}$ compared to the base model.

Bioavailability

Bioavailability was determined for the base model and the model with the worst-case scenario parameters by simulating an individual infant of 0.25 years old and 5.13 kg receiving doxorubicin or paclitaxel containing breast milk during four consecutive maternal doses of doxorubicin (2 weeks interval) or paclitaxel (1 week interval) as oral and i.v. administration. Additionally, the difference in peripheral venous blood exposure between the base model and the model with the worst-case scenario parameters after oral administration was determined.

Simulations

A population of 500 European (International Commission on Radiological Protection [ICRP], 2002[22]) infants aged 0 to 1 years was used to predict chemotherapy exposure in plasma and intestinal tissue of infants following feeding of breast milk from paclitaxel or doxorubicin-treated mothers. Age was classified in three groups 0–0.25, 0.25–0.5, and 0.5–1, this classification is justified by the maturation of CYP enzymes and renal function that is most prominent during the first half year after birth. Amounts of chemotherapy in breast milk were based on previously developed population PK models for the prediction of chemotherapy distribution to breast milk.[15] Simulations were performed using the parameter values that resulted in the highest systemic exposure. $AUC_{0\text{-inf}}$ of plasma, intestinal tissue and heart tissue (for doxorubicin only) were calculated with the trapezoidal rule. The $AUC_{0\text{-inf}}$ in tissue implies all interstitial and intracellular paclitaxel or doxorubicin within the intestinal wall or heart. Additionally, simulations were divided in age groups to separately evaluate age-dependent differences in exposure. Exposure was predicted for breastfeeding during the entire cycle and with discarding the breast milk through multiple days after maternal administration.

Software

PBPK model development was performed in PK-Sim, which is part of the open source software OSP suite (version 11.0, www.open-systems-pharmacology.org) and R (version 4.2.1) was used for processing the data and graphical and statistical diagnostics.[20]

RESULTS

Worst-case scenario oral absorption parameter values

A sensitivity analysis was performed for oral absorption parameters to find values that resulted in the highest systemic exposure, results are presented in Tables 1 and 2 and Figures S1 and S2. For both paclitaxel and doxorubicin an increase in specific intestinal permeability had the most impact on peripheral venous blood exposure followed by a decrease in the fraction unbound. Paclitaxel peripheral venous blood exposure was higher with the inclusion of a food (breast milk) effect. In contrast to paclitaxel, the highest peripheral venous blood exposure for doxorubicin resulted from co-administration without food (breast milk). The calculation method for the partition coefficient did not result in different peripheral venous blood exposures for either paclitaxel or doxorubicin (Table 2; Table S1). However, intestinal exposure was higher with the Rodgers and Rowland method for paclitaxel and with the PK-Sim 2003 method for doxorubicin. Reducing the specific hepatic clearance of doxorubicin by −50% resulted in a slightly higher peripheral venous blood exposure. A decrease in the doxorubicin-specific DNA reference concentration parameter, a parameter specifically used in the doxorubicin model of Hanke et al., resulted in higher C_{max} (Figure S2) and slightly higher peripheral venous blood exposure (Table 2). A decrease in DNA concentration in the intestines was the main orchestrator of this effect and a decrease in DNA concentration in other tissue had minimal effect. A lower pH in the ileum and jejunum resulted in higher peripheral venous blood exposures for paclitaxel. Extension of the GIT transit time in both the small and large intestines resulted in higher peripheral venous blood exposures for doxorubicin and, for paclitaxel, this was only the case for the small intestine. Based on these results the worst-case scenario parameters we included for paclitaxel were specific intestinal permeability +100% (6.96×10^{-6} cm/min), fraction unbound −25% (2.25% unbound), the Rodgers and Rowland method for partition coefficient, with a food effect, lower GIT pH by 1–2 units (ileum and jejunum) and GIT transit time +25% (small intestine). The included worst-case scenario parameters for doxorubicin were specific intestinal permeability +100% (2.92×10^{-7} cm/min), fraction unbound −25% (19.7% unbound), specific hepatic clearance −50%

TABLE 1 The paclitaxel $AUC_{0\text{-inf}}$ for each parameter that was evaluated in the sensitivity analysis and the difference from the base model (%) in descending order for the peripheral blood difference from base model.

Paclitaxel	$AUC_{0\text{-inf}}$ (μM * h) peripheral blood	$AUC_{0\text{-inf}}$ (μM * h) large intestine	$AUC_{0\text{-inf}}$ (μM * h) small intestine	Peripheral blood exposure difference from base model (%)	Large intestine exposure difference from base model (%)	Small intestine exposure difference from base model (%)
Specific intestinal permeability +100%	0.023	2.0	20.7	186	73	97
Specific intestinal permeability +50%	0.018	2.2	21.4	146	82	100
Fraction unbound −25%	0.017	2.7	21.4	134	100	100
GIT transit time small intestine +25%	0.013	2.4	23.0	106	90	107
GIT pH upper ileum of 5.8	0.013	2.7	22.5	105	100	105
GIT pH lower ileum of 6.0	0.013	2.7	22.2	104	100	104
GIT pH lower jejunum of 5.5	0.013	2.7	22.1	103	100	103
GIT pH upper jejunum of 5.0	0.013	2.7	21.6	101	100	101
GIT transit time large intestine +25%	0.013	2.9	21.4	101	106	100
Base model	0.013	2.7	21.4	100	100	100
GIT pH duodenum of 4.8	0.013	2.7	21.4	100	100	100
GIT transit time stomach +25%	0.013	2.7	21.4	100	100	100
Calculation method for the partition coefficient PK-Sim	0.013	2.0	15.6	100	73	73
Without food	0.012	2.3	21.7	99	85	101
Fraction unbound +25%	0.010	2.7	21.4	80	100	100

Abbreviations: $AUC_{0\text{-inf}}$, area under the plasma-concentration time curve extrapolated until infinity; GIT, gastrointestinal tract.

