Orthopaedic Anesthesia
Part 1. Commonly Used Anesthetic Agents in Orthopaedics

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Abstract
Anesthesia is a broad discipline; for orthopaedic applications, the type and location of the planned orthopaedic procedure is important in the selection of the most appropriate anesthetic agent and technique. The purpose of this overview is to: 1. highlight the role of several anesthetic agents commonly used in an orthopaedic setting and 2. to familiarize the orthopaedist with those techniques of regional anesthesia that have implications for emergency rooms and other ambulatory settings. Because the subject matter is expansive in scope, it is necessary to address each of the above objectives separately, in two different articles. Part 1 describes anesthetic agents, whereas Part 2 encompasses techniques of administering regional anesthesia.

Throughout both articles, a few terms will resurface as reference points of discussion; understanding these terms will help place the various anesthetic agents and techniques in the appropriate context. Pain is an unpleasant subjective phenomenon with sensory and emotional components and is triggered by actual or potential tissue damage. Analgesia is relief from pain, whereas sedation is depression of awareness and responsiveness. There are two levels of sedation: one in which the patient maintains the airway reflex and the ability to cooperate per the clinician’s requests (conscious sedation); and another in which both of these abilities are lost (unconscious or deep sedation). Anxiolysis, a key element in sedation, is relief from uneasiness. Autonomic reflexes are responses to trauma and are comprised of tachycardia, tachypnea, hypertension, lacrimation, and neuroendocrine responses. Management of these reflexes provides a stable setting for performing medical procedures and decreases patient morbidity and mortality. General anesthesia induces analgesia, sedation, amnesia, suppression of autonomic reflexes, and muscle relaxation, whereas regional anesthesia is more site specific.

Analgesics: Opioids
Acquired from the opium poppy (Papaver somniferum L.), opiates include the natural products morphine and codeine, and several synthetic derivatives, including meperidine and fentanyl (Table 1). Used singly, opiates primarily have analgesic and sedative properties. Although lacking intrinsic amnesic effects, they interact synergistically with sedative hypnotics (e.g., propofol) and are commonly used in such combinations for loss of consciousness and tolerance of
noxious stimuli (e.g., skin incisions, reflexes to airway manipulation).

**Mechanism of Action**

The analgesic effects of opioids are a result of their binding to endogenous endorphin receptors ($\mu, \sigma, \kappa$) in the central nervous system (CNS), and subsequently achieving two objectives: 1. blocking ascending nociceptive pathways\(^1\) and 2. augmenting descending pain inhibitory pathways.\(^2\) Of the first objective, blocking ascending pathways, it is important to note that opioids are very selective for nociceptive pain fibers. These pathways carry noxious stimuli from peripheral receptors to transmitter (T) cells in the spinal cord, which then ascend and relay the information to the brain. Within this pathway, opioids inhibit T cells at the level of the spinal cord. Nociceptive pain is distinct from neuropathic pain, which is elicited by direct injury to neural structures. Since opioids lack amnesic effects, the anesthesiologist may need to administer additional agents to achieve deeper levels of sedation. The second objective, augmentation of descending pain inhibitory pathways, is achieved by diminishing the effects of GABA-ergic fibers that ordinarily suppress this endogenous analgesic system. Once opioids stimulate $\mu$ receptors located in the mesencephalon and medulla, GABA-ergic inhibition is reduced, and the descending fibers are now free to act on T cells that carry ascending nociceptive stimuli through the spinal cord. The result is that tolerance of pain and level of comfort are much improved. Regarding choice of opioid, the decision is governed by minimization of adverse effects, reduction of supplemental drugs, and the desire to achieve rapid titration.

**Morphine**

The oldest, least expensive, and most established member of this class, morphine has a prolonged effect (3 to 4 hours) that makes it ideal for alleviating continuous dull pain associated with traumatic injuries or lengthy invasive procedures that require systemic analgesia. The main drawback of morphine is the time to analgesic effect, achieved roughly 5 minutes post-administration. This makes morphine more difficult to titrate to pain than other opioid alternatives (e.g., fentanyl). An intravenous loading dose of 0.05 to 0.10 mg/kg, followed by 0.80 to 10.0 mg/hr (titrated to pain) via the same route, is typical.

