Developmental pharmacology of the brain
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Pharmacotherapy aims to attain safe and effective drug prescription. During maturation or development, this should be based on integrated knowledge concerning both the evolving physiological characteristics of the infant who will receive the drug and the pharmacokinetic and pharmacodynamic characteristics of the compound considered. Consequently, developmental clinical pharmacology is as dynamic and diverse as the pediatric patients we are entitled to take care for, and covariates explaining the variability are at least as relevant as the median estimates, even not taking the fetal brain development into account.

Covariates of pharmacokinetics (PK, i.e. concentration-time profiles) can predict the exposure time course reasonable accurate and need to be considered before issues related to maturational pharmacodynamics can be explored. Moreover, maturational trends for specific enzymes, organ or clearance routes are not similar. This will be illustrated based on the differences between hepatic and renal maturation, and on the impact of pharmacogenetics on drug disposition and effects in early life. More specific, the distribution volume of the central nervous system compartments and the blood brain permeability may also display maturation and disease related differences, resulting in either faster appearance (passive permeability, drug transporter activity) or delayed efflux (drug transporter activity) from the central nervous system to the systemic compartment. For opioids, the lipophilic character will drive the delay in onset.

The subsequent link between PK and PD, (i.e. pharmacodynamics, concentration effect profile) remains much less explored. We aim to illustrate the complexity and the need for neonatal clinical pharmacology based on the gap between current and likely best clinical practice. The balance and the trends in guidelines related to either oxygen administration or body temperature reflect these difficulties. The trends in perinatal steroid use or hypothyroidism are similar cases. Finally, there is an issues about formulations in neonates, containing e.g. ethanol, propylene glycol or other excipients.

Anaesthetic-induced developmental neurotoxicity exists in animal models, raising the possibility of similar effects in humans. Clinical evidence for developmental anaesthetic neurotoxicity is inconclusive, and will be difficult to obtain. Neonatal anaesthesia is also complicated by physiological and pathological derangements that can contribute to neurological injury. The ontogeny of drug receptors commonly 'used' in pediatric anesthesia is much less explored, but can be essential when considering e.g. the GABA receptor activity or the mu-opioid receptor. The loop diuretic bumetanide blocks the neuronal NKCC1 co-transporter and is thought specifically to suppress seizures in the immature brain, but may also have additional, population specific toxicity. The use of mu-opioid agonists is a difficult balance between uncertainties related to assessment, the need to alleviate pain and the knowledge that opioid exposure in itself has side effects. The side effects likely are both short term and long term and both may display a dose-related trend. Pathophysiology related to the Sotos syndrome at least illustrates that these receptors have their functions and relevance, that is manipulated by both exogenous and endogenous compounds. Based on the available data, it seems appropriated that analgosedatives should not merely be considered toxic drugs but rather acknowledged as context-dependent modulators of neural plasticity.

At the other end of pediatric life, alcohol exposure and binge drinking during adolescence are not only epidemiological predictors for future problems during adulthood. Based on epidemiological studies and animal experimental findings, there seems to be another window of vulnerability with prolonged, persistent effects. The same holds true of adolescent pharmacology, and can be illustrated based on the differences in outcome and side effects when e.a. antidepressants are considered in adolescents. In conclusion, drugs – especially those commonly administered by anesthesiologists – should be considered as context-dependent modulators of cerebral activity and plasticity. Consequently, in the setting of a pediatric patient, this context does include developmental issues since this cerebral activity in itself may affect the further development. Prospective studies should focus on outcome studies that include exposure-time observations, exposure-effect observations as well as context (e.g. clinical characteristics, co-morbidity, co-medication) related data.

Suggested literature