Effect of ALlopurinol in addition to hypothermia for hypoxic-ischemic Brain Injury on Neurocognitive Outcome
Hypoxic-ischemic encephalopathy

- 1-2 / 1000 newborn suffer from moderate to severe HIE
- 700-1,500 neonates / year in Germany
  5,000-10,000 neonates / year in Europe
  (... worldwide up to 1 Mio. infants / year)
- Therapeutic hypothermia is the only established treatment for HIE
- Despite therapeutic hypothermia, 40% of infants with moderate HIE suffer from death or severe disability
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There is an urgent need for additional treatment options!!!
Hypoxic-ischemic encephalopathy
Pathophysiology: phases of HIE evolution

Graph deleted
Reperfusion-injury (O₂-radicals, inflammation) and excitatory injury result in 2° energy failure and apoptosis

Johnston et al., Lancet Neurol 2011
Birth asphyxia reperfusion/ reoxygenation/ excitatory /inflammatory damage

Treatment strategies

hypothermia

+ further (pharmacological) intervention(s)

F.v.Bel, Utrecht
Further treatment options in addition to hypothermia currently investigated:

- Xenon (anti-excitatory)
- Erythropoietin (anti-apoptotic)
- Melatonin (anti-oxidative?)

Any additional treatment options?
Origine of Oxygen Radicals in HIE

Allopurinol
Animal data supporting Allopurinol for HIE

- Xanthine-oxidase mediated oxygen radical injury largely occurs *early after* ischemia
- Allopurinol administered *after* inducing hypoxia-ischemia reduces brain injury in 7-day-old rats [Palmer, Pediatr Res 1993].
- Vasogenic edema (MRI) was reduced [Peeters-Scholte, Pediatr Res 2003]
- Cerebral energy state was preserved in allopurinol-treated piglets [Peeters-Scholte, Exp Brain Res 2004].
Clinical Data supporting Allopurinol for HIE

Metaanalysis of 3 RCTs [Chaudhari, Cochrane 2008]

P: Neonates with HIE (together n=114)
I: Allopurinol (up to 4h after birth)
C: Standard / Placebo (without hypothermia)
O: death or disability (2 studies)
T: at 1-2 years of age

Reduction of death/disability from 65% to 25% in allopurinol-group in infants with moderate HIE
[Kaandorp, Arch Dis Child 2012].
Favorable risk/benefit-ratio

No evidence of severe harm from allopurinol:
- in 138 neonates following antenatal allopurinol
- in 58 neonates following postnatal allopurinol
- In 155 infants undergoing cardiac surgery

“The available data have not raised major safety concerns related to use in newborn infants.”
[Cochrane Rev 2008]
Key Challenge with ALBINO study

Xanthine oxidase-mediated production of superoxide radicals occurs within minutes of reperfusion
[Ono Brain Res 2009]
The ALBINO project

Aims to investigate:

P: In (near) term infants with severe perinatal acidosis and/or asphyxia
I: the effect of very early allopurinol (within 30 min after birth) in addition to therapeutic hypothermia
C: in comparison with placebo
O: on death and neurodevelopmental impairment
T: assessed at 2 years of age

How could that be realized?
Can parents give informed consent within that time frame??
Deferred Consent for the ALBINO-study

- Anticipated potential benefit from early administration
- Favorable risk/benefit-ratio
- Minimal burden from study–driven examinations
- Impossible to get meaningful consent before administration of study medication
“Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.“.
Community Engagement

Press release: inform community by mass media

Basic Information: inform parturients in prenatal clinics/obstetric practices/delivery units etc. (Flyer/Poster including link to study homepage and full parent information)
Verification that opt-out was *not* chosen

Before opening the container with study medication investigators shall verify:

- that the parents understand the local language (or English),
- that they have been informed about the study
- that had *not* expressed the wish of non-participation after having received the information
Deferred Consent for the ALBINO-study

Formal written informed consent after 1st dose
(written information + oral explanation + time for reflection + signature of both parents (if applicable) as usual)
**Planned Recruitment for the ALBINO-study**

We aim:

- to involve 60-80 study centers in Europe
- to screen 1200 infants with umbilical arterial pH < 7.0 or need for resuscitation
- to recruit 846 infants
- to assess at least 684 infants at 2 years
- within 2 years
The ALBINO team

ALBINO-Coordinator for Poland: Jan Mazela
University of Poznan
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We seek NICUs throughout Europe who might be willing to participate!!!