**Meperidine**

Meperidine (Demerol) has one-tenth the potency of morphine, variable grades of pain relief and no clear advantage over the other opioid alternatives. Meperidine is mentioned here due to its paradoxical popularity in the emergency department. Normeperidine (a metabolite of meperidine) has a longer half-life than its parent molecule and, thus, will quickly accumulate to dangerous levels with repeated dosing, leading to adverse CNS stimulation. Meperidine reaches peak effect 5 to 10 minutes post-administration, with a duration of action of 2 to 3 hours. It can be given in any form, including intravenous, oral, subcutaneous, or intramuscular.

**Fentanyl**

The last opioid considered, fentanyl, has a rapid uptake (30 to 60 seconds) and a short time to peak effect (2 to 3 minutes post-administration), making it easily titratable to pain. Because fentanyl is 7000 times more lipophilic and 100 times more potent than morphine, dosing is comparably lower (1 $\mu$g/kg administered slowly), with sedation often occurring at 3 to 4 $\mu$g/kg. Fentanyl is typically combined with a sedative-hypnotic drug (e.g., propofol) and a muscle relaxant to initiate general anesthesia. When used as an adjunct for maintenance of anesthesia, fentanyl decreases the amount of inhaled agent (e.g., isoflurane, N\(_2\)O) required. Its short duration (20 to 30 minutes), however, necessitates either constant infusion (0.5 to 5.0 $\mu$g/kg/hr) or intermittent boluses (25 to 50 $\mu$g every 15 to 30 minutes). It is important to note, however, that its short duration of action is due to its tendency to redistribute to body fat. In the event that these fat reserves become saturated with fentanyl, as would occur during prolonged infusion, then emergence can become delayed. Although fentanyl has a longer half-life than morphine, because of its redistribution feature, fentanyl is the preferred analgesic agent in procedures of short duration.

**Table 1** Opioid Analgesics, Summary

<table>
<thead>
<tr>
<th>Agent</th>
<th>Onset</th>
<th>Duration</th>
<th>Advantage</th>
<th>Drawback</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>5 minutes</td>
<td>3-4 hours</td>
<td>Great for continuous dull pain, lengthy procedures. Inexpensive. The gold standard in the PACU.</td>
<td>Normeperidine quickly accumulates, elicits side effects.</td>
</tr>
<tr>
<td>Meperidine</td>
<td>5-10 minutes</td>
<td>2-3 hours</td>
<td>Not recommended for routine use.</td>
<td>Short duration requires repeat dosing for maintenance of anesthesia.</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>2-3 minutes</td>
<td>20-30 minutes</td>
<td>Easy to titrate to pain. Ideal for short procedures. Used for synergy with typical induction agents (e.g., propofol).</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) blocking ascending nociceptive pathways

\(^2\) augmenting descending pain inhibitory pathways
Side Effects
The most serious adverse effect of opioids concerns respiration. Depressive effects on central ventilatory drive, mucociliary flow, and respiratory reflexes, renders the patient vulnerable to respiratory tract infections and aspiration pneumonitis. Notable risk factors to this end are high doses (e.g., 20 to 50 µg/kg of fentanyl), co-administration with sedative agents (which also have depressive effects on ventilation), and older patient age. Postoperative nausea and vomiting should also be anticipated due to opioid stimulation of the area postrema of the medulla. In addition, opioids influence central hemodynamic control centers, resulting in bradycardia and hypotension.

Naloxone: An Opioid Antagonist
Like the opioids, naloxone has a strong affinity for the µ receptor, but without the downstream analgesic effects. As a competitive antagonist, naloxone can reverse the effect of opioids within 1 to 3 minutes of intravenous administration, making it the optimal choice for restoring spontaneous ventilation in patients with hypoventilation following opioid administration. The duration of action is short (30 to 60 minutes) and dose-dependent; therefore, repeated dosing may be warranted in the presence of longer-acting opioids. Typically, boluses of 0.5 to 1.0 µg/kg administered intravenously in 2 to 3 minute intervals (for a total of 1.0 to 2.0 µg/kg) will restore ventilation without compromising the desired analgesic effects of opioids.

