Sunday, March 10, 2002

7:00 - 8:30 am

The Baxter Breakfast

Moderator: Myron Yaster, MD

Oral Analgesics in Children

Julia C. Finkel, MD

Oral Analgesic Use in Children

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Objectives: 1) Review pharmacologic advances in oral analgesic options for children. 2) Compare safety, efficacy, and side-effect profiles of the different groups of agents. 3) Describe rational regimens for oral analgesia in acute, chronic and neuropathic painful conditions. Reviewed specifically are NSAIDs, atypical opioids, opioids and the adjunctive agents gabapentin and dextromethorphan.

Prostaglandin Synthesis Inhibitors
(Acetaminophen and conventional NSAIDs)

Acetaminophen:

The most commonly prescribed analgesic in infancy and childhood for mild to moderate pain. It is frequently administered in combination with an opioid for moderate to moderately severe pain to take advantage of its opioid sparing effect. Its mechanism of action is primarily through its inhibition of central cyclo-oxygenase. Unlike the conventional NSAIDs, it has no peripheral anti-inflammatory effect. Therapeutic serum concentration levels are achieved within 15 to 30 min after oral ingestion.[1] The optimum serum concentration producing analgesia in children has not been determined, however, it is higher than the concentration producing antipyresis (10 □g/ml). A single loading dose of 20 mg/kg po results in a peak serum concentration of approximately 20З□g/ml and a level > 10 □g/ml for 3-4h. There is evidence suggesting that greater morphine sparing can be achieved with higher doses.[2] Toxicity is seen when peak serum concentration reaches greater than 150 mg/ml. The recommended dose to maintain therapeutic serum levels is a 20 mg/kg loading dose, then 15 mg/kg 4-6 hourly to a maximum of 90 mg/kg/day (60 mg/kg/mg in neonates).

References:

1. Prescott LF. Kinetics and metabolism of paracetamol and phenacetin. Br J Clin Pharmac 1980; 10:291-298.
2. Korpela R, Korvenoja P, Meretoja OA: Morphine-sparing effect of acetaminophen in pediatric day-case surgery.Anesthesiology 1999;91:442-7

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs):

Though many NSAIDs do not have appropriate pediatric labeling, they experience widespread use in the pediatric population. The MSO_4-sparing effect is approximately 30%.

NSAIDs non-selectively inhibit cyclooxygenase which is necessary for the conversion of arachidonic acid to prostaglandins. Disruption for this process reduces the prostaglandins mediating inflammation as well as those involved with homeostatic functions such as platelet aggregation, renal blood flow and prostaglandin mediated protection of the gastric mucosa which accounts for all the attendant risks of using NSAIDs.

Pharmacokinetics:

In general, all NSAIDs are rapidly absorbed orally. Peak plasma concentrations occur within 2-3h. They are highly protein bound to albumin and are oxidized by the liver by cytochrome P-450 or conjugated by glucuronide.

Individual Drugs:

The most commonly used agents are:

Ibuprofen has an antipyretic and anti-inflammatory effect in children at a dose of 5-10 mg/kg (max daily dose 40 mg/kg/day) and is given on a q 6h schedule. It comes in tablet and liquid form which makes it useful as part of a preoperative premed in young children.

Naproxen is given as 5-7.5 mg/kg bid (max daily dose 15 mg/kg/day).

Ketorolac is available as an intravenous injection, and 10 mg tablets. The optimum dose of oral ketorolac in children is not known. Its bioavailability of 80%, suggests that 1mg/kg should establish a serum concentration similar to a 0.25 to 0.5 mg/kg IV bolus.

Tramadol HCl:

Tramadol is a synthetic 4-phenyl-piperidine analogue of codeine. Its mechanism of action, however, is tri-fold and not strictly that of an opioid. Tramadol and the only pharmacologically active M_1 metabolite posses a weak affinity for the m-opioid receptor and has a reuptake inhibitory effect on serotonin and noradrenaline (NA). Increased synaptic levels of 5-HT decrease excitability of spinal nociceptive activity and the NA antinociceptive effect is via alpha-2 adrenoreceptor mechanisms.[1,2] Tramadol has been postulated to also have a peripheral analgesic effect because of its ability to decrease propofol injection pain.[3] The synergism of opioid and monoaminergic mechanisms results in a significant reduction in the side effects profile relative to opioids and extends the analgesic benefit to opioid insensitive pain.[2]

In the U.S., tramadol is only formulated as a 50 mg tablet though virtually everywhere else in the world, it is available in po liquid, iv and suppository form. Many of the studies done to date in children have been done outside the U.S. using these other formulations. A po liquid formulation is anticipated in this country in the near future. FDA trials for pediatric labeling have been completed over this past year.

Pharmacokinetics: (following oral absorption in adults)

Bioavailability is 20% following single dose and 90% in multiple dose studies. Peak serum concentration occur within 2h. V_D is 306 l. The elimination half-life is 5h for tramadol and 9h for the M_1 metabolite.[4] The drug is metabolized in the liver (~85%) and is renally excreted (90%).

Adverse effects:

Tramadol is generally well tolerated in clinical trials. The most common side effects reported are (1.6-6.1% incidence), nausea (more with IV than po), dizziness, drowsiness, sweating, vomiting and dry mouth.[5]

The incidence of side effects with tramadol children is significantly less than in adults.[6] Tramadol should not be used in patients receiving MAO inhibitors because of its monoamine uptake inhibition.

Based on studies done outside the U.S. in children ∅12 mos, a dose of 1-2 mg/kg po q 4-6h is used (max 8 mg/kg/day).[7,8,9] Results of a recently completed multicenter trial examining tramadol 1-2 mg/kg in children and adolescence ages 7-16 revealed a side effect profile of vomiting 10%, nausea 9%, pruritus 7% and rash 4%.(*Anesthesiology 2001;95:A1233*)

Dose: Efficacy has been demonstrated with a dose of 1-2 mg/kg every 6h with a maximum of 8 mg/kg/day. In the above mentioned trial comparing 1 vs. 2 mg/kg po in postoperative patients ages 7-16, the 2mg/kg group required 50% less rescue opioid. (*Anesthesiology 2001;95:A1232*)

Tramadol promising analgesic for both acute and chronic pediatric pain management given its low side effect profile relative to opioids and NSAIDs and as new formulation are made available in the U.S., its versatility of use in this population will expand.

References:

1. Schug SA, Dickenson AH, Strauburger W, et al.: Current concepts on the mechanisms of action of tramadol. In: Abstract Booklet on Symposium "Current concepts on the mechanisms of action of tramadol". 9th World Congress on Pain, Austria Center Vienna, 25 August 1999.
2. Shipton EA: Tramadol-Present and Future. Anaesth Intensive Care 2000;28:363-374.

