Lidocaine for seizure control in (pre)term neonates

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Objective

Development of an optimal dosing strategy for lidocaine in preterm and term neonates using population PK modeling and simulation.

Introduction

Lidocaine is an effective anticonvulsant against neonatal seizures that persist in spite of first-line anticonvulsant therapy. Lidocaine toxicity, especially cardiac arrhythmias, can be life-threatening. For term neonates an optimal dosing regimen has been developed. However, lidocaine pharmacokinetics (PK) may be different in preterm neonates because of differences in maturation of hepatic metabolic enzymes and body composition.

Methods

A population pharmacokinetic (PK) analysis was performed using NONMEM 6.2 using the FOCE-I method. The influence of body size (weight, WT) and maturation (gestational age, GA, and postnatal age, PNA) on PK parameters was assessed. The starting point of model development was to incorporate the effect of body size using allometric scaling.

Results

163 plasma concentrations from 48 normothermic neonates (WT 0.84-4.46 kg, GA 25-42.7 weeks, PNA 0-10 days) were analysed. 19 neonates (38%) had a GA of less than 34 weeks (i.e. prematurity). A one-compartmental PK model was selected. The effects of body size (allometry) and gestational age and postnatal age (maturation) on PK could not be described independently because of their close relationship (fig 1).

Both effects were captured by the significant relationship between WT and clearance (CL) and distribution volume (V), see equations 1 and 2.

$$CL = CL_{STD} \cdot \left(\frac{WT}{3}\right)^{\alpha} \quad \text{(eq. 1)} \qquad V = V_{STD} \cdot \left(\frac{WT}{3}\right)^{\beta} \quad \text{(eq. 2)}$$

CL_{STD} and V_{STD} are centred to an individual with a bodyweight of 3 kg. Parameter estimates are shown in table 1.

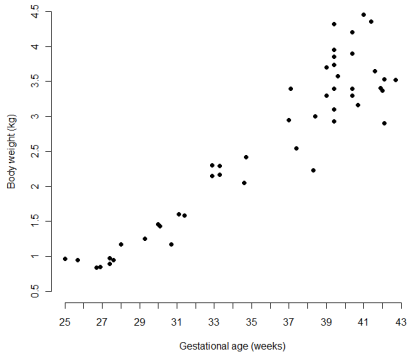

Fig 1. Distribution of body weight versus gestational age in our dataset.

PK parameter estimates are shown in table 1.

Table 1. PK parameter estimates

Parameter	Parameter estimate*
CL_{STD} (L/h)	1.41 (CV 7.78%)
V_{STD} (L)	8.95 (CV 4.13%)
α (power coefficient of WT on CL)	1.32 (CV 13.5%)
β (power coefficient of WT on V)	1.13 (CV 5.50%)

*CV(%) obtained from covariance step by NONMEM

Large interindividual variability (IIV) on CL (49.4%, CV 14.2%) was found. IIV on V was smaller (19.4%, CV 23.1%). A new dosing strategy was developed based on simulations (fig 2.). This resulted in 31% less plasma concentrations exceeding 9 mg/L, mainly for neonates with a body weight of less than 3 kg.

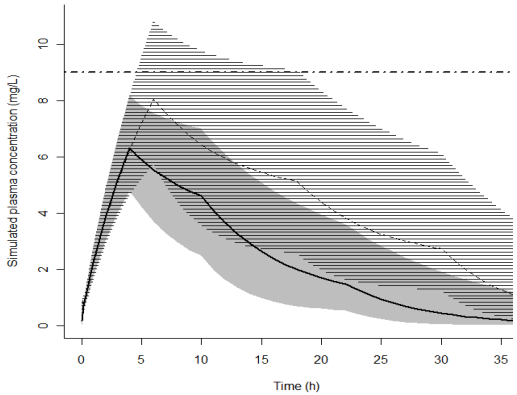

Figure 2. Time versus predicted plasma concentrations. 10% and 90% percentiles with median are shown for new (solid grey area) and former (dashed black area) dosing regimen based only on data in term neonates. Avoidable concentration: >9 mg/L

In the new strategy first an initial bolus of 2 mg/kg in 10 minutes was administered, followed by the regimen as displayed in table 2.

Table 2. New dosing strategy

Body weight (kg)	Infusion (during 4h)	1st dose reduction (during 6h)	2nd dose reduction (during 12h)
0.8 - 1.5	5 mg/kg/h	2.5 mg/kg/h	1.25 mg/kg/h
1.6 - 2.5	6 mg/kg/h	3 mg/kg/h	1.5 mg/kg/h
2.6 - 4.5	7 mg/kg/h	3.5 mg/kg/h	1.75 mg/kg/h

Main conclusions

1) Body size and maturation were both captured in an exponential relationship between CL and V and WT
2) The estimated power coefficients were >1, suggesting a strong effect of maturation on the PK of lidocaine during the first 10 days after birth.