Table 2  Sedatives, Summary

<table>
<thead>
<tr>
<th>Agent</th>
<th>Onset</th>
<th>Duration</th>
<th>Advantage</th>
<th>Drawback</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>2-3 minutes</td>
<td>60 minutes</td>
<td>Easily titrated. Synergistic interaction with opioids and sedative-hypnotics (e.g., propofol) translates into reduced dosage.</td>
<td>Respiratory depression enhanced when co-administered with agents that also reduce ventilation (e.g., opioids).</td>
</tr>
<tr>
<td>Ketamine</td>
<td>30-60 seconds</td>
<td>15-20 minutes</td>
<td>Wide safety margin, respiration minimally affected, versatile (brief/prolonged procedures), dose dependent therapeutic response.</td>
<td>Hallucinations upon emergence (preventable). Hypertension. Lacrimation.</td>
</tr>
<tr>
<td>Propofol</td>
<td>30 seconds</td>
<td>5-10 minutes</td>
<td>Easy to titrate, can be used for induction, as well as maintenance of anesthesia.</td>
<td>Dose dependent respiratory, cardiovascular depression.</td>
</tr>
</tbody>
</table>

Sedatives: Benzodiazepines, Ketamine, Propofol

In addition to pain relief (i.e., analgesia), depression in awareness is another important component of balanced anesthesia. Common choices to this end are benzodiazepines, ketamine, and propofol (Table 2).

Benzodiazepine Sedation
This group has anxiolytic, hypnotic (i.e., sleep inducing), anticonvulsant, and muscle-relaxing properties that are desired in preoperative, intraoperative (local/regional), as well as postoperative settings. Benzodiazepines are relatively safe and reliable agents of conscious sedation and anterograde amnesia, and they preserve hemodynamic stability.

Mechanism of Action
Benzodiazepines act centrally by binding to GABA$_\alpha$ receptors and altering their structures so that the receptor’s affinity for its ligand, GABA, is enhanced. Subsequent activation causes a chloride influx that hyperpolarizes the membrane, making the cell less excitable. The GABA$_\alpha$ receptor has an intrinsic limit relative to the degree to which its conformation can be altered, and this accounts for the considerable safety margin of benzodiazepines. However, long-term use can result in downregulation of the GABA$_\alpha$ receptors altogether, the basis for the development of tolerance. Flumazenil is an agent that binds to the same site as the benzodiazepines but without eliciting the downstream changes that lead to an increased affinity in receptors for GABA, resulting in flumazenil serving as a benzodiazepine antagonist.

Midazolam
Of the several different benzodiazepines in clinical use (e.g., lorazepam and diazepam), midazolam is the preferred constituent of balanced anesthesia. Relative to the other agonists in this family, midazolam has a rapid onset (30 to 60 seconds, reaching peak effect in 2 to 3 minutes) and a short duration (approximately 60 minutes). Administration is usually in 1 to 2 mg doses, and can easily be titrated to effect every 5 to 7 minutes. Furthermore, its synergistic interaction with other hypnotics (e.g., propofol) as well as opioids, translates into reduced dosage requirements during co-administration. This potentiation effect is particularly advantageous, given how the analgesic actions of opioids nicely complement the sedative and amnesic effects of benzodiazepines.

Side Effects
Although minimal, the most notable side effect of midazolam is its dose-dependent depression of respiration.
This effect can become enhanced when co-administered with other respiratory depressants (e.g., opioids). Because midazolam and its active metabolites accumulate in blood, close supervision is recommended when administering in repeated boluses or via continuous infusion. Undesired effects of midazolam are reversible with the benzodiazepine antagonist, flumazenil.

**Flumazenil: A Benzodiazepine Antagonist**

Flumazenil is a competitive antagonist and takes effect within 2 minutes post-administration, reaching full effect within 10 minutes. Duration of action is dose-dependent, and its half-life is shorter than that of the benzodiazepines. Therefore, the duration of action of the agonist should be used to guide dosing. For adults, 0.1 to 0.2 mg administered intravenously, for a total of 3 mg, is typical (0.02 mg/kg in children). Like the benzodiazepines, flumazenil has a fairly high safety margin.

