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Drug dosing during hypothermia: to adjust, or not to adjust, that is the question

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Hypothermia is a proven neuroprotective therapy in neonates with moderate to severe hypoxic ischemic encephalopathy (HIE). Recent randomized control trials have demonstrated that whole body cooling to 33 to 34°C for 72 hours when initiated within 6 hours after birth of infants with a greater than 35 week gestational age increases survival and the rate of survival-free-disability.^{1,2} The efficacy of therapeutic hypothermia has led to expanded clinical implementation, and has resulted in the need for an understanding of the effects of reduced body temperature on drug disposition. This fact is particularly true in HIE patients due to the longer duration (up to 72 hours) of hypothermia and the difficulty in identifying adverse drug events from disease pathogenesis in neonates.

Preclinical studies have demonstrated that therapeutic hypothermia to 33°C generally reduces hepatic drug metabolism and increases plasma concentrations of several drugs. The most extensively studied pathway evaluated so far has been the cytochrome P450 (CYP) enzymes which have generally reduced activity under cooled conditions.³⁻⁵ More recent studies have suggested that such reductions in CYP activity are potentially drug and isoform specific⁶ and therefore, should be evaluated for the individual drugs with the greatest potential for adverse effects. In addition, several recent studies have reported elevated plasma concentrations of morphine⁷ and phenytoin⁸ in neonates and elevations in midazolam^{9,10}, vecuronium¹¹, and phenytoin¹² concentrations in adults receiving therapeutic hypothermia; however, specific dosing recommendations are still lacking.

The significant hurdle in translating the known preclinical observations into precise dosing recommendations in cooled patients is the need for clinical studies of sufficient size to allow for accurate, testable dosage adjustments as they relate to drug response. To date, most clinical reports involve small numbers of subjects with the goal of retrospectively evaluating if the known preclinical alterations in drug concentrations are observed in critically ill patients. Specifically, evaluation of drugs administered as part of routine care is complicated by the inter-patient differences in severity of concomitant disease; differences in drug dose and timing of administration; differences in the timing of dose and blood levels relative to the initiation of hypothermia; and lack of randomization.

One approach to overcome these barriers is to utilize population pharmacokinetic modeling, known as pharmacometrics. Through this approach differences in drug administration timing

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and dosage that occur as part of routine care can be accounted for and useful population and individual level exposure characteristics can be generated despite limited concentration sampling. Pharmacometrics is an emerging discipline that uses mathematical models to control for known sources of variance (such as age and weight) in order to evaluate if given factor (such as differences in body temperature) can significantly account for previously unexplained variability within a given patient population. This approach preserves the within individual correlation, therefore allowing for the determination of random inter-individual variability. The incorporation of patient specific covariates that explain that variability further parses between individual variability into those that are predictable (i.e., changes with age) versus the unpredictable (random effects). The power of pharmacometrics lies in the fact that once a given source of variability is identified, simulations can be conducted to guide larger clinical trials that validate and ultimately produce predictive algorithms to optimize patient dosing.

In this issue of *Pediatric Critical Care Medicine*, Shellhaas and colleagues utilized population pharmacokinetic approaches to evaluate phenobarbital concentrations in a retrospective cohort of 20 hypothermic and 19 normothermic HIE neonates.¹³ The aim of this study was to determine if therapeutic hypothermia explained a significant portion of the variance in phenobarbital pharmacokinetics when accounting for maturational differences in these patients. Phenobarbital is eliminated via multiple routes that include CYP2C, glucuronidation, and direct renal excretion pathways. The authors observed that body weight and age were significant covariates on phenobarbital clearance, whereas the temperature group assignment did not influence the phenobarbital pharmacokinetics. These results contrast that of Filippi et al. who reported that phenobarbital plasma concentration and half-life were elevated in 19 neonates with HIE as compared to historical control values. However, these findings are consistent with a preclinical study demonstrating isoform-specific changes in CYP metabolism that demonstrated greater effects of hypothermia on CYP2E1 and CYP3A with little effect CYP2C metabolism in the rat cardiac arrest model.⁶

The authors should be commended for utilizing pharmacometric techniques to estimate pharmacokinetic parameters rather than reporting concentration values alone and for evaluating a commonly used, highly relevant drug in this vulnerable patient population. There are some limitations of this work that should be noted. As detailed by the authors in the discussion section, the retrospective nature of this study did not allow for modeling concentrations as a continuous function of body temperature or the assessment of the temporal relationship between temperature and blood levels. Understanding time-temperature relationship may be particularly important for a drug with a long half-life such as phenobarbital because plasma concentrations may not significantly differ at early time periods after reaching target temperature, whereas, later time points, even into the post-rewarming period, may be significantly altered. This phenomenon was recently demonstrated with phenytoin where cooling differences in drug concentrations were most significant during rewarming and extended long into the post-rewarming period.⁸ These later time periods may be most important for increased adverse drug reaction risks because blood levels may remain elevated at a time period when receptor response returns to normal. This hypothesis suggests that future prospective studies to evaluate drug disposition and response during hypothermia should be designed such that temperature can be included as a continuous covariate and such that the rewarming and post-rewarming periods are evaluated, particularly for drugs with long terminal half-lives.

As we move forward, population-based pharmacokinetic modeling should be incorporated into future studies in pediatrics and studies should ideally focus on larger cohorts of subjects evaluated over longer periods of time after cooling. Such approaches will allow for the definitive identification of drugs with altered disposition and will allow for the creation of

specific dosing algorithms to optimize drug therapy in patients receiving therapeutic hypothermia.

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