Knowledge of pharmacology improves outcomes in children

Brian Anderson, Starship Children’s Hospital, New Zealand

Anaesthesia dosing in children (and particularly infants) should be based on pharmacokinetic-pharmacodynamic considerations and adverse effects profiles. Disease processes and treatments in this group are distinct from adults. Absorption, distribution, and clearance change dramatically during this period because of maturation of enzyme, anatomical, physiological, pathology and cerebral processes. Paediatric anaesthesia morbidity and mortality has historically been highest in this age group (1) and continues to be so (2), some of which was attributed to poor understanding of developmental pharmacology (3, 4); this facet continues to plague the specialty (5).

An ignorance of developmental pharmacology resulted is seizures in infants receiving continuous epidural bupivacaine.(4) Immature clearance resulted in raised drug concentrations. However, other aspects of pharmacology besides clearance enzyme maturation are also important (6). Reduced gastric emptying (and clearance) in infants dictates longer dosing intervals. Changing body composition with age alters volume of distribution. Muscle bulk changes influence NMBD dose (7). Reduced alpha-1 acid glycoprotein (AAG) concentrations in those under 6 months increase in total plasma concentrations for low to intermediate extraction drugs such as bupivacaine, suggesting less dose of thiopentone or bupivacaine. Regional blood flow changes contribute to MAC age related changes in children.

Children’s responses to drugs have much in common with the responses in adults once developmental PK aspects are considered.(8) The perception that drug effects differ in children arises because these drugs have not been adequately studied in paediatric populations who have size and age related effects as well as different diseases. However, neonates and infants do have altered pharmacodynamics. Catecholamine, calcium, prokinetic and bronchodilator response all change with age. One problem is that effect measures are commonly more difficult to assess in children than adults e.g. depth of anaesthesia, sedation or pain in neonates. Adverse effects also differ. Propofol may cause profound hypotension in neonates (9), while verapamil may contribute to cardiac standstill (10).

Recent literature has examined the PK of alternative routes (e.g. nasal (11-13) or oral (14)) for old drugs. The PK of old drugs has been further re-examined in children. Thiopentone (15), etomidate (16), methadone (17), diclofenac (18), paracetamol (19) and paracoxib (20) have all been re-scrutinised, allowing us greater dose accuracy. The Holy Grail of clinical pharmacology is prediction of drug PK and PD in the individual patient.(21) This requires knowledge of the covariate effects that contribute to variability. PK sources such as size, age, organ function, pharmacogenetics, circadian rhythms and drug interactions have been extensively investigated (22). Pharmacodynamic variability is equally important and those covariates are slowly being investigated. Disease processes (23, 24), ethnicity (25) and environment (26, 27) have recently been shown as influential. Characterisation of these PK, PD and adverse effect profiles allows us better understanding and dose precision of the drugs we commonly use.

References

21 Anderson BJ. My child is unique; the pharmacokinetics are universal. Paediatr Anaesth 2012.