**Ketamine Sedation**

Ketamine, a phencyclidine (PCP) analog, combines dissociative anesthesia, analgesia, and amnesia into a state called dissociative anesthesia. The dissociative component, which is unique to ketamine, is due to somatic sensory input being prevented from reaching awareness centers in the brain and is marked clinically by nystagmus and a glassy-eyed stare. Although the eyes remain open and the patient is not entirely unconscious, response to very basic commands is minimal. Moreover, its efficacy as a potent pain reliever does not come at a cost of compromising respiration.

**Mechanism of Action**

While the full mechanism of action of ketamine is yet unclear, the following details have been elucidated. The principal mechanism by which ketamine disorganizes thought and memory is by attenuating the response of the NMDA (N-methyl-D-aspartate) receptor to the stimulatory neurotransmitter glutamate. The NMDA receptor is the main excitatory receptor in cortical association areas, and depression of its action results in dissociation and sedation. Although this same mechanism may also account for the analgesic effects of ketamine, interaction with CNS opiate receptors is also believed to contribute to the alleviation of pain. The end effect is a sedative disorganization in thought and memory, as well as relief from nociceptive pain.

Compared to other anesthetic agents, the safety margin of ketamine is relatively broad. As mentioned, respiration is minimally affected. Blood pressure, however, is often increased. In addition to its wide safety margin, another advantage of ketamine over other anesthetics is that it elicits different therapeutic responses depending on the dose used. Low doses induce analgesic and anxiolytic effects that are useful for minor procedures (e.g., debridement and dressing changes); slightly higher doses elicit sedation and amnesia in addition to relief from pain and anxiety, features that are applicable to more involved procedures (e.g., closed reductions); in still higher doses, the combined effects of ketamine enable prolonged surgical procedures.

Although ketamine can be used in multiple settings, including the operating room during general anesthesia, the most common use is in the emergency department or the battlefield for brief painful procedures. To minimize the risk of dose-related adverse effects, a dilute solution of ketamine should be employed (dilute 100 mg/mL of ketamine with sufficient saline or D5W to yield a final concentration of 10 to 50 mg/mL). When used as an adjunct to regional anesthesia, 0.5 mg/kg is commonly combined with a benzodiazepine to minimize adverse effects. During prolonged, painful procedures, an induction dose of 2.0 mg/kg is usually administered intravenously over a span of 60 seconds. At this dose, there exists a potential for impairing airway reflexes, and it would be prudent to have equipment and personnel available to manage the airway (e.g., intubation, ventilation, etc.) in this setting. With this approach, the onset time is approximately 30 seconds post-administration and is marked by glazed eyes and nystagmus. Duration of the effect is approximately 15 to 20 minutes. For maintenance purposes, 0.5 to 1.0 mg/kg administered every 10 minutes is usually adequate, although this can be adjusted as required.

The intramuscular route is also an option for children for whom the intravenous route may be more traumatic. Analgesia alone is elicited at 1 mg/kg using this approach; complete dissociation occurs at slightly higher doses (3 to 7 mg/kg). Onset of action occurs within 5 minutes post-administration and lasts up to 30 minutes. If the response to the initial dose is insufficient, then 2 to 5 mg/kg administered intramuscularly every 10 minutes is appropriate. Compared to the intravenous route, because volume restrictions are a limitation with the intramuscular route, it is best to start with a more concentrated solution of ketamine (100 mg/mL).

**Side Effects**

The most prominent adverse effect of ketamine is that of hallucinations upon emergence. However, co-administration with midazolam or other benzodiazepines attenuates side effects of both agents without compromising desired results. Also, ketamine-related adverse emergence reactions occur less frequently in the pediatric population, making the drug a good choice in this group. Because the above mentioned potential complications are either preventable or manageable, ketamine is a superior agent to other sedatives in emergency cases.

**Propofol Sedation**

Propofol is a sedative-hypnotic, with some amnesic but no analgesic properties. Although it may be co-administered for maintenance of anesthesia, its rapid onset, ease of titration, rapid recovery, fewer postoperative complications (e.g., nausea, vomiting, residual drowsiness), and the fact
that it can be used for short or long procedures has made propofol a more popular choice than benzodiazepines or barbiturates for induction of anesthesia in the ambulatory setting.

