Anesthesiologists are constantly looking for new drugs that are safe and effective with least amount of unwanted side effects. Several drugs have revolutionized the practice of pediatric anesthesia in the last decade. These include local anesthetics (ropivacaine, levobupivacaine), inhalational agents (desflurane, sevoflurane), intravenous agents (propofol, etomidate) vasoactive drugs (fenoldopam) cardiac drugs with inotropic and lusiotropic effects (neseritide, levosimendan) pulmonary vasodilators, antifibrinolytic (aprotinin) drugs and sedatives (dexmedetomidine).

Newer local anesthetic drug combinations for cutaneous analgesia such as the S-Caine patch have allowed the clinician to produce quicker sensory block prior to intravenous cannulation in children and adolescents while avoiding the problem of vasoconstriction that was inherent with the use of EMLA. This novel delivery device, (manufactured by ZARS Inc., Salt Lake City, Utah, U.S.A.), is a eutectic mixture of lidocaine and tetracaine that uses a controlled heating system to accelerate transcutaneous delivery of local anesthetics. The efficacy and tolerability of the S-Caine patch was investigated in 64 children (3-17yr). The results of this study demonstrated that a 20-minute application of S-Caine patch is effective in lessening pain associated with venipuncture procedures. Adverse events following S-Caine patch application were mild and transient. (1)

In epidural blockade, newer drugs (ropivacaine, levobupivacaine) and newer additives other than narcotics (s-ketamine, clonidine) to local anesthetics have similarly changed the face of regional anesthesia. Bupivacaine has been used extensively in adults and children for epidural and other regional blockade despite its potential for cardiotoxicity. Ropivacaine and levobupivacaine are similar in their efficacy for sensory blockade while having less motor blockade and a safer cardiotoxicity profile compared to bupivacaine.

Technological limitations of current pump or catheter-based systems have paved the way for continuous delivery systems and extended-duration techniques for pain relief. Among these are morphine sulfate sustained-release liposome injection (Morphine SR, DepoMorphine) and the Patient-Controlled Transdermal System (PCTS, E-TRANS). Longer lasting epidural morphine was recently approved for use in the treatment of pain after major surgery by the FDA. Single-dose Extended Release Epidural Morphine (single-dose EREM) (DepoDur, Endo Pharmaceuticals) is a formulation of morphine that is encapsulated in a novel multichambered liposomal delivery system (DepoFoam, SkyePharma). Once inside the epidural space the liposomal membranes slowly...
reorganize and break down, resulting in a gradual predictable release of morphine into the epidural space. A single epidural bolus of 2 ml has been shown to provide significant postoperative analgesia for at least 48 hours. (PCTS) for fentanyl administration (E-TRANS; ALZA Corporation) is a transdermal system attached to the patient's arm or upper chest; a button on the device is controlled by the patient to deliver doses of fentanyl. The needle-free PCTS uses an iontophoretic drug delivery process, in which low-level current is applied to enable the transport of ionizable compounds across the skin for local systemic therapy. In a study comparing fentanyl HCl PCTS with conventional IV patient-controlled analgesia (PCA) morphine, PCTS was found to be as safe and effective as PCA for the treatment of postoperative pain. (2,3)

Studies in adults have proven that newer vasoactive drugs like fenoldopam (Corlopam) can be used successfully for lowering blood pressure and improving renal blood flow. (4) Fenoldopam can be used to provide controlled hypotension during spinal surgery in children and adolescents. (5) A recent multicenter study evaluating different concentrations of fenoldopam infusion in infants and children showed that fenoldopam dosages up to 1.0 - 1.2 mcg/kg/min caused clinically significant reductions in MAP but dosages greater than 1.0 - 1.2 mcg/kg/min conveyed little additional benefit with regard to lowering MAP (6)

The use of antifibrinolytic like aprotinin, a protein serine inhibitor has revolutionized the management of coagulopathies in adults and pediatric patients undergoing cardiopulmonary bypass or other major orthopedic surgeries with inherent blood loss. The benefit of aprotinin in decreasing inflammation and blood loss outweighs the minimal risks involved in its use. (7) Recombinant factor VIIa (rFVIIa; Novo Seven(R), Novo Nordisk, Bagsvaerd, Denmark) (Eptacog Alfa) yet another costly drug that was originally introduced for treatment of hemophilic patients who had developed inhibitors against factor VII have been evaluated in the control of excessive bleeding following surgery for congenital heart disease in pediatric patients (8). In addition to inducing hemostasis in patients with severe hemophilia and inhibitors, it has been found to control hemorrhage associated with severe trauma and surgery in patients with basically normal hemostatic mechanisms. It augments the generation of thrombin on activated platelets and facilitates the formation of a tight, stable fibrin plug that is resistant to premature lysis (9) It has been increasingly used in a variety of non-hemophilia bleeding/hemorrhagic situations such as post cardiac pediatric patients with excess blood loss with great efficacy. (10) Another area where bleeding can be life threatening is in pediatric neurosurgical patients who undergo resection of brain tumors. A study in eight pediatric patients reported that recombinant factor VIIa (rFVIIa) was successfully used to control intraoperative bleeding during surgical resection of their brain tumors (11)

