Knowledge driven pharmacotherapy in neonates

A perinatal research agenda is needed

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Maturational physiological changes are most prominent in early life, variability is the key feature of clinical pharmacology in infancy: maturational physiology drives maturational pharmacology. A search through Saudi Medical Journal illustrates that such a maturational pattern has also been described for theophylline.[1] However, providing safe and effective drug therapy to infants requires knowledge integration of both pharmacokinetics (PK) and pharmacodynamics (PD), concentration-(side) effect of drugs.[2] We can illustrate this based on PK and PD data on paracetamol in neonates. Weight or size was the most important covariate of paracetamol PK, with minor additional contributions of age or hyperbilirubinemia.[3] Based on these PK findings, a dosing regimen to reach analgesic plasma concentrations similar to adult levels was suggested. The concentration-(side) effect profile PD of this dosing regimen was subsequently evaluated.[3]

Similar efforts can be carried out for other compounds, and should be tailored to the regional needs and disease characteristics. This is because the incidence of preterm birth is increasing throughout the world. Moreover, the burden of mortality and morbidity after admission in a neonatal intensive care unit remains high, and is mainly driven by hyaline membrane disease, respiratory distress, and peripartal asphyxia.[4] Consequently, there is an urgent need to build a perinatal research agenda, tailored to the regional needs, and their burdens of disease when the topics are considered.

Such a research agenda on perinatal pharmacology should apply for state of the art research methods. As major progress has been made to achieve studies in neonates and young infants both feasible and relevant. Population modelling using non-linear mixed effect modelling is the preferred tool to achieve. This approach allows the analysis of sparse and unbalanced datasets and it enables exploration of the impact of different covariates (weight, age, disease, co-medications).[5] Using such approaches, PK-PD studies can be suggested in the most efficient manner to obtain maximum information with the highest precision. Once the model is developed, validations should be performed. If the model performs well, simulations can be used to define a dosing regimen and the dosing regimen needs to be challenged in a prospective clinical trial as a final step of the process.[5]

In conclusion, knowledge driven pharmacotherapy is a very effective tool to improve outcome, also for infants and neonates. A perinatal research agenda should cover the major causes of mortality and morbidity in a given region, but should also be performed using state of the art methodology since this ensures feasibility and efficiency of studies, but also maximal validity, namely, robustness, of the collected information.

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