Procedural Sedation Curriculum
Nationwide Children's Hospital
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Module 2: Basics of Anesthesia

Introduction

Intraopeative anesthetic are can be provided by one of 5 techniques which include local anesthesia (somewhats referred to as "local only", monitored anesthesia care (MAC), peripheral nerve blockade, neuraxial techniques (spinal or epidural anesthesia), and general anesthesia. Local anesthesia involves the infiltration of a surgical site with a local anesthetic agent to render the site insensitive to pain. This may be done solely by the surgeon without the involvement of an anesthesia provider. Monitored anesthesia care (MAC) involves monitoring a patient with standard monitors according to the American Society of Anesthesiologisgts (ASA monitors, see below) and administering a sedative and/or analgesic agent intravenously to provide anxiolysis, sedation, and analgesia. MAC is frequently combined with either infiltration of the surgical site with a local anesthetic agent or a regional anesthetic technique. MAC is provided using a combination of a drug with amnestic properties (midazolam or propofol) combined with a drug to provide analgesia (an opioid such as fentanyl). During MAC, spontaneous ventilation is maintained during the procedure thereby eliminating the need for endotracheal intubation and controlled ventilation. The depth of sedation may range a state in which the patient is awake and relaxed with the ability to respond to verbal stimuli to a state of deep sedation where a painful stimulus is required to elicit a response. Peripheral nerve blockade and neuraxial anesthesia are frequently considered together under the title of regional anesthesia. A peripheral nerve block involves the placement of a local anesthetic agent around a nerve or group of nerves (plexus) to render specific dermatomes insensitive to pain. Examples of plexus blockade include cervical plexus blocakde for superficial and deep neck surgery, brachial plexus blockade for upper extremity or shoulder procedures, or lumbar plexus blockade for hip or leg surgery.[1-3] Intravenous regional anaesthesia, the Bier block, is another example of a peripheral nerve block that can be used to provide surgical anesthesia. A Bier block involves the intravenous injection of a dilute local anesthetic into a

vein of an extremity after that extremity has been exsanguinated by wrapping it with a bandage and then occlusion with a tourniquet. Although the latter technique is generally successful and easy to accomplish, it may not be feasible in younger children except when combined with deep sedation. Given the use of an occlusive tourniquet, its duration is limited to 60-70 minutes due to tourniquet pain. The major concern with the Bier block is that the dose of local anesthetic used approaches the toxic limits and should the tourniquet fail, cardiovascular or CNS consequences from the local anesthetic agent may occur. Neuraxial anesthesia involves the injection of a local anesthetic agent into either the subarachnoid or epidural space. This reasults in blockade of the spinal cord and its accompanying nerve roots to render an entire region of the body (lower abdomen, pelvis, perineum, or lower extremities) insensitive to pain. Examples of neuraxial anesthesia include spinal, epidural, and caudal anesthesia.[4,5] In infants and children, a regional anesthetic technique such as a peripheral nerve block or epidural anesthesia can be used instead of general anesthesia in patients with co-morbid diseases which significnatly increase the risk of anesthesia. More frequently, the regional anesthetic technique is combined with a general anesthetic as part of a balanced anesthetic technique and continued into the postoperative period by use of a continuous infusion via the catheter to provide postoperative analgesia.

When a general anesthesia is used, it should include the 4 requisites of amnesia, analgesia, muscle relaxation, and attenuation of the sympathetic nervous system's response to surgical trauma. The phases of general anesthesia include induction, maintenance, and emergence. The induction of anesthesia can be carried out with the intravenous administration of an anesthetic agent (thiopental, propofol, ketamine or etomidate) or via the inhalation route with an inhalational anesthetic agent such as sevoflurane. Advantages of an intravenous induction include the rapid onset of anesthesia and avoidance of issues associated with inhlation induction including claustrophobia from anesthesia mask placement and the odor of the inhalational anesthetic agent. In pediatric patients, the inhalation induction of anesthesia is frequently

chosen to avoid the need for obtaining intravenous access on an awake child. However, when inhalation induction is carried out without intravneous access, airway and cardiovascular issues may arise which may mandate immediate treatment without intravenous access. In such cases, if intravenous access cannot be rapidly obtained, it may be feasible to use the intramuscular (IM) route for a select number of medications (atropine, succinylcholine). However, more aggressive resuscitation such as the administratio of epinephrine for hemodynamic compromise may require the use of intraosseous access (IO).[6] Fortunately, the majority of problems during inhalation induction can be easily reversed with appropriate airway techniques or the administration of IM medications. Hemodyanmic compromise including cardiac arrrest was more common with the use of halthane given its negative inotropic and chronotropic properties.[7] However, halothane is no longer used in the practice of anesthesia, having been replaced by sevoflurane. Even if intravenous access is present, the inhalational induction of anesthesia may be chosen as it allows the maintenance of spontaneous ventilation even during deep planes of anesthesia (deep enough to allow for direct laryngoscopy and endotracheal intubation). Such a technique may be used if there is a question regarding the ability to bag-valve-mask ventilate the patient such as patients with compromised airways from infection, tumor or anatomic abnormalities. Following anesthetic induction, one progresses into the maintenance phase of general anesthesia. This is can by the administratio of intravenous agentgs, inhalational agents or most likely, the a combination of the two. An example of a balanced technique includes some cominbation of inhalational (nitrous oxide and an inhaltional anesthetic agent), a continuous infusion of an intravenous anesthetic (propofol), a nondepolarizing neuromuscular blocking agent (NMBA), and an opioid. In most circumstances, the choice of maintenance anesthesia is based on the presence of comorbid features and the preferences of the anesthesiologists.

Preoperative Evaluation

Regardless of the type of procedure, the patient's status, and the anesthetic technique that is planned, a preoperative evaluation should be performed. In many centers, such an evaluation is performed well in advance of the anticipated surgical procedure in a specialized clinic to allow for specific preoperative interventions or preparation that may be required to allow for the safe completion of the anesthetic care and surgical procedure. Alternatively, in low risk patients without accompanying comorbid diseases, the preoperative evalution can be performed the day of surgery. The latter may also be required for patients admitted to the hospital or those presenting for emergent or urgent surgical procedures.

The preoperative evaluation includes a history of present illness, past medical problems including drug allergies, a past surgical and anesthetic history, and a review of the patient's current and possibly prior medical record and medication list. For elective surgical procedures, the status of co-morbid conditions should be optimized prior to the surgical procedure. The latter may not be feasible for urgent or emergent cases. The physical examination is directed primarily at the central nervous system, cardiovascular system, and respiratory system including an examination of the airway. The preoperative evaluation can identify many of the patients with a difficult airway which may preclude successful endotracheal intubation using standard techniques of direct larygnoscopy. An airway history should be obtained seeking medical, surgical, and anesthetic factors that may indicate a difficult airway. Examination of previous anesthesia records is helpful although a patient's airway may change with changes in weight or the development of co-morbid conditions. A physical examination of the airway is performed to detect physical characteristics associated with a difficult airway such as a large tongue, small mouth, short neck (shortened thyromental distance), recessed mandible, limited extension or flexion of the neck, limited mouth opening, and difficulty visualizing the uvula and tonsillar pillars when the patient opens their mouth. The latter is assessed with the Mallampati grading system so that

visualization of the entire uvula and tonsillar pillars (Mallampati grade) suggests that endotracheal intubation will be umcomplicated while failure to visual the tonsillar pillars and the soft palate (Mallampati class IV) is suggestive that endotracheal intubtion will be difficult. Based on the preopearitive evaluation, an American Society of Anesthesiologists (ASA) Physical Status classification is assigned to the patient based on their comorbid features and associated medical conditions (Table 1).[8] The physical classification is based on the physical condition of the patient and does not include the planned surgical procedure. Laboratory tests and additional investigations are ordered based on the positive findings obtained during the history and physical examination and on the complexity of the surgical procedure.[9] The routine preoperative testing of all patients for elective surgery has been shown to be unjustified and expensive. In the absence of comorbid conditions, for surgical procedures with limited chance of significant blood loss, no laboratory or radiologic evaluation is necessary. Although commonly performed, routine testing of coagulation function has been shown to be of limited value without an anetecedant history of bleeding problems.[10] The most common coagulation disorder that may casue problems intraoperatively is von Willebrand's disease which cannot be identified on routine coagulatio screening which includes a prothrombin time (PT), partial thromboplastin time (PTT), and an international normalized ratio (INR). Another area of ongoing controversy is the need for routine preoperative pregnancy testing in post-menarchal patients. Given the theoretical potential for anesthetic agents to be teratogenic and the risks of spontaneous abortion, the history should include specific questioning about the potential for pregnancy including the patient's last menstrual cycle. In addition, there is increasing use of a point-of-care urine pregnancy testing in many centers. Further testing such as pulmonary function tests, electrocardiography, and echocardiography are based solely on the presence of co-morbid conditions. Following the preoperative visit including the history and physical examination. The planned management of anesthesia is discussed with each patient, and risks and

possible complications are reviewed. Options and plans for postoperative pain management are discussed. The answering of questions and obtaining an informed consent complete the preoperative evaluation.

