Received: 26 July 2019 | Revised: 8 September 2019 | Accepted: 10 September 2019

DOI: 10.1111/bcp.14136

ORIGINAL ARTICLE

# Lidocaine as treatment for neonatal seizures: Evaluation of previously developed population pharmacokinetic models and dosing regimen

Laurent M.A. Favié[1,2] | Alwin D.R. Huitema[1,3] | Marcel P.H. van den Broek[4] | Carin M.A. Rademaker[1] | Timo R. de Haan[5] | Henrica L.M. van Straaten[6] | Sinno H.P. Simons[7] | Monique Rijken[8] | Debbie H.G.M. Nuytemans[5] | Toine C.G. Egberts[1,9] | Floris Groenendaal[2,10] on behalf of the PharmaCool study group*

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

[2]Department of Neonatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

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

[4]Department of Clinical Pharmacy, St. Antonius Hospital, Nieuwegein, The Netherlands

[5]Department of Neonatology, Emma Children's Hospital, Amsterdam University Medical Center, Amsterdam, The Netherlands

[6]Department of Neonatology, Isala Clinics, Zwolle, The Netherlands

[7]Department of Pediatrics, Division of Neonatology, Erasmus University Medical Centre-Sophia Children's Hospital, Rotterdam, The Netherlands

[8]Department of Neonatology, Leiden University Medical Center, Leiden, The Netherlands

[9]Department of Pharmacoepidemiology and Clinical Pharmacology, Faculty of Science, Utrecht University, Utrecht, The Netherlands

[10]UMC Utrecht Brain Center, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

**Aims:** Lidocaine is used to treat neonatal seizures refractory to other anticonvulsants. It is effective, but also associated with cardiac toxicity. Previous studies have reported on the pharmacokinetics of lidocaine in preterm and term neonates and proposed a dosing regimen for effective and safe lidocaine use. The objective of this study was to evaluate the previously developed pharmacokinetic models and dosing regimen. As a secondary objective, lidocaine effectiveness and safety were assessed.

**Methods:** Data from preterm neonates and (near-)term neonates with and without therapeutic hypothermia receiving lidocaine were included. Pharmacokinetic analyses were performed using non-linear mixed effects modelling. Simulations were performed to evaluate the proposed dosing regimen. Lidocaine was considered effective if no additional anticonvulsant was required and safe if no cardiac adverse events occurred.

**Results:** Data were available for 159 neonates; 50 (31.4%) preterm and 109 term neonates, of whom 49 (30.8%) were treated with therapeutic hypothermia. Lidocaine clearance increased with postmenstrual age by 0.69%/day (95% confidence interval 0.54–0.84%). During therapeutic hypothermia (33.5°C), lidocaine clearance was reduced by 21.8% (7.26%/°C, 95% confidence interval 1.63–11.2%) compared to normothermia (36.5°C). Simulations demonstrated that the proposed dosing regimen leads to adequate average lidocaine plasma concentrations. Effectiveness and safety were assessed in 92 neonates. Overall effectiveness was 53.3% (49/92) and 56.5% (13/23) for neonates receiving the proposed dosing regimen. No cardiac toxicity was observed.

A complete list of non-author contributors appears in the Acknowledgements section.

The authors confirm that the Principal Investigators for this paper are Timo R. de Haan and Floris Groenendaal and that they had direct clinical responsibility for patients.

**Correspondence**
Laurent M.A. Favié, Department of Clinical Pharmacy, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX, Utrecht, The Netherlands.
Email: l.m.a.favie@umcutrecht.nl

**Funding information**
ZonMw, Grant/Award Numbers: 40-41500-98-900, 40-41500-98-9002

**Conclusion:** Lidocaine pharmacokinetics was adequately described across the entire neonatal age range. With the proposed dosing regimen, lidocaine can provide effective and safe treatment for neonatal seizures.

**KEYWORDS**
clinical pharmacology, drug utilization, mass spectrometry, modelling and simulation, neonatology, pharmacometrics

## 1 | INTRODUCTION

Neonatal seizures are signs of a serious neurological disorder in the neonatal period and are often caused by underlying brain pathology such as hypoxic–ischaemic encephalopathy (HIE), central nervous system infections or intracranial haemorrhage.[1-3] Neonatal seizures are associated with an increased risk of long-term morbidity, including epilepsy and neurodevelopmental disorders possibly by adding damage to an already lesioned brain.[4-8] Therefore, effective treatment of seizures in neonates is important to prevent and reduce brain damage.[9-12]

**Lidocaine**, an amine derivative of **cocaine**, is commonly used as a local anaesthetic and as a class 1b antiarrhythmic drug in both paediatric and adult patients.[13-16] However, it is also used as an anticonvulsant in neonates refractory to 1 or more other antiepileptic drugs (AEDs) such as phenobarbital and midazolam.[17] Lidocaine has proven to be effective in several observational studies in both term and preterm neonates and is favoured as a second- or third-line anticonvulsant therapy in several European countries. The most important safety risk of the use of lidocaine is cardiac toxicity (bradycardia, arrhythmias or asystole), most likely to occur at plasma concentrations exceeding 9 mg/L.[18-22]

Lidocaine is metabolised in the liver by the **cytochrome p450 (CYP) enzyme system**, predominantly by **CYP1A2** and to a lesser extent by **CYP3A**. Monoethylglycinexylidide (MEGX) is the most prominent metabolite and is eliminated renally. Accumulation of MEGX has been associated with recurrent seizure activity.[23] An effect of gestational age (GA), postnatal age (PNA) and/or postmenstrual age (PMA) on the pharmacokinetics (PK) for lidocaine and MEGX can be expected given the physiological changes responsible for maturation of CYP1A2 and CYP3A activity as well as the development of renal function in neonates.[24,25]

Therapeutic hypothermia (TH), lowering the neonates' core temperature to 33–34°C for 72 h is the standard of care for term and near term neonates (GA ≥ 36 weeks) with HIE to reduce the incidence of death and neurological disabilities.[26,27] This controlled hypothermia treatment can, however, have an additional effect on lidocaine clearance due to a possible reduction in organ perfusion and/or reduction in hepatic enzymatic activity secondary to TH.[28-32]

Previous studies from our group have investigated lidocaine PK in both preterm and term neonates with and without TH treatment. Lidocaine clearance was lower in preterm neonates compared to term neonates.[33] As GA in this population is closely related to body weight (BW), a novel dosing regimen differentiated by BW was proposed for safe (lidocaine plasma concentrations <9 mg/L) and effective lidocaine use across the entire neonatal population (Table 1). Compared to the previously used dosing regimens, the loading phase was reduced from 6 to 4 h.[18,33] In (near-) term neonates, TH was found to reduce lidocaine clearance by 24% compared to normothermia. Therefore, a further reduction of the loading phase to 3.5 h during TH is incorporated in this dosing regimen.[34]

However, we have only been able to investigate lidocaine PK in relatively small numbers of neonates and never simultaneously across the entire neonatal treatment spectrum. Furthermore, the effectiveness of the previously developed dosing regimen has not been evaluated.