Glanzmann thrombasthenia is a very rare inherited platelet function disorder in which bleeding may be extremely difficult to stop. Recombinant factor VIIa has been shown to be effective as alternative treatments for arresting bleeding in Glanzmann thrombasthenia. (12)
In the arena of resuscitation there has been an added interest in the use of **vasopressin** and amiodarone. In the clinical setting, arginine vasopressin has been shown to improve coronary perfusion pressure (13) and hasten the return of spontaneous circulation and increase the 24-h survival rate (14). In a recently published animal study, resuscitation of pigs from bupivacaine induced toxicity, was more successfully achieved when a combination of epinephrine with vasopressin was used instead of either drug alone. (15)

Newer inotropic drug **levosimendan** (Simdax) also referred to as an inodilator, (with both inotropic and pulmonary vasodilation properties) has been used successfully in children with depressed cardiac function. It is a new calcium sensititizer developed for short-term intravenous treatment of congestive heart failure. The pharmacokinetic profile of levosimendan in children with congenital heart disease is similar to that in adult patients with congestive heart failure. (16)

**Nesiritide** is a recombinant formulation of brain-type natriuretic factor. Preliminary experience in the adult population and children suggests that nesiritide may be an effective agent in the treatment of decompensated congestive heart failure. In one study, the authors after a retrospectively review of their experience with nesiritide in 5 pediatric patients in the ICU reported a trend toward increased cardiac output.(17) Plasma BNP and ANP reflect pressure and volume loads to the pulmonary artery and right ventricle and may help to identify children with ventricular septal defect complicated by pulmonary hypertension that demands early intervention and promises to be useful in evaluating surgical indications (18).

**Phosphodiesterase inhibitors:** Inhaled nitric oxide (NO) induces vasorelaxation by increasing intracellular concentrations of cyclic guanosine monophosphate (cGMP). Cyclic GMP is metabolized by phosphodiesterases. Phosphodiesterase up regulation and accelerated cGMP clearance may contribute to the sub optimal responses to iNO and rebound pulmonary hypertension after iNO withdrawal. Selective inhibitors of type V phosphodiesterase, (the predominant enzyme type in the pulmonary circulation) such as sildanafil (Viagra) and zaprinast can selectively decrease pulmonary vascular resistance when given alone as well as significantly augment the effects of iNO and prostacyclin and its analogues. Newer pulmonary vasodilators such as epoprostenol (prostacyclin, Flolan) emerging after recent trials in adult patients have shown a reduction in mortality and functional improvement in pediatric patients. (19)

Sildenafil has been successfully administered both orally and by inhalation after nebulization and have shown to improve exercise tolerance and cardiac index in adult patients with PPH. (20) Oral Sildanafil has been used successfully to reduce the incidence of pulmonary hypertensive crises after congenital heart surgery and to prevent post iNO withdrawal pulmonary hypertension (21). Orally administered endothelin antagonists like bosentan (Tracleer) and sixtasentan have been used successfully in adult patients in the management of pulmonary artery hypertension and studies are underway in children to evaluate their efficacy. (22) Initial studies have shown that the pharmacokinetics of bosentan in pediatric patients with pulmonary arterial hypertension and healthy adults are similar (23). It undergoes extensive hepatic metabolism. Bosentan-induced hepatotoxicity
is common and must be monitored carefully. Prostacyclin (PGI2) analogues in the form of inhaled aerosolized Iloprost have become a useful and less expensive alternative to inhaled nitric oxide. Iloprost has a longer duration of action than prostacyclin and has action on the pulmonary circulation equivalent to that of inhaled NO(24). Treprostinil is a stable prostacyclin analogue with a longer half-life than prostacyclin and can be administered via an insulin pump for chronic therapy (25).

Finally in the postoperative period after an open-heart surgery or an extensive spine operation, sedation and weaning of ventilated patients has always been a problem because of the side effects of respiratory depression inherent with the currently available sedatives. Into this arena has emerged dexmedetomidine, an alpha 2-adrenoreceptor agonist with unique features of producing quality of sedation similar to sleep but with “easy and calm arousability”. (26) Published studies in children are few but the results show the unique features of this drug. At a dose of 0.25 microg/kg/h, dexmedetomidine was approximately equivalent to midazolam at 0.22 mg/kg/h. At 0.5 microg/kg/h, dexmedetomidine provided more effective sedation as demonstrated by the need for fewer bolus doses of morphine, a decrease in the 24-hour requirements for supplemental morphine. (27) In another clinical scenario, dexmedetomidine provided effective sedation during spontaneous ventilation in two patients, reversed the clinical signs and symptoms of withdrawal from illicit substances in one patient, and was effective in the treatment of post anesthesia emergence delirium and shivering in two additional patients. (28)

Dexmedetomidine has been used as a primary anesthetic for brain mapping of the cortical speech area in children undergoing awake craniotomy. General anesthesia with the laryngeal mask airway was used for parts of this procedure not requiring patient cooperation to decrease the duration of wakefulness and to obtund the surgical stimulation. The asleep-awake-sleep technique provided adequate sedation and analgesia throughout the surgery and allowed the patient to complete the necessary neuropsychological tests (29)

Dexmedetomidine has also been reported to be used successfully to treat cyclic vomiting syndrome (CVS) in pediatric patients (30)

In conclusion many new drugs are now available to pediatric anesthesiologists to enhance perfect approach to perioperative management of children.
References:


