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Anaesthetic Agents for Advanced Regional Anaesthesia

A North American Perspective

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Contents

Abstract

Interest in the use of regional anaesthesia, particularly peripheral nerve blocks (PNBs) and continuous PNBs, has increased in recent years. Accompanying this resurgence in interest has been the development of new local anaesthetics and additives designed to enhance block duration and quality. This manuscript provides a literature-based review on accepted uses of local anaesthetics and adjuncts for a variety of regional anaesthesia techniques. A brief review of local anaesthetic pharmacodynamics describes the action of these drugs in preventing nerve depolarisation, thus blocking nerve impulses. Toxic adverse effects of local anaesthetics, specifically CNS and cardiac manifestations of excessive local anaesthetic blood concentrations and the direct neurotoxic properties of local

anaesthetics, are discussed generally and specifically for many commonly used local anaesthetics. Clinically useful ester and amide local anaesthetics are evaluated individually in terms of their physical properties and toxic potential. How these properties impact on the clinical uses of each local anaesthetic is explored. Particular emphasis is placed on the long-acting local anaesthetic toxic potential of racemic bupivacaine compared with levobupivacaine and ropivacaine, which are both levorotatory stereoisomers. Guidelines for using ropivacaine and mepivacaine, based on the authors' experience using advanced regional anaesthesia in a busy practice, is provided. Finally, epinephrine (adrenaline), clonidine and other local anaesthetic additives and their rationale for use is covered along with other future possibilities.

Recent advances involving peripheral nerve stimulation techniques and stimulating needles that accommodate perineural catheter placement have renewed interest in limb-specific advanced regional anaesthesia. Regional anaesthesia has developed beyond traditional neuraxial techniques (spinals and epidurals), and now peripheral nerve blocks (PNBs) and continuous PNBs (CPNBs) are commonplace in many institutions. Compared to general anaesthesia with opioid-based perioperative pain management, regional anaesthesia can provide benefits of superior pain control,[1] improved patient satisfaction,[2] decreased stress response to surgery,[3] reduced operative and postoperative blood loss,[4] diminished postoperative nausea and vomiting,[5,6] and, possibly, reduced costs,[7] among other benefits. This article reviews the most common local anaesthetics and adjunct medications used in the performance of regional anaesthesia today, with particular emphasis on medications used for the increasingly popular techniques of PNB and CPNB.

1. Basic Review of Local Anaesthetic Pharmacodynamics

The value of local anaesthetics comes from the ability of these medications to prevent membrane depolarisation of nerve cells. Local anaesthetics block nerve impulses by inhibiting passage of sodium through the sodium channels in the cell membrane, thus preventing depolarisation of the cell. The sodium channel is most susceptible to local anaesthetic binding in the open state and, thus, frequently stimulated nerves tend to be more easily blocked. The ability of a given local anaesthetic to block a nerve is related to the length of the nerve exposed to local anaesthetic, the diameter of the nerve and the presence of myelination. Small or myelinated nerves are more easily blocked then large or unmyelinated nerves. Because myelinated nerves only need to be exposed to local anaesthetic at nodes of Ranvier, a significantly smaller proportion of the myelinated nerve needs to be exposed to local anaesthetic (approximately three consecutive nodes) for successful block.[8]

The structures of local anaesthetics are characterised by having both lipophilic and hydrophilic ends (amphipathic molecule) connected via a hydrocarbon chain. The linkage between the hydrocarbon chain and the lipophilic aromatic ring classifies local anaesthetics as being either ester (-CO- link) or amide (-NHC- link) local anaesthetics. This distinction relates to the site of metabolism for the local anaesthetic and to the potential for it to cause allergic reactions

The functional characteristics of local anaesthetics are determined by the dissociation constant (pK_a), lipid solubility and protein binding. The pK_a

is the pH at which a solution of local anaesthetic is in equilibrium with half in the neutral base (salt) and half in the ionised state (cation). Most local anaesthetics have a pK_a >7.4. Since the neutral base form of the local anaesthetic is more lipophilic it can penetrate nerve membranes faster. As the pK_a of a local anaesthetic rises, the percentage in the ionised state increases and the onset of the block is slowed.[9] Once the local anaesthetic has passed through the cell membrane it is exposed to the more acidic axioplasmic side of the nerve favouring the ionised state. It is the ionised form of the molecule that binds the sodium channel and blocks conduction.

The potency of local anaesthetics is determined by lipid solubility. As lipid solubility increases, the ability of the local anaesthetic molecule to penetrate connective tissue and cell membranes increases, thus the increase in potency.[10]

The duration of action for local anaesthetics is determined by protein binding. Local anaesthetics with high affinity for protein binding remain bound to nerve membranes longer, resulting in an increased duration of action. Binding to serum α1-acid glycoproteins and other proteins also decreases the availability of the drug in the blood, reducing the potential for toxicity in primary organs. The free fraction of local anaesthetic in the blood is increased in conditions of acidosis or decreased serum protein, thus heightening the potential for toxicity.[11]

2. Local Anaesthetic Toxicity

Shortly after Carl Köller introduced cocaine for regional anaesthesia of the eye in 1884 and physicians worldwide began injecting cocaine near peripheral nerves, reports of 'cocaine poisoning' began appearing in the literature. Local anaesthetics are indispensable to the successful practice of regional anaesthesia and physicians who use these techniques must be familiar with the signs and symptoms of local anaesthetic toxicity. Initial excitatory symptoms of local anaesthetic toxicity are manifestations of escalating drug concentration in the CNS, specifically the amygdala. Increasing local anaesthetic concentrations begin to block inhibitory pathways in the amygdala resulting in unopposed excitatory neuron function. This is seen clinically as symptoms of muscular twitching, visual disturbance, tinnitus, light-headedness or tongue numbness.[12] Extreme patient anxiety, screaming or concerns about imminent death have also been proposed as indicators of toxicity.[13,14] As the blood concentration of local anaesthetic increases, without intervention these initial symptoms will progress to generalised tonic-clonic convulsions, coma, respiratory arrest and death.

The cardiovascular system, though significantly more resistant to local anaesthetic toxicity than the CNS, will exhibit arrhythmias and eventual collapse as local anaesthetic concentrations increase. The relationship between the blood concentration of a particular local anaesthetic that results in convulsions and the concentrations needed to cause circulatory collapse is called the circulatory collapse-CNS ratio. As this ratio becomes smaller, the increase in blood local anaesthetic concentration leading to the transition from convulsions to circulatory collapse decreases. Generally, this ratio tends to be small in the more potent, long-acting local anaesthetics (bupivacaine and ropivacaine) compared with intermediate- and shorter-acting drugs (mepivacaine and lidocaine). The more potent a local anaesthetic is, the greater potential it has for causing cardiac depression and arrhythmias.[15]

Local anaesthetics have been shown to be myotoxic *in vivo*, although little evidence is available to support a discussion of the clinical relevance of the phenomenon. Nevertheless, practitioners using local anaesthetic for PNB or CPNB should consider the myotoxic potential of these medications in cases of unexplained skeletal muscle dysfunction. The my-

Table I. Recommended techniques and conditions for minimising the risk of local anaesthetic intravascular injection

Standard monitoring with audible oxygen saturation tone
Oxygen supplementation
Slow, incremental injection: 10–15 seconds every 5mL
Gentle aspiration for blood before injection and every 5mL
Initial injection of local anaesthetic test dose containing at least epinephrine (adrenaline) 5–15μg with observation for heart rate change >10 beats per minute, blood pressure changes >15mm Hg or ECG lead II T-wave amplitude decrease of 25%
Pretreatment with benzodiazepines increases the seizure threshold to local anaesthetic toxicity
Patient either awake or sedated, but still able to maintain meaningful communication with the physician
Resuscitation equipment and medications readily available at all times

onecrosis that can develop is believed to be a result of increased intracellular calcium levels from cell local anaesthetic exposure. The damage is reversible with cessation of the local anaesthetic infusion.[16]

Local anaesthetics have also been demonstrated to be neurotoxic *in vitro*, but the clinical significance of these findings remains theoretical. Kitagawa et al.[17] demonstrated that disruption of nerve cell membranes by highly concentrated local anaesthetics may be due to solubilisation. This is attributed to the detergent nature of local anaesthetics and may cause irreversible injury. Radwan et al.[18] examined the neurotoxicity of lidocaine, bupivacaine, mepivacaine and ropivacaine on growing neurons, demonstrating a collapsing effect by all these agents on neural growth cones, possibly leading to a disturbance in the developing nervous tissue.

