How to translate neuro-cognitive and behavioural outcome data in animals exposed to paracetamol to the human perinatal setting?

K Allegaert 1,2,3, J van den Anker 4,5,6

1Department of Development and Regeneration, KU Leuven, Belgium
2Department of Pharmacy and Pharmaceutical Sciences, KU Leuven, Belgium
3Department of Clinical Pharmacy, Erasmus MC, Rotterdam, The Netherlands
4Department of Pediatrics, Pharmacology and Physiology, Children’s National Medical Center, Washington, DC, USA
5Intensive Care, Erasmus Medical Center-Sophia Children’s Hospital, Rotterdam, The Netherlands
6Department of Pediatric Pharmacology, University Children’s Hospital Basel, Basel, Switzerland

Background: Epidemiological observations link perinatal paracetamol (acetaminophen) exposure to impaired neuro-cognition and behavior, but animal models may assist to better understand mechanisms.

Methods: To provide an overview on preclinical data and mechanisms explored, we conducted a structured literature search on animal models and neuro-cognition and behavioural outcome following perinatal paracetamol exposure.

Results: This search resulted in 20 papers [rat (n=9), zebrafish larvae (n=6), mice (n=5)], published between 2009-2020. Eight discussed pregnancy/fetal paracetamol exposure, 6 juvenile, 6 studies combined pregnancy and juvenile exposure. Most papers (n=16) described paracetamol exposure without indication, so rather toxicity models, except for an induced fever and repetitive needle pricking (rat), brain injury (mice), and a zebrafish nociception model.

Reported outcomes related to biochemistry (mono-amines, amino-acids, protein expression), anatomy (teratogen, morphology, nuclear size) or behaviour (spatial memory, motor, social behaviour and exploration, sexual behaviour).

On mechanisms, the cumulative data support an interesting ‘cannabinoid’ hypothesis to link paracetamol to neuro-cognitive and behavioural outcome. Besides limited species diversity, there is relevant within-species paracetamol dosing variability (dose, duration) with undocumented exposure.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Journal</th>
<th>Species</th>
<th>Condition</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allegaert &amp; Anker</td>
<td>2020</td>
<td>Prenatal</td>
<td>Rat</td>
<td>Fetal</td>
<td>Paracetamol exposure to the human perinatal setting.</td>
</tr>
</tbody>
</table>

Conclusions: Toxicology models should shift to clinical indications, as non-exposure is the obvious safest setting in the absence of an indication. Besides pain and fever related to the, this should include perinatal brain injury, as there is animal experimental evidence that cannabinoids are neuroprotective in newborn brain injury or asphyxia, further supported by evidence in non-perinatal models of paracetamol-related neuroprotective effects.