The aim of the present study was, therefore, to evaluate the previously developed population PK models and proposed dosing regimen in a larger dataset encompassing preterm neonates and (near-) term neonates with and without TH treatment. As a secondary objective, antiepileptic treatment effectiveness and the incidence of cardiac toxicity were assessed.

**What is already known about this subject**

- Lidocaine is an effective anticonvulsant in neonates, but is also associated with cardiac toxicity.
- Several small studies have described lidocaine pharmacokinetics in various neonatal populations.
- Based on these studies, a lidocaine dosing regimen was developed for safe and effective lidocaine use.

**What this study adds**

- Lidocaine pharmacokinetics was described across the entire neonatal age range, with postmenstrual age and body temperature influencing lidocaine clearance.
- Evaluation of the previously developed dosing regimen shows that lidocaine can provide safe and effective treatment for neonatal seizures.

**TABLE 1** Proposed lidocaine dosing regimen[33,34]

| | Bolus | | Loading phase | | Maintenance phase I | | Maintenance phase II | |
|---|---|---|---|---|---|---|---|---|
| **Weight** | **Dose** | **Duration** | **Dose** | **Duration** | **Dose** | **Duration** | **Dose** | **Duration** |
| *Normothermia* | | | | | | | | |
| < 1.6 kg | 2 mg/kg | 10 min | 5 mg/kg | 4 h | 2.5 mg/kg | 12 h | 1.25 mg/kg | 12 h |
| 1.6–2.6 kg | 2 mg/kg | 10 min | 6 mg/kg | 4 h | 3 mg/kg | 12 h | 1.5 mg/kg | 12 h |
| > 2.6 kg | 2 mg/kg | 10 min | 7 mg/kg | 4 h | 3.5 mg/kg | 12 h | 1.75 mg/kg | 12 h |
| *Hypothermia* | | | | | | | | |
| < 2.5 kg | 2 mg/kg | 10 min | 6 mg/kg | 3.5 h | 3 mg/kg | 12 h | 1.5 mg/kg | 12 h |
| ≥ 2.5 kg | 2 mg/kg | 10 min | 7 mg/kg | 3.5 h | 3.5 mg/kg | 12 h | 1.75 mg/kg | 12 h |

## 2 | PATIENTS AND METHODS

### 2.1 | Setting and study population

For the current study, data collected in the multicentre prospective cohort SHIVER study[34] and from a historical dataset collected as part of routine clinical care[33] (both previously published) were combined with data collected from patients who were included in the multicentre prospective cohort PharmaCool study and a novel dataset collected for routine clinical care. The SHIVER study and the PharmaCool studies both included (near-)term neonates treated with TH for HIE; neonates with congenital disorders were excluded. Full in- and exclusion criteria for both studies have been published previously.[35,36] Both studies were approved by the Ethics Committees of the participating centres and in both studies, written parental informed consent was obtained for each included neonate. The datasets collected during routine clinical care consisted of preterm and term neonates receiving lidocaine for treatment of neonatal seizures at the Neonatal Intensive Care Unit (NICU) of the University Medical Center Utrecht/Wilhelmina Children's Hospital between 2004 and 2018. An overview of the included neonates in the 2 studies and the 2 clinical care cohorts is shown in Table 2.

### 2.2 | Lidocaine dosing

In all neonates, lidocaine was prescribed as second- or third-line AED for seizures refractory to midazolam and/or phenobarbital. Lidocaine was administrated as continuous intravenous infusion according to local clinical protocols. In the SHIVER and PharmaCool studies, choice of therapy or dosing regimen was not influenced by the study protocol. Neonates in the second clinical care cohort received the proposed dosing regimen from 2015 onwards.

### 2.3 | Sampling and bioanalysis

In the SHIVER and PharmaCool studies, once daily blood samples were drawn on days 2–5 after birth. In the 2 clinical care cohorts, blood samples were drawn between 4 and 6 h and between 10 and 12 h after start of lidocaine administration. Plasma concentrations of lidocaine and MEGX in both studies and both cohorts were determined using a validated liquid chromatography–tandem mass spectrometric assay at the Clinical Pharmaceutical and Toxicological Laboratory of the Department of Clinical Pharmacy of the University Medical Center Utrecht, the Netherlands.[37] The lower limit of quantification (LLQ) for both lidocaine and MEGX was 0.2 mg/L.

**TABLE 2** Overview of the included neonates per study and cohort

| | Time period | No. of patients | Age groups, TH yes/no | Dosing regimen(s) | Sampling |
|---|---|---|---|---|---|
| Clinical care cohort 1 | 2004–2008 | 46 | Preterm and term neonates, no TH | See[33] | 4–6 h and 10–12 h after start of lidocaine |
| SHIVER study | 2008–2010 | 21[a] | (Near-)term neonates, all treated with TH | See[34] | Once daily on days 2–5 after birth |
| PharmaCool study[b] | 2010–2014 | 22 | (Near-)term neonates, all treated with TH | Various, none receiving the proposed dosing regimen | Once daily on days 2–5 after birth |
| Clinical care cohort 2[b] | 2010–2018 | 70 | Preterm and term neonates, 6 treated with TH | Various, 23 neonates receiving the proposed dosing regimen | Between 4-6 h and between 10-12 h after start of lidocaine |

Abbreviation: TH = therapeutic hypothermia

[a]one patient from in the SHIVER study was excluded because the exact timing of TH could not be retrieved.

[b]included for assessment of effectiveness and safety.