TABLE 2 The doxorubicin $AUC_{0\text{-inf}}$ for each parameter that was evaluated in the sensitivity analysis and the difference from the base model (%) in descending order for the peripheral blood difference from base model.

Doxorubicin	$AUC_{0\text{-inf}}$ (μM * h) peripheral blood	$AUC_{0\text{-inf}}$ (μM * h) large intestine	$AUC_{0\text{-inf}}$ (μM * h) small intestine	Peripheral blood exposure difference from base model (%)	Large intestine exposure difference from base model (%)	Small intestine exposure difference from base model (%)
Specific intestinal permeability +100%	0.129	2.89	2.19	204	94	115
Specific intestinal permeability +50%	0.096	3.01	2.05	152	97	108
Fraction unbound −25%	0.083	3.09	1.90	131	100	100
Without food	0.074	3.12	2.93	117	101	154
GIT transit time large intestine +25%	0.073	3.81	1.95	116	123	103
GIT transit time small intestine +25%	0.071	3.07	2.60	113	99	136
Hepatic clearance −25%	0.069	3.17	1.96	109	102	103
DNA reference concentration −25%	0.064	3.09	1.91	101	100	100
DNA intestinal reference concentration −25%	0.064	3.09	1.91	101	100	100
Calculation method for the partition coefficient PK-Sim	0.063	4.21	2.59	100	136	136
Base model	0.063	3.09	1.90	100	100	100
DNA reference concentration +25%	0.063	3.10	1.90	100	100	100
DNA other tissue reference concentration −25%	0.063	3.10	1.90	100	100	100
GIT transit time stomach +25%	0.063	3.09	1.91	100	100	100
Fraction unbound +25%	0.052	3.11	1.90	82	101	100

Abbreviations: $AUC_{0\text{-inf}}$, area under the plasma-concentration time curve extrapolated until infinity; GIT, gastrointestinal tract.

(1.16 L/min), the PK-Sim method for partition coefficient (base model), without a food effect, intestinal DNA concentration −25%, and GIT transit time +25% (small and large intestines).

Bioavailability

Bioavailability increased between the base model to the model with the worst-case scenario parameters from 10% to 23% and from 13% to 38% for paclitaxel (Figure 1) and doxorubicin (Figure 2), respectively. This resulted in an increase in peripheral venous blood exposure between the base model and the model with the worst-case scenario parameters of 187% and 355% for paclitaxel and doxorubicin, respectively.

Paclitaxel simulations with the worst-case scenario parameters

The final simulation of paclitaxel administration through breast milk in infants using the worst-case scenario parameters resulted in a peripheral venous blood $AUC_{0\text{-inf}}$ of 0.042 ± 0.092 μM*h (Figure 3), which is 0.1%–0.8% of the $AUC_{0\text{-inf}}$ observed in adults (5–40 μM*h) after a short infusion (<6 h) of doses between 50 and 250 mg/m^2.[23] The upper 95th percentile of the predicted C_{max} values of 3.48 nM were reached in peripheral venous blood corresponding with 0.4%–1.7% of the C_{max} observed in on-treatment adults (210–830 nM) at doses between 110 and 200 mg/m^2.[24] The highest C_{max} values were observed in the population younger than 0.25 years old (Figure S3). No clinical data of i.v. paclitaxel administrations in children younger than 1 year was found. Furthermore, peripheral venous blood concentrations only marginally exceeded the lowest in vitro cell death half-maximal inhibitory concentration (IC_{50}) found in literature of 2.5 nM (after a 24 h exposure).[25,26] Local exposure in the intestines was higher with an $AUC_{0\text{-inf}}$ of 23.0 ± 5.8 μM*h and 2.1 ± 0.6 μM*h for small and large intestines, respectively (Figure 3). The upper 95th quantile of the predicted C_{max} values were also higher at 981 and 37 nM for small and large intestines, respectively.