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6. Ratcliffe S, Repas C. A comparison of adverse effects of tramadol in children and adults. 3rd International Symposium of Paediatric Pain 1994;182.
7. Bamigbade TA, Langford RM: The clinical use of tramadol hydrochloride. Pain Reviews 1998;5:155-182.
8. Bosenberg A, Ratcliffe S: The respiratory effects of tramadol in children under halothane anaesthesia. Anaesthesia 1998;53:960-964.
9. Barsoum MW. Comparison of the efficacy and tolerability of tramadol, pethidine, and nalbuphine in children with postoperative pain. Clin Drug Invest 1995;9:183-190.

Oral Opioid Analgesia
Codeine, Oxycodone, Hydrocodone, Methadone, MSO_4

Typically used when transitioning from parenteral opioids in inpatients and for postoperative and chronic pain management. They are frequently used in combination with acetaminophen or NSAID.

Oral administration of opioids is confounded by the interindividual variation in bioavailability of drug which makes equianalgesic conversation or assumptions about equipotent between agents ("MSO_4" equivalents) impossible. They are all agonist at the μ opioid receptor. The consideration made in choosing one or another would include formulation (liquid vs. tablet) combination with acetaminophen or NSAID and potency in patients requiring higher dose and tolerability.

Adverse effects within this group and are similar for equipotent dose given and is dose related. With the preparation that come in fixed combination with acetaminophen, aspirin or ibuprofen, these NSAIDs but not exceeds recommended doses in those whose requirements have excalated.

<u>Codeine</u>:
Most commonly used oral opioid in pediatrics. Rapidly absorbed from GI tract. PO bioavailability of 60 to 70%. Peak serum concentration 1-2h. 10% undergoes hepatic demethylation to morphine MSO_4, though 10-20% of the population lacks the enzyme for demethylation. It is available as a elixir and in tablet form. Dose 0.8-1 mg/kg q 4h.

Oxycodone and Hydrocodone:
Semisynthetic opioids. PO bioavailability 50-60%. Peak serum concentration reached 1-2h t ½ η 2.5 to 4h. Dose 0.1 mg/kg q 3-4h. Hydrocodone comes as an elixir in combination with acetaminophen (167mg acetaminophen/2.5 mg per 5 ml). OxyContin q 12 hr sustained release available in 10,20,40,& 80 mg tablets. Must be swallowed whole and not crushed.

MSO_4
Frequently used in oncology population. Bioavailability 15-64%. Doses (not approved for Peds). Moderate to severe pain 0.2 to 0.5 mg/kg/dose q 4-6h (immediate release), 0.3-0.6 mg/kg/dose po q 12h (controlled release).

References:

1. Kalso E. Vainco A. Morphine and oxycodone hydrochloride in the management of cancer pain. Clin Pharmacol Ther 1990;47:649-646.
2. Beaver WT, Wallenstein SL, Rogers A, et al. Analgesic studies of codeine and oxycodone in patients with cancer. II. Comparisons of intramuscular codeine and of oral with intramuscular oxycodone. J Clin Pharm Ther 1978;207:92-100.

Methadone:

A synthetic opioid agonist with unique properties that make it suitable for acute perioperatve use, chronic pain therapy and possibly the most suitable opioid to use when addressing neuropathic pain because of the d-isomers inhibitory activity at the NMDA receptor.

The analgesic half-life is 4-6h with single dose but the duration may be increased to 12h with chronic dosing. The plasma half-life is 15-60h with outliers to 120h. It has a large V_D and is 60-90% protein bound to AAG.

The range of oral methadone administered to hospitalized children with cancer pain or with injuries due to trauma in one series of 180 was 0.1- 1.1 mg/kg /day[1]. In another series of children < 10 yr of age, the initial daily dose of methadone ranged from 0.2-0.4 mg/kg b.i.d.-t.i.d. with a max of 1 mg/kg/day[2].

References:

1. Shir Y et al. Methadone is safe for treating hospitalized patients with severe pain. Can J Anesth 48:11:1109-1113;2001
2. Shir Y et al. Oral methadone for the treatment of severe pain in hospitalized children: a report of five cases. Clin J of Pain 1998;14:350-3.

Dextromethorphan:

The N-methyl-D-aspartate (NMDA) receptor antagonists have been shown to modulate somatic and neuropathic pain [1,2] by attenuating the process of central sensitization and windup response to noxious stimuli.[3] Several studies have indicated that only secondary hyperalgesia is attenuated[4] with, but a recent study demonstrated attenuation of both primary and secondary thermal hyperalgesia.[5] Dextromethorphan (DM) is a low affinity, non-competitive NMDA antagonist. It is the d-isomer of the codeine analogues, levorphanol and is used primarily as an antitussive. It has an established safety record when orally administered as 1 mg/kg/day.[6] DM is rapidly metabolized in the liver and transformed to dextrorphan which is more active than DM as an NMDA antagonist. Its oral bioavailability is only 10%.

Studies demonstrating the efficacy of DM as an analgesic adjunct have presented conflicting finding. In general, however, a beneficial role for DM as part of a multi-modal analgesic approach for mainly acute pain has been demonstrated.[7] Two pediatric studies examining the use of DM for T & A patients produced conflicting results. In the first, Rose et al. in a randomized double-blind, placebo controlled trial compared DM 0.5 mg/kg, 1 mg/kg and placebo in children 6-12 years. All patients received MSO4 0.075 mg/kg I.V., acetaminophen 25-35 mg/kg PR, ondansetron, and dexamethasone 0.5 mg/kg IV. No difference in CHEOP's, behavior or VAS scores were found and there was no difference in parental satisfaction.[8] In a subsequent study by Dawson et al. children 3-13 yrs were randomized to receive DM 1 mg/kg vs. placebo 30" prior to surgery. Pts received MSO_4 0.025 mg/kg and dexamethasone 0.1 mg/kg

In this study, significantly fewer patients in the DM group required no additional MSO_4 compared with the placebo group (P=0.03). Of those requiring MSO_4 the, mean dose requirement was significantly lower in the DM group and was therefore found to be MSO_4 sparing.[9] It was suggested that these contradictory findings resulted from the larger MSO_4 and dexamethasone dose obviating a difference in postoperative analgesic requirements.

We currently are examining the use of DM as an adjunct to accelerate opioid weans in children who have developed tolerance (typically after prolonged ICU stay) and in patients whose opioid requirements rapidly escalate despite opioid rotation and the use of other adjuvant agents. The doses used are typically 1 mg/kg PO q 6h to q 8h without side effects to date.