Dosing is primarily guided by the weight of the patient and the clinical effect being sought. For a typical adult patient, general anesthesia can be induced with a dose of 2 to 2.5 mg/kg, administered at a rate of approximately 40 mg every 10 seconds. The clinical effect can then be maintained using intermittent propofol boluses of 20 to 50 mg, given as needed, or constant infusion at a rate of ~100 to 200 µg/kg/min (6 to 12 µg/kg/hr).

**Mechanism of Action**

Although the mechanism of action remains largely unclear, it is believed that the sedative-hypnotic effect of propofol is achieved through potentiating the effect of GABA at the GABA<sub>A</sub> receptor. In the hippocampus and the prefrontal cortex, for example, this potentiation and subsequent binding of GABA hyperpolarizes the cell making the release of acetylcholine less likely. Lack of acetylcholine neurotransmission in this region yields a sedative effect.<sup>13,14</sup>

For hypnosis purposes, 2.5 mg/kg IV is typical. Propofol is highly titratable, achieving peak effect about 90 seconds post-administration. Its duration of action spans 5 to 10 minutes. Subhypnotic doses are recommended for inducing amnesia (2 mg/kg/hr) or sedation (0.5 to 1.0 mg/kg/hr). If the patient is premedicated with an opiate or benzodiazepine, then adherence to the lower end of the above-mentioned range is advised. Following the previously mentioned induction doses, 100 to 200 µg/kg/hr will usually suffice for maintenance purposes. This infusion rate can be altered to suit individual needs.<sup>15</sup>

**Side Effects**

One interesting side effect of propofol is pain during injection. This discomfort can be minimized with concomitant administration of intravenous lidocaine (1 mL of a 1% solution). Also associated with propofol is a dose-dependent apnea experienced during induction of anesthesia and can be further increased with concomitant use of opioids. This depressive effect is minimized at doses used for maintenance of anesthesia. Cardiovascular influences are similarly dose-dependent and depressive in nature. Although heart rate remains unchanged, cardiac output and arterial blood pressure both decrease. Again, this effect can be minimized by decreasing the rate of infusion. As a result of these side effects, especially those on respiration, there is current debate regarding the credentials required to safely utilize propofol as a non-anesthesiologist.<sup>16-18</sup>

**Inhalants**

**Nitrous Oxide Inhalation**

Nitrous oxide provides surgical sedation and significant analgesia at concentrations of 25% to 50% (mixed in oxygen). For general anesthesia, a higher concentration (40% to 70%) is required. Although nitrous oxide alone may be adequate for brief procedures, in cases involving moderate to severe pain, its minimal alveolar concentration (MAC) of greater than 100% dictates its use as an adjunct with other agents for both induction and maintenance of anesthesia. When used in this capacity, nitrous oxide reduces the MAC of other inhaled anesthetics.<sup>19-21</sup> The MAC of an inhaled drug is an indicator of its potency and is the concentration of that agent required to block (in 50% of a test population) the ability to voluntarily withdraw in response to painful stimulus. The additive effect of nitrous oxide is not limited to gaseous mixtures and also occurs when co-administered with intravenous propofol, a commonly used induction agent.<sup>22-24</sup>

As mentioned, nitrous oxide can be used to induce general anesthesia. In children, a common means to this end is by combining nitrous oxide with sevoflurane (an inhaled anesthetic agent that will be further described in the discussion to follow). For example, a child can be started on 60% nitrous oxide at a gas flow rate of 6 L/min, and sevoflurane can then be co-administered at steadily increasing concentrations. Once response to verbal commands is lost, intubation and mechanical ventilation can be employed. Time to induction using this approach is approximately 2 minutes although this can be hastened either by increasing the flow of gas or the concentration of sevoflurane.<sup>25</sup> In adults, however, induction of anesthesia is usually achieved using intravenous propofol. This is secondary to the fact that, in contrast to children, the adult patient group has intravenous catheters placed prior to going to the operating room. Induction using intravenous medications is faster than inhalation alternatives.