Discarding breast milk after maternal administration of paclitaxel

Discarding breast milk for multiple days after maternal administration of paclitaxel resulted in a decrease in peripheral venous blood $AUC_{0\text{-inf}}$ of 71%, 86%, and 92% when 1, 2, or 3 days were discarded, respectively (Figure 3). For peripheral venous blood C_{max}, a decrease of 80%, 92%, and 96% were predicted when 1, 2, or 3 days were discarded, respectively. Discarding 1 day of breast milk is sufficient to reduce peripheral venous blood C_{max} to concentrations lower than the in vitro cell death IC_{50} values (Figures 3 and

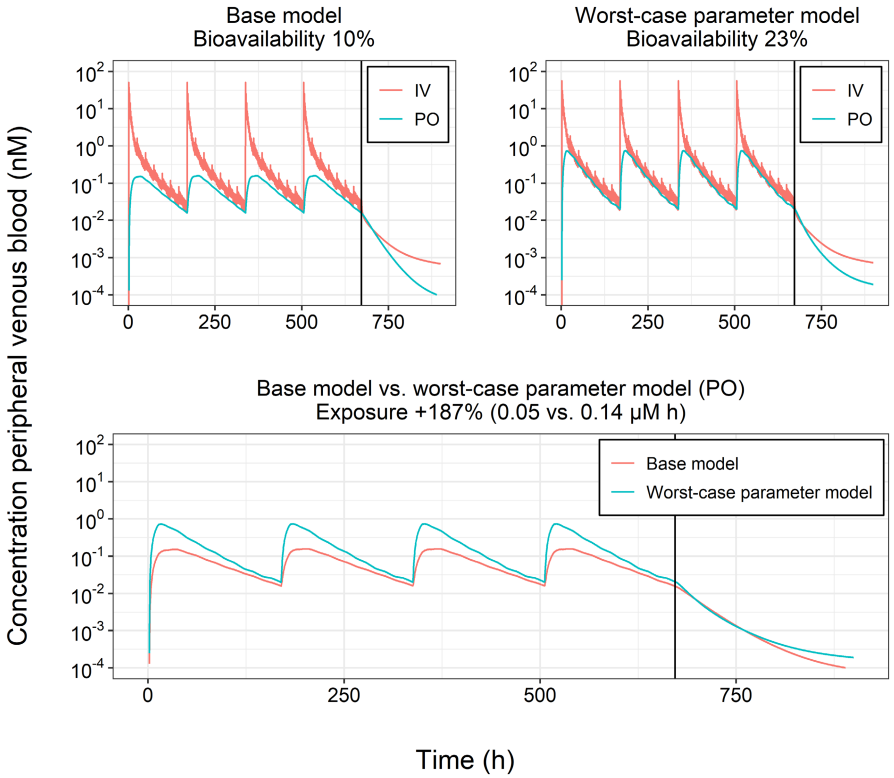

FIGURE 1 IV and oral (PO) paclitaxel administration in the base model and the model with the worst-case scenario parameters with corresponding bioavailability and a comparison in the peripheral venous blood exposure of the base model and worst-case parameter model after oral administration. Bioavailability and differences in exposure were calculated using the $AUC_{0\text{-inf}}$. The black vertical lines represent the time of the last administered dose. $AUC_{0\text{-inf}}$, area under the plasma-concentration time curve extrapolated until infinity.

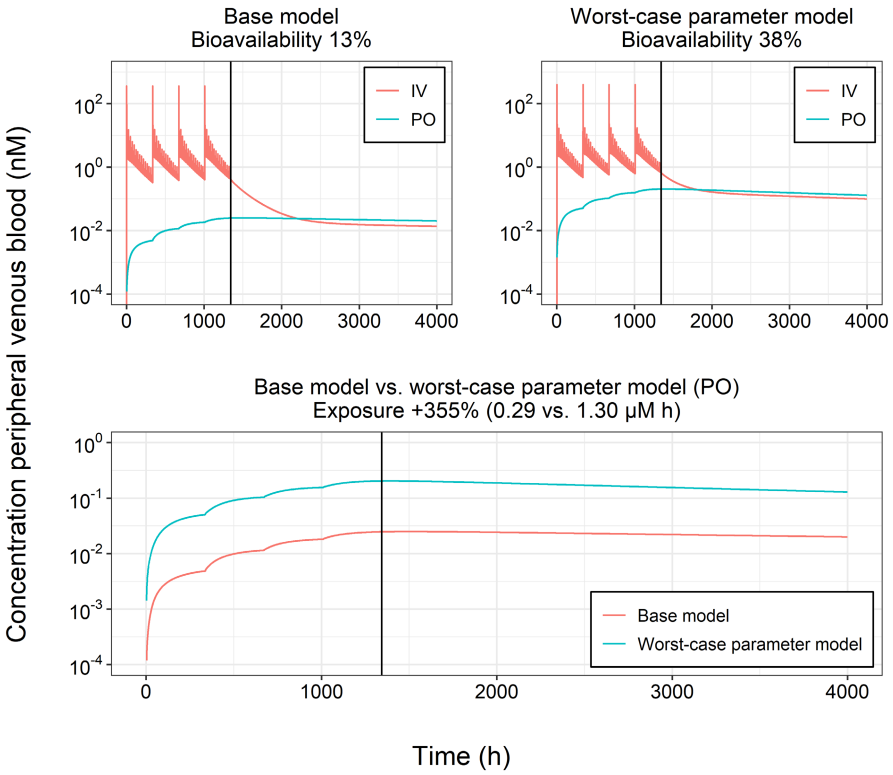

FIGURE 2 IV and oral (PO) doxorubicin administration in the base model and the model with the worst-case scenario parameters with corresponding bioavailability and a comparison in the peripheral venous blood exposure of the base model and worst-case parameter model after oral administration. Bioavailability and differences in exposure were calculated using the $AUC_{0\text{-inf}}$, bioavailability calculated with $AUC_{0\text{-4000h}}$ were much lower at 4% and 20% for the base model and worst-case parameter model, respectively. The black vertical lines represent the time of the last administered dose. $AUC_{0\text{-inf}}$, area under the plasma-concentration time curve extrapolated until infinity.