References:

1. Kawamata T, Omote K, Kawamata M, Namiki A. Premedication with oral dextromethorphan reduces postoperative pain after tonsillectomy. Anesth Analg 1998; 86:594-7.
2. Nelson KA, Park KM, Robinovitz E, Tsigos C, Max MB. High dose oral dextromethorphan vs. placebo in painful diabetic neuropathy and post-therapeutic neuralgia. Neurology 1997; 48:1212-8.

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4. Ilkjaer S, Dirks J, Brennum J, et al. Effect of systemic N-methyl-D-aspartate receptor antagonist (dextromethorphan) an primary and secondary hyperalgesia in humans. Br J Anaesth 1997;79:600-5.
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8. Rose JB, Guy R, Cohen DE, Schreiner MS. Preoperative oral dextromethorphan does not reduce pain or analgesic consumption in children after adenotonsillectomy. Anesth Analg 1999;88:749-53.
9. Dawson GS, Seidman P, Ramadan HH. Improved postoperative pain control in pediatric adenotonsillectomy with dextromethorphan. Laryngoscope 2001;111:122-26.

Gabapentin in Pediatric Patients with Neuropathic Pain

Gabapentin was first introduced in the United States in 1993 as a second-generation antiepileptic drug for treatment of partial complex seizures. Its current off-label use for neuropathic pain management in children is thought to resemble its use in the adult population.[1]

Use of gabapentin for chronic pediatric pain conditions were first reported by McGraw.[2,3] The first report was of a 9 yr old with erythromelalgia and second was of a 12 yr girl with neuropathic pain. Subsequent clinical trials have addressed its efficacy in the treatment of post-herpetic neuralgia[4] and diabetic neuropathy.[4,5,6]

Pharmacokinetics:

The mechanism of gabapentin's anti-hyperalgesic effect is unknown. Gabapentin interacts with the system L transporter and alters the synthesis and release of GABA in the brain and exhibits high affinity binding to voltage-activated sodium channels.[7] The oral bioavailability is 50 to 60%.[8] Elimination occurs via renal excretion as unchanged drug with a half-life of 5 to 7 hours.[8]

Dosage Guidelines for Pediatric Pain Management:

Analgesic onset and dose response was reviewed in a case series of twelve patients ages 7 to 17 yrs by McClain et al.[5] Gabapentin was administered for various neuropathic pain states. A staring dose of 5 to 10 mg/kg/day was administered and the dose was increased q 48h after tid dosing (in contrast to the adult qd) without significant side effects (day 1qd, day 2 bid, day 3 tid). For children weighing less than 20 kg, the starting individual dose was no greater than 100 mg/d. The onset of analgesia was found to occur as early as day 3 of tid administration. All patients were reported to have marked pain relief within 2 weeks of starting therapy. The target dose is 15 to 30 mg/kg/day. Once pain reduction is achieved, the dose escalation is stopped and therapy is continued for a minimum of 6 weeks and ideally for a minimum of 3 months after resolution of symptoms to avoid recrudescence.[1]

Dosing Schedule for Gabapentin

Day	Morning	Midday	Bedtime
1			5 mg/kg; max = 300 mg
2	5 mg/kg		5 mg/kg
3	5 mg/kg	5 mg/kg	5 mg/kg
4	5 mg/kg	5 mg/kg	5 mg/kg
5	7 mg/kg	7 mg/kg	7 mg/kg
6	7 mg/kg	7 mg/kg	7 mg/kg
7	10 mg/kg	10 mg/kg	10 mg/kg

McClain B, et al. Anesthesiology 1999;91(3A):A927

Side effects of gabapentin may include somnolence, dizziness, ataxia, fatigue, nystagmus, all of which remit with a reduction in dose. Overall, gabapentin has a more favorable side effect profile than the tricyclic antidepressants (dry mouth, sedation lethargy) which are regarded as the first line therapy for neuropathic pain.[9] Further pediatric clinical trials are needed to confirm these initial clinical impressions.

References:

1. McClain BC, Ennevar S: The use of gabapentin in pediatric patients with neuropathic pain. Seminars in Anesthesia 2000;19(2):83-87.
2. McGraw T, Kosek P: Erythromelalgia pain manage with gabapentin. Anesthesiology 86:988-990, 1997.
3. McGraw T, Brett R: Gabapentin for treatment of neuropathic pain in a 12 year-old girl. Clin J Pain 1998;14(4):354-356.
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8:30 - 10:30 am

Update in Pediatric Cardiac Anesthesia: New Myths

Moderator: Anne M. Lynn, MD

Anesthesia Agents and Myocardial Function
Dean B. Andropoulos, MD

Anesthetic and Stress Ablation
Peter C. Laussen, MBBS

Neuroprotection
C. Dean Kurth, MD

Anesthetic Agents and Myocardial Function in Congenital Heart Disease

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A wide variety of anesthetic regimens are used for patients with congenital heart disease (CHD) undergoing cardiac or non-cardiac surgery, procedures in the cardiac catheterization laboratory, or other diagnostic or therapeutic procures such as magnetic resonance imaging. The goal of all of these regimens is to produce general anesthesia or adequate sedation, while preserving systemic cardiac output and oxygen delivery. Many of these patients have limited cardiac reserve, and if a cardiac arrest or other adverse cardiac event occurs, successful resuscitation is less frequent than in patients with normal hearts.[1] Thus, intelligent selection of regimen and dosage, with the patient's unique pathophysiology of their cardiac lesion in mind, along with requirements for the particular procedure they are undergoing, is essential. This lecture reviews the effects on hemodynamics and myocardial contractility of anesthetic agents commonly used for patients with congenital heart disease.

Volatile Agents

In vitro studies of effects on contractility in isolated adult human atrial fibers indicate that the order of direct myocardial contractility depressant effect is halothane >> sevoflurane = isoflurane = desflurane.[2] Differences among these agents occur because of differing effects on calcium flux through L-type Ca^{++} channels, both transarcolemmal, and in the sarcoplasmic reticulum (SR). Halothane reduces Ca^{++} flux through the sarcolemma more than isoflurane, with the net result that there is less intracellular Ca^{++} available to bind to the troponin-actin-myosin complex producing myocyte contraction. Another mechanism is that halothane, but not isoflurane, directly activates ryanodine-sensitive sarcoplasmic reticulum Ca^{++} channels, thereby reducing Ca^{++} storage in the SR and making less available for release during contraction. The effects of sevoflurane and desflurane on Ca^{++} flux are similar to isoflurane.[2]

The effects of these anesthetic agents on myocardial contractility and hemodynamics have been evaluated in children with normal hearts.[3-6] Holzman et al. compared the effects of halothane and sevoflurane on echocardiographically derived indices of contractility, using stress-velocity and stress-shortening indices to eliminate the effects of loading conditions.[3] Wodey et al. performed a similar study on infants and also compared Doppler-derived cardiac indexes.[4] In both studies, halothane caused a significantly greater decrease in contractility than sevoflurane at 1 and 1.5 MAC. In the latter study, cardiac index (CI) was preserved with sevoflurane, but was significantly decreased with halothane. Isoflurane's effect has been studied echocardiographically in infants and young children with normal

hearts,[5-6] and found to have a similar profile to halothane, namely a decrease in cardiac index and systolic and mean blood pressure. It is important to note that infants from the newborn period up to an age of approximately 6 months[7] exhibit an exaggerated degree of depression of myocardial contractility and blood pressure in response to all volatile agents, but especially halothane. This is likely due to the immaturity of the Ca^{++} release and reuptake system, necessitating higher levels of free cytosolic Ca^{++} to be available to bind to the troponin-actin-myosin complex to produce myocyte contraction. Because all volatile agents interfere with the release of Ca^{++}, their effects are more pronounced in young infants.