## 2.4 | Population PK analyses

PK analyses were performed using non-linear mixed effects modelling NONMEM (version 7.3, Icon Development Solutions).[38] Lidocaine hydrochloride doses were converted to lidocaine base and consecutively, all units of dose and concentration for lidocaine and MEGX were converted to μmol and μmol/L, respectively for the purpose of the PK analysis. If the measured concentration for 1 of the compounds was below the LLQ, it was fixed to LLQ/2 (i.e. 0.1 mg/L for both compounds); samples with measurements below LLQ for both lidocaine and MEGX were excluded from analysis.[39] As the fraction (F) of lidocaine converted to MEGX was unknown, MEGX parameters were estimated relative to F. Based on the previous publications, a 1-compartment model for lidocaine with a consecutive 1-compartment model for MEGX were used as structural models.[33,34] BW was used as a descriptor for body size and was related to PK parameters using allometric relationships with an exponent of 0.75 on clearance and an exponent of 1 on volume of distribution.[40] GA, PNA, PMA and body temperature were tested as covariates on clearance. Body temperature was tested as a continuous variable using a dynamic model as described previously.[36] Inclusion of covariates was guided by effect size, biological plausibility and statistical significance.

Interindividual variability was modelled using a proportional model and tested on all parameters. To account for data below LLQ, both proportional and additive error models were used to model residual unexplained variability in which the additive error was fixed on LLQ/2. Separate error models were used for lidocaine and MEGX. Parameter precision was assessed with sampling importance resampling.[41] Both graphical (e.g. goodness-of-fit plots) and statistical model evaluation procedures were used to assess model adequacy.

## 2.5 | Dosing regimen evaluation

To evaluate the previously developed dosing regimen, a simulation dataset was created by replicating the patient characteristics of each neonate included in the original dataset 7 times. The observed lidocaine plasma concentrations from neonates receiving the proposed dosing regimen were compared to the predicted lidocaine plasma concentrations using this simulation dataset and the parameter estimates from the PK model as reported by Van den Broek et al.[33] Additionally, simulations were conducted using the final parameter estimates from the PK model developed in this study and proposed dosing regimen. Mean peak lidocaine plasma concentrations <9 mg/L were considered effective and safe. The peak lidocaine plasma concentration was established as the highest plasma concentration reached during lidocaine treatment. Additionally, accumulation of MEGX should be avoided to reduce the occurrence of adverse effects related to MEGX; however, an upper limit cannot be established based on literature.

## 2.6 | Antiepileptic effectiveness and cardiac events

Antiepileptic effectiveness and incidence of cardiac events were assessed for neonates in the PharmaCool study and in the second cohort for clinical care as these have been published previously for the other datasets (Table 2).[18,34] Lidocaine was considered effective for seizure control if no additional antiepileptic drug was needed after lidocaine therapy, including dose increases of AEDs started prior to lidocaine therapy. Incidence of cardiac toxicity such as bradycardia, arrhythmias or asystole was based on spontaneous reports by the local investigators or the treating physicians in the patient's study files or clinical care records.

## 2.7 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY.

# 3 | RESULTS

## 3.1 | Patient characteristics

In total, 159 neonates were included in this study (SHIVER *n* = 21, PharmaCool *n* = 22, clinical care cohort 1 *n* = 46, clinical care cohort 2 *n* = 70, Table 2). Fifty neonates (31.4%) were born prematurely (<36 weeks GA) and 49 (30.8%) received TH (GA 36–42 weeks). Patient characteristics are presented in Table 3. Lidocaine and/or MEGX plasma concentrations were determined in 444 samples.

## 3.2 | Population PK analyses

PkK parameter estimates of the final model are shown in Table 4. GA but not PNA was identified as covariate for both lidocaine and MEGX clearance. However, combining GA and PNA into PMA as covariate on clearance for both compounds provided a better fit of the data. Average lidocaine clearance for a neonate of 3.5 kg at PMA 40 weeks was 1.77 L/h (95% confidence interval [CI] 1.63–2.03) whereas average lidocaine clearance for a neonate of 1 kg at PMA 25 weeks was 0.191 L/h (PMA effect 0.69%/day, 95% CI 0.54–0.84%). During TH, lidocaine clearance was reduced

**TABLE 3** Patient characteristics

| Parameter | Patients (*n* = 159) |
|---|---|
| Gestational age (weeks), mean ± SD | 37.0 ± 4.84 |
| Prematurity[a]; *n* (%) | 50 (31.4%) |
| Body weight; kg, mean ± SD | 2.89 ± 1.05 |
| Male; *n* (%) | 86 (54.1%) |
| Treated with TH[b]; *n* (%) | 49 (30.8%) |

Abbreviation: TH = therapeutic hypothermia
[a]Neonates born with a gestational age <36 weeks.
[b]All neonates treated with TH were born with a gestation age ≥36 weeks

**TABLE 4** Final model pharmacokinetic parameter estimates and SIR results

| | Lidocaine | | MEGX[a] | |
|---|---|---|---|---|
| ***Parameter*** | ***Estimate*** | ***SIR[b] 95% CI*** | ***Estimate*** | ***SIR[b] 95% CI*** |
| Cl, l/h[c] | 1.77 | 1.63–2.03 | 1.51 | 1.37–1.73 |
| V, l[c] | 9.32 | 8.49–9.63 | 15.8 | 13.6–18.7 |
| PMA on Cl, %/d | 0.690 | 0.581–0.837 | 0.350 | 0.114–0.805 |
| TEMP[d] on Cl, %/°C | 7.26 | 1.63–11.2 | NA | NA |
| *Interindividual variability* | | | | |
| Cl, variance (RSD) | 0.231 (48.1%) | 0.211–0.336 | 0.237 (48.7%) | 0.148–0.368 |
| V, variance (RSD) | 0.0673 (25.9%) | 0.0365–0.0956 | 0.478 (69.1%) | 0.346–0.672 |
| *Residual variability* | | | | |
| Additional, mg/L | 0.1 (fixed) | NA | 0.1 (fixed) | NA (fixed) |
| Proportional, variance (RSD) | 0.0379 (19.5%) | 0.0274–0.0431 | 0.0550 (23.5%) | 0.0445–0.0754 |

Final model:

$Cl_{LIDOCAINE} = 1.77 \times (BW/3.5)^{0.75} \times (1 + 0.0069 \times (PMA - 280)) \times (1 + 0.0726 \times (TEMP\text{-}36.5))$

$V_{LIDOCAINE} = 9.32 \times (BW/3.5)^{1}$

$Cl_{MEGX}/F_{MEGX} = 1.51 \times (BW/3.5)^{0.75} \times (1 + 0.0035 \times (PMA - 280))$

$V_{MEGX}/F_{MEGX} = 15.8 \times (BW/3.5)^{1}$

[a]MEGX estimates are relative to formation fraction F.