NPO Guidelines

Although the aspiration of gastric contents is an uncommon event, the consequences may be severe including pneumonitis, respiratory failure or even death. Classical teaching states that the severity of the aspiration injury relates to the volume aspirated as well as its pH with severe complications occurring with the aspiration of a voluem ≥ 0.4 mL/kg or a pH ≤ 2.5. Although aspiration may occur in any setting, patients at risk include parturients, obese patients, diabetics, patients who have received opioids, patients with gastrointestinal disease (reflux, obstruction), patients with altered mental, patients with intra-abdominal pathology (acute abdominal emergencies including appendicitis) and patients in whom difficult airway management is anticipated. These factors may predispose to aspiration by limiting the patient's ability to protect their own airway, decreasing the normal barrier to aspiration (lower esophageal sphincter tone), increasing gastric volume or delaying gastric emptying.[11,12] Patients who have the highest incidence of perioperative aspiration are those with a high ASA physical status classification (III, IV or V) and those having emergency surgery. The majority of aspirations occur during the induction of anesthesia or following tracheal extubation when the patient has lost their protective airway reflexes.

Classically, keeping patients *nil per os* (NPO) has been the mainstay of therapy to prevent acid aspiration. In the past, patients were fasted for 8-12 hours before surgery to reduce the volume of gastric contents at the time of induction of anesthesia and to decrease the risk of aspiration pneumonitis. This preoperative fast does not take into account differences in gastric emptying of clear liquids and solids. More

recently based on several investigations, there has been a significant revision in the perioperative fasting rules especially for infants and children. It has been demonstrated that clear liquids have a gastric emptying time of 1-2 hours while solids have an unpredictable gastric emptying time that may be greater than 6 hours.[13-16] The ingestion of clear liquids up to 2 hours before surgery does not increase gastric fluid volume or acidity.[13-16] As a result, the liberalization of guidelines for ingestion of clear liquids for elective surgery of otherwise healthy patients has been recommended.[17,18] A survey of anesthesiologists in the United States has shown that 69% have either changed their NPO policy or are flexible in their practice in allowing clear liquids before elective operations in children.[19] Suggested guidelines as recommended by the American Society of Anesthesiologists for patients with no known risk factors include no solid food for at least 6 hours before surgery and unrestricted clear liquids until 2 hours before surgery. Oral medications may be given 1-2 hours before surgery with a small sip of water.

Although on theoretical grounds, several maneuevers may be indicated in patients with risk factors for acid aspiration, there is limited if any evidence-based medicine to demonstrate their efficacy in preventing perioperative aspiration. Many centers routinely use preoperative medications to decrease the acidity of the gastric fluid (H_2-antagonists or proton pump inhibitors) and speed gastric emptying (metoclopramide). To be effective, it is recommended that these medications be administered 60-90 minutes prior to anesthetic induction. Alternatively, a non-particulate antacid (sodium bicitrate) can be given immediately prior to anesthetic induction, a common practice in obstetrical anesthesia. Additionally, in patients at risk for acid aspiration, rapid sequence induction is practiced. This involves the use of a rapidly acting neuromuscular blocking agent (see below) with an anesthetic induction agent and the application of cricoid pressure. As the cricoid is the only complete ring of the trachea, it can be gently pushed posteriorly to effectively occluded the esophagus and prevent passive regurgitation of gastric contents when consciousness is lost during anesthetic induction. This practice is commonly referred to as rapid sequence induction or intubation (RSI). In its pure form, RSI involves preoxygenation, the administration of medications for neuromuscular blockade and anesthetic induction, and the performance of endotracheal intubation without bag-valve-mask ventilation as the latter may distend the stomach and predispose to regurgitation. A modification of this technique, known as a modified RSI, uses gentle bag-valve-mask ventilation to maintain oxygenation while waiting for the anesthetic agents to take effect. The modified RSI may be used more commonly in pediatric anesthesia as even brief periods of apnea without bag-valve-mask ventilation may result in precipitous decreases in oxygenation due to the low functional residual capacity and high metabolic rate for oxygen in young children and infants.

Preoperative Medication

There are several categories and uses of preoperative medications (table 2). The most common use of a preoperative medication is to provide sedation and anxiolysis prior to transport to the operating room. Preparing the patient for surgery includes psychological preparation and frequently pharmacological premedication. Psychological preparation includes the preoperative visit and an interview by the anesthesiologist. Pharmacological premedication may be given orally or rarely intramuscularly, 1-2 hours, before the induction of anesthesia or intravenously in the immediate preoperative period. Popular choices include benzodiazepines such as midazolam or occassionally, α_2-adrenergic agonists such as clonidine or dexmedetomidine. A frequently used agent and route of administration is the oral administration of the benzodiazepine, midazolam to ease separation from parents and improve mask acceptance for inhalation induction. This is generally necessary when children are at least 9-18 months of age and begin to manigest stranger anxiety. Given alterations in bioavailability when administered by the oral route, doses of 0.3-0.5 mg/kg are required.

Additional preoperative medications may be used in patients with certain co-morbid features including the use of H_2-antagonists, proton pump inhibitors or motility agents to increase gastric pH and decrease gastric volume in patients at risk for acid aspiration while inhaled β-adrenergic agonists (albuterol) or anticholinergic agents (ipratropium) may be administered to patients with reactive airway diseases (asthma, recent upper respiratory infection, or chronic obstructive pulmonary diseases). Anticholinergic agents may be used to dry airway secretions in patients requiring fiberoptic intubation.

Monitoring

The standards for intraoperative anesthetic monitoring have been outlined by the American Society of Anesthesiologists. The same monitoring standards are the same regardless of whether the case entails a general anesthetic, regional anesthetic (peripheral nerve block, spinal or epidural), or monitored anesthesia care. The standards according to the ASA include an oxygen analyzer, non-invasive blood pressure cuff, continuous ECG, pulse oximeter, end-tidal carbon dioxide analyzer, precordial or esophageal stethoscope, temperature probe, and a ventilator disconnect alarm. Based on the medical condition of the patient and the surgical procedure, more elaborate, invasive monitoring may be added to these standard monitors such as a urinary catheter, catheters for measuring intraarterial, central venous, and pulmonary artery pressures, and transesophageal echocardiography. Although there are no strict guidelines dictating which patients should have invasive monitors placed, there have been recommendations set forth for the adult population. These recommendations must be taken within the context of the fact that there are limited data comparing outcomes in patients managed perioperatively with or without pulmonary artery (PA) catheters.[20,21] The ASA recommends considering three variables including disease severity, magnitude of the surgical procedure, and practice setting when assessing benefit versus risk of PA catheters.[22] Additional information regarding structural and functional issues of the mycardium may be obtained by the use of transesophageal echocardiography (TEE). TEE is being used more frequently in the adult population with the development of specific curriculum to teach the skills necessary for performance of TEE during cardiac anesthesia fellowships. The latter has been followed by the American Board of Anesthesiology recognizing such training and providing the opportunity for credentialling through the completion of a written examination. The strongest indications for perioperative transesophageal echocardiography which are supported by evidence-based medicine include cardiac surgery procedures such as repair of valvular lesions (insufficiency or stenosis) or congenital lesions, assessments and repairs of thoracic aortic aneurysms and dissections, pericardial

window procedures, and the repair of hypertrophic obstructive cardiomyopathy.[23]   For noncardiac surgery, intraoperative transesophageal echocardiography is indicated to evaluate acute, persistent, and life-threatening hemodynamic disturbances in which ventricular function and its determinants are uncertain and have not responded to treatment especially when placement of a PA catheter is not feasible.

In addition to standard ASA monitors, there is growing interest in the development and potential use of "depth of anesthesia" monitors. Although controversial, the potential impact of such monitors is highlighted by the results of several trials which demonstrate that intraoperative awareness may occur in anywhere from 0.1-0.2% of all patients with even higher incidences in specific procedures including trauma, cardiac, obstetrical, and emergency surgery.   Several manufacturers have marketed or are developing monitors which provide the anesthesia provider with a numerical value against which anesthetic agents are titrated. There are currently 5 such monitors including the Bispectral Index (BIS monitor, Aspect Medical, Newton, MA), the Narcotrend (MonitorTechnik, Bad Bramstedt, Germany), which is currently available only in Europe; Patient State Analyzer (PSA 4000, Baxter Healthcare, Deerfield, IL); SNAP (Everest Medical, Minneapolis, MN); and Auditory Evoked Potential Monitor (AEP Monitor, Danmetter Medical). To date, the one that has received the most clinical use is the BIS monitor. The BIS is a modified electroencephalographic monitor that uses a preset algorithm based on intraoperative data obtained from adults to evaluate the electroencephalogram. The BIS number is determined from three primary factors, including the frequency of the electroencephalographic waves, the synchronization of low and high frequency information, and the percentage of time in burst suppression. Part of the simplicity and attraction of the BIS monitor is that the depth of sedation/anesthesia is displayed numerically, ranging from 0 to 100, with 40-60 being a suitable level of anesthesia to ensure amnesia and lack of recall. With the use of BIS monitoring, a decreased incidence

of awareness has been demonstrated as well as a decrease in the total amount of anesthetic agent used.[24-26] Additional studies have suggested faster recovery times and faster discharge times from the post-anesthesia care unit; all of which may translate into reduced perioperative costs.[26,27] Although not considered the standard of care as of yet for intraoperative anesthesia care, the ASA does recommend the availability of such monitors whenever general anesthesia is provided. Given the success of such monitors in the perioperative arena, there is ongoing interest in the application of such technology in the ICU and the procedural sedation arena.[28-30]

The Pharmacology of Anesthetic Agents

LOCAL ANESTHETIC AGENTS: The local anesthetic agents can be divided into two chemically distinct classes: esters and amides. Local anesthetic agents in the amino ester class include procaine, chloroprocaine, and tetracaine. Amino amides used clinically include lidocaine, mepivacaine, prilocaine, bupivacaine, levobupivacaine, and ropivacaine. Several clinically important differences exist between these two classes of local anesthetic agent including site of metabolism, plasma half-lives, adverse effect profile (CNS versus cardiac toxicity), and allergic potential. Amino esters are metabolized by plasma cholinesterases while amino amides undergo hepatic metabolism.

The mechanism of action for the majority of local anesthetic agents involves blockade of sodium channels in the nerve membrane thereby preventing depolarization. The non-ionized portion of the local anesthetic agent penetrates the lipid membrane while the ionized portion reversibly blocks the inner aspect of the sodium channel. Local anesthetic agents differ in intrinsic potency, onset of action, duration of action, and their ability to produce differential sensory and motor blockade. Potency is determined primarily by lipid solubility (high lipid solubility = potency).[31] Bupivacaine and tetracaine are examples of local anesthetic agents with high lipid solubility and hence high potency. The onset of

action is determined primarily by the pK_a with onsent being most rapid in those agents with a pKa closest to physiologic pH.[32,33] With a pKa close to physiologic pH, the percentage of the unionized form is greater thereby increasing passage through the nerve membrane. Lidocaine has a pK_a of 7.7 and at a pH of 7.4, 35% exists in the unionized base form yielding a relatively rapid onset of blockade. In contrast, tetracaine has a pK_a of 8.6 with only 5% in the unionized form at a tissue pH of 7.4, resulting in a slower onset of blockade than lidocaine. Duration of action is determined primarily by the degree of protein binding to receptors in the sodium channel.[34] Local anesthetic agents bind to protein receptors in the sodium channels. High protein binding and therefore a prolonged duraiton of action are characteristic of bupivacaine, levobupivacaine, tetracaine, and ropivacaine. Duration of action is also influenced by the degree of vasodilation produced by the local anesthetic.[35] Vasodilatation results in increased blood flow to the area and therefore an increased removal of the agent from the depot in the tissues. The local anesthetic agents also differ in their differential effects on sensory versus motor nerves. Bupivacaine and ropivacaine demonstrate this property, which is very beneficial for postoperative analgesia administered through an epidural catheter so that patients are able to ambulate with minimal discomfort.

When performing regional anesthesia, the goal is to place the local anesthetic agent as close to the nerve or plexus that needs to be anesthetized. A recent addition to the armamentarium of the anesthesiologist has been the use of ultrasound to visualize the individual nerve roots or the plexus that is to be anesthetized.[37-40] This technology is also being used for neuraxial techniques including spinal and epidural anesthesia. The advantages of this technology are not only an increased success rate of various regional anesthetic techniques, but also the ability to provid blockade with a decreased dose of the local anesthetic agent. Additional factors that must considered when using these agents are themaximal allowable dose of the agent, the impact when a vasoconstrictor such as epinephrine is added

to the soluation, and the effect of the site of administration.   Increasing the dose of a local anesthetic (increased concentration or volume) yields a faster onset of effect, a longer duration of action, and a greater depth of blockade.[41]   However, higher plasma concentrations of the local anesthetic agent will also be achieved thereby increasing the risks of toxicity (see below).

Given the catastrophic effects of local anesthetic toxicity, mechanism to avoid it and prevent its occurrence are mandatory during the peformance of regional anesthetic techniques in infants and children.   Epinephrine (0.5 µg/ml or a concentration of 1:200,000) is added to the local anesthetic solution during performance of a regional anesthetic technique to cause local vasoconstriction thereby decreasing the vascular absorption of the drug and also to serve as a marker of inadvertant systemic injection.[41-43] However, the ability of epinephrine to prolong the duration of action depends on the local anesthetic used and the site of administration.   More importnatly, epinephrine is used as a marker for inadvertant systemic injection.   Even with negative aspiration for blood, there is the potential for inadvertant intravascular administration thereby suggesting the use a test dose. The test dose entails the administration of 3 mL of the 5 µg/mL epinephrine solution or a total epinephrine dose of 15 µg. If this amount of epinephrine is injected intravascular, it can generally be detected by changes in heart rate, blood pressure, or the ST-T wave segments of the electrocardiogram and thereby alert the practitioner that inadvertant intravascular injection is occurring.[44]

The site of injection of the local anesthetic agent also has a significant impact on the clinical effects including duration of action and vascular uptake (plasma concentrations). The shortest durations of action occur with either intrathecal injection for spinal anesthesia or subcutaneous administration. The longest duration of action and onset of blockade are seen with major peripheral nerve blocks (brachial or lumbar plexus plexus blockade).[45,46] The vascular absorption of the local anesthetic agent and its plasma concentration are also dependent on the site of administration. The highest plasma concentration occurs following an intercostal nerve block or interpleural analgesia followed in order caudal epidural, lumbar or thoracic epidural, brachial plexus, peripheral nerve blockade, subarachnoid, and subcutaneous infiltration.[47] During performance of regional anesthesia, the greatest risk of morbidity and mortality results from the achievement of toxic plasma concentraitons of the drug. Local anesthetic-induced systemic toxicity affects the central nervous system (CNS) and the cardiovascular (CV) system. The differential effects on these two organ systems and the plasma concentration at which toxic effects are noted vary according to the agent. With most local anesthetic agents, CNS toxicity occurs at doses and blood levels below those that produce CV toxicity. The latter provides some degree of safety as the CNS symptoms (seizures) are generally more amenable to treatment than the CV effects (arrhythmias and conduction blockade). Death from local anesthetic toxicity is most commonly the result of the cardiovascular effects of these agents with adverse effects on cardiac electrical and mechanical activity.[48] Bupivacaine produces cardiac arrhythmias by inhibiting the fast sodium channels and the slow calcium channels in the cardiac membrane. Hypercarbia, acidosis, and hypoxia potentiate the negative chronotropic and inotropic effects of high plasma concentrations of local anesthetic agents.These effects are so profound that resuscitative measures for ventricular tachycardia/fibrillation including standard ACLS protocols may be ineffective. Anecdotal case reports have suggested the potential role of various agents such as amiodarone for refractory ventricular arrhythmias. More

recently, anecdotal human data and animal studies have suggested that intralipid solutions may be used to bind the local anesthetic agent thereby resulting in return of spontaneous circulation. Current recommendations from the ASA include easy and ready access to 20% intralipid solutions whenever large doses of local anesthetic agents are used for regional anesthetic techniques. Given the risks of morbidity and mortality from local anesthetic toxicity, avoidance of toxicity is the goal through the careful calculation of the dose, use of the lowest necessary dose (concentration and volume), use of a test dose with epinephrine to identify inadvertant intravascular injection, intermittent aspiration to identify vascular penetration, and slow incremental injection of the dose.

INTRAVENOUS ANESTHETIC AGENTS: The intravenous anesthetic agents in common clinical use include the barbiturates, (thiopental, mehohexital, and thiamylal), propofol, etomidate, and ketamine. These agents are used to induce (bolus administration) and/or maintain (continous infusion) the general anesthetic state. In lower doses, agents in this class such as propofol can be used by continuous infusion to provide MAC while maintaining spontaneous ventilation. Although any of the intravenous anesthetic agents will induce anesthesia, the choice of the agent and its dose are based on the clinical scenario, the anticipated duration of the surgical procedure, and the patient's underlyng hemodynamic status.

Thiopental, propofol, and etomidate mediate their anesthetic properties through interactions with the $GABA_A$ receptor complex. These interactions lead to enhanced activity of the inhibitory neurotransmitter system, γ-aminobutyric acid (GABA).[49-52] Activation of the $GABA_A$ receptor increases the transmembrane movement of chloride resulting in hyperpolarization of the postsynaptic cell membranes. Ketamine's analgesic and anesthetic effects are the result of its interactions with the N-methyl-D-aspartate (NMDA) system which is activated by glutamate, an excitatory transmitter as well as other sites within the CNS including those involved with opioid and cholinergic transmission.[53-55]

The intravenous anesthetic agents result in somewhat varying end-organ effects. The barbiturates, propofol, and etomidate reduce cerebral metabolism ($CMRO_2$), cerebral blood flow (CBF), and ICP. As such, they are valuable agents in the practice of neuroanesthesia or in critically ill patients with increased ICP. When compared with propofol or the barbiturates, etomidate may be preferred in patients with abnormal cardiovascular function as it provides greater hemodynamic stability. As a result, etomidate maintains cerebral perfusion pressure (CPP = MAP - ICP) whereas propfol and thiopental may decrease MAP through their effects on systemic vascular resistance (vasodilatation) as well as direct negative inotropic properties. Thiopental and perhaps etomidate and propofol may possess "neuroprotective" properties secondary to reducing $CMRO_2$, which improves the ability of the brain to tolerate incomplete ischemia during procedures such as carotid endarterectomy or the temporary occlusion of cerebral arteries during an aneurysm repair.[56,57] Ketamine's direct effects on ICP remain controversial with the older literature suggesting that ketamine may directly increase cerebral blood flow and ICP. However, recent studies suggest that ketamine has limited effects on CBF and ICP especially when given in combination with other anesthetic agents including midazolam.[72-74] Propofol, midazolam, and the barbiturates have similar effects on the electroencephalogram (EEG). Initial, low doses with low brain concentrations result in transient high-frequency activity followed by lower-frequency, higher-amplitude waveforms at high brain concentrations, and eventually burst suppression and even electrical silence with high enough doses. These effects which are similar to those produced by the potent inhalational anesthetic agents have been studied in enough detail and are consistent enough that algorithms have been developed which can analyze the EEG patterns and thereby determine the depth of anesthesia. These algorithms are used by several different monitoring systems to provide modified EEG monitors which are clinically used to evaluate the depth of anesthesia. Although

controversial, it is these monitors that are purported to have efficacy in avoiding intraoperative awareness during anesthetic care.

Most intravenous anesthetics have anticonvulsant properties. Various of the barbiturates and propofol have been incorporated algorithms for the treatment of refractory status epilepticus.[61,62] Opposite effects are generally seen with etomidate which can produce involuntary myoclonic movements from an imbalance of inhibitory and excitatory influences in the thalamocortical tract. Etomidate also stimulates the EEG resulting in increased amplitude and frequency.[63] Myoclonic movements and opisthotonic posturing have also been reported following the administration of propofol. These movements are attributed to propofol's antagonism at glycine receptors in subcortical structures.

The intravenous anesthetic agents also have dose dependent effects on ventilatory function. Thiopental, propofol, etomidate, and midazolam result in a decrease of tidal volume and minute ventilation as well as a rightward shift of the CO_2 response curve. As with many of the end-organ effects of the anesthetic agents, the respiratory depressant effects may be magnified in patients with comorbid conditions (chronic respiratory or cardiovascular disease) and when coadministerend with other medications which are respiratory depressants (inhalational anesthetic agents, opioids, phenothiazines). Given these effects on central control of ventilation, a transient period of apnea generally occurs following an anesthetic induction dose of any of these agents. In contrast to the respiratory effects of propofol, etomidate and the barbiturates; in the absence of co-morbid diseases, ketamine can generally be expected to result in minimal respiratory depression in clinically relevant doses and may preserve airway protective reflexes.[64,65] Ketamine also stands apart from the other intravenous anesthetic agent in that the release of endogenous catecholamines following its administration results in bronchodilatation thereby making it a suitable induction agent in patients who are actively wheezing or at risk for reactivity during airway manipulation. Propofol has also been shown to have beneficial airway effects in patients with airway reactivity. In a prospective trial, 77 adult patients were randomized to receive one of three agents: propofol (2.5 mg/kg), etomidate (0.4 mg/kg) or thiopental

(5 mg/kg) for anesthetic induction and tracheal intubation.[66] Following endotracheal intubation, respiratory resistance was lower with propofol when compared to either etomidate or thiopental. Additional evidence for the beneficial effects of propofol on airway reactivity are provided by Pizoz et al. who randomized asthmatic or non-asthmatic patients to anesthetic induction with thiopental/thiamylal (5 mg/kg), methohexital (1.5 mg/kg), or propofol (2.5 mg).[67] In asthmatic patients, the incidence of wheezing was 45% with thiopental/thiamylal, 26% with methohexital, and 0% with propofol. In non-asthmatic patients, the incidence of wheezing was 16% with thiopental/thiamylal and 3% with propofol. The potential beneficial effects of propofol on airway reactivity are further supported by animals studies.[68,69] The proposed mechanism for these effects are a decrease of intracellular inositol phosphate resulting in a depression of intracellular calcium availability.

During anesthtetic induction or maintenance, the intravenous anesthetic agents can depress the cardiovascular system resulting in hypotension by various mechanisms. These include a reduction of central and/or peripheral autonomic nervous system activity, blunting compensatory baroreceptor reflexes, decreasing preload, systemic vasodilatation or directly depressing myocardial contractility. Hemodynamic function during the induction of anesthesia may also be affected by co-morbid cardiovascular disease, intravascular volume status, resting sympathetic nervous system tone, concomitant medications (angiotensin converting enzyme inhibitors, β-adrenergic antagonists), and the administration of other agents used for anesthetic care including opioids and benzodiazepines. An induction dose of thiopental causes a variable decrease in cardiac output, systemic vascular resistance, and MAP. The decrease in cardiac output is the result of vasodilation as well as direct myocardial depression. This effect is generally well tolerated in patients with adequate cardiovascular function, but can be exaggerated with pre-exisiting cardiovascular disease necessitating the use of a lower dose of thiopental or preferably the use of alternative agents in patients with compromised cardiovascular

function. Propofol demonstrates cardiovascular depressant effects similar to or greater than those of thiopental. Propofol is a direct myocardial depressant and reduces systemic vascular resistance. Significant cardiovascular responses following propofol are more common with high doses, in hypovolemic patients, in elderly patients, and in patients with significant cardiovascular disease.[71,72] The deleterious cardiovascular effects of propofol can be attenuated by the administration of calcium chloride (10 mg/kg).[73] Additional cardiovascular effects from propofol may result from its augmentation of central vagal tone leading to bradycardia, conduction disturbances, and asysole.[74,75] The negative chronotropic effects of propofol are more common when it is administered with other medications known to alter cardiac chronotropic function (fentanyl or succinylcholine). Although the relative bradycardia may be beneficial in elderly patients at risk for myocardial ischemia, it may be detrimental if cardiac output is heart rate dependent.

In contrast to the negative inotropic effects of propofol and the barbiturates, etomidate causes minimal cardiovascular depression and may be used for anesthetic induction in patients with significant cardiovascular disease.[76,77] As etomidate has little effect on systemic vascular resistance, it may be used in patients with cyanotic congenital heart disease in whom pulmonary blood flow is dependent on mean arterial pressure. Although suppression of adrenal cortical function occurs even following a single bolus dose of etomidate through inhibition of the activity of 17-α hydroxylase and 11-β hydroxylase, it remains controversial whether such effects are of clinical significance.[78,79] However, the risk:benefit ratio of this effect much be entertained when etomidate is chosen for anesthetic induction. Additionally, although still used as a single induction dose in patients with co-morbid cardiovascular disease, repeated doses or continuous infusions are not recommended.[80]

The cardiovascular effects of ketamine are different from those of the other intravenous anesthetic agent. Ketamine stimulates the cardiovascular system by activation of the sympathetic

nervous system and the release of endogenous catecholamines.[81] Anesthetic induction doses of ketamine (1-2 mg/kg) generally increase heart rate and MAP. Although the indirect effects of ketamine include the release of endogenous catecholamines and stimulation of the sympathetic nervous system, ketamine is a direct myocardial depressant. In most clinical scenarios, the indirect effects compensate for the direct negative inotropic effects. However, in critically ill patients who have depleted their endogenous catecholamines, cardiovascular collapse may occur.

The pharmacokinetic profile of the intravenous anesthetic agents is characterized by a rapid onset of CNS effects secondary to the high lipid solubility of these agents and the high percentage of cardiac output perfusing the brain. The termination of the central CNS effect results from redistribution of the drug from the central to the peripheral compartment. It is not dependent on primary metabolism and elimination of the drug from the body. Most intravenous anesthetics are metabolized in the liver and excreted in the kidney. Some metabolites are active, such as desmethyldiazepam (diazepam) and norketamine (ketamine), and may result in prolonged effects especially with repeated dosing or the use of continuous infusions. There is a wide variation in the elimination half-lives of intravenous anesthetic agents because of differences in clearance. Drugs with short elimination half-lives include propofol, etomidate, ketamine, and midazolam whereas thiopental has a long elimination half-life. Propofol is widely used, especially in ambulatory surgery centers, because of its short duration of action, fast recovery time, and early discharge potential.[82,83] This rapid recovery results in less "hang-over" effect or residual drowsiness following outpatient surgical procedures thereby facilitating return to work and resumption of activities of daily life.

OPIOIDS: There are various roles for the opioids in the perioperative and anesthetic of patients. The commonly used opioids are pure agonists that are selective for μ (mu) opioid receptors located at

discrete sites throughout the spinal cord and the CNS.[84] However, they are generally combined with either with an inhalational anesthetic agent or an intravenous anesthetic agent (total intravenous anesthesia or TIVA). This combination is necessary as even when administered in doses sufficient to produce profound analgesia and apnea, the opioids do not consistently produce amnesia in healthy patients.[85] Therefore other agents are required to ensure amnesia during the intraoperative care of patients. Intraoperatively, the opioids are used to blunt the sympathetic stress response to surgical trauma, decrease the requirements for inhalational or intravenous anesthetic agents, and provide postoperative analgesia.

Although discrete differences in the chemical structure exist in the intravenous opioid agents; when used clinically, the clinically relevant differences include their potency, onset of action, duration of action, lipid solubility, hemodynamic effects, and metabolic fate (table 3).[86,87] During the conduct of general anesthesia, the synthetic agents including fentanyl and its derivatives are frequently chosen given their brief duration of action, ability to effectively blunt the hemodynamic changes related to the surgical stress response, and limited cardiovascular effects. However, other opioids including morphine may be chosen given their longer duration of action with the ability to provide postoperative analgesia during the transition from general anesthesia to the awake state (emergence). Morphine is the least lipophilic of the commonly used opioids and therefore it has a slower onset of action than the more lipophilic synthetic opioids such as fentanyl. Morphine, like all of the opioids except for remifentanil, undergoes hepatic metabolism. In part, morphine is converted to morphine-6-glucoronide (M6G), a water soluble metabolite with a potency far greater than that of the parent compound. However, given that it is water solubility, M6G does not rapidly pass through the blood-brain barrier into the CNS and therefore has limited clinical effects. In patients with renal insufficiency or failure, a signicant amount of M6G can accumulate and result in respiratory depression.

Meperidine, has a potency that is approximately 10% that of morphine with a similar half-life of 2-3 hours. Hepatic metabolism produces normeperidine, a metabolite which may accumulate in renal insufficiency. High plasma concentrations of normeperidine may cause seizures. Given these concerns and the higher incidence of psychomimetic effects with meperidine, our current clinical practice does not include its use except in low doses (10 mg) to treat post-anesthesia shivering. Hydromorphone has a potency that is 6-8 times that of morphine with a half-life of 2-3 hours. As there are no active metabolites of hydromorphone, it may be an effective alternative to morphine in patients with renal insufficiency. When compared with morphine, hydromorphone causes less histamine release and may be an effective alternative agent when pruritus occurs with morphine use.

The synthetic opioids including fentanyl, sufentanil, and alfentanil are very potent, highly lipid-soluble drugs with rapid onsets of action and short durations of action. Hepatic metabolism does not result in active metabolites. Fentanyl is 100 times as potent as morphine while sufentanil has 10 times the potency of fentanyl. The pharmacokinetics of fentanyl and sufentanil are similar with both drugs being short-acting at low doses and longer-acting at higher doses. Alfentanil is less potent than sufentanil and fentanyl and has a very rapid onset of action and short duration of action. Because its elimination half-life is substantially less than that of sufentanil and fentanyl, it is suitable for multiple dosing and continuous infusions and is popular for ambulatory surgery in many centers. Remifentanil is the newest of the synthetic opioids. It is the first true ultrashort-acting opioid.[88] It has a rapid onset of activity, undergoes ester metabolism, which results in a short, predictable duration of action. Its elimination half-life is 8-10 minutes and its potency is comparable to fentanyl. It is administered as a continuous infusion and remains short acting regardless of the duration of the infusion. Unlike the other opioids which have longer half-lives and a variable duration of effect in neonates and infants, the

duration of action and half-life of remifentanil is constant across all age ranges thereby making it a suitable agent in neonatal anesthesia.

The opioids play a key role in anesthesia practice. Fentanyl, sufentanil, and alfentanil are common components of various anesthetic techniques. They have replaced their predecessors (morphine, meperidine) because of their faster onsets of action, shorter and more predictable duration of action, and minimal hemodynamic side effects. For general anesthesia they reduce the surgical stress response and the associated cardiovascular responses to endotracheal intubation and surgical stimulation. They potentiate the hypnotic effects of barbiturates and benzodiazepines. They produce a dose-related decrease in the need for the potent inhalational anesthetic agents thereby facilitating recovery from prolonged anesthetic cases. High-dose opioid techniques are commonly used in cardiac surgery because the synthetic opioids produce a smooth induction process, provide hemodynamic stability, suppress the hemodynamic responses to various surgical stimulations, reduce the production of stress hormones, and provide a smooth transition to mechanical ventilation at the end of the case.

As with all medications used in the practice of anesthesia, there are several adverse effects relaed to opioid administration. Opioids produce a dose-related depression of the ventilatory response to CO_2 and blunt the response to hypoxia through a direct effect on the medullary respiratory centers.[89] Increasing plasma concentrations result in a slowing of the respiratory rate that is initially offset by an increase in tidal volume. Equianalgesic doses of all opioids (fentanyl, morphine, meperidine, etc) produce equivalent degrees of respiratory depression. Opioid-induced respiratory depression is antagonized by pain, movement, and opioid antagonists such as naloxone. When postoperative respiratory depression related to opioids occurs, small incremental doses of naloxone (1 μg/kg every 2 to 3 minutes) may be used to reverse opioid-induced respiratory depression without reversing analgesia. Given that the clinical half-life of naloxone is 20-30 minutes, repeated doses or a continuous infusion

may be needed if longer acting opioids (morphine, meperidine or hydromorphone) have been administered. Longer acting opioid antagonists (nalmefene) are now clinically available; however, there is limited clinical experience with their use in the pediatric population. Opioid reversal using naloxone can result in undesirable or dangerous hemodynamic responses such as hypertension, tachycardia, and myocardial infarction. The potential for such effects must be weighed against the anticipated benefits of opioid reversal.

Opioids generally produce minimal cardiovascular effects at usual analgesic doses. With higher doses, when combined with other anesthetic drugs, or in patients with comorbid features, opioids may produce bradycardia and a decrease in SVR resulting in hypotension. The synethic opioids may result in bradycardia from stimulation of the central nuclei of the vagus nerve leading to prolonged AV conduction and direct depression of the SA node while peripheral vasodilation results from depression of the vasomotor centers in the medulla.[90,91] Patients with elevated levels of sympathetic tone (hypovolemia, CHF) are more likely to become hypotensive after opioids. Although anesthetic techniques using high doses of the synthetic opioids may result in bradycardia and peripheral vasodilation, given that there is no direct negative inotropic effects, these technqiues are effective for patients with myocardial pathology including patients undergoing cardiovascular surgery in whom high doses of fentanyl (25-75 µg/kg) is a frequently chosen anesthetic technique. Decreases in blood pressure with such techniques result from adecrease in SVR and are usually easily treated with a direct acting α-adrenergic agonist such as phenylephrine. Morphine may result in more profound venodilatation leading to decreased venous return, decreased cardiac output and hypotension. Meperidine, given its structural similarity to atropine, may result in a mild tachycardia.

THE INHALATIONAL ANESTHETIC AGENTS: A unique aspect of intraoperative anesthetic care is the administration of inhalational anesthetic agnets including nitrous oxide (N_2O), halothane, enflurane, isoflurane, sevoflurane, and desflurane. Although their anesthetic properties are similar, the potent inhalational anesthetic agents can be divided into 2 chemically distinct clasess (alkanes and ethers). Halothane is an alkane (a 2 carbon chain) while the other 4 agents (enflurane, isoflurane, desflurane, and sevoflurane) are ethers. The potent inhalational anesthetic agents are volatile liquids and are administered to the patient via a vaporizor on the anesthesia. Nitrous oxide is administered either from a central hospital source or from E cylinders on the anesthesia machine. Flows of nitrous oxide and oxygen are mixed in varying concentrations and then directed through the vaporizer to pick up the desired concentration of the potent inhalational anesthetic agent.

The potency of inhalational anesthetic agents is measured by MAC (minimum alveolar concentration). MAC is defined as the percent of the inhalational anesthetic agent that is required to prevent 50% of patients from moving in response to a surgical stimulus. The lower the MAC, the more potent the inhalational agent. Halothane is the most potent inhalational anesthetic agent, followed in order by isoflurane, enflurane, sevoflurane, and desflurane. Nitrous oxide has a very low potency (MAC of 110%) and must be combined with other intravenous sedatives/analgesics/anesthetics or a potent inhalational anesthetic agent to fulfill the prerequisites (unconsciousness, analgesia, muscle relaxation, decrease in sympathetic nervous system activity) of a general anesthestic. As 1.5 to 2.5 MAC of an agent is required to maintain anesthesia solely with a potent inhalational anesthetic agent; in most clinical scenarios, 1.0-1.5 MAC of an inhalational anesthetic agent is combined with N_2O, opioids or intravenous anesthetic agents to provide maintenance anesthesia during a surgical procedure.

Nitrous oxide (N_2O) was the first of the inhalational anesthetic agents to be discovered. Although there hae s been a decline in its use with the introduction of newer inhalational anesthetic agents with a low blood-gas solubility coefficients (deslfurane, sevoflurane), it remains a common component of intraoperative anesthetic regimens and is also used in some centers for procedural sedation. Depending on the concentration administered, N_2O can provide sedation and analgesia or a weak anesthetic level. In concentrations of 70%, N_2O will render the majority of patients amnestic and provide moderate to significant analgesia. However, only minor surgical procedures can be performed with N_2O and O_2 alone and its amnestic properties are not a given thereby necessitating its combination with other agents. When used as the sole agent, N_2O causes minimal respiratory and cardiac depression.[92] Recovery from N_2O sedation is rapid given its low blood-gas solubility coefficiemt. Durig recovery, high concentrations of O_2 are needed to avoid diffusion hypoxia.[93] As N_2O diffuses from the blood into the alveoli, its alveolar concentraiton rises therby, singleby decreasing the effective concentration of oxygen which can lead to "diffusion hypoxia". With used for procedural sedation on repeated occassions, N_2O can lead to inactivation of methionine synthetase, an enzyme necessary for vitamin B_{12} metabolism leasding to bone marrow impairment with megaloblastic anemia and deterioration of the posterior columns of the spinal cord and neurologic impairment.[94,95] These effects may occur not only in patients, but also in healthcare workers with chronic exposure thereby mandating effective scavenging of exhaled gases to avoid environmental pollution whenever N_2O is administered. Given solubility differences, N_2O diffuses into and expands gas-containing closed spaces in the body (obstructed bowel, pneumothorax, middle ear, pneumocephalus, and air embolus).[96]

When administered in appropriate inspired concentrations, all of the potent inhalational anesthetic agents (halothane, isoflurane, enflurane, desflurane, and sevoflurane) provide the basic components of a general anesthetic including amnesia, analgesia, skeletal muscle relaxation, and control of the sympathetic nervous system. Despite their use for over 150 years in clinic anesthetic care, the exact site and mechanism of action of these agents remains elusive. Recent work suggests that the stabilization of critical proteins, possibly the receptors of neurotransmitters.[97] Although these agents provide general anesthesia, their end-organ effects can be quite varied thereby dictating their use in various clinical scenarios. In infants and children, given the potential stress that may be inflicted by placement of an intravenous cannula, anesthetic induction may be carried out by the inhalation route with placement of the intravenous cannula after the patient is anesthetized. As halothane and sevoflurane are less pungent to the airway than the other agents, they are the only agents used for the inhalation induction of anesthesia. Although halothane had been the time honored agent for inhalation induction of anesthesia in infants and children, it has recently been removed from the market and replaced by sevoflurane due to its significantly lower incidence of bradycardia, myocardial depression, and cardiac arrest. In fact, surverys evaluating the etiology of cardiac arrest during general anesthesia in infantas and children have implicated halothane as the primary factor responsible for many of these events.

All of the potent inhalational anesthetic agents cause a dose-related depression of cardiovascular and respiratory function. With increasing anesthetic depth, there is a rightward shift of the CO_2 response curve with a progressive decrease in alveolar ventilation characterized by a reduction in tidal volume in spontaneously breathing patients and an increase in $PaCO_2$. Beneficial effects on the airways include a direct effect on bronchial smooth muscle with bronchodilatation making them an effective

agent both intraoperatively and outside of the outside of the operating room for the treatment of patients with refractory status asthmaticus.[98]

The potent inhalational anesthetic agents decrease mean arterial pressure, myocardial contractility, and myocardial oxygen consumption. The exact changes in cardiac output, systemic vascular resistance, and heart rate vary from agent to agent and with the inspired concentration of the agent that is administered. Isoflurane and desflurane result primarily in vasodilatation and a decrease in SVR with reflex tachycardia. Direct negative chronotropic effects predominate with sevoflurane and halothan leading to a lowering of heart rate. As mentioned previously, this effect is less with sevoflurane than with halothane. Because of its alkane structure, halothane sensitizes the myocardium to catecholamines and can cause dysrhythmias especially when there is associated hypercarbia or high circulating catecholamines. The latter is of clinical significance when epinephrine-containing local anesthetic agents are admintered to patients anesthetized with halothane.

The potent inhalational anesthetic agents cause a dose-dependent decrease in CNS activity, depressing EEG activity, and reducing cerebral metabolic oxygen consumption. Enflurane and sevoflurane can activate the EEG and produce clinical and EEG evidence of seizure activity at high concentrations. Such problems are more exacerbated by the presence of hypocarbia when may occur if there is hyperventilation during anesthetic induction. CBF increases via a reduction in cerebral vascular resistance, which can lead to an elevation in ICP in patients with compromised intracranial compliane. The effect on ICP is least with isoflurane and can be blunted by hyperventilation and hypocarbia. These effects make isoflurane a common choice for neurosurgical anesthesia. These agents also have peripheral neuromuscular effects, they potentiate the effects of the neuromuscular blocking agents, and along with succinylcholien are trigerring agents for malignant hyperthermia.

In addition to the parent compound, metabolic products may be responsible for the toxicity of the potent inhalational anesthetic agents agents. Fifteen to 20% of halothane is metabolized compared to 5-10% for sevoflurane, 2-3% for enflurane, 0.2% for isoflurane, and less than 0.1% for desflurane. In the early days of inhalational anesthesia, hepatic toxicity was a significant concernt and existed into the modern era with halothane. Hepatotoxicity occurs from an immune-mediated reaction following exposure to halothane, enflurane, isoflurane, or desflurane.[99-102] However, given the limited metabolim of enflurane, isoflurane, and desflurane, the risk of hepatotoxicity is extremely low. The mechanism of hepatoxicity relates to the metabolic product, TFA or trifluroacetic acid, acting as a hapten. It binds to hepatocytes and induces an immune-mediated hepatitis. The metabolic pathway of sevoflurane is different and does not result in the production of TFA. Risk factors for halothane-hepatis include prior anesthetic exposure, female gender, age $\geq$ 35 years, and obesity.[103,104]

Albeit rare, specific issues related to renal function must be considered during anesthetic care. Most importantly, alterations related to cardiac output due to the inhalational anesthetic agents may seconardily decrease renal blood flow and result in renal damage. As with other end-organs, the kidneys may be damaged by the agent itself or its metabolites. Additionally, both enflurane and sevoflurane contain flouride around their carbon atoms which can be released during metabolism.[105] Fluoride concentrations in excess of 50 μmol/L can result in decreased glomerular filtration rate and renal tubular resistance to vasopressin with nephrogenic diabetes insipidus. Although high levels of serum fluoride may occur following the prolonged administration of sevoflurane, clinical signs of nephrotoxicity are extremely rare. This is postulated to be the result of the low blood:gas partition coefficient of sevoflurane and its rapid elimination from the body or the fact that sevoflurane unlike older agents such as methoxyflurane does not undergo metabolism in the kidney, but only in the liver. Therefore, unlike methoxyflurane, there is no local renal release of fluoride thereby limiting the risk of toxicity. Although

high serum flouride concentrations have been documented with prolonged enflurane administration, this agent is no longer commonly used in clinical anesthesia practice. An additional concern regarding the potential nephrotoxicity of the potent inhalational agents is unique to sevoflurane, in particular a unique metabolite, a vinyl ether also known as compound A. Compound A is produced during the metabolism of sevoflurane and its reaction with the soda lime in the carbon dioxide absorber of the anesthesia machine.[106-108] Compound A concentrations are increased by several factors including a high inspired concentration of sevoflurane, low fresh gas flows through the system (less than 2 liters per minute), increasing temperatures of the soda lime canister, decreased water content of the CO_2 absorbent, and high concentrations of potassium or sodium hydroxides in the CO_2 absorbent. Although of potential concern when studied in laboratory animals, there are no clinical data to suggest the nephrotoxic potential of compound A thereby suggesting that such concerns should not limit the use of sevoflurane even in patients with pre-existing renal dysfunction.

NEUROMUSCULAR BLOCKING AGENTS: The reader is referred to module 3 for a complete review of the use of neuromuscular blocking agents (NMBAs). The following section will deal briefly with those aspects of NMBA administration which relate specifically to perioperative anesthetic care. Intraoperatively, skeletal muscle relaxation may be required for the successful complete of a surgical procedure (exploratory laparotomy), may be required briefly for endotracheal intubation, or may be used to ensure patient immobility in situations where inadvertant movemement may be detrimental (craniotomy). Although frequently administered during the perioperative period, many surgical procedures can be performed without the administration of NMBAs NMBA's have no effect on the level of consciousness, provide neither amnesia nor analgesia, and do not alter the dose of other medications required to induce and maintain general anesthesia. When NMBA's are used, the patient

requires an adequate level of general anesthesia and in the intensive care unit an adequate level of sedation. This is especially important since clinical signs of inadequate anesthesia (movement) are abolished. It is also important to recognize that the airway must be controlled when NMBA's are used These agents are contraindicated if there is any concern regarding one's ability to control ventilation. One additional caveat regarding the administration of NMBAs is that although problems are rare, NMBA's are high on the list of agents responsible for intraoperative anaphylactoid reactions (along with antibiotics and latex).

Neuromuscular blockade may be used only to facilitate endotracheal intubation or may be continued throughout the surgical procedure to provide surgical relaxatioln. When ongoing neuromuscular blockade is required, incremental doses which are approximately $1/4^{th}$ to $1/5^{th}$ of the initial intubating dose are administered based on the response obtained using neuromuscular blockade monitoring. Alternatively, a conintuous infusion of short or intermediate acting agents is occassionally used.

Given that repetitive doses or an infusion may result in excessive levels of neuromuscular blockade, monitoring of neuromuscular transmission is used to predict optimal conditions for endotracheal intubation, adequacy of surgical muscle relaxation, effectiveness of reversal of neuromuscular blockade, and to guide dosing of NMBA's during intraoperative care. The goal of such monitoring is to allow incremental titration of NMBA's to maintain the desired level of blockade while maintaining sufficient neuromuscular function to allow reversal of residual neuromuscular blockade at the completion of the surgical procedure.

To accomplish monitoring of neuromuscular blockade, a supramaximal electrical stimulation from a peripheral nerve stimulator is delivered to electrodes placed over the distribution of peripheral nerve. This can be accomplished using the ulnar nerve at the wrist or elbow, the common peroneal nerve as it passes over the head of the fibula, or the facial nerve. As any of these involve electrical stimulation, they are painful and should only be performed in an appropriately anesthetized patient. Although various patterns of electrical stimulation of the peripheral nerve (single twitch, train-of-four or TOF, double burst suppression, tetanus, and post-tetanic stimulation) have been advocated in the literature, TOF monitoring remains the technique used most commonly in clinical anesthesia practice. Two electrical stimuli are delivered each second for 2 seconds to give 4 twitches or a train-of-four. Despite its acceptance and use in every day anesthesia practice, TOF monitoring is relatively non-specific in that up to 70-80% of the acetylcholine receptors must be blocked in order to achieve any visible decrement in the TOF. The goal of monitoring is to ensure that some residual neuromuscular function is present at the completion of the surgical procedure so that the effects can be reversed. The goal of reversal is for the patient to sustain minute ventilation and maintain a patent airway to allow for tracheal extubation.[109,110] In most clinical circumstances, 1 or 2 twitches of the TOF must be present to allow for effective pharmacologic reversal. A TOF of 0.7 or greater, where the fourth twitch is 70% or more of the height of the first twitch, is evidence of adequate reversal. Other tests of adequacy of reversal include a sustained response to tetanus, a sustained head lift for 5 to 10 seconds, and strong grip strength. In infants, sustained hip flexion is a useful clinical sign. Patients demonstrating profound blockade (no response to electrical stimulation) should not be reversed until some evidence of return of neuromuscular function has occurred. Despite adequate reversal, recurrence of partial paralysis resulting in respiratory insufficiency or upper airway obstruction may occur during the postoperative period. Reversal of residual neuromuscular blockade is accomplished using drugs that inhibit

acetylcholinesterase (edrophonium, neostigmine, or pyridostigmine). By inhibiting acetylcholinesterase, these medications result in the accumulation of acetylcholine at the nicotinic (neuromuscular junction) and muscarinic sites thereby increasing the competition between acetylcholine and the NMBA for the α subunits of the nicotinic cholinergic receptor. As these medications also inhibit acetycholinesterase at muscarinic sites, they must be coadministered with an anticholinergic agent such as atropine or glycopyrrolate to prevent bradycardia or asystole.   An inadequate response to the anticholinesterase medication with residual weakness may be secondary to excessive blockade at the time of reversal, allowing inadequate time since the administration of the reversal drug, an altered acid–base or electrolyte status, hypothermia, effects of other medications, or impaired clearance of NMBA's from the plasma secondary to renal or hepatic dysfunction.

Intraoperative Anesthetic Care

MAINTENANCE ANESTHESIA: The current chapter has discussed the periopearative care of a surgical patient from the preoperative evaluation through premedication, monitoring, and the induction of general anesthesia. Once the airway has been secured and ventilation/oxygenation established, maintenance anesthesia is provided for the duration of the surgical procedure. Given the variety of inhalational anesthetic agents, intravenous anesthetic agents, opioids, and NMBAs available, there are several combinations of agents which can be used to provide the prerequisites of general anesthesia. The choice of agent varies widely and is determined by personal preferences and experiences of the anesthesia provider, the patient's comorbid features such as their underlying cardiovascular function, the anticipated duration of the surgical procedure, the postoperative requirements (will the patient's trachea be extubated at the completion of the procedure, is ongoing postoperative analgesia required?), and the

operative setting (is rapid turnover of cases desireable and are rapid awakening and hospital discharge needed?).

In most scenarios, the baseline level of anesthesia is provided by either a potent inhalational anesthetic agent or propofol and supplemented with intermittent dosing or a continuous infusion of an opioid. If ongoing neuromuscular blockade is required, a continuous infusion of a short acting agent or intermittent dosing of an intermediate to long acting agent can be used. Although controlled ventilation is most commonly practiced, there are many surgical procedures for which spontaneous ventilation is acceptable. The use of spontaenous ventilation is more common in the outpatient setting where endotracheal intubation is less common and general anesthesia is provided using a mask or an LMA. In addition to commonly monitored hemodynamic parameters, spontaneous ventilation provides a very effective means of assessing the depth of anesthesia, respiratory rate and provides the optimal parameter for dosing of opioids. When spontaneous ventilation is used, opioids can be dosed based on the patient's respiratory rate to ensure that an appropriate amount is administered to provide postoperative analgesia while avoiding overdosing and postoperative respiratory depression.

INTRAOPERATIVE FLUID MANAGEMENT: In addition to monitoring hemodynamic and respiratory function, the anesthesiologist must also maintain fluid, electrolyte and glucose homeostasis during anesthetic care. Intraoperative fluid management uses isotonic crystalloid solutions such as lactated Ringer's (LR) normal saline (NS) or Plasmalyte® to provide ongoing maintenance fluids and replace preoperative deficits, intraoperative third space losses, and blood losses when blood therapy is not necessary. Third space losses may be relatively trivial during superficial procedures (2-3 mL/kg/hr) or significant (10-15 mL/kg/hr) for intra-abdominal procedures. Although generally considered an isotonic fluid, LR has only 130 mEq of sodium per liter and therefore is relatively contraindicated in

patients at risk for cerebral edema including the multiple trauma patient. Large volumes of NS, although effective in supporting the serum sodium, can result in a dilutional acidosis. These issues have led to the consideration of using a combiantion of NS and LR or the use of a more balanced solution such as Plasmalyte® which contains 140 mEq/L of sodium, physiolgoic amounts of chloride and gluconate/acetate as buffers. Given their distrubtion between the intravascular and extravascular space, if blood therapy is not administered, blood loss is routinely replaced as 3 mL of crystalloid for each 1 mL of blood loss. Alternatives to isotonic crystalloid solutions include synthetic and natural colloids such as hydroxyethyl starch, albumin, or gelatins (these are not currently available in the United States). As with resuscitation in other areas, there are currently no studies demonstrating the superiority of any of these solutions over standard isotonic crystalloids and it is likely that the crystalloid-colloid debate will continue for many years. Potential drawbacks to the use of hydroxyethyl starch solutions including hetastarch solutions (Hespan® or Hexted®) includes the potential for platelet dysfunction when amounts greater than 15-20 mL/kg are administered. This reversible platelet dysfunction results from alterations in the efficacy of von Willebrand factor by the hydroxyethyl starch solutions.

During the postoperative period, especially in pediatric patients, given the potential for the development of postoperative hyponatremia, fluids more hypotonic than ½ normal saline are rarely indicated. For short surgical procedures when a Foley catheter is not inserted, aggressive fluid therapy with replacement of the preoperative deficit is not necessarily required since bladder distention during emergence from anesthesia may be quite uncomfortable for the patient. Additionally, specific surgical procedures such as intracranial neurosurgical procedures and thoracic procedures or underlying cardiovascular dysfunction may mandate that the patient "be kept dry" to improve the intraoperative and postoperative course. However, in many other surgical procedures especially intra-abdominal cases, burn debridement or other cases with significant third space losses, the administration of significant

amounts of isotonic crystalloids may be required to maintain intravascular volume status. Except for the neonatal population or patients chronically receiving parenteral nutrition fluids, dextrose containing fluids are rarely administered. In high risk patients, those receiving glucose containing fluids, and diabetics, intermittent monitoring of blood glucose may be indicated. Although a review of the perioperative care of the diabetic patient is beyond the scope of this chapter, recent evidence has demonstrated that the posoperative outcome of such patients may be improved by tight perioperative glucose control. With the availability of rapid bedside testing, the rapid and intermittent determination of blood glucose concentrations is feasible.