In a recent report of the Pediatric Perioperative Cardiac Arrest Registry[8] halothane alone or in combination was deemed to be responsible for l of the medication related cardiac arrests. Isoflurane was responsible for none, and sevoflurane for 4% of the medication related cardiac arrests.

In a study of 40 preterm neonates (mean postconceptual age 32 weeks) undergoing a variety of procedures (9 PDA ligation), Friesen et al.[9] found that after atropine and pancuronium (which increased HR 8-12%), 0.5% halothane maintained heart rate at baseline levels, and decreased systolic blood pressure by 25%, and isoflurane 0.75% also maintained heart rate but decreased systolic BP by 30%.

The volatile have also been assessed in patients with congenital heart disease.[10-15] Glenski et al. used echocardiography to compare the effects of isoflurane and halothane on hemodynamics and M-mode derived measures of contractility.[10] Contractility was preserved with isoflurane and depressed with halothane. Knobelsdorff et al. compared incremental halothane induction with immediate 8% sevoflurane induction in infants with CHD, and reported a significantly greater decrease in ejection fraction (EF) with halothane.[11] This report, however, concerned only the first 10 minutes after induction, and no reference was made to end-tidal concentrations of anesthetic agents. Girota et al.[12] compared 8% sevoflurane with 4% halothane for induction of anesthesia and tracheal intubation in patients with congenital heart disease and observed a 25% decrease in systolic blood pressure in the halothane group versus a 15% decrease in the sevoflurane group.

Our study using transthoracic echocardiography compared halothane, isoflurane, sevoflurane[13] in 54 children with congenital heart disease reported that 1 and 1.5 MAC halothane produces significant myocardial depression, resulting in a decline in mean arterial pressure *(*MAP:22 and 35%), ejection fraction (EF--15 and 20%) and cardiac output (CO: 17 and 21%*)* in patients 1 month to 13 years with two ventricles undergoing cardiac surgery. Sevoflurane maintained both CO and heart rate (HR), and had less profound hypotensive (MAP decrease 13 and 20%) and negative inotropic (EF preserved at 1 MAC, 11% decrease at 1.5 MAC) effects compared with halothane. Isoflurane, in concentrations as high as 1.5 MAC, preserved CO and EF, had less suppression of MAP (22 and 25%) than halothane, and increased HR (17 and 20%) and decreased systemic vascular resistance (SVR: 20 and 22%).

We also assessed the effects of these agents on pulmonary (Qp) and systemic (Qs) blood flow in 30 patients with two ventricles and left to right shunts.[9] Halothane, isoflurane, and sevoflurane did not change Qp:Qs as measured by echocardiography, despite the study design that made baseline measurements with FiO_2 .21, and with FiO_2 1.0 at 1 and 1.5 MAC anesthetic concentrations.

Russell et al.[15] compared halothane with sevoflurane in the pre-bypass period in 180 children with a variety of cardiac diagnoses, including 14 with single-ventricle physiology. The incidence of significant hypotension, bradycardia, and arrhythmia requiring drug treatment with atropine, phenylephrine, epinephrine, or ephedrine was higher with halothane (two events per patient vs. one) and the serum lactate increased slightly with halothane.

The propensity of halothane to cause dysrhythmias in normal children is well known. Blayney et al.[16] in a recent controlled study in pediatric patients with normal hearts undergoing dental surgery, noted a 48% incidence of dysrhythmias by Holter analysis with incremental halothane, versus 12% in the sevoflurane group. Forty percent of the halothane patients had ventricular dysrhythmias, including 12% with short runs of ventricular tachycardia. All dysrhythmias in the sevoflurane group were single supraventricular ectopic beats. Viitanen et al.[17] compared halothane 5% and sevoflurane 8% induction followed by maintenance levels in 1 to 3 year olds undergoing adenoidectomy. The overall incidence of dysrhythmias with halothane was 23% vs. 6% with sevoflurane; all sevoflurane dysrhythmias were supraventricular. There was a 47% incidence of tachycardia with sevoflurane (HR>170) vs. 26% with halothane. In a study by Green et al.[18] however, even sevoflurane induction, either with a circuit primed with 8% sevoflurane, or in incremental increases up to 8%, caused a 20% incidence of junctional bradycardia (less than 80 beats/min) in infants, mean age 7.5 months. An abstract by Girotra et al.[12] cites a 60% incidence of dysrhythmias with 4% halothane induction, versus 0% with 8% sevoflurane during induction in patients with congenital heart disease. Isoflurane, when utilized in children for electrophysiologic studies and radiofrrequency ablation for supraventicular tachycardia, did not affect sinoatrial or atrioventricular node conduction, and all arrhythmias were easily induced.[19]

Some practitioners consider halothane to be indicated in ventricular outflow tract obstruction conditions, such as Tetralogy of Fallot (TOF) or hypertrophic cardiomyopathy (HCM), where depressed contractility and maintenance of baseline heart rate may be desirable to allow for a longer ejection time to reduce obstruction to outflow.[20] This advantage of halothane may well be offset by a greater decrease in mean arterial pressure, which could increase right to left shunting in TOF, or the gradient across the left ventricular outflow tract in HCM. And, loss of sinus rhythm, more likely with halothane, is poorly tolerated by many of these patients. Despite this theoretical debate, these agents have both been used for TOF with success,[21,22] and no controlled studies have addressed this question.

To summarize the ability of the three most commonly utilized volatile agents to maintain cardiovascular stability in patients with two ventricles with congenital heart disease, taking into account contractility, cardiac output, and maintenance of normal sinus rhythm,

isoflurane and sevoflurane are most likely to maintain stability whereas halothane is less likely. Halothane and sevoflurane cause minimal airway irritation and thus can be used for inhaled induction of anesthesia; however in view of the available data it would appear that there is little evidence for the continued use of halothane for this purpose in patients with congenital heart disease. Isoflurane has even less effect on contractility and hemodynamics than sevoflurane, and thus is considered by many to be the best maintenance agent, especially in light of its lower cost.