A variety of anaesthesia textbooks publish maximum recommended dosages for local anaesthetics in an attempt to prevent high-dose injections leading to toxicity. Because local anaesthetic toxicity is related more to intravascular injection, rather than total dose, some physicians have suggested maximum dose recommendations are irrelevant.[12,19] In the authors' practice, resident anaesthetists or anaesthesiologists are often reminded that it is not a question of 'if' an intravascular injection will occur, just a question of 'when'. With this admonition in mind, prudent practitioners of regional anaesthesia will select techniques designed to minimise intravascular injection while always being prepared with appropriate treatments for its eventual occurrence. The site of local anaesthetic injection also affects the blood concentrations of local anaesthetic realised.[20] Blood absorption of local anaesthetic is greatest from intercostal > caudal > epidural > brachial plexus > femoral – sciatic > subcutaneous > intra-articular > spinal.[12] Taking these factors into consideration, recommended techniques and conditions for local anaesthetic injection are listed in table I.[21,22]

When local anaesthetic toxicity does develop, swift intervention with supportive care can be lifesaving. If symptoms of CNS toxicity are noted, immediate termination of local anaesthetic injection may prevent the development of seizures. Should seizures occur, patient care should include airway maintenance, supplemental oxygen and termination of the seizure with propofol 25–50mg or thiopental sodium 50mg.[22,23] In situations involving local anaesthetic toxicity that lead to cardiovascular collapse, prompt institution of advanced cardiac life support (ACLS) protocols can be lifesaving.[22]

3. Common Local Anaesthetics in Regional Anaesthesia

3.1 Esters

3.1.1 Procaine – pK_a 8.9

Procaine is one of the oldest ester local anaesthetics still in clinical use. It continues to be used for short-duration procedures requiring local anaesthetic infiltration of mucous membranes. Because pro-

caine is rapidly metabolised by plasma cholinesterase within seconds, toxicity is extremely rare even after achieving high serum concentrations.[24] Despite a long history of use in spinal anaesthesia, procaine has fallen out of favour. Studies have shown procaine to produce a poorer quality of spinal anaesthesia and more incidents of nausea than lidocaine.[25,26] In the US, procaine is uncommonly used for spinal anaesthesia and not used for epidural anaesthesia. The low toxicity of procaine allows large volumes of this local anaesthetic to be injected for peripheral nerve blockade. Unfortunately, this local anaesthetic has a short duration coupled with a slow onset, which has reduced its usefulness when compared with other short-acting local anaesthetics such as lidocaine.

3.1.2 Chloroprocaine – pK_a 9.0

Chloroprocaine, like procaine, has a low potential for toxicity because of rapid plasma cholinesterase metabolism. The exceptionally short half-life of the drug in the bloodstream allows practitioners to use high concentrations to overcome the relatively high pK_a and achieve fast onset rates clinically. Chloroprocaine was initially favoured for short-acting epidural anaesthesia, especially in parturients, because of its low toxicity. Initial enthusiasm for the local anaesthetic was tempered in the 1980s when reports of neurological injury following unintended intrathecal injection of chloroprocaine began to appear in the literature.[27,28] Initially, neurotoxicity was attributed to the use of sodium bisulfite as a preservative in early formulations, which has since been removed in current preparations.[28,29] Other authors have disputed this and suggest that neurotoxicity from unintentional intrathecal injection of chloroprocaine is attributable to the local anaesthetic.[30] Notwithstanding the controversy, chloroprocaine continues to be used and studied for both spinal, epidural and intravenous regional anaesthesia applications with clinical success.[28,31-33]

The use of chloroprocaine in PNBs is uncommon because of the short duration of action. Some practitioners will mix chloroprocaine with other longer-acting local anaesthetics, such as bupivacaine, when a block that sets up quickly but is of long duration is desired. Unfortunately, mixtures of this type are often unpredictable and can result in blocks that are significantly shorter than would be expected if long-acting local anaesthetic had been used alone.[34,35] Chloroprocaine, compared with the commonly used lidocaine, may be a better choice for subcutaneous skin analgesia for venous cannulation or regional block needle placement since it is associated with less pain on injection.[36]

3.1.3 Tetracaine – pK_a 8.6

The development of tetracaine was based on the recognition that lipid solubility was related to potency and duration of action in local anaesthetics. Modification of procaine with hydrophobic moieties resulted in tetracaine, a molecule 100 times more lipid soluble with a resulting substantial increase in potency.[37] Tetracaine is a popular local anaesthetic for spinal anaesthesia and compares favourably to bupivacaine (also commonly used for spinal anaesthesia) with a faster onset time and a higher spinal level spread of anaesthesia with no difference in haemodynamics.[38] Tetracaine has also been shown to be efficacious for infant (including premature infant) spinal anaesthesia as an alternative to general anaesthesia.[39] Tetracaine is more neurotoxic in the rabbit intrathecal space than other long-acting local anaesthetics (bupivacaine and ropivacaine).[40] It has also been associated with cauda equina syndrome in patients when concentrations >1% are used for spinal anaesthesia.[41] Interestingly, compared with other long-acting local anaesthetics, tetracaine does not appear to have any selective cardiac toxicity, even with large dosages and seizure activity.[37] Other regional anaesthesia uses for tetracaine include skin analgesia with 4% tetracaine gel (amethocaine – approved in Europe but not the US),[42] ophthalmo-

logical procedures,[43] nasal surgery[44] and other topical applications. Dose limits (100mg for an average adult) restrict the usefulness of tetracaine for epidural or PNBs because of the larger volumes typically needed for these blocks.