For maintenance of anesthesia, an often used inhalant mixture is comprised of nitrous oxide and a volatile anesthetic (e.g., isoflurane, desflurane, or sevoflurane). Because of the low solubility of nitrous oxide (blood-gas partition coefficient is 0.47), desflurane, and sevoflurane, recovery from anesthesia is more rapid than other alternatives (e.g., propofol), while the quality of anesthesia is comparable.<sup>26,27</sup> A blood-gas partition coefficient is an indicator of the solubility of an agent given two solvents, blood and air. Drugs with high blood-gas partition coefficients are highly dissolved in blood, which in this case serves as an inactive reservoir that prevents the medication from reaching its intended target: the brain. A coefficient of 0.47 means that at equilibrium a milliliter of blood holds 0.47 times as much nitrous oxide as a milliliter of alveolar gas. Low solubility agents (such as nitrous oxide) rapidly reach equilibration of alveolar, blood, and brain concentrations. This translates into rapid onset as well as recovery once the mask is removed. A rapid time to effect and recovery allows the clinician to easily adjust dosing to fit the patient’s situational needs,
Isoflurane Inhalation

Isoflurane, a volatile anesthetic, is primarily used to maintain general anesthesia. Sedation can be achieved at a concentration of 0.4%, and the MAC for anesthesia is 1.2%. Typically, surgery concentrations range from 1% to 2.5%.

Relative to other volatile anesthetics (e.g., desflurane, sevoflurane), isoflurane has a higher blood-gas partition coefficient (1.4) and, thus, a longer recovery time. This negates one of the main theoretical advantages volatile anesthetics have over intravenous propofol.28

Isoflurane has an onset of 7 to 10 minutes. Its pungent odor is a key impairment to a faster inhalation rate. As is true for the other volatile anesthetics, postoperative nausea and vomiting is a significant adverse effect during the early stages of recovery29 and is one of the main drawbacks of volatile inhalants compared to the propofol alternative.

Sevoflurane Inhalation

Being that this anesthetic is less irritating to the airway and, thus, less cough-provoking than the other volatile inhalants,30 sevoflurane can be used for both induction and maintenance of general anesthesia. Compared to the induction of anesthesia using intravenous propofol, while induction with 8% sevoflurane occurs more slowly, it is less expensive and emergence from anesthesia occurs more rapidly.31 Sedation is triggered at a concentration of 0.6%, while the MAC for anesthesia is 2.6%. Sevoflurane has an onset time of 2 minutes, and, due to a low blood-gas partition coefficient (0.66),32 its time to recovery is equally as rapid.

Desflurane Inhalation

Due to its high vapor pressure, desflurane requires administration through a heated vaporizer to ensure that the agent is fully converted from liquid to gas prior to inhalation. This drug is primarily used for maintenance of anesthesia. As was the case with isoflurane, the pungency of this gas renders it impractical for induction of anesthesia. Sedation is achieved at a concentration of 2.4%, while the MAC for anesthesia ranges from 6.0% to 7.3%.

A blood-gas partition coefficient of 0.4533 (lower than the other inhalant anesthetics described) allows desflurane to not only take effect faster (onset time of 1 to 2 minutes), but allows for a more rapid emergence34 than isoflurane and sevoflurane. The faster emergence time holds true when desflurane is co-administered with nitrous oxide (this combination is compared to an isoflurane-nitrous oxide mixture35 and also when desflurane alone is compared to intravenous propofol).36 The main drawback of desflurane, however, is a higher incidence of postanesthesia nausea and vomiting when compared with isoflurane, sevoflurane, and propofol.28,37

Local Anesthetics

Local anesthetics block voltage-gated sodium channels, thereby impeding axons from generating the necessary action potentials to transmit stimuli from the periphery to the CNS (Table 3). As a result of selectivity for smaller, myelinated fibers that fire at high frequency, local pain and temperature fibers are much more sensitive to these agents than pressure, proprioceptive, and motor fibers.