4). A similar decrease in $AUC_{0\text{-inf}}$ and C_{max} was predicted for the small and large intestines, except for the C_{max} in the large intestine which decreased by 56%, 82%, and 91% when 1, 2, or 3 days were discarded, respectively. Discarding 3 or 5 days of breast milk was sufficient to reduce intestinal C_{max} to between 5 and 10 or one to fivefold higher than the in vitro cell death IC_{50} values, respectively (Figure 4).

Doxorubicin simulations with the worst-case scenario parameters

The final simulation of doxorubicin ingestion through breast milk in infants using the worst-case scenario parameters resulted in a peripheral venous blood $AUC_{0\text{-inf}}$ of 1.4 ± 1.0 µM*h (Figure 5). The upper 95th quantile of the predicted C_{max} values of 0.74 nM were reached in peripheral venous blood corresponding to 0.1%–1.8% of the C_{max} observed in on-treatment children (40–550 nM) between 11 and 56 weeks old after an i.v. administration of 0.5–1.6 mg/kg doxorubicin (Figure 6). Furthermore, peripheral venous blood concentrations did not exceed the lowest in vitro cell death IC_{50} value found in literature of 7.5 nM (after 72 h exposure),[27] but persisted over a duration of more than 2000 h (Figure 5). Differences in exposure between age groups were minimal for doxorubicin (Figure S4). Tissue exposure was markedly higher for doxorubicin, with $AUC_{0\text{-inf}}$ values of 5.5 ± 34.2, 242 ± 146, and 942 ± 336 mM*h for the heart, and small and large intestines, respectively (Figure 5), between ~4000 and 240,000-fold higher than peripheral venous blood exposure. The upper 95th quantile of the predicted C_{max} values were also much higher at 2.4, 106, and 140 µM for the heart, and small and large intestines, respectively.

Discarding breast milk after maternal administration of doxorubicin

Peripheral venous doxorubicin blood $AUC_{0\text{-inf}}$ values were lowered by 60%, 72%, and 79% when 1, 2, or 3 days of breast milk were discarded, respectively (Figure 5). For peripheral venous blood C_{max} values, a decrease of 62%, 71%, and 81% were predicted when 1, 2, or 3 days were discarded, respectively. No milk had to be discarded to reduce peripheral venous blood C_{max} to concentrations lower than the in vitro cell death IC_{50} values (Figures 4 and 5). A similar decrease in $AUC_{0\text{-inf}}$ and C_{max} values was predicted for the heart, and small and large intestines when 1, 2, or 3 days were discarded. Discarding 1 or 3 days of breast milk was sufficient to reduce C_{max} in the heart to between one and five or less than or equal to onefold of the in vitro cell death IC_{50} values, respectively (Figure 4). Discarding 10 or 12 days of breast milk was sufficient to reduce intestinal C_{max} to between five and 10 or one to fivefold of the in vitro cell death IC_{50} values, respectively.