Nitrous Oxide

In patients with congenital heart disease recovering from surgery, Hickey et al.[23] administered 50% N_20 and observed a decrease of 9% in heart rate, 12% in mean arterial pressure, and 13% in systemic cardiac index. However, mean pulmonary artery pressure and pulmonary vascular resistance were not significantly changed in these well-ventilated patients with a $PaC0_2$ of 34-35, and pH of 7.47-7.49, even in patients with elevated pulmonary vascular resistance at baseline. This report of 14 patients represents the total number of patients with congenital heart disease in which N_2O administration has been carefully studied. Despite this paucity of information, extensive clinical experience has demonstrated N_2O to be safe and effective, particularly as an adjunct to inhaled induction of anesthesia for congenital heart surgery.

Narcotic Agents

Fentanyl and sufantanil have been studied as a sole anesthetic in patients with congenital heart disease. Hickey and Hansen, et al.[24-27] provided the basis for this technique with a series of studies in neonates and infants under one year of age undergoing complex repairs ranging from the Norwood operation to complete repair of two ventricle lesions. Fentanyl doses of 50-75 mcg/kg, and sufantanil doses of 5 to 40 mcg/kg, administered with pancuronium 0.1-0.15 mg/kg, provided excellent hemodynamic stability with minimal changes in heart rate and blood pressure throughout the anesthetic. Fentanyl at 25 mcg/kg also eliminated the increase in pulmonary artery pressure and resistance in response to suctioning in infants recovering from cardiac surgery. Moore et al.[28] demonstrated that 5, 10, or 20 mcg/kg sufentanil in children 4-12 years of age had no effect on echocardiographically derived ejection fraction in patients undergoing repair of two ventricle lesions. Increases in heart rate and blood pressure and stress hormones were more effectively blunted by the 10 and 20 mcg/kg doses. Glenski et al.[10] reported M-mode echocardiographic measures of contractility as well as blood pressure and heart rate responses during anesthesia for cardiac surgery in children. They compared fentanyl at 100 mcg/kg, or sufentanil at 20 mcg/kg in children 6 months to 9 years of age. Measurements were made at three different times: after a premedication with morphine and scopolamine, after induction, and after tracheal intubation. These narcotic agents decreased both EF and shortening fraction (SF) after induction, but they returned to or above baseline after intubation.

Midazolam is often added to fentanyl anesthesia to provide sedation and amnesia, as a substitute for low dose volatile anesthetic agent, particularly in hemodynamically unstable patients and young infants, where the myocardial depressant effects of volatile agents are more pronounced. We studied fentanyl and midazolam in two different clinically utilized dose regimens for congenital heart disease[13] in patients with two ventricles. Vecuronium was used for muscle relaxation in order to isolate the effects of the other two agents on hemodynamics. Measurements of cardiac output and contractility were made by echocardiography. Fentanyl/midazolam caused a significant decrease in cardiac output (21 and 22%) despite preservation of contractility. Compromise of cardiac output was predominantly due to a decrease in heart rate (19 and 22%), given minimal changes in stroke volume and systemic vascular resistance. Co-administration of a vagolytic agent such as atropine[29] or pancuronium would likely preserve cardiac output. The added effect of midazolam on echocardiographic indices of contractility has not been previously reported; however, increased inotropic support requirements have been documented in infants undergoing cardiac surgery with the addition of midazolam bolus totaling 0.3 mg/kg, and infusion of 0.1 mg/kg/hr intraoperatively.[30]

Remifantanil is a synthetic ultra-short acting narcotic agent metabolized by plasma esterases with half-life 3 to 5 minutes that appears to be independent of the duration of infusion.[31] It would appear to be particularly useful for short non-cardiac procedures with intense stimulation where narcotic analgesia and it hemodynamic stability would be desirable, yet where rapid emergence is also important. Remifentanil at 0.25 mcg/kg/min has been demonstrated to provide equivalent analgesia and hemodynamic profile when compared to epidural bupivacaine during N_2O/isoflurane anesthesia for major abdominal or lower extremity surgery in children.[32] Donmez et al[54] reported a series of 55 children undergoing cardiac catheterization with a remifentanil infusion of 0.1 mcg/kg/min. This regimen maintained excellent cardiovascular stability, with minimal changes in heart rate, blood pressure or oxygen saturation. 58% of patients required additional sedation with midazolam or ketamine. Apnea was infrequent, and time to recovery score of Ó5 (10 point scale) was only 2-4 minutes. Long cardiac catheterization procedures could potentially benefit from this agent. Its use has been reported for atrial septal defect repair, where patients are extubated in the operating room.[33] It apparently does not bind to the cardiopulmonary bypass circuit,[34] and its clearance in children before and after cardiopulmonary bypass appears to be predictable within a narrow range, making it a potentially useful agent for "fast-track" anesthesia and early extubation for simple surgical procedures. Despite these advantages, nausea/vomiting, and bradycardia/hypotension,[32] as with other synthetic μ-receptor agonists, are a prominent feature of the adverse event profile.

Propofol

Williams et al.[35] measured the hemodynamic effects of propofol in 31 patients 3 months to 12 years at a dose of 50-200 mcg/kg/min undergoing cardiac catheterization. They found that propofol significantly decreased mean arterial pressure and systemic vascular resistance; however systemic cardiac output, heart rate, and mean pulmonary artery pressure, as well as pulmonary vascular resistance, did not change. In patients with cardiac shunts, the net result was a significant increase in the right to left shunt, a decrease in the

left to right shunt, and decreased Qp:Qs, resulting in a statistically significant decrease in PaO_2 and SaO_2, as well as reversal of the shunt from left to right to right to left in two patients. Lebovic et al.[36] in another study of patients undergoing cardiac catheterization, demonstrated that 4 of 10 propofol (9 of whom had intracardiac shunting) patients experienced a decrease in heart rate of greater than 20%, and 7 of 10 a decrease in mean arterial pressure of 20% or more. 4 of 10 experienced a decrease in arterial saturation of 5% or more from baseline.

Zestos et al.[37] studied 26 patients undergoing congenital heart surgery with cardiopulmonary bypass who were selected for early extubation in the ICU. They were begun on a propofol infusion at 50 mcg/kg/min after cardiopulmonary bypass, and were compared to a placebo control group who received intralipid. The infusions were discontinued upon leaving the operating room, and morphine was given as needed for pain. Both the time to tracheal extubation (33 vs.63 minutes) and the number of morphine doses (1 vs. 2.3) were significantly less in the propofol group. No hemodynamic depression was observed in this study. Another recent study with a similar protocol for propofol infusion after weaning from bypass demonstrated that 72 of 103 children undergoing simple and complex surgery were extubated within 9 hours of ICU admission.[38]

Ketamine

Ketamine has been a mainstay of induction of general anesthesia in patients with congenital heart disease.[39,40] It can be administered IV or IM. It will reliably maintain heart rate, blood pressure, and systemic cardiac output at a dose of 1-2 mg/kg IV, or 5-10 mg/kg IM in patients with a variety of congenital heart diseases, including Tetralogy of Fallot.[27] The question about exacerbation of pulmonary hypertension has been addressed in two important studies. Morray et al.[41] demonstrated that in cardiac catheterization patients, 2 mg/kg ketamine caused a minimal (<10%) increase in mean pulmonary artery pressure, and ratio of pulmonary to systemic vascular resistance (Rp:Rs), with no change in direction of shunting or Qp:Qs. Hickey et al.,[42] in postoperative cardiac surgery patients whose tracheas were still intubated but were breathing spontaneously with normal $PaCO_2$, demonstrated that ketamine 2 mg/kg had no effect on pulmonary artery pressure or calculated pulmonary vascular resistance (PVR), either in patients with normal or elevated baseline PVR. Two cardiac catheterization laboratory studies reporting increases in PVR in some patients were both performed at 5000 feet altitude, confounding the results.[43,44]

IM induction of anesthesia and muscle relaxation may be achieved with ketamine 5 mg/kg/ succinylcholine 4 mg/kg, and atropine 20 mcg/kg in the same syringe. This regimen is useful for small patients without IV access in whom inhalational induction of anesthesia may produce undesirable hemodynamic effects. Endotracheal intubation can usually be achieved in 3-5 minutes, and attention can be turned to establishing intravenous access with the airway secure and a stable hemodynamic state.

In summary, ketamine is an attractive choice for IV or IM induction of anesthesia in patients with congenital heart disease with good or moderately limited hemodynamic reserve, including those with pulmonary hypertension or cyanosis. However, it is a direct myocardial depressant, and care must be taken in patients with severely limited cardiac

reserve with depressed myocardial contractility, who may be chronically receiving ß-adrenergic or similar agents, or whose own endogenous sympathomimetic stimulation is maximal in an attempt to maximize cardiac output because of a severely compromised hemodynamic status.

Etomidate

Of all of the available IV induction agents, etomidate consistently demonstrates the smallest amount of direct myocardial depression in several in vitro models. There are few published reports of the hemodynamic effects of etomidate in children with congenital heart disease. A study of 20 patients in the cardiac catheterization laboratory with a variety of congenital defects found that etomidate at 0.3 mg/kg bolus followed by an infusion of 26 mcg/kg/min had similar effects as ketamine 4 mg/kg followed by an infusion of 83 mcg/kg/min, namely a slight increase in heart rate but no change in mean arterial pressure during induction or the 60 minute infusion.[45] Sarkhar et al.[46] studied etomidate bolus 0.3 mg/kg in 12 children undergoing cardiac catheterization for device closure of ASD, or radiofrequency ablation of atrial arrythmias. There were no significant changes in any hemodynamic parameter, including heart rate, mean arterial pressure, filling pressures, vascular resistances, Qp:Qs, or mixed venous oxygen saturation. A case report of stable hemodynamics in a pediatric patient with end-stage cardiomyopathy receiving a second anesthetic four weeks after cardiovascular collapse with ketamine induction demonstrates the utility of the drug in this population.[47] Etomidate has been utilized for induction of anesthesia in adults with congenital cardiac conditions such as ruptured aneurysm of the sinus of valsalva, and cesarean section in a patient with uncorrected coronary artery to pulmonary artery fistula, and been demonstrated to be devoid of cardiovascular effects in these patients.[48,49]

Thus it would appear that etomidate is best utilized in patients with the most limited cardiac reserve. It seems to be particularly useful in teenagers or adults with poorly compensated palliated congenital heart disease presenting for cardiac transplantation, or revision of previous surgeries. New water soluble preparations, or other formulations of etomidate[50,51] may eliminate the troubling side effects of pain on injection and phlebitis.

Barbiturates

The rapid acting barbiturates, including thiopental, are direct myocardial depressants. In a recent study using adult human atrial muscle strips, thiopental, at clinically relevant concentrations seen after standard IV induction of anesthesia, reduced contractility by 25-50%.[52] Thiopental also causes venodilation and pooling of blood in the periphery. The mechanism for these cardiovascular effects probably has to do with interference of Ca^{++} flux across the sarcolemmal membrane, or alteration of the nitric oxide synthase pathway.[53] Hemodynamic homeostasis is mediated by baroreceptor reflex-induced sympathetic stimulation. Patients with limited reserves, and maximally stimulated sympathetic responses or down-regulated ß-adrenergic receptors do not do well with barbiturate anesthetic inductions.

In summary, intravenous induction of anesthesia with barbiturates in patients with congenital heart disease should be reserved for those patients with good cardiac reserves and intact baroreceptor reflexes, who can tolerate a reduction in contractility, and a possible reduction in arterial pressure.

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Anesthesia and Stress Ablation

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In general terms the "stress response" refers to the metabolic and hormonal changes that result from critical illness, surgery and trauma. It is a systemic reaction to injury, with hemodynamic, endocrinologic and immunologic effects (Table 1).

Systemic response to Injury
Autonomic nervous system activation:
Catechol release
Hypertension, tachycardia, vasoconstriction
Endocrine response:
Anterior Pituitary:
⇒ACTH, GH
Posterior Pituitary:
⇒Vasopressin
Adrenal Cortex:
⇒Cortisol, aldosterone
Pancreas:
⇒Glucagon
Insulin resistance
Thyroid:
⇔⇓ $T_{4/3}$
Metabolic response:
Protein catabolism
Lipolysis
Glycogenolysis / gluconeogenesis
Hyperglycemia
Salt and water retention
Immunologic responses:
Cytokine production
Acute phase reaction
Granulocytosis

Although the stress response evolved to allow injured animals to survive by catabolizing stored fuels, it can be argued whether this response is necessary, or even beneficial, after surgery. Stress and adverse postoperative outcome have been linked closely in critically ill newborns and infants. This is not surprising given their precarious balance of limited metabolic reserve and increased resting metabolic rate. Metabolic derangements such as altered glucose homeostasis, metabolic acidosis, salt and water retention, and a catabolic state contributing to protein breakdown and lipolysis, are commonly seen following major stress in sick neonates and infants (1). This complex of maladaptive processes may be associated with prolonged mechanical ventilation courses and ICU stay, as well as increased morbidity and mortality.