[b]Ten iterations; no. of samples 1000, 1000, 1000, 1000, 1000, 1000, 2000, 2000, 2000, 2000; no. of resamples 200, 200, 400, 400, 500, 500, 1000, 1000, 1000, 1000.

[c]Estimates for neonate with a birth weight of 3.5 kg and PMA 40 weeks.

[d]In neonates treated with TH, TEMP was set to 33.5°C during TH with rewarming at 0.4°C/h. Normothermia for all neonates was set to 36.5°C.

Abbreviations: Cl = clearance; V = volume of distribution; PMA = postmenstrual age; TEMP = body temperature; SIR = sampling importance resampling; NA = not applicable; RSD = relative standard deviation; TH = therapeutic hypothermia; MEGX = monoethylglycinexylidide

by 21.8% compared to normothermia (7.26%/°C, 95% CI 1.63–11.2%). No effect of TH on clearance of MEGX could be identified. Model evaluation demonstrated that the final models adequately described the data. Goodness-of-fit plots of observed *vs* population and individual predicted concentrations showed no systematic deviation and the weighted residuals were homogeneously scattered for both lidocaine and MEGX (Figures S1–S4).

### 3.3 | Dosing regimen evaluation

Figure 1 shows that the observed lidocaine plasma concentrations from 22 normothermic neonates receiving the proposed dosing regimen were comparable to the predicted lidocaine plasma concentrations for normothermic neonates. Only 1 neonate received the proposed dosing regimen while treated with TH. Therefore, comparing the observed lidocaine plasma concentrations to the predicted range during TH was not sensible. Lidocaine plasma concentrations achieved with the proposed dosing regimen (Table 1) were predicted using a simulation dataset of 1113 patients and the final PK parameter estimates. Both with and without TH, mean lidocaine peak plasma concentration was well below 9 ml/L (Figure 2) and no accumulation of MEGX occurred. During normothermia, 20.0% of simulations reached a lidocaine plasma concentration above 9 mg/L (4.7% >11 mg/L). During TH, lidocaine plasma concentrations exceeding 9 mg/L were reached in 31.8% of simulations (12.8% >11 mg/L).

### 3.4 | Antiepileptic effectiveness and cardiac events

Effectiveness and safety were assessed in 92 neonates. Overall, lidocaine was considered an effective anticonvulsant in 53.3% (49/92) of neonates. Of the 26 neonates without TH who were unresponsive to lidocaine 13 had meningitis, and 7 a major haemorrhage. Other diagnoses included asphyxia (4) GNAO1 mutation (1), and tuberous sclerosis (1). Lidocaine appeared to be most effective in term neonates not treated with TH. The predicted lidocaine plasma concentrations at the end of the loading phase did not differ between effective and ineffective treatment (Figure 3). The proposed dosing regimen was administered to 23 neonates (25.0%). Within this subgroup, effectiveness was 56.5% (13/23) and lidocaine effectiveness appeared to be greater in (near-)term neonates than in preterm neonates. Effectiveness with the previous dosing regimens was 52.2% (36/69). Lidocaine effectiveness is summarised in Table 5. No cardiac adverse events were reported.

## 4 | DISCUSSION

This study successfully described lidocaine PK in a large dataset combining both preterm and term neonates with and without TH treatment. PMA and TH were identified as significant covariates on lidocaine clearance. The final parameter estimates for lidocaine clearance and volume of distribution obtained in this study are largely consistent with the previous findings, which confirms the previously

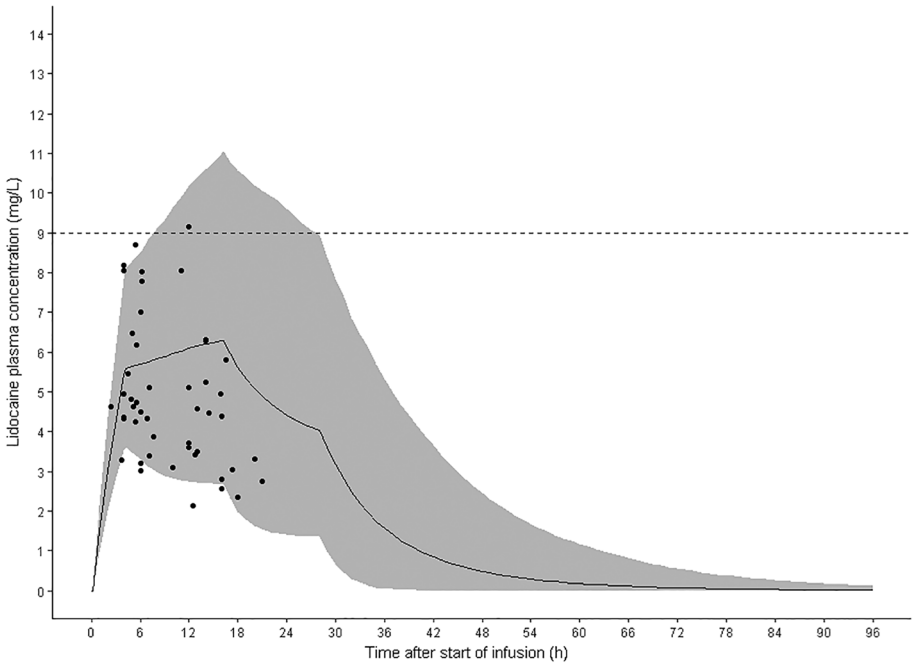


**FIGURE 1** Evaluation of the dosing regimen presented in Table 1 in 22 normothermic neonates. Black dots represent the observed lidocaine plasma concentrations. Solid line indicates the mean lidocaine plasma concentration and dark grey area represents the 95% prediction interval simulated with the final parameter estimates as reported by Van den Broek *et al*[33]