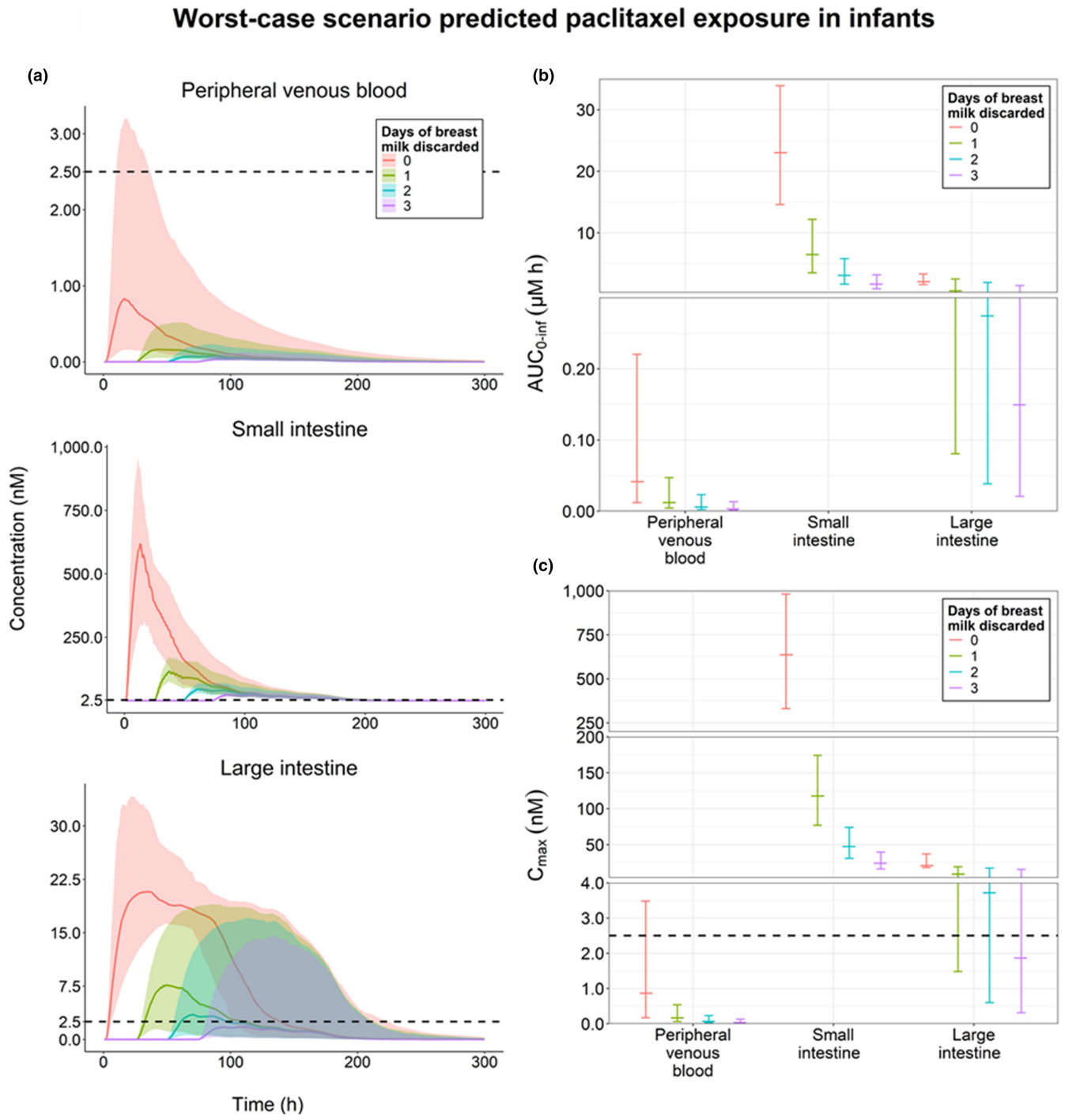

FIGURE 3 Simulation results with worst-case scenario predictions of paclitaxel exposure in a population of 500 infants between 0 to 1 years old. Concentration-time curves (a), $AUC_{0\text{-inf}}$ (b) and C_{max} (c) for peripheral venous blood, and small and large intestines for the situations in which 0, 1, 2, or 3 days of breast milk are discarded after maternal administration with 90% prediction intervals. The horizontal dashed line represents the lowest in vitro cell death half-maximal inhibitory concentration for paclitaxel found in literature (2.5 nM, after a 24 h exposure). $AUC_{0\text{-inf}}$, area under the plasma-concentration time curve extrapolated till infinity; C_{max}, peak concentrations.

DISCUSSION

A PBPK modeling approach enabled us to predict systemic and tissue (heart and intestines) exposure in infants after oral administration of paclitaxel and doxorubicin containing breast milk. Systemic exposure in the worst-case scenario was negligible and did not exceed in vitro cell death IC_{50} values associated with cytotoxic effects,[25,27] although tissue exposure did. Systemic exposure corresponded with less than 2% of on-treatment exposure for both paclitaxel and doxorubicin. By discarding breast milk for the first 3 days after maternal infusion of

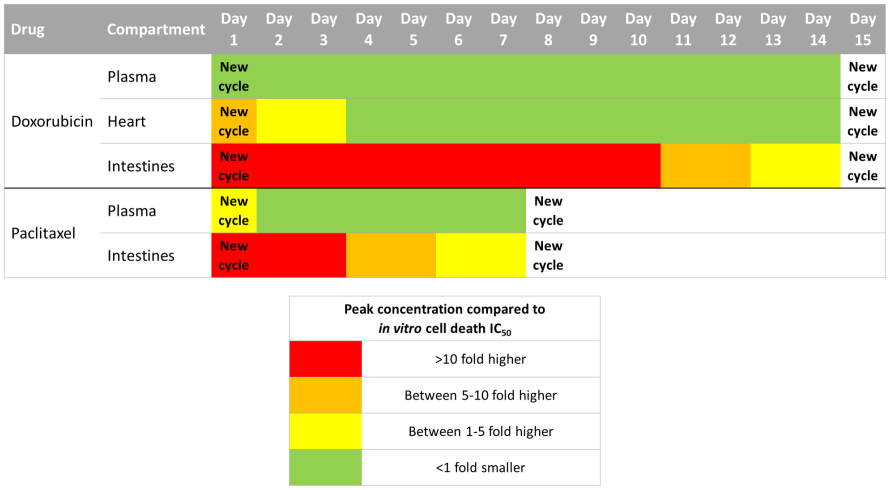

FIGURE 4 Days of breast milk that have to be discarded after maternal chemotherapy administration (new cycle) to prevent worst-case scenario predicted paclitaxel and doxorubicin concentrations of the upper 95th quantile of the predicted C_{max} values in the breastfed infant population to reach greater than 10, between five and 10, between one and five and less than onefold levels of in vitro cell death IC_{50} in plasma, heart (doxorubicin only) or intestines. In vitro cell death IC_{50} used are 2.5 and 270 nM for paclitaxel and doxorubicin, respectively. Concentrations in the 4th cycle were used for doxorubicin because of accumulation over cycles. We chose to use a 7 and 14 day cycle for paclitaxel and doxorubicin, respectively, because these are the most frequently used schedules. $AUC_{0\text{-inf}}$, area under the plasma-concentration time curve extrapolated till infinity; C_{max}, peak concentrations; IC_{50}, half-maximal inhibitory concentration.