The stress response to surgical stimulation has been extensively investigated in both pediatric and adult patients. It has been the subject of numerous reviews and presentations, and often generates vigorous discussion as noted at the recent SPA meeting and articles / editorial in A&A (2-4). Although somewhat mired in dogma, there is little doubt that anesthesia has a pivotal role in attenuating this process in the acute phase. However it is important to review the effect of anesthesia with respect to the surgical stimulus and the likelihood of ongoing or postoperative stresses. There are differences

in the activation and magnitude of the response for patients undergoing non-cardiac surgery and cardiac surgery prior to cardiopulmonary bypass (CPB), and with the response seen in patients once exposed to a bypass or an ECMO circuit.

Further, it is important to distinguish between suppression of the endocrine response and attenuation of hemodynamic responses to stress. Because of their direct effects on the myocardium and vascular tone, anesthetic agents can readily suppress the hemodynamic side-effects of the endocrine stress response. The same is true when inotropic and vasoactive agents are administered during anesthesia. However, the postoperative consequences of the endocrine stress response, in particular fluid retention and increased catabolism, remain unabated. Relying on hemodynamic variables to assess the level of "stress" is therefore often inaccurate. Metabolic indices such as hyperglycemia and hyperlactatemia are also indirect markers of "stress", particularly as they are influenced by other factors such as fluid administration and cardiac output.

Activation of the stress response

1. Neuro-endocrine pathways:

The endocrine stress response is activated by afferent neuronal impulses from the site of injury, traveling via sensory nerves through the dorsal root of the spinal cord to the medulla and hypothalamus. Anesthesia can therefore have a substantial modulating effect on the neuro-endocrine pathways of the stress response by virtue of providing analgesia and loss of consciousness.

Non-Cardiac surgery:

Outcomes after major surgery in neonates and infants may be improved when the stress response is attenuated. This was initially reported in two controlled, randomized trials comparing N_2O / O_2 / curare anesthesia with or without fentanyl in neonates undergoing PDA ligation(5), and with or without halothane in neonates undergoing general surgery (6). Morphine premedication has been reported to reduce ACTH and cortisol rises in children undergoing adenoidectomy (7). Fentanyl doses as low as 10 mcg/kg may be sufficient for effective baseline anesthesia in neonates, although larger doses are necessary for prolonged anesthesia. A bolus dose of 10-15 mcg/kg has been demonstrated to effectively ameliorate the hemodynamic response to tracheal intubation in neonates (8). Infants undergoing major non-cardiac surgery using fentanyl doses less than 10 mcg/kg demonstrate significant neuro-humoral responses despite maintaining hemodynamic stability; this response can be ameliorated when combined with a regional epidural anesthetic technique (9-11).

Cardiac surgery

The effect of surgical stress has been particularly evaluated in neonates and infants undergoing cardiac surgery (12), with the focus on high-dose opioid anesthesia to attenuate this response (13,14). A conclusion from these studies supported the notion that reducing the stress response with large-dose opioid anesthesia, and extending this into the immediate postoperative period, was important to reduce the morbidity and mortality associated with congenital heart surgery in neonates.

These studies were performed over a decade ago. During the intervening period, there have been substantial changes in the perioperative management of children with heart disease as well as the management of cardiopulmonary bypass in general; along with these changes

outcomes have considerably improved. Further, it has been well demonstrated that high-dose opioid anesthetic techniques do not consistently block the endocrine stress response to cardiac surgery. To evaluate this further, however, it is necessary to separate pre-bypass and bypass responses.

1. Pre bypass:

Recent studies in neonates, infants and older children undergoing cardiac surgery have demonstrated attenuation of the *pre-bypass* endocrine and hemodynamic response to surgical stimulation with a variety of anesthetic techniques. These have included:

- High-dose fentanyl (50 mcg/kg) either by bolus or infusion (15,16),
- High-dose bolus fentanyl (25-150 mcg/kg) with or without low dose isoflurane (17),
- Combined general anesthesia with epidural caudal opioids (18,19)

Based upon the lack of significant stress responses reported in these studies, it is reasonable to conclude that there was appropriate neuraxial inhibition in these patients and that they were adequately anesthetized during this pre-bypass phase of surgery. There were no significant postoperative complications (from hemodynamic and pulmonary complications through to awareness) reported in the studies.

It is not possible to conclude, however, that one technique is superior to another. No specific dose response between opioid plasma level and level of hormone or metabolic stress response has been established. Nor a specific benefit for the method or route of opioid administration, i.e. bolus, continuous infusion or regional technique. There are conflicting reports as to the potential benefit of adding a benzodiazepine to an opioid based technique in pediatric patients undergoing cardiac surgery (15,16,20). In addition, the type of surgical approach (mini- vs. full sternotomy) has not been reported to effect the measured stress response in children (21).

2. Bypass:

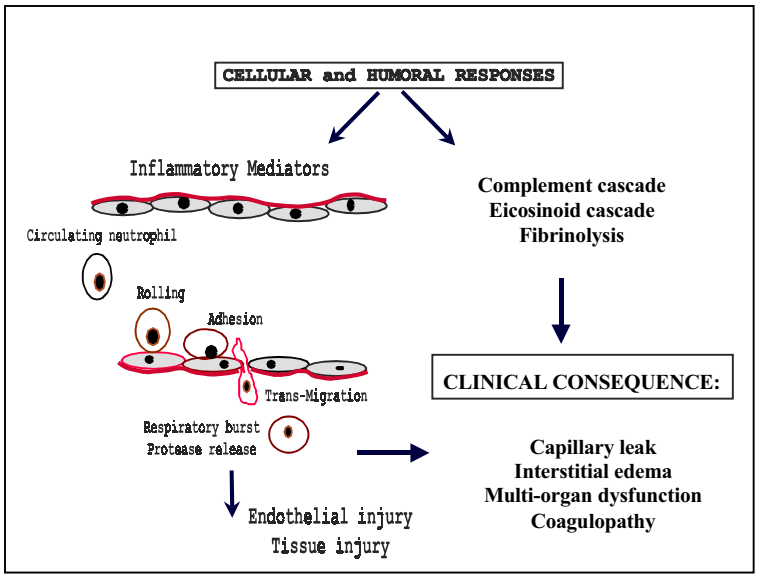
The initiation of the endocrine stress response may be from a myriad of causes and the relative contributions are speculative. Besides the surgical stimulus, additional factors include the effects of cardiopulmonary bypass (CPB), i.e. hypothermia, contact activation, hemodilution and non-pulsatile flow (22-24). Distinct to the effect of anesthesia in the pre-bypass phase, anesthesia techniques have *not* been demonstrated to consistently obtund the responses to bypass (14,16,18). This is primarily because bypass initiates a *second mechanism* for establishing the stress response independent of surgical stimulation, namely the acute phase response and inflammatory cytokine release.

