Pediatric RESEARCH

COMMENT

Translation from animal to clinical studies, choosing the optimal moment

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We want to thank Davidson et al.[1] for their comments and thoughts as reflected in their commentary, "When is a potential new neuroprotective treatment ready for translation?", on our publication concerning 2-iminobiotin following perinatal asphyxia.[2]

Their criticism focuses on the limited animal data of 2-iminobiotin as a neuroprotective compound in combination with therapeutic hypothermia (TH). They therefore recommend more animal studies before translation to human efficacy trials.

Although the above-mentioned considerations are sound and understandable, an important issue may be overlooked here: direct translation from animal data to clinical care may not provide the ultimate answer! This is best illustrated with the development of TH itself, where depth of hypothermia and duration of this treatment was started on animal data, but clinical studies were necessary to "fine tune" the depth and duration in the clinical setting. Moreover, other compounds and drugs thought to be promising for add-on therapy for TH, such as rhEPO, allopurinol and several others, are not thoroughly and methodically tested along the lines as suggested by the authors of this editorial, but are now in phase II and III studies.

HOW SOUND IS THE EVIDENCE ON 2-IMINOBIOTIN?

2-Iminobiotin has been investigated in several small as well as large animal models conducted by different laboratories.[3–7] Also in in vitro models of neonatal hypoxic-ischemic encephalopathy (HIE), using human neuronal cells, neuroprotective properties of 2-iminobiotin during normothermia, as well as in combination with hypothermia were reported.[8,9] Dose-escalation studies were performed in large animals models[7] and in humans.[10] Besides being a selective neuronal and inducible nitric oxide inhibitor, a secondary mechanism of action was postulated on the downregulation of apoptosis-related proteins based on the neuroprotective results of 2-iminobiotin in NOS naïve cells in vitro.[9] Indeed as far as we know, no human evidence for the duration of upregulation of iNOS after HIE is present. However, in rat studies it was shown that iNOS was upregulated from 6 to 48 h after transient focal cerebral ischemia.[11] For that reason in the 2-STEP study 2-iminobiotin was dosed for 48 h in part B of the study.

HOW AND WHEN TO TRANSLATE FROM ANIMAL TO CLINICAL STUDIES?

In general, most scientists working in the HIE field agree that after establishment of proof of concept in in vitro trials or experiments in small animals, preferably from different laboratories, the potential neuroprotective drug has to be tested in a large animal model, where electrocortical brain activity, MRI or MRS techniques and histology can be performed. Additionally, long-term behavioral studies in (mainly small) animals and dose-escalation studies in large animal models are advised before translation to the neonate with HIE can be initiated.

Since enzyme systems, receptors and pharmacodynamic properties of a treatment can function differently across species, a trade-off has to be made whether additional research in animals has to be performed or translation to neonates can be started. In our opinion this decision to translate or not is mainly dependent on the safety and potential efficacy of the treatment, established in preclinical and phase 1 trials, and the chances to get a clear, timely, and translatable result from additional preclinical experiments.

DESIGN OF CLINICAL TRIALS FOR HIE

We agree with the authors that for many reasons it will be difficult to perform a robust trial to demonstrate efficacy. Furthermore, in the case of HIE, not a single treatment will render optimal neuroprotection, but a combination treatment facing the different aspects of delayed cell damage and repair.[12] For that reason umbrella and basket trial designs, as used in oncology, might need to be considered as a more effective way to approach clinical trials for HIE.[13]

With the above taken into account, in our opinion, 2-iminobiotin is potentially an effective neuroprotective drug to be used following HIE, and is at least as rigorously studied as other promising drugs before translation to human clinical studies. Additional animal studies would delay the clinical assessment of this potential therapy even further.

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ADDITIONAL INFORMATION

Competing interests: C.M.P.C.D.P.-S., F.v.B. and F.G. are the inventors of 2-iminobiotin as a neuroprotective agent in neonates with hypoxic-ischemic encephalopathy. C.M.P.C.D.P.-S. and H.T. are shareholders and consultants of Neurophyxia BV. P.V. is employed at LAP&P Consultants BV. All other authors declare no conflicts of interest.

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