Postoperative Care

POSTOPERATIVE ANALGESIA: Various factors may interfere with the delivery of effective postoperative analgesia. Inadequate pain relief following surgery generally results from inappropriate methods of administration rather than ineffective analgesic agents. Although frequently used in the past for the delivery of opioids in the delivery of postoperative analgesia, the intramuscular route should be abandoned as several factors result in inadequate analgesia including variable absorption and unpredictable plasma opioid concentrations in addition to the child's reluctance to ask for pain medications due to the pain associated with IM injections.[111] Fortunately, the area of acute and postoperative analgesia has been an area of intense research which has resulted in the development of new techniques and refinement of treatment strategies.[112] Current modalities to provide better postoperative analgesia include intravenous patient-controlled analgesia (PCA) and the use of epidural and spinal local anesthetics and/or opioids. Although introduced into the adult population, these techniques are now widely applied across all age ranges in pediatric patients. PCA involves the self administration of small doses of opioids to obtain and mataintain analgesia. Analgesia occurs when the plasma opioid concentration reaches the minimum effective analgesic

concentration (MEAC). With PCA, patients titrate the opioid to their own MEAC and can thereby maintain consistent analgesia.[113-115] Numerous studies have demonstrated improved analgesia, fewer adverse effects, and decresed opioid consumption with the use of PCA. Prior to the initiation of PCA, the patient receives a loading dose of the opioid administered either intraoperatively or postoperative as multiple small doses of an opioid to achieve the MEAC. Once this is accomplished, the PCA is started and a dose of opioid is self administered at a specific interval or lockout period (generally 5-10 minutes) as needed by the patient. Additionally, a continuous infusion can be added to the PCA regimen although it has been suggested that this negates the safety feature of PCA in which no opioid is delivered if the patient is too sleepy to push the button. With the continuous infusion, opioid is infused regardless of the patient's demand, which may increase the incidence of adverse effects including respiratory depression.

In addition ot the use opioids, acetaminophen and non-steroidal anti-inflammatory agents (NSAIDs) play a significant role in the control of postoperative pain. NSAIDs, acetaminophen, and salicylates act through the inhibition of the enzyme cyclo-oxygenase thereby blocking the synthesis of prostaglandins. In distinction to opioids, these agents demonstrate a ceiling effect so that once a specific plasma concentration is achieved, no further analgesia is provided by increasing the dose. These agents are classified according to their chemical structure as: 1) para-amino phenol derivatives (acetaminophen), 2) NSAID's (ibuprofen), and, 3) salicylates (acetylsalicylic acid, choline magnesium trisalicilate).[116] When considering the para-aminol phenol derivatives, acetaminophen has a significant role in the management of acute pain while phenacetin is no longer used given its potential toxicity profile (renal papillary necrosis). Although currently available only as an oral or rectal medication in the United States, the prodrug (propacetamol) is available in Europe and elsewhere throughout the world for intravenous administration. FDA approval is anticipated soon for the use of intravenous acetaminophen in the United States. Commonly used NSAID's include either ibuprofen for oral

administration or ketorolac for intravenous administration. An intravenous preparation of ibuprofen has recently received FDA approval for the treatment of pain an the control of fever in adults. The reader is referred to reference #116 for a more in-depth discussion of the prostaglandin synthesis inhibitors.

The prostaglandin synthesis inhibitors are used alone for minor pain, combined with weak opioids (codeine or oxycodone) for oral administration to control moderate pain or added to parenteral opioids and regional anesthetic techniques for severe pain. In the last scenario, their use does not replace opioids or neuraxial techniques, but rather provides adjunctive analgesia thereby lowering the total amount of opioid required. As the majority of opioid-related adverse effects are dose-related, modalities that decrease total opioid consumption play a significant role in decreasing or preventing opioid-associated adverse effects. When used for this purpose, the prostaglandin synthesis inhibitor is administered around-the-clock and not on a prn basis.

Regional anesthetic techniques including either neuraxial blockade (epidural or spinal analgesia) or peripheral nerve blockade can be continued into the postoprative period to provide effective analgesia while avoiding the potential adverse effects associated with parenteral opioid therapy. Epidural and spinal local anesthetics provide profound analgesia; however, undesirable side effects of the use of high concentrations of local anesthetics include blockade of the sympathetic nervous system with hypotension, urinary retention, blockade of motor function, and risks of local anesthetic toxicity from systemic absorption. Epidural and spinal opioids can provide intense, segmental, localized analgesia without sensory, motor, or sympathetic nervous system effects although their adverse effects profile may include respiratory depression, nausea, pruritus, sedation, and urinary retention. As a result, a combination of low-dose epidural local anesthetics and opioids are commonly used to take advantage of their synergistic effects and limit the side effects of each. Fentanyl and morphine are commonly used opioids, and bupivacaine is the usual local anesthetic of choice. The lipid solubility of the opioid

predicts its clinical behavior. Fentanyl is very lipid soluble, penetrating the dura and rapidly binding to spinal cord opioid receptors, producing a fast onset of action but a short duration of action. Significant vascular absorption of fentanyl also occurs, decreasing its epidural effect and reducing its advantage over parenteral administration. Morphine is lipid insoluble and has a slower onset of action, but a much longer duration of action.   However, given its hydrophilic nature, morphine remains in the cerebrospinal fluid for a longer period of time with cephalad spread and the risks of delayed respiratory depression for up to 24 hours after neuraxial administration thereby mandating ongoing monitoring of respiratory function during this time. Other methods of postoperative analgesia include the use of long acting local anesthetic agents for either wound infiltration or peripheral nerve blockade. Examples of peripheral nerve blockade include brachial plexus blocks for upper extremity pain, femoral nerve blocks for femur and knee surgeries, sciatic nerve blocks for analgesia below the knee, and intercostal nerve blocks for thoracic and abdominal surgeries. Options include the placement of a catheter to allow for a continuous infusion during the postoperative period and provide long-term analgesia for up to 3-5 days.

Conclusions

The perioperative care of pediatric patients begins dwith the preparation of the operating room site as well as the preoperative evaluation of the patient. The complexity of the latter varies tremendously based on the presence of co-morbid conditions. These co-existing conditions as well as the requirements of the surgical procedure influence the techniques used for intraoperative monitoring. In its simplest form, a general anesthesia includes amnesia, analgesia, muscle relaxation, and attenuation of the sympathetic nervous system's response to surgical trauma. The phases of general anesthesia include induction, maintenance, and emergence. The induction of anesthesia can be carried out with the intravenous administration of an anesthetic agent or via the inhalation route with an inhalational anesthetic

agent such as sevoflurane. In pediatric patients, the inhalation induction of anesthesia is frequently chosen to avoid the need for obtaining intravenous access on an awake child. Following anesthetic induction, one progresses into the maintenance phase of general anesthesia. This may include the administration of intravenous agents, inhalational agents or most likely, the a combination of the two. Following the successful completion of the surgical procedure, a plan is determined for the postoperative delivery of analgesia including some combination of intravenous opioids, agents to inhibit prostaglandin formation or a regional anesthetic technique. For complex surgical procedures, tracheal intubation and mechanical ventilation may be continued into the postoperative period while tracheal extubation and resumption of spontaneous ventilation is the general rule for the majority of surgical procedures. Regardless of the type of anesthesia administered, close monitoring of hemodynamic and respiratory function is continued into the postoperative period either in the ICU or a specialized post-anesthesia care unit.

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Table 1: American Society of Anesthesiologists (ASA) Physical Status Classification

Classification	*Description*	*Example*
1	Normal healthy patient	-------------------------
2	Mild systemic disease with no functional limitation	Mild asthma, acyanotic congenital heart disease (atrial septal defect)
3	Severe systemic disease with functional limitation	Sickle cell disease, cystic fibrosis, palliated cyanotic congenital heart disease
4	Severe systemic disease that is a constant threat to life	Advanced stages of muscular dystrophy, cyanotic congenital heart disease with pulmonary hypertension
5	Moribund patient not expected to survive without operation	Perforated bowel with sepsis and shock
6	Brain-dead patient; organs are being removed for donor purposes	---------------------------------
E	Emergency operation	------------------------------------

Table 2: Types and Uses of Premedications

Type of medication	Purpose
Benzodiazepine	Sedation, anxiolysis, amnesia – eases parental separation
Alpha$_2$-adrenergic agonists (clonidine, dexmedetomidine)	Sedation, anxiolysis – decrease intraoperative anesthetic needs
Opioids	Analgesia during invasive procedures
Anticholinergic agent (atropine, glycopyrrolate)	To prevent bradycardia, blunt airway reflexes, dry secretions
Inhaled β-adrenergic agonists (albuterol) and anticholinergic agents (ipratroprium)	Prevention or relief of bronchospasm
Inhaled lidocaine	Prevent airway reflexes during awake fiberoptic intubation, direct laryngoscopy or bronchoscopy
H$_2$-antagonists, proton pump inhibitors	Decrease pH of stomach contents
Promotility agents such as metoclopramide	Decrease volume of gastric secretions
Anti-emetic agents (scopolamine patch, neurokinin-1 inhibitors)	Prevention of perioperative nausea and vomiting

Table 3: Potency and Half-life of Opioids

Agent	**Potency**	**Half-life**	**Active metabolites**
Morphine	1	2-3 hours	Yes
Meperidine	0.1	2-3 hours	Yes
Hydromorphone	5	2-4 hours	No
Oxymorphone	10	2-4 hours	No
Methadone	1	12-24 hours	No
Fentanyl	100	20-30 minutes	No
Sufentanil	1000	20-30 minutes	No
Alfentanil	20	10-15 minutes	No
Reminfentanil	100	5-8 minutes	No