Based on structural differences, there exists two primary classes of local anesthetics: aminesters and aminomides. The ester group (e.g., procaine) is metabolized in plasma, generating the by-product para-aminobenzoic acid (PABA), which is very antigenic and may explain the relatively higher incidence of hypersensitivity reactions associated with this category of local anesthetics. In contrast to the esters, the amides (e.g., lidocaine and bupivacaine) are metabolized in the liver to inactive agents that are hypoallergenic, and, therefore, seemingly present a fitting alternative. However, a side effect of the amides is vasodilation that requires co-administration of epinephrine in order to produce an effect of useful duration. Preservatives added to either the amide local anesthetic or its epinephrine additive are structurally similar to PABA and elicit adverse reactions similar to those triggered by the ester drugs. Therefore, if a patient is allergic to ester local anesthetics, then a preservative-free amide local anesthetic is the next viable option.38

When considering the extent of area to be anesthetized, the anticipated duration of the procedure, and the optimal

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Local Anesthetics (Lidocaine and Bupivacaine), Summary</th>
</tr>
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<tbody>
<tr>
<td>Agent</td>
<td>Concentration</td>
</tr>
<tr>
<td>----------</td>
<td>---------------</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>1% solution</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>0.25% solution</td>
</tr>
<tr>
<td>0.50% solution</td>
<td></td>
</tr>
</tbody>
</table>

A blood-gas partition coefficient of 0.45 (lower than the other inhalant anesthetics described) allows desflurane to not only take effect faster (onset time of 1 to 2 minutes), but allows for a more rapid emergence than isoflurane and sevoflurane. The faster emergence time holds true when desflurane is co-administered with nitrous oxide (this combination is compared to an isoflurane-nitrous oxide mixture and also when desflurane alone is compared to intravenous propofol). The main drawback of desflurane, however, is a higher incidence of postanesthesia nausea and vomiting when compared with isoflurane, sevoflurane, and propofol. The faster emergence time holds true when desflurane is co-administered with nitrous oxide (this combination is compared to an isoflurane-nitrous oxide mixture and also when desflurane alone is compared to intravenous propofol). The main drawback of desflurane, however, is a higher incidence of postanesthesia nausea and vomiting when compared with isoflurane, sevoflurane, and propofol. Therefore, if a patient is allergic to ester local anesthetics, then a preservative-free amide local anesthetic is the next viable option. When considering the extent of area to be anesthetized, the anticipated duration of the procedure, and the optimal
time to onset of anesthesia, it is important to take note of the following principles that influence the activity of local agents.

**Protein Binding and Lipid Solubility**
Most drugs exhibit an affinity for plasma proteins, either albumin or α1-acid glycoprotein. While an unbound drug can readily equilibrate in terms of concentration between plasma and peripheral tissue levels, a drug that is bound remains in this compartment until released from plasma proteins. Because they are able to elude inactivation by metabolic enzymes in peripheral tissues while being freed incrementally to act at target sites, anesthetic agents that are bound by plasma proteins have a longer duration of action. The prolonged duration of effect of bupivacaine is a direct result of its high affinity for plasma proteins.

The lipid solubility of a drug determines its ability to penetrate the nerve membrane. A lipophilic local anesthetic is more likely to reach its target site than a charged alternative. As a result, the amount of drug required to attain clinical effect is lower, and this translates into improved potency. The potency of bupivacaine reflects its high lipid solubility.

**Dose and Volume**
Generally speaking, as dosage is increased, duration of action is lengthened, and time to onset is hastened. Also, the regional spread of anesthesia is increased when a larger volume of local agent is used. So in an attempt to prolong duration or hasten onset, if the volume of solution administered is increased, then anesthesia over a larger area ought to be anticipated. Alternatively, it is possible to achieve the same objectives (extending the duration and accelerating the onset of anesthesia) by keeping the volume constant and simply increasing the concentration of solution (e.g., from a 1% solution to a 2% solution).

**Additives**
Another idea that deserves mention is that of additives that can be co-administered with local anesthetics, with the intent of altering their activity. Three such agents are aimed at either prolonging the duration or hastening the onset of the block.

Epinephrine elicits vasoconstriction and decreases the rate of vascular uptake of the local agent and, thus, prolongs its duration. Furthermore, by increasing heart rate, epinephrine serves as a marker of inadvertent intravascular injection so that systemic side effects (e.g., central nervous toxicity) can be averted in time. Commercially prepared solutions of local anesthetics (e.g., lidocaine and bupivacaine) with epinephrine are available in 1:100,000 ratios (10 µg/mL) to 1:200,000 ratios (5 µg/mL).

