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Drugs for neuroprotection after birth asphyxia: Pharmacologic adjuncts to hypothermia

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ABSTRACT

An adverse outcome is still encountered in 45% of full-term neonates with perinatal asphyxia who are treated with moderate hypothermia. At present pharmacologic therapies are developed to be added to hypothermia. In the present article, these potential neuroprotective interventions are described based on the molecular pathways set in motion during fetal hypoxia and following reoxygenation and reperfusion after birth. These pathways include excessive production of excitotoxins with subsequent over-stimulation of NMDA receptors and calcium influx in neuronal cells, excessive production of reactive oxygen and nitrogen species, activation of inflammation leading to inappropriate apoptosis, and loss of neurotrophic factors. Possibilities for pharmacologic combination therapy, where each drug will be administered based on the optimal point of time in the cascade of destructive molecular reactions, may further reduce brain damage due to perinatal asphyxia.

Introduction

Perinatal asphyxia in the near-term and full-term infant is still one of the most important causes of neonatal death and adverse motor and cognitive outcome and has an incidence of 2–20 in every 1000 live born infants, depending in which part of the world they are born.[1,2]

There is increasing evidence that not only the actual period of antenatal and/or perinatal hypoxia-ischemia (HI) affects the neuronal cells, but also reoxygenation and reperfusion upon and after birth add substantially to delayed apoptotic and necrotic neuronal cell death due to secondary energy failure. This delayed brain damage may proceed up to days or even weeks after birth.[3,4]

At the same time this biphasic or even triphasic pattern of brain damage creates a "therapeutic" window, which is believed to range from birth up to 6 h of life, during which neuroprotective strategies can prevent or reduce the full consequences of delayed brain damage.[4–6] Up to now, the only established postnatal therapy to achieve this goal to a certain extent is moderate hypothermia.[7,8] Although the composite adverse outcome was reduced, an adverse

Herewith the authors of this article, Frank van Bel, MD and Floris Groenendaal, MD, declare that Frank van Bel and Floris Groenendaal are, together with Cacha Peeters-Scholte, inventors of 2-iminobiotin as neuroprotective agent for neonates with cerebral hypoxia-ischemia. They have any financial or personal relationships with other people or organizations that could potentially and inappropriately influence their work and conclusions. They further declare to have no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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Table – Information of dosages of drugs and gasses used or being used in (ongoing) clinical studies investigating pharmacologic neuroprotection after perinatal hypoxia-ischemia.

Drug or gas	Dosage
Maternal allopurinol	
Torrance et al.[30]	500 mg iv; IT: 10 min
Kaandorp et al.[26]	500 mg iv; IT: 10 min
Postnatal allopurinol	
Van Bel et al.[62]	20 mg/kg/iv < 4 h (IT: 10 min); repeat 20 mg/kg/iv after 12 h
Benders et al.[99]	20 mg/kg/iv < 4 h (IT: 10 min); repeat 20 mg/kg/iv after 12 h
Gunes et al.[63]	20 mg/kg/iv < 6 h (IT: 10 min); repeat every 12 h (total 120 mg/kg)
Postnatal 2-iminobiotin (CT: NCT01626924)	0.2 mg/kg/dose iv, <6h, repeat every 4 h up to 6 doses in 20 h
Postnatal rhEPO	
Elmahdy et al.[82]	2500 U/kg/sc < 6 h;repeated daily for 5 days
Zhu et al.[83]	300 U/kg or 500 U/kg/sc < 48 h; every other day for 2 week
Wu et al.[84] (+HT) *Postnatal*	250, 500, 1000, or 2500 U/kg/iv < 24 h; up to 6 doses every 48 h
Darbepoetin	
Baserga et al.[88] (+HT)	2 or 10 μg/kg/iv < 12 h; second dose at day 7
Postnatal xenon ventilation	
TOBYXe study (+HT) (CT: NCT00934700)	30% Xenon gas for 24 h (start < 6 h)
CoolXeno 3 study(+HT) (CT: NCT02071394)	50% Xenon gas for 18 h (start < 5 h)
Postnatal Topiramate	
NeoNATI study (+HT) (CT: NCT1241019)	10 mg/kg/orally-at admission; repeat at days 2 and 3
Postnatal MgSO4	
Hemen study (+HT) (CT: NCT02499393)	250 mg/kg/iv < 6 h (IT: 60 min); repeat on days 2 and 3.

CT, www.ClinicalTrials.gov; HT, hypothermia; IT, infusion time.

outcome of 45% is still high[8] and it is conceivable that the outcome can be improved further when moderate hypothermia will be combined with other neuroprotective strategies.

In order to achieve this goal it is important to delineate the potentially harmful cascade of molecular pathways induced by fetal hypoxia and upon and after reoxygenation and reperfusion. With this knowledge additional pharmacotherapeutical interventions can be considered which may be capable to inhibit these destructive mechanisms. In this article we will particularly focus on those pharmacological interventions which can be expected to be effective in the human infant within the near future. Information of proposed dosages of the drugs and gasses discussed in this article will be provided, when available, in a separate table (Table).

Destructive molecular pathways initiated during and after HI

1. Fetal hypoxia, an important determinant of perinatal asphyxia, sets in motion the excessive production of excitatory neurotransmitters which gives rise to the activation of N-methyl D-aspartate (NMDA)- and voltage-regulated ion channels on the cell membranes resulting in a surge of extracellular calcium into neuronal and microglial cells and astrocytes.[9,10] This will not only lead to direct cell damage but also to a drop in the intra-and intercellular pH leading to production of pro-radicals liberated from their binding proteins and accumulation of xanthine.
2. Upon reoxygenation and reperfusion xanthine will be metabolized to uric acid at the expense of excessive formation of the superoxide free radical ($O_{2-}^{\bullet}$), which plays a central role in the further formation of free radicals and toxic compounds[11–13]: it reacts with pro-radicals such as non-protein bound iron to form the very toxic hydroxyl free radical ($OH^{\bullet}$).[14] It furthermore reacts with nitric oxide ($NO^{\bullet}$), because of the HI-increased formation of neuronal and later also inducible nitric oxide synthase (nNOS; iNOS),[15,16] to form the toxic peroxynitrite ($ONOO^{-}$).

   The initially high levels of excitatory neurotransmitters and the surge of free radicals, especially upon and early after reperfusion and reoxygenation contribute to activation of transcription factors such as nuclear factor kappa B (NFkB) and c-jun N-terminal kinase (JNK) with subsequent activation of an inflammatory response with abundant formation of pro- and anti-inflammatory cytokines, and leading to production of iNOS setting in motion a pre-apoptotic pathway with further (delayed) brain damage.[17–19]
3. Finally, a substantial part of the delayed brain damage is related to downregulation of the formation of neurotropic, maturational, and growth factors inhibiting neurogenesis and repair.[20,21]

In the Figure A, the four patterns of above mentioned destructive molecular pathways are schematically depicted as a function of postnatal age. The proposed pharmacological