chemotherapy the systemic and tissue exposures were reduced even further with a decrease of 90% and 80% for paclitaxel and doxorubicin, respectively. With regard to the clinical implications, our results were derived from the worst-case scenario, which predicted an exposure that was 2.87 and 4.55-fold higher than the base model, which is probably a better predictor for clinical exposure, for paclitaxel and doxorubicin, respectively (Figures 1 and 2). Nevertheless, safety in this population is of high importance and the worst-case scenario presented in Figure 4 should be leading for clinical application. In regard to Figure 4, the observed concentrations in the intestines stand-out, because they are high relative to observed in vitro cell death IC_{50} values.[25,27] Put into perspective, clinical trials of paclitaxel in an oral formulation have been conducted where patients were orally administered doses of 30 mg twice daily (~1 mg/kg/day).[28] Similar clinical trials with oral docetaxel show that GIT toxicity is comparable to that seen with i.v. administered docetaxel.[29] In relation, infants would ingest 0.035 mg/kg (no discarding) or 0.002 mg/kg (first day discarded) through breast milk, which is thus 3.5 or 0.2% of clinical mg/kg doses in adults, respectively. Despite the much lower doses in infants, there is insufficient information to assure that toxic events will not occur. Furthermore, no mutagenic effects have been identified for paclitaxel, suggesting minimal risk for mutations that could permanently alter the infants DNA.[30] However, for doxorubicin, mutagenic effects have been reported.[31] Although no conclusive information can be given on infant safety due to potential high local exposure, the discouragement shown in previous reports might be considered exaggerated. For example, in 2019, Codacci-Pisanelli et al.[32] observed prolonged persistence of doxorubicin, doxorubicinol, and cyclophosphamide in breast milk. With the caption: "Please abstain!" breastfeeding was discouraged for at least 6 weeks after treatment. Now with more data and modeling approaches to extrapolate our findings to a breastfed infant population, the fine-tuned breast milk discarding strategy might provide the solution for chemotherapy-treated mothers with a desire to breastfeed their infants.

We developed a PBPK model where we used a worst-case scenario for the amount of chemotherapy in breast milk, absorption-related parameters and parameters that we considered to have a high uncertainty. Hereby, we aimed to minimize the risk of underpredicting infant exposure. Nevertheless, the models lacked important properties, such as the effect of active transport in the intestines on the absorption and exposure to the active metabolite doxorubicinol. Paclitaxel and doxorubicin are both substrates for transporters in the intestines, such as the ABCG2 and ABCB1, and it is likely that absorption is influenced by these transporters. Differences in transporter expression between infants and adults due to maturation and the scarce literature on the oral absorption of these drugs complicate the implementation of a reliable transporter effect into the model. However, ABCB1 and ABCG2 are both located at the apical side of the intestinal