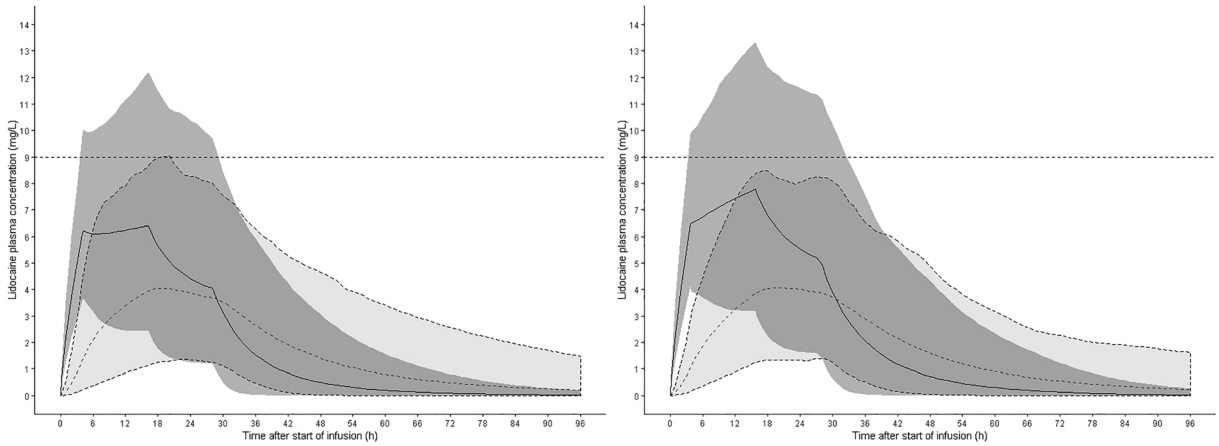


**FIGURE 2** Simulated lidocaine and monoethylglycinexylidide plasma concentrations for normothermic (left) and hypothermic (right) neonates with the final parameter estimates obtained in this study and dosing regimen presented in Table 1. Solid line indicates the mean lidocaine plasma concentration; dark grey area represents the 95% prediction interval. Dotted lines and light grey area indicate the mean MEGX plasma concentration and 95% prediction interval. horizontal dotted line indicates the suggested upper limit for lidocaine of 9 mg/L

identified PK parameters.[18,33,34] Evaluation of the proposed dosing regimen showed that average lidocaine plasma concentrations are well below the potential toxic upper limit of 9 mg/L for all neonates. Lidocaine effectiveness did not differ between the proposed and previous dosing regimens and no cardiac toxicity occurred.

Lidocaine is metabolised by the liver and its metabolites, including MEGX, are subsequently eliminated via the kidneys. PMA is identified as a covariate for maturation of both lidocaine and MEGX clearance. PMA was found to be a descriptor for maturation of morphine clearance, a hepatically cleared drug, by Knøsgaard et al.[42] and for glomerular filtration rate by Rhodin et al.[43] Both studies included data from neonates as well as older children and adults and incorporated PMA using a sigmoidal Hill equation. The $TM_{50}$, the PMA at which clearance is 50% of the mature value, was estimated in both studies to be around 55 weeks. Our study was comprised of only neonatal data with a minimum PMA of 25 weeks and maximum PMA of 42.7 weeks. In this age range, the sigmoidal Hill equations approach linearity. Therefore, we decided to include PMA as a linear effect in this study.

TH reduced lidocaine clearance by 21.8% compared to normothermia. This is consistent with our findings in a previous study.[34] Lidocaine is qualified as a drug with a high hepatic extraction ratio, with hepatic perfusion as rate limiting step for metabolism.[44] During hypothermia, hepatic blood flow is decreased due to a decrease in cardiac output and stroke volume.[29-32] Therefore, we hypothesise

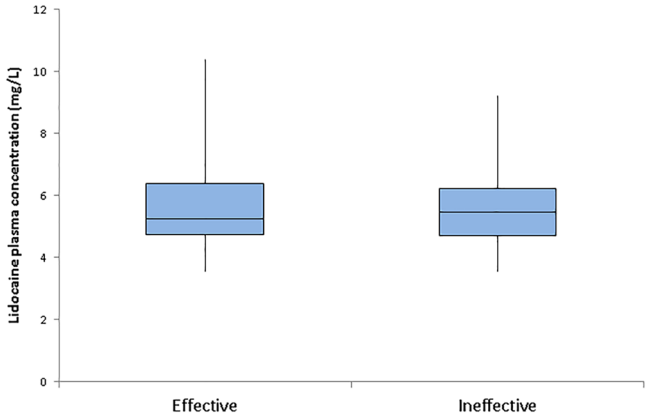


**FIGURE 3** Predicted lidocaine plasma concentrations at the end of the loading phase in neonates where lidocaine was effective (left) and ineffective (right). Horizontal lines represent the median plasma concentration; blue boxes represent the interquartile ranges; vertical lines indicate the highest and lowest plasma concentration

**TABLE 5** Effectiveness of lidocaine as antiepileptic drug

| | Effective, *n* (%) | Ineffective, *n* (%) |
|---|---|---|
| All patients (*n* = 92) | 49 (53.3%) | 43 (46.7%) |
| *GA <36 weeks (n = 28)* | *11 (39.3%)* | *17 (60.7%)* |
| *GA ≥ 6 weeks, NT (n = 36)* | *27 (75.0%)* | *9 (25.0%)* |
| *GA ≥ 6 weeks, TH (n = 28)* | *11 (39.3%)* | *17 (60.7%)* |
| Novel dosing regimen (*n* = 23) | 13 (56.5%) | 10 (44.5%) |
| *GA <36 weeks (n = 6)* | *3 (50%)* | *3 (50%)* |
| *GA ≥36 weeks (n = 17)* | *10 (58.8%)* | *7 (41.2%)* |

Abbreviations: GA = gestational age, NT = normothermia, TH = therapeutic hypothermia

that reduced blood flow during TH is primarily responsible for decreased lidocaine clearance. However, an additional or synergistic effect of TH on activity of CYP enzymes cannot be excluded based on this data. Renal perfusion is also dependent on cardiac output, but an effect of TH on clearance of MEGX has not been identified. Although an effect of TH on other renally cleared drugs and metabolites has been noted, this finding is consistent with the current knowledge regarding MEGX clearance.[34,36,45,46]

Simulations performed with the final PK estimates from the present study show that the proposed dosing regimen as depicted in Table 1 leads to acceptable average lidocaine plasma concentrations for both normothermic preterm and term neonates as well as term neonates treated with TH. The large interpatient variability will lead to plasma concentrations exceeding the supposed threshold for cardiac toxicity of 9 mg/L in some neonates for an acceptable period. Additionally, the proposed dosing regimen was validated by comparing the observed lidocaine plasma concentrations from neonates receiving this regime to the predicted concentrations based on the original PK model.[33] In 22 normothermic neonates the observed plasma concentrations fall largely within the predicted range. Unfortunately, this validation could not be performed for neonates treated with TH due to insufficient data.