2. Inflammatory cytokines

Cytokines are produced from activated leukocytes, fibroblasts and endothelial cells as an early response to tissue injury and have a major role in mediating immunity and inflammation. Cytokine production reflects the degree of tissue trauma or injury. They stimulate the production of acute phase proteins in the liver (i.e. CRP, fibrinogen, ζ2-macroglobulin and other anti-proteinases), stimulate the adhesion molecule cascade, increase protein catabolism and augment release of ACTH from the anterior pituitary (25,26).

In addition to direct tissue injury, exposure of blood to foreign surfaces is also a potent stimulus for cytokine production and, with this, the stress response. It is well recognized that that exposure of blood elements to the non-epithelialized cardiopulmonary bypass circuit, along with ischemic-reperfusion injury, induces a systemic inflammatory response. The effects of the interactions of blood components with the bypass circuit is magnified in children because of the

large bypass circuit surface area and priming volume relative to patient blood volume. Humoral responses include activation of complement kallikrein, eicosanoid, and fibrinolytic cascades. Cellular responses include platelet activation and an inflammatory response with an adhesion molecule cascade that stimulates neutrophil activation and release of proteolytic and vasoactive substances.



The clinical consequences of activating these pathways include increased interstitial fluid, generalized capillary leak, and potential multi-organ dysfunction. In the circumstances of limited hemodynamic reserve, end organ dysfunction following bypass and limited oxygen delivery or extraction within the tissue beds, an additional increase in metabolic rate and oxygen demand may be poorly tolerated.

Over the years, numerous strategies have evolved to limit the effect of this endothelial injury that results from the systemic inflammatory response. Of these, the most important strategy is limiting the time spent on bypass and limiting the use of deep hypothermic circulatory arrest. This is clearly dependent, however, on surgical expertise and preference, and in certain situations DHCA is necessary to effect surgical repair. In the early experience of bypass in neonates and infants, the use of high-dose opioid anesthesia to modulate the stress response was perceived to be one of the few clinical strategies available that was associated with the demonstrable improvement in morbidity and mortality (14). More recently, it has been demonstrated that opioids *do not* in fact modify the endocrine or metabolic stress response initiated by CPB; despite this, mortality and morbidity continues to remain low. Gruber et al demonstrated a significant increase in stress hormone levels in infants during CPB compared to pre-bypass levels although there was no change in plasma fentanyl concentrations (15).

With the advances in perioperative diagnosis and management, along with techniques of cardiopulmonary bypass and surgical expertise, the impact of the systemic inflammatory response and ischemic-reperfusion injury on multi-organ dysfunction is much less apparent. Altering pump prime composition to maintain oncotic pressure and hematocrit, the use of ultrafiltration during rewarming or immediately after bypass, and the use of antioxidants such as mannitol or antiflammatory agents such as methyprednisalone, are all important in limiting the clinical consequences of the inflammatory response.

Whereas the neonate may be more labile to changes in intravascular pressures, pulmonary vascular resistance and cardiac output than older children, in fact the neonate is quite capable of coping with the *acute phase* of surgical stress. It is less common nowadays to see patients in the immediate post-bypass period with extensive peripheral edema and along with that impaired ventricular function, reactive pulmonary hypertension and substantial alterations in

lung compliance and airway resistance. An example of this is the incidence of postoperative pulmonary hypertensive events. Pulmonary hypertensive crisis were more common a decade or more ago in infants who had been exposed to weeks or months of high pulmonary pressure and flow, such as for truncus arteriosis, complete atrioventricular canal defects and transposition of the great arteries with ventricular septal defects. High-dose opioids were an important component of management for patients at risk for pulmonary hypertensive crises, however, this occurs much less frequently nowadays when patients are operated upon at an earlier age and are therefore less likely to have significant or irreversible changes in the pulmonary vascular bed. Therefore, changes in surgical practice, and in particular the timing of surgery, has meant that the longer-term pathophysiologic consequences of various defects are less apparent than what they were ten to twenty years ago. *A strategy of large-dose opioid anesthesia to blunt the stress response appears to be a less critical determinant of outcome.*

Anesthesia and CPB

General anesthesia with high- and low-dose opioid techniques and regional epidural opioids have not demonstrated consistent attenuation of the stress response during hypothermic bypass. A recent retrospective review of intrathecal and epidural local anesthetics administered in combination with general anesthesia for congenital cardiac surgery speculated that there was more effective attenuation of the stress response (4). However, hormone levels were not reported and it remains to be determined whether this technique has a substantial modulating effect on the inflammatory response.

Of course, another possibility for the increase in stress hormones occurring during CPB is lighter level of anesthesia (27,28). A number of factors contribute to the potential increased risk during cardiac surgery, in particular altered anaesthesia drug pharmaco-kinetics and -dynamics related to hypothermia and cardiopulmonary bypass. While the incidence of awareness during cardiac anaesthesia for children is unknown, the factors contributing to awareness in adult patients also occur during paediatric anesthesia.

Assessment of the depth of anaesthesia during cardiopulmonary bypass (CPB) is difficult. While patient movement or changes in autonomic and metabolic responses are possible indices, these are affected by anaesthetic drugs, the surgical repair, the conduct of CPB, vasoactive agents, cardiovascular manipulation, and hypothermia. A recent study attempted to evaluate BIS monitoring of consciousness in children during bypass; although a significant increase in BIS during rewarming from mild hypothermic CPB was demonstrated, there were no clinical or somatic signs to indicate a lighter plane of anaesthesia, and no patients demonstrated evidence for explicit recall (18).

Conclusion

The choice of a particular anesthesia technique is often an individual or institutional preference. Nevertheless, techniques should not be mired in dogma, as has been the case for high-dose opioid anesthesia and bypass inflammatory / stress responses. Anesthesia effectively obtunds the neuraxial and endocrine response to surgery, but it is unable to suppress or defeat the powerful responses generated when blood comes in contact with artificial surfaces or during ischemia/reperfusion. Preoperative condition, surgical procedure and expertise, and the planned / anticipated post operative course are the fundamental decision making variables. There are multiple ways to achieve the same end result.

Continuing opioids into the immediate postoperative period are no longer critical determinants of outcome after pediatric cardiac surgery. They should be used to provide analgesia, sedation and comfort, but not viewed as a panacea. They are not muscle relaxants, nor anti-hypertensive agents. On the other hand, overdosing with opioids simply prolongs the duration of mechanical ventilation, delays establishing nutrition, possibly increases the risk for sepsis, and induces tolerance and acute withdrawal phenomena.

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