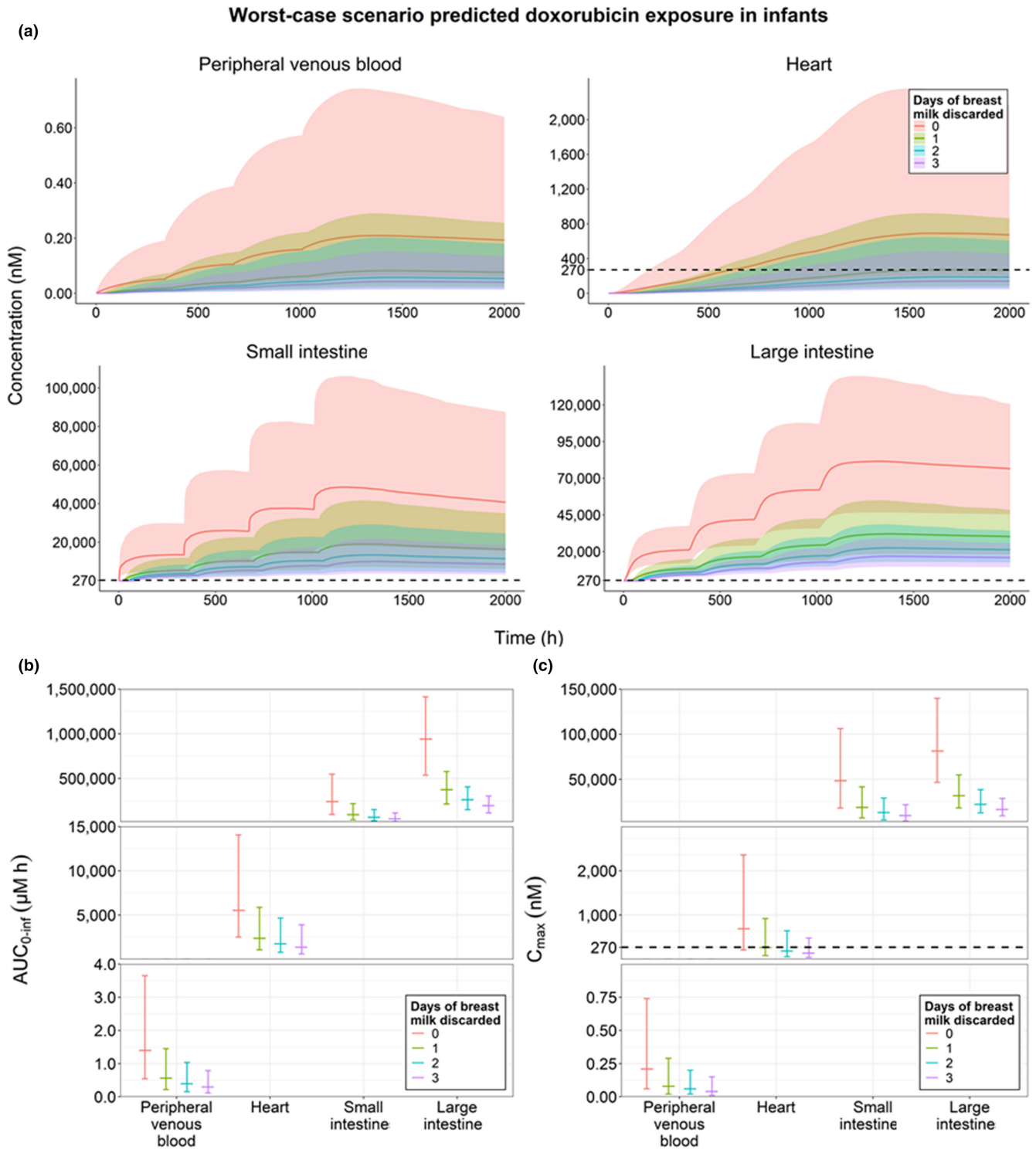

FIGURE 5 Simulation results with worst-case scenario predictions of doxorubicin exposure in a population of 500 infants between 0 and 1 years old. Concentration-time curves (a), $AUC_{0\text{-inf}}$ (b) and C_{max} (c) for peripheral venous blood, heart, small and large intestines for the situations in which 0, 1, 2 or 3 days of breast milk are discarded after maternal administration with 90% prediction intervals. The horizontal dashed line represents the lowest in vitro cell death IC_{50} for doxorubicin found in literature (270 nM, after a 72 h exposure). $AUC_{0\text{-inf}}$, area under the plasma-concentration time curve extrapolated till infinity; C_{max}, peak concentrations; IC_{50}, half-maximal inhibitory concentration.

membranes, which would cause the substrates to be excreted into the intestines and result in a lower bioavailability. For other cells, like in the blood–brain barrier, ABCB1 and ABCG2 are also located on the apical side of the cell and excretes substrates back into the systemic circulation, thereby reducing tissue concentrations and

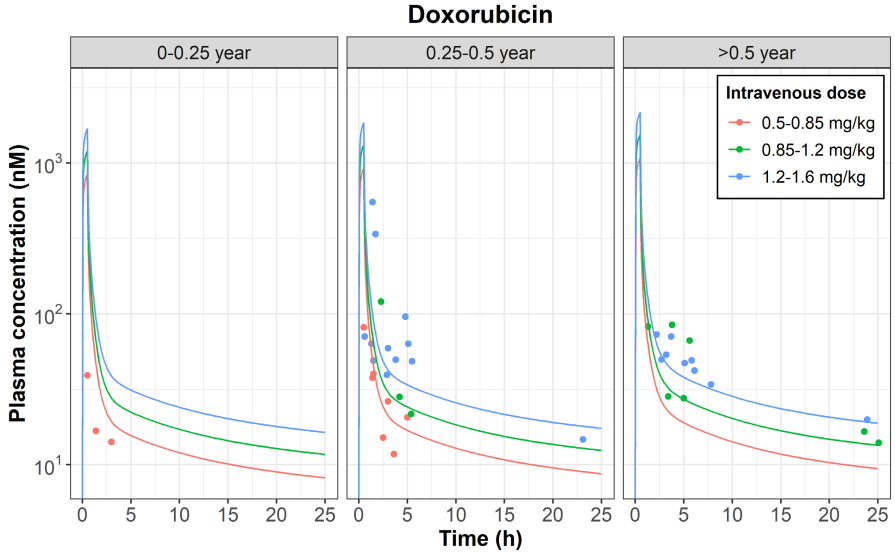

FIGURE 6 Clinical plasma concentrations of doxorubicin in on-treatment children between 11 and 56 weeks old (dots) after administration of a doxorubicin infusion with a duration between 0.07 and 4.5 h. Lines are simulations in infant of 0.25, 0.5 and 1 years old with the worst-case parameter model after a doxorubicin infusion of 0.7 (red), 1 (green), and 1.4 mg/kg with a duration of 0.5 h. Note that infusion duration is shorter for some of the simulations than for some of the clinical plasma concentrations and that the worst-case parameters in the model are absorption related and therefore have minimal effect on exposure after i.v. administration.

correlated toxicities. Because we aimed to assume the worst-case scenario the excretion effect of the transporters was disregarded. With regard to the active metabolite doxorubicinol, distribution to breast milk and absorption in the infant GIT is likely similar to that of doxorubicin. Doxorubicinol concentrations observed in postpartum women have been reported as half that of doxorubicin.[33] Taking into account a 1.5 to twofold safety margin on top of the doxorubicin concentration is therefore likely to suffice. Furthermore, our sensitivity analysis assumed the worst-case scenario for the systemic exposure and this does not necessarily imply the worst-case scenario in the intestines, possibly resulting in a reduced intestinal exposure. However, in the sensitivity analysis, increase in systemic exposure was most dependent on the increase of the specific intestinal permeability. This parameter represents the surface area-normalized transcellular permeability of the innermost layer of the intestinal wall. An increase in this parameter therefore results in higher systemic exposure but also higher intestinal exposure. As a result, the worst-case scenario for systemic exposure also resulted in higher intestinal exposures compared to the base model. Furthermore, it is important to highlight that there was no information available concerning colostrum drug concentrations, which impacts the precise dosage for administration due to the other composition of colostrum and potential difference in concentrations. Consequently, we have omitted a specific colostrum subpopulation from our analysis. As such, it is essential to exercise caution when extrapolating our findings to this specific population.