Anticonvulsant effectiveness for lidocaine was assessed in 92 neonates in whom effectiveness was not reported previously. No relationship between effectiveness and lidocaine plasma concentrations at the end of the loading phase could be identified. This could be explained by the high heterogeneity in seizure aetiology in this population. Some neonates respond to lidocaine treatment while others are refractory to it, irrespective of the lidocaine plasma concentration. A higher lidocaine success rate was noted in (near-) term neonates. This is consistent with a retrospective study with 413 term and preterm neonates where a significantly lower success rate was observed in preterm *vs* term neonates (55.3 *vs* 76.1%); overall antiepileptic effectiveness of lidocaine was 71.4%.[19] Seizure control in our study was lower but did not differ between the proposed and the old dosing regimen. In neonates treated with TH, however, lidocaine responds rate was markedly lower in the present study compared to Van den Broek et al. (39.3 *vs* 91%).[34] The majority of data on neonates treated with TH comes from the PharmaCool study (22/28, 78.6%). In the PharmaCool study, data were only collected for 5 days after birth which might have created a selection bias. As lidocaine was administered mostly as third-line anticonvulsant after phenobarbital and midazolam in this population, only neonates who resorted to lidocaine treatment relatively early were included. It could be argued that these were neonates with more severe HIE unresponsive to any antiepileptic treatment. Mortality for neonates receiving lidocaine in the PharmaCool study was 77.3% (17/22), confirming the highly moribund prognosis. Additionally, Van den Broek et al.[34] defined effectiveness as a reduction of electrographic seizure burden of >80% within 4 h of commencing lidocaine instead of no need for additional anticonvulsants after lidocaine therapy and thus a shorter time frame for detecting treatment failure.

Cardiac toxicity was not seen in any neonate included in this study. Although lidocaine associated cardiac toxicity has been described, it is extremely rare and fatal incidents have only occurred when lidocaine was used concomitantly with phenytoin.[20,23,47,48] Lidocaine cardiac toxicity has been associated with plasma concentrations exceeding 9 mg/L. However, the relationship between toxicity and plasma concentration is based on anecdotal evidence in adults with coronary disease and might not be valid for neonates.[49,50] Additionally, neonates undergoing TH might be even less susceptible to cardiac side effects. Lidocaine inhibits **voltage-dependent sodium channels** on the cardiomyocyte, which are only available during the systolic phase.[34,51] During TH, the heart frequency is reduced compared to normothermia, thereby reducing the potential for cardiotoxicity. However, to minimise the chance of cardiac toxicity, lidocaine should not be co-administered with phenytoin or to neonates with congenital heart disease.[22]

Possible limitations of this study are the lack of clinical precision in the diagnoses of efficacy as we could not incorporate electrographic confirmation of lidocaine (in)effectiveness. However, the use of (no) additional AEDs can be used as a surrogate marker for efficacy. Additionally, the incidence of cardiac adverse events in this study was based on spontaneous reports. This introduces a

risk of bias due to underreporting. However, it is unlikely that any major cardiac event would have been omitted from the patient (study) records.

## 5 | CONCLUSION

This study describes lidocaine PK across the entire neonatal age range, with PMA and TH as significant covariates on clearance. The previously developed proposed dosing regimen leads to lidocaine plasma concentrations within the desired range with comparable effectiveness to the older regimens. No cardiac toxicity occurred. With the developed dosing regimen, lidocaine can be a safe and effective add-on anticonvulsant in preterm and term neonates with and without TH.

### ACKNOWLEDGEMENTS

The following PharmaCool study group members are non-author contributors: Mieke J. Brouwer PhD[2], S.M. Mulder-de Tollenaer MD, PhD[6], L.J.M. Groot Jebbink - Akkerman MD, PhD[6], Jeroen Dudink MD, PhD[9], Rogier C.J. de Jonge MD, PhD[9], Annelies A. Bos MD, PhD[9], Affiliations correspond with author affiliations.

The authors would like to thank Mark de Groot and Ylfa van Bergen for contributions with regard to data management and Frank van Bel for critical appraisal of the manuscript.

The PharmaCool study was funded with a grant from the Netherlands Organization for Health Research and Development (ZonMw) Priority Medicines for Children grant number: 40-41500-98-9002.

### CONTRIBUTORS

L.F.: data collection, data analyses, data interpretation, wrote the manuscript; A.H.: data analyses, data interpretation, reviewed and revised the manuscript; M.B.: study design, data collection, data interpretation, reviewed and revised the manuscript; C.R., T.E.: study design, data interpretation, reviewed and revised the manuscript; T.R.: study design, data collection, reviewed and revised the manuscript; H.S., S.S., M.R.: data collection, reviewed and revised the manuscript; D.M.: study conduct, reviewed and revised the manuscript; F.G.: study design, data collection, data analyses, data interpretation, reviewed and revised the manuscript. All authors contributed to and approved the final version of the manuscript.

### COMPETING INTERESTS

There are no competing interests to declare.

### ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

### ORCID

*Laurent M.A. Favié* https://orcid.org/0000-0002-4894-5236

### REFERENCES

1. Oh A, Thurman DJ, Kim H. Independent role of neonatal seizures in subsequent neurological outcomes: a population-based study. *Dev Med Child Neurol*. 2019 Jun;61(6):661-666. https://doi.org/10.1111/dmcn.14174
2. Mulkey SB, Swearingen CJ. Advancing neurologic Care in the Neonatal Intensive Care Unit with a neonatal neurologist. *J Child Neurol*. 2014;29(1):31-35. https://doi.org/10.1177/0883073812469051
3. Tekgul H. The current etiologic profile and neurodevelopmental outcome of seizures in term newborn infants. *Pediatrics*. 2006;117(4):1270-1280. https://doi.org/10.1542/peds.2005-1178
4. Ronen GM, Buckley D, Penney S, Streiner DL. Long-term prognosis in children with neonatal seizures: a population-based study. *Neurology*. 2007;69(19):1816-1822. https://doi.org/10.1212/01.wnl.0000279335.85797.2c
5. Glass HC, Glidden D, Jeremy RJ, Barkovich AJ, Ferriero DM, Miller SP. Clinical neonatal seizures are independently associated with outcome in infants at risk for hypoxic-ischemic brain injury. *J Pediatr*. 2009;155(3):318-323. https://doi.org/10.1016/j.jpeds.2009.03.040
6. Glass HC, Hong KJ, Rogers EE, et al. Risk factors for epilepsy in children with neonatal encephalopathy. *Pediatr Res*. 2011;70(5):535-540. https://doi.org/10.1203/PDR.0b013e31822f24c7
7. Pisani F, Piccolo B, Cantalupo G, et al. Neonatal seizures and postneonatal epilepsy: a 7-y follow-up study. *Pediatr Res*. 2012;72(2):186-193. https://doi.org/10.1038/pr.2012.66
8. Pisani F, Cerminara C, Fusco C, Sisti L. Neonatal status epilepticus *vs* recurrent neonatal seizures: clinical findings and outcome. *Neurology*. 2007;69(23):2177-2185. https://doi.org/10.1212/01.wnl.0000295674.34193.9e
9. Miller SP, Weiss J, Barnwell A, et al. Seizure-associated brain injury in term newborns with perinatal asphyxia. *Neurology*. 2002;58(4):542-548. https://doi.org/10.1212/WNL.58.4.542
10. McBride MC, Laroia N, Guillet R. Electrographic seizures in neonates correlate with poor neurodevelopmental outcome. *Neurology*. 2000;55(4):506-514. https://doi.org/10.1212/WNL.55.4.506
11. Glass HC, Nash KB, Bonifacio, et al. Seizures and magnetic resonance imaging–detected brain injury in newborns cooled for hypoxic-ischemic encephalopathy. *J Pediatr*. 2011;159(5):731-735e1. https://doi.org/10.1016/j.jpeds.2011.07.015
12. van Rooij LGM, Toet MC, van Huffelen AC, et al. Effect of treatment of subclinical neonatal seizures detected with aEEG: randomized. *Controlled Trial Pediatrics*. 2010;125(2):e358-e366. https://doi.org/10.1542/peds.2009-0136
13. Shahid S, Florez ID, Mbuagbaw L. Efficacy and safety of EMLA cream for pain control due to venipuncture in infants: a meta-analysis. *Pediatrics*. 2019 Jan;143(1). pii: e20181173. https://doi.org/10.1542/peds.2018-1173
14. Nagendrababu V, Setzer FC, Veettil SK, Pulikkotil SJ, Suresh A, Bhatia S. Efficacy of local anaesthetic solutions on the success of inferior alveolar nerve block in patients with irreversible pulpitis - a systematic review and network meta-analysis of randomized clinical trials. *Int Endod J*. 2019;52(6):1-11. https://doi.org/10.1111/iej.13072
15. Panchal AR, Berg KM, Kudenchuk, et al. 2018 American Heart Association focused update on advanced cardiovascular life support use of antiarrhythmic drugs during and immediately after cardiac arrest: an

update to the American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2018 Dec 4;138(23):e740-e749. https://doi.org/10.1161/CIR.0000000000000613

