Analgesics and hypnotics (for children)
Dr Tom Hansen, Odense, Denmark

Albeit far from perfect, there is a growing body of pharmacological experience with the use of analgesic and hypnotic drugs in neonates, infants and children. Growth and development are two major aspects of children not readily apparent in adults. Pharmacodynamic differences in infancy remain poorly defined, and neonatal pharmacokinetic-pharmacodynamic analyses that might elucidate such differences are few, partly because of a paucity of effective pharmacodynamic measures.

Most analgesic and hypnotic drugs are lipophilic substances and thus require transformation into water-soluble substances for the body to be able to excrete the substances in the urine or bile. Pharmacokinetic variations within the paediatric population are significant and have implications for the dosage and intervals of analgesics and hypnotics. For example, body composition affects the volume of distribution of drugs. The higher body water content in neonates and infants results in a larger volume of distribution of water-soluble drugs and the potential for a longer elimination half life (and duration of action). Smaller fat and muscle stores in neonates result in higher plasma concentrations of drugs because there is less drug uptake by these pharmaco-dynamically inactive sites. With a higher percentage of cardiac output going to organ systems known as vessel rich group (e.g. the brain) in neonates and young infants, the brain concentration of drugs may be higher in neonates than in older children and adults. Further, it is the general belief that an immature blood-brain barrier in neonates may further facilitate (hydrophilic) drug transportation in to this pharmacologically active site. Protein binding of drugs is reduced in neonates compared with older children and adults because of lower plasma levels and reduced binding affinity of albumin and α1-acid glycoprotein. Drugs that are highly protein bound, such as opioids, will be present in a higher unbound concentration in plasma, leading to increased effects and/or toxicity. Hepatic metabolism of drugs involves either phase 1 reactions (oxidation, reduction, hydroxylation, and hydrolysis) or phase 2 reactions (conjugation). The cytochrome P-450 system is the most important phase 1 enzyme family and is responsible for the metabolism of many analgesics and hypnotics. At birth, the hepatic enzymes responsible for drug metabolism are immature; resulting in a reduced clearance of drugs. The levels of these hepatic enzymes quickly increase to adult levels in the first few months of life. Drug clearance in the 1 to 6-year-old age group is often higher than adult levels possibly because of the larger hepatic mass relative to body weight and higher doses and shorter intervals of analgesics may be required. The renal excretion of drugs depends on renal blood flow, glomerular filtration rate, and tubular secretory function, all of which are decreased in neonates, especially in the young neonate and in premature infants. Renal function reaches adult levels by 1 year of age. With decreased renal function, parent compounds or active drug metabolites can accumulate to toxic levels, e.g. the morphine-6-glucuronide metabolite.

In this talk, I will summarize the most recent pharmacological data about analgesics and hypnotics, including local anaesthetics, NSAIDS and paracetamol, with particular focus placed on intravenous administration of opioids and hypnotics. The current important issue of the long-term effects of these drugs is also focus of this talk.

Contact:
Tom G. Hansen, MD, PhD,
Department of Anaesthesiology and Intensive Care
Odense University Hospital
DK-5000 Odense
Denmark
Email: tomghansen@dadlnet.dk or tom.g.hansen@rsyd.dk