Another essential consideration is the predicted intestinal exposure, especially for doxorubicin which was much higher than the systemic exposure. It is difficult to relate these tissue exposure values to clinical toxicity and tolerability, and to validate whether these exposures are comparable to the clinical situation or whether they are a consequence of the model assumptions. In general, clinical relationships between local toxicity and drug exposure are typically based on systemic exposure, because tissue exposure data are often not available and are more difficult if not impossible to determine. Therefore, very limited tissue exposure-toxicity relationships are available, which makes it difficult to draw conclusions regarding toxicity based on predicted concentrations in tissues. As an alternative we looked into in vitro cell death IC_{50} values as a measure of toxicity, which also poses a number of problems. First, the in vitro cell death IC_{50} is often based on cancer cell line data. Unlike healthy cells, cancer cells are likely more susceptible to chemotherapy-induced toxicity because of their deficient processes to detect and correct errors in their faster cell replication, likely resulting in a lower in vitro cell death IC_{50}. However, it is important to note that the specific cell death IC_{50} value can vary depending on the type of cancer or healthy cells, the chemotherapy used, and other factors, such as the stage of the cell cycle or the presence of other mutations or genetic alterations.[34] Second, cell death IC_{50} values are probably also lower in vitro compared to in vivo due to a different environment of the cells. The in vivo environment contains many different potential binding partners for anticancer agents resulting in

lower unbound concentrations, as well as a more densely packed group of cells, making it more difficult for the drugs to reach every cell and inflict damage. Third, the cell death IC_{50} assumes a fixed time of exposure and longer exposure of cells to chemotherapy will result in more toxicity.

Nevertheless, due to a lack of more detailed data on exposure-toxicity relationships, we compared the orders of magnitude between tissue concentrations and cell death IC_{50} values. This would mean that, without discarding, breast milk concentrations in the small intestine are more than a 100-fold higher than cell death IC_{50} values for both paclitaxel and doxorubicin. Discarding strategies can reduce this to concentrations close to cell death IC_{50} values for paclitaxel within 6 days, but for doxorubicin this requires discarding at least 13 days of breast milk. This results from a predicted strong tissue accumulation of doxorubicin in the PBPK model. In the base model, a binding partner for doxorubicin was implemented to describe doxorubicin binding to DNA as the cause of the extensive distribution into and slow elimination from DNA-rich body tissues.[19] The binding partner was implemented in eight DNA-rich compartments, including the intestines. Subsequently, a DNA reference concentration was estimated based on observed plasma concentrations after an i.v. administration. Authors already warned for an overestimation of the DNA binding partner in the included compartments due to leaving out the DNA binding partner in other compartments. Furthermore, the model was not evaluated for oral administration, administration through the GIT therefore probably results in excessive binding of doxorubicin to its DNA binding partner in the intestines. This further supports the decision to reduce the intestinal DNA concentrations by 25% based on the sensitivity analysis. In addition, the model was designed to predict on-treatment doxorubicin plasma concentrations with higher concentrations over a shorter period of time. Although the base model of doxorubicin may not yet be optimal for the predictions following oral administration, we expect that the concentrations are overpredicted rather than underpredicted, thereby not violating our aim to assume the worst-case.

To conclude, it is difficult to predict what the toxic effect of concentrations higher and lower than in vitro cell death IC_{50} values will be, especially after prolonged exposure. The risks of adverse events in the intestines remain nevertheless substantial, even after discarding breast milk during 10 and 4 days after maternal administration of doxorubicin or paclitaxel, respectively. Nevertheless, previously reported breastfeeding interruption can probably be shortened. Our results suggest that toxicity related to the systemic exposure is expected to be negligible. The next step would be a safety assessment that requires clinical observations from infants that are breastfed during paclitaxel or doxorubicin treatment, for which our results provide the evidence-base for physicians to make a well-informed decision in consultation with mothers. Our analysis suggests that particularly gastrointestinal adverse events should be monitored and most caution is advised for the infants younger than 3 months, due to immature metabolic and renal function resulting in higher exposure.

AUTHOR CONTRIBUTIONS

D.D., J.H.B., A.D.R.H., S.B., G.J.V., F.A., and T.P.C.D. wrote the manuscript. D.D., T.P.C.D., and A.D.R.H. designed the research. D.D. performed the research. D.D. analyzed the data.

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CONFLICT OF INTEREST STATEMENT

The authors declared no competing interests for this work.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

ORCID

David Damoiseaux https://orcid.org/0000-0002-2348-5923
Gareth J. Veal https://orcid.org/0000-0002-1897-8678
Thomas P. C. Dorlo https://orcid.org/0000-0003-3076-8435

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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