Results The development of HIE stage 3 was significantly lower in Anapleoxia group (8%) than in the Normothermia group (28%) (p=0.052, RR=0.285). Fifteen neonates in the anapleoxia group had normal outcome versus only 9 in the normothermia group (p=0.049, RR=0.5). The incidence of mortality (12% vs 16%, p=0.264, RR=0.75) complications and baseline characteristics were comparable.

Conclusions Anapleoxia if allowed to persist for 72 hours after birth, alleviates the ill effects of hypoxic ischemic insult and results in improved outcome in the neonates particularly the neurodevelopmental outcome at 6 months of age.

Background and Aims Therapeutic moderate hypothermia for neuroprotection in asphyxiated newborns can influence pharmacokinetics and pharmacodynamics. Lidocaine is administered if seizures persist despite initial therapy. Because cardiotoxicity is a potential risk of lidocaine, dose adjustment under hypothermia might be necessary to prevent toxicity. The aim was to evaluate the effect of hypothermia on lidocaine pharmacokinetics and to evaluate the efficacy and safety under hypothermia.

Methods Hypothermic data were obtained from the SHIVER-study. Term born newborns with perinatal asphyxia and encephalopathy with lidocaine therapy were included. Therapeutic hypothermia (33.5°C, for 72 hours) was applied within 6 hours after birth. Lidocaine dosing under hypothermia was reduced; initial dose 2 mg/kg in 10 minutes, followed by an infusion of 4 mg/kg/h during 6 hours. Subsequently the infusion was reduced to 2 mg/kg/h during 12 hours, and then stopped.

Data from normothermic newborns were obtained from a previously published study (van den Broek et al., 2011). Pharmacokinetic modelling was performed using NONMEM.

Results 22 hypothermic newborns were included and were compared with 26 normothermic newborns. Based on a one-compartmental model with allometric relationships, lidocaine clearance was decreased by 24% under hypothermia, while relative metabolite formation was unchanged. During hypothermia no effect of lidocaine on heart frequency could be observed and the observed efficacy, i.e. decrease of seizure activity, was 78%.

Conclusion Hypothermia has a clinically relevant effect on lidocaine clearance. The dosing regimen needs to be adjusted under hypothermia in order to maintain efficacy and to prevent adverse events. This model is currently validated.
Background and Aims

Excessive glutamate release followed by N-methyl-D-aspartate receptor (NMDAR) activation displays an important cascade in the pathophysiology of perinatal brain injury. We have previously shown that dextromethorphan, a low-affinity NMDAR antagonist, is neuroprotective in an animal model of neonatal excitotoxic brain injury. Of interest, dextromethorphan also shows agonistic properties at the sigma-1 receptor (σ1R). Sigma-1 agonists have given beneficial results in animal models of adult brain injury.

Aim of the study

To evaluate the effect of the selective σ1R agonist 2-(4-morpholinetyl)-1-phenylcyclohexanecarboxylic acid (PRE-084) in neonatal excitotoxic brain injury.

Results

A single intraperitoneal injection of 0.1 μg/g (low dose) or 10 μg/g (high dose) bodyweight (bw) PRE-084, given 1 h after the excitotoxic insult, significantly reduced lesion size in cortical gray matter 24 h and 120 h after the insult. Repeated injections of 0.1 μg/g PRE-084 proved to be equally effective. PRE-084 treatment resulted in a decrease in cell death indicated by reduced TUNEL positivity and caspase-3 activation. PRE-084 reduced the number of isolectin B4-positive, activated microglial cells. Quantitative real-time PCR analysis showed no effect on σ1R gene expression at 1, 4, 8, 12, 24 and 48 h after intracranial ibotenate injection compared to healthy controls. In vitro PRE-084 protected against glutamate-induced morphological and functional changes in primary hippocampal neurons.

Conclusion

We demonstrate that systemic treatment with the selective σ1R agonist PRE-084 protects against NMDAR-mediated excitotoxic brain damage.

CIRCULATING PROGENITOR CELLS IN PRETERM NEONATES WITH CNS INJURY - A PRELIMINARY REPORT

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Background and Aims

The assumption that the circulating progenitor cells participate in a chemotactic way in the endogenous regeneration effort after damage of body tissues is controversial and the exact type of the cells involved remains unknown, especially when referring to damages of the Central Nervous System (CNS). We assume that preterm neonates who undergo CNS injury respond in a similar way, and we investigate the progenitor cell populations that might be related to the devastating event.

Methods

25 preterm newborns were enrolled (gestation age ≤32 weeks). 10 of them underwent severe perinatal stress with metabolic acidosis and developed CNS injury (IVH III or higher, PVL or infarct), whereas 15 of them were assumed as controls with no obvious CNS injury. Peripheral blood was collected at days 1, 3, 9, 18 and 45 after birth and analyzed using flow cytometry. Cell populations of interest were EPCs (Endothelial progenitor cells, CD34+/CD133+/CD184+), HSCs (Hematopoietic stem cells, CD34+/CD184+/CD45+) and VSELs (Very Small Embryonic-Like SCs, CD34+/CD184+/CD45+)..

Results

EPCs were significantly increased in the group with CNS injury at days 1.9 and 18 and VSELs were marginally increased at day 1 and significantly at day 9. HSCs showed no specific variation.

Conclusion

Circulating progenitor cells seem to play a role in the endogenous regeneration effort. Enhancing this effect might prove to be a good therapeutic practice in the future, whereas delineation of the timeframe of this effect would be essential. Larger studies are needed, as well as correlation with chemooattractants and long-term outcome is necessary.

SEIZURE BURDEN AND NEUROBEHAvIORAL SCORES AFTER THERAPEUTIC HYPOTHERMIA IN THE NEWBORN PIGLET

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Background

Therapeutic hypothermia (TH) is standard of care in newborns with hypoxic-ischemic encephalopathy (HIE). Although the predictive value of amplitude-integrated EEG (aEEG) after HIE has been studied, the predictive value of aEEG during TH remains to be established.

Aim

To study aEEG characteristics and timing of recovery of neurobehavior in a newborn piglet model of HIE following TH.

Methods

Newborn piglets (N=14) were subjected to 50 min hypoxia-ischemia and survived to 72h. Animals were randomly assigned to hypothermia (N=6) or normothermia for 24h after hypoxia-ischemia (N=6). aEEG was continuously recorded until ~40h post-insult and at 48 and 72h post-insult. Background pattern aEEG and presence of seizures were analysed. Neurobehavior was scored from 40 until 72h post-insult.

Results

In hypothermic piglets aEEG background pattern recovered to continuous low voltage (CLV) within 2h post-insult until 36h post-insult. Normothermic piglets recovered within 2h post-insult to continuous normal voltage (CNV) until 36h, where there was a decrease in background pattern to CLV aEEG recovered to CNV in both groups by 72h post-insult. Seizures were recorded in a proportion of 40% in normothermic piglets.

Conclusion

aEEG characteristics during therapeutic hypothermia allow prediction of post-hypoxic-ischemic encephalopathy neurobehavioral outcome in the newborn piglet model.