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COMMENT

The unintended consequences of acetaminophen use for ductal closure in premature infants

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The use of acetaminophen (paracetamol) for patent ductus arteriosus (PDA) closure in premature infants is steadily creeping into clinical practice. The vasoconstrictive effect of paracetamol on ductal tissue is achieved through inhibition of the peroxidase moiety of prostaglandin H_2 synthase responsible for metabolising arachidonic acid (AA), thereby inhibiting prostaglandin production.[1] Since the first report of its potential utility for PDA constriction by Hammerman et al. in 2011,[2] there has been a steady stream of clinical trials and observational studies demonstrating the efficacy of acetaminophen in promoting ductal closure.[3] Those studies have been a catalyst for its increasing use in the clinical field as a primary therapeutic intervention, when contra-indications to conventional non-steroidal anti-inflammatory drugs (NSAIDS, indomethacin and ibuprofen) exist, or following failure of closure after NSAIDS prior to referral for PDA ligation as a last ditch effort to avoid surgical intervention.

However, most of those clinical studies lack robust safety data for the use of acetaminophen in the premature population. In addition, those studies lack comprehensive monitoring of the cardiovascular system to enable the close study of the extra-cardiac physiologic consequences of acetaminophen-mediated PGE_2 inhibition in the premature neonatal population. Liver toxicity associated with acetaminophen use remains a concern. A recent Cochrane review has highlighted the potential for adverse neurodevelopmental outcomes following antenatal and early postnatal exposure to acetaminophen and has called for the implementation of robust long-term follow-up to be integrated into any future trials.[3] The link between early acetaminophen exposure and adverse neurodevelopmental outcome including autism spectrum disorder can be explained by the early depletion of the hepatic primary pathways for metabolising acetaminophen: glucuronidation and sulfation. "When the capacity to metabolise through the primary pathways is depleted or saturated, the fraction of the dose converted to reactive metabolites increases and the secondary metabolic pathways become increasingly involved". Activation of secondary metabolic pathways can lead to oxidative stress resulting in neurotoxicity.[4]

The study by Hostovsky et al.[5] in this issue of *Pediatric Research* highlights yet another potential unintended consequence of acetaminophen use in the premature population. In this in vitro study, the group demonstrated that acetaminophen increases pulmonary and systemic vasomotor tone via peroxynitrite generation. This timely study further highlights the pitfalls of introducing a therapeutic intervention into clinical practice before robust safety data become available or a thorough understanding of its complete physiological impact becomes established. Inhibition of cyclo-oxygenase (COX)-dependent dilators (prostaglandins) will lead to an increase in the tone of resistance-level pulmonary arteries. In addition, a shift from cox-dependent dilator production to cox-dependent constrictor production (thromboxane) can also be another explanation to this observed phenomenon. Other animal studies also suggest that chronic exposure to hypoxia can exacerbate this shift from dilator to constrictor production.[6,7] Those mechanisms require further exploration in an experimental and clinical setting.

There are important clinical implications to this observation. It is possible that some of the mitigation of shunt volume seen in infants exposed to acetaminophen stem from the potential increase in pulmonary vascular resistance (PVR), thereby reducing the gradient across the shunt rather than due to a reduction in PDA diameter.[8] Recent advances in echocardiography methods in the neonatal field have facilitated a more comprehensive assessment of pulmonary hemodynamics. The ratio of pulmonary artery acceleration time (PAAT), to right ventricular ejection time (RVET), referred to as PAATi is a reliable and valid measurement of PVR in neonates and children. Recent clinical studies demonstrated excellent intra- and inter-observer reproducibility for PAAT and PAATi measurements in preterm infants.[9] Those measurements should be used in future clinical trials.

The longer term impact of this phenomenon requires careful investigation. Future clinical trials investigating the efficacy and safety of acetaminophen use for PDA closure should pay close attention to this possible side effect. Robust echocardiography-based longitudinal assessment of pulmonary haemodynamics is required in order to confirm this association, study its clinical impact, and monitor the longer term outcome. Until those safety data become available, the use of acetaminophen for ductal closure should be limited to the research setting or in exceptional clinical circumstances where the risk−benefit ratio for this treatment is thoughtfully considered.

ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

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