16. Duff JP, Topjian A, Berg MD, et al. 2018 American Heart Association focused update on pediatric advanced life support: an update to the American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2018 Dec 4;138(23):e731-e739. https://doi.org/10.1161/CIR.0000000000000612
17. Donovan MD, Griffin BT, Kharoshankaya L, Cryan JF, Boylan GB. Pharmacotherapy for neonatal seizures: current knowledge and future perspectives. *Drugs*. 2016;76(6):647-661. https://doi.org/10.1007/s40265-016-0554-7
18. Malingré MM, Van Rooij LGM, Rademaker CMA, et al. Development of an optimal lidocaine infusion strategy for neonatal seizures. *Eur J Pediatr*. 2006;165(9):598-604. https://doi.org/10.1007/s00431-006-0136-x
19. Weeke LC, Toet MC, van Rooij LGM, et al. Lidocaine response rate in aEEG-confirmed neonatal seizures: retrospective study of 413 full-term and preterm infants. *Epilepsia*. 2016;57(2):233-242. https://doi.org/10.1111/epi.13286
20. Lundqvist M, Ågren J, Hellström-Westas L, Flink R, Wickström R. Efficacy and safety of lidocaine for treatment of neonatal seizures. *Acta Paediatr Int J Paediatr*. 2013;102(9):863-867. https://doi.org/10.1111/apa.12311
21. Hellström-Westas L, Westgren U, Rosén I, Svenningsen NW. Lidocaine for treatment of severe seizures in newborn infants: I. clinical effects and cerebral electrical activity monitoring. *Acta Paediatr Scand*. 1988;77(1):79-84.
22. Yozawitz E, Stacey A, Pressler RM. Pharmacotherapy for seizures in neonates with hypoxic ischemic encephalopathy. *Pediatr Drugs*. 2017;19(6):553-567. https://doi.org/10.1007/s40272-017-0250-4
23. Van Rooij LGM, Toet MC, Rademaker CMA, Groenendaal F, de Vries LS. Cardiac arrhythmias in neonates receiving lidocaine as anticonvulsive treatment. *Eur J Pediatr*. 2004;163(11):637-641. https://doi.org/10.1007/s00431-004-1513-y
24. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental Pharmacology — drug disposition, action, and therapy in infants and children. *N Engl J Med*. 2003;349(12):1157-1167. https://doi.org/10.1056/NEJMra035092
25. van den Anker J, Reed MD, Allegaert K, Kearns GL. Developmental changes in pharmacokinetics and pharmacodynamics. *J Clin Pharmacol*. 2018;58(3):S10-S25. https://doi.org/10.1002/jcph.1284
26. Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cooling for newborns with hypoxic ischaemic encephalopathy. *Cochrane Database Syst Rev*. 2013;58:385-385. https://doi.org/10.1002/14651858.CD003311.pub3
27. Groenendaal F, Casaer A, Dijkman KP, et al. Introduction of hypothermia for neonates with perinatal asphyxia in the Netherlands and flanders and the dutch-flemish working group on neonatal neurology. *Neonatology*. 2013;104(1):15-21. https://doi.org/10.1159/000348823
28. Van den Broek MPH, Groenendaal F, Egberts ACG, Rademaker CMA. Effects of hypothermia on pharmacokinetics and pharmacodynamics. *Clin Pharmacokinet*. 2010;49(5):277-294. https://doi.org/10.2165/11319360-000000000-00000
29. Sehgal A, Linduska N, Huynh C. Cardiac adaptation in asphyxiated infants treated with therapeutic hypothermia. *J Neonatal-Perinatal Med* February. 2019;12(2):117-125. https://doi.org/10.3233/NPM-1853
30. Eriksen VR, Trautner S, Hahn GH, Greisen G. Lactate acidosis and cardiac output during initial therapeutic cooling in asphyxiated newborn infants. *PLoS ONE*. 2019 Mar 14;14(3):e0213537. https://doi.org/10.1371/journal.pone.0213537
31. Yoon JH, Lee E, Yum, et al. Impacts of therapeutic hypothermia on cardiovascular hemodynamics in newborns with hypoxic-ischemic encephalopathy: a case control study using echocardiography. *J Matern Neonatal Med*. 2018;31(16):2175-2182. https://doi.org/10.1080/14767058.2017.1338256
32. Gebauer CM, Knuepfer M, Robel-Tillig E, Pulzer F, Vogtmann C. Hemodynamics among neonates with hypoxic-ischemic encephalopathy during whole-body hypothermia and passive rewarming. *Pediatrics*. 2006;117(3):843-850. https://doi.org/10.1542/peds.2004-1587
33. Van Den Broek MPH, Huitema ADR, Van Hasselt JGC, et al. Lidocaine (lignocaine) dosing regimen based upon a population pharmacokinetic model for preterm and term neonates with seizures. *Clin Pharmacokinet*. 2011;50(7):461-469. https://doi.org/10.2165/11589160-000000000-00000
34. Van den Broek MPH, Rademaker CMA, van Straaten HLM, et al. Anticonvulsant treatment of asphyxiated newborns under hypothermia with lidocaine: efficacy, safety and dosing. *Arch Dis Child Fetal Neonatal Ed*. 2013;98(4):F341-F345. https://doi.org/10.1136/archdischild-2012-302678
35. De Haan TR, Bijleveld YA, van der Lee JH, et al. Pharmacokinetics and pharmacodynamics of medication in asphyxiated newborns during controlled hypothermia. *The PharmaCool Multicenter Study BMC Pediatr*. 2012 May 22;12:45. https://doi.org/10.1186/1471-2431-12-45
36. Favié LMA, Groenendaal F, van den Broek MPH, et al. Pharmacokinetics of morphine in encephalopathic neonates treated with therapeutic hypothermia. *PLoS ONE*. 2019 Feb 14;14(2):e0211910. https://doi.org/10.1371/journal.pone.0211910
37. ter Weijden E, van den Broek MPH, Ververs FFT. Easy and fast LC–MS/MS determination of lidocaine and MEGX in plasma for therapeutic drug monitoring in neonates with seizures. *J Chromatogr B*. 2012;881–882:111-114. https://doi.org/10.1016/j.jchromb.2011.11.030
38. Keizer RJ, Karlsson MO, Hooker A. Modeling and simulation workbench for NONMEM: tutorial on Pirana, PsN, and Xpose. *CPT Pharmacometrics Syst Pharmacol*. 2013;2(6):1-9;e50. https://doi.org/10.1038/psp.2013.24
39. Beal SL. Ways to fit a PK model with some data below the quantification limit. *J Pharmacokinet Pharmacodyn*. 2001;28(5):481-504. https://doi.org/10.1023/A:1012299115260
40. Holford N, Heo YA, Anderson B. A pharmacokinetic standard for babies and adults. *J Pharm Sci*. 2013;102(9):2941-2952. https://doi.org/10.1002/jps.23574
41. Dosne AG, Bergstrand M, Harling K, Karlsson MO. Improving the estimation of parameter uncertainty distributions in nonlinear mixed effects models using sampling importance resampling. *J Pharmacokinet Pharmacodyn*. 2016;43(6):583-596. https://doi.org/10.1007/s10928-016-9487-8
42. Knøsgaard KR, Foster DJR, Kreilgaard M, Sverrisdóttir E, Upton RN, van den Anker JN. Pharmacokinetic models of morphine and its metabolites in neonates: systematic comparisons of models from the literature, and development of a new meta-model. *Eur J Pharm Sci*. 2016;92:117-130. https://doi.org/10.1016/j.ejps.2016.06.026
43. Rhodin MM, Anderson BJ, Peters, et al. Human renal function maturation: a quantitative description using weight and postmenstrual age. *Pediatr Nephrol*. 2009;24(1):67-76. https://doi.org/10.1007/s00467-008-0997-5
44. Stenson RE, Constantino RT, Harrison DC. Interrelationships of hepatic blood flow, cardiac output, and blood levels of lidocaine in man. *Circulation*. 1971;43(2):205-211. https://doi.org/10.1161/01.CIR.43.2.205
45. Bijleveld Y, Mathôt R, van der Lee J, et al. Population pharmacokinetics of amoxicillin in term neonates undergoing moderate hypothermia. *Clin Pharmacol Ther*. 2018;103(3):458-467. https://doi.org/10.1002/cpt.748

46. Bijleveld YA, de Haan TR, van der Lee, et al. Evaluation of a system-specific function to describe the pharmacokinetics of Benzylpenicillin in term neonates undergoing moderate hypothermia. *Antimicrob Agents Chemother*. 2018 Mar 27;62(4). pii: e02311-17. https://doi.org/10.1128/AAC.02311-17
47. Hellström-Westas L, Svenningsen N, Westgren U, Rosén I, Lagerström P-O. Lidocaine for treatment of severe seizures in newborn infants. II. Blood concentrations of lidocaine and metabolites during intravenous infusion. *Acta Paediatr*. 1992;81(1):35-39. https://doi.org/10.1111/j.1651-2227.1992.tb12075.x
48. Weeke LC, Schalkwijk S, Toet MC, van Rooij LGM, de Vries LS, van den Broek MPH. Lidocaine-associated cardiac events in newborns with seizures: incidence, symptoms and contributing factors. *Neonatology*. 2015;108(2):130-136. https://doi.org/10.1159/000430767
49. Lie KI, Wellens HJ, van Capelle FJ, Durrer D. Lidocaine in the prevention of primary ventricular fibrillation. A double-blind, randomized study of 212 consecutive patients. *N Engl J Med*. 1974;291(25):1324-1326. https://doi.org/10.1056/NEJM197412192912504
50. Gianelly R, von der Groeben JO, Spivack AP, Harrison DC. Effect of lidocaine on ventricular arrhythmias in patients with coronary heart disease. *N Engl J Med*. 1967;277(23):1215-1219. https://doi.org/10.1056/NEJM196712072772301
51. Weirich J, Antoni H. Rate-dependence of antiarrhythmic and proarrhythmic properties of class I and class III antiarrhythmic drugs. *Basic Res Cardiol*. 1998;93(10):s125-s132. https://doi.org/10.1007/s003950050236

## SUPPORTING INFORMATION

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

**How to cite this article:** Favié LMA, Huitema ADR, van den Broek MPH, et al. Lidocaine as treatment for neonatal seizures: Evaluation of previously developed population pharmacokinetic models and dosing regimen. *Br J Clin Pharmacol*. 2020;86:75–84. https://doi.org/10.1111/bcp.14136