Another commonly used additive, clonidine, also prolongs the duration of action of local anesthetics. Compared to epinephrine, however, its potentiation of bupivacaine is especially longer in duration.10 In terms of dosage, using 0.5 µg/kg avoids side effects without compromising its intended function.

The third additive, sodium bicarbonate, is frequently added to lidocaine. By alkalinizing the local environment, it enables more lidocaine (a weak base) or other similar local anesthetic to exist in an uncharged form. Because the uncharged form is more lipophilic, it readily traverses the nerve cell membrane to provide pain relief of faster onset. A 44 mEq/50 mL solution of sodium bicarbonate is usually mixed with lidocaine in a 1:10 ratio and with bupivacaine in a 1:50 ratio (e.g., 0.1 mL bicarbonate plus 5 mL bupivacaine).

**Anatomy**
The third factor that affects the activity of local anesthetics is the site of injection. Anatomic variations influence the rate of diffusion of the drug through tissues, as well as their uptake and delivery to the intended site by vascular structures. These elements, in turn, impact both the time to onset and the duration of action of the anesthetic agent. Therefore, in order to accelerate the onset of action of a brachial plexus block akin to the same agent administered intrathecally, it is necessary to either increase its dose or co-administer an additive.

Two of the most commonly used local anesthetics are lidocaine and bupivacaine. Although both are potent, lidocaine has a more rapid onset and can be used for local infiltration, in a regional block, or as an epidural agent. Bupivacaine is slower in onset, but is the longer-acting alternative, and by manipulating its concentration, it may be possible to separate motor and sensory blocks.

**Approximate Dosing Guidelines**
Because the following figures have been arrived at by extrapolation from animal experiments, case reports, and clinical experiences, and are not necessarily a product of randomized or controlled studies, it is important to appreciate the potential for variability and, therefore, use these numbers as approximate guidelines rather than conclusive measurements.40 For peripheral nerve blocks, lidocaine is typically employed at concentrations of 1% to 2%, while the analogous range for bupivacaine is 0.25% to 0.50%. For minor blocks involving single nerves (e.g., radial or ulnar nerve blocks), 5 to 20 mL of a 1% lidocaine solution (50 to 200 mg) has an onset of 4 to 7 minutes and a duration of 1 to 2 hours (2 to 3 hours with epinephrine). A similar volume of 0.25% bupivacaine solution (12.5 to 50 mg) has a slower onset of 20 minutes but a longer duration of 3 to 6 hours (4 to 8 hours with epinephrine). For major nerve blocks involving more than one nerve (e.g., brachial plexus blocks or three-in-one block), 30 to 50 mL of 1% to 2% lidocaine solution (with epinephrine) has an onset of 10 to 20 minutes and a duration of 2 to 4 hours. A similar volume of 0.25% to 0.5% bupivacaine has an onset of 15
to 30 minutes and a duration of 6 to 12 hours, although effects lasting as long as 17 to 24 hours have also been reported.41,42 The figures listed have been 70 kg for adults. For children or patients with risk factors (e.g., hepatic impairment, any degree of heart block, or congestive heart failure), doses should be decreased accordingly. The maximal dose of lidocaine is 3 to 5 mg/kg (7 mg/kg when co-administered with epinephrine), up to 300 mg in a single dose. Analogous figures for bupivacaine are 2 to 2.5 mg/kg (3 to 3.5 mg/kg with epinephrine), up to 400 mg in 24 hours.

In terms of adverse effects, local anesthetics can depress the action of the heart by blocking sodium channels, thus resulting in arrhythmias and hypotension. Their effect on the CNS can be either inhibitory or excitatory (if inhibitory fibers are hindered) and lead to seizures. Administering doses beyond the maximum figures mentioned or inadvertent intravascular injection are two modes by which these nonallergic, toxic responses can be elicited.43 Care must be taken with regard to these issues when using local agents.

Disclosure Statement
None of the authors have a financial or proprietary interest in the subject matter or materials discussed, including, but not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony.

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