3.2 Amides

3.2.1 Lidocaine – pK_a 7.7

With a low pKa and moderate water and lipid solubility, lidocaine is the most versatile and widely used local anaesthetic. Subcutaneous infiltration of lidocaine is the favoured analgesic technique for many percutaneous procedures (such as venous cannulation).[45] Despite a long history of being selected as the preferred agent for short-duration spinal anaesthesia, intrathecal lidocaine use has become controversial. In 1993, Schneider et al.[46] described severe radicular back pain following a hyperbaric lidocaine spinal anaesthetic, which would subsequently be termed transient neurologic syndrome (TNS). Since this first description, multiple clinical studies have reported on the increased incidence of TNS following intrathecal lidocaine, and a review of 14 trials (1349 patients) concluded that the risk of TNS following spinal anaesthesia with lidocaine was significantly higher than with bupivacaine, prilocaine or procaine.[47] Even with overwhelming evidence documenting the presence of TNS, the mechanism for TNS development in humans remains unknown.[48,49] Although TNS has been reported with other local anaesthetics, because of the compelling evidence linking lidocaine with TNS, authors have questioned the continued use of lidocaine intrathecally, especially when alternative short-acting spinal local anaesthetic solutions are available.[50-53]

Lidocaine 0.5% is the most common local anaesthetic used for intravenous regional anaesthesia.[54] The low pK_a facilitates distribution of the local anaesthetic into the exsanguinated extremity.

With regard to epidural anaesthesia, lidocaine 2% is popular for caesarean sections and other major operations of the abdomen and lower extremities because of its low systemic toxicity, rapid onset and intermediate length of duration. As a result of the low pK_a of lidocaine, a theoretical concern developed in obstetric patients over the possibility that lidocaine (and other local anaesthetics) could pass into the fetus and become sequestered in its ionic form (ion trapping) leading to toxic concentrations. The lower infant pH compared with maternal pH tends to favour lidocaine in its cationic form which does not readily pass through membranes. Although this phenomenon is a consideration when using local anaesthetics in parturients, recent studies have not suggested a clinical significance in terms of fetal outcome.[55,56] In a rat model, epidural injections of lidocaine are significantly less neurotoxic than intrathecal injections.[57] Certainly, less controversy surrounds epidural use of lidocaine.

Lidocaine use for PNB has also been described.[58] Most physicians prefer longer-acting local anaesthetics for PNB, allowing the duration of analgesia to extend well into the postoperative recovery period.

3.2.2 Mepivacaine – pK_a 7.6

Experiments with the piperidine ring of cocaine combined with the xylidine component of lidocaine resulted in the pipecolyl xylidine family of local anaesthetics and led to the development of mepivacaine in 1957. Other modifications of the pipecolyl xylide group subsequently led to the development of bupivacaine (butyl substitution) and ropivacaine (isopropyl substitution).[59] In terms of function and toxicity, mepivacaine is often compared with lidocaine. In dogs, mepivacaine has been shown to be less cardiotoxic than lidocaine.[60] Mepivacaine can be used for infiltration anaesthesia as it has a similar onset to lidocaine but a longer duration. Because of concern over neurotoxicity and TNS associated with lidocaine, mepivacaine has been proposed as an

alternative local anaesthetic for spinal anaesthesia in the ambulatory surgery environments.[61] In a freshwater snail model, mepivacaine was found to be one of the least neurotoxic local anaesthetics tested.[62] Although TNS has been reported in patients following mepivacaine spinals, the incidence is significantly less compared with lidocaine spinals.[53,63] Intrathecal mepivacaine has also been described as an acceptable local anaesthetic alternative for caesarean delivery.[64]

Epidural anaesthesia has been described with mepivacaine.[65,66] Mepivacaine is usually avoided in obstetric epidural analgesia because of accumulation of the drug in the fetus as a result of poor metabolism of mepivacaine by the fetus.[67]

In addition to low toxicity, mepivacaine has other properties that make it an attractive local anaesthetic for intermediate-acting PNB, particularly in high-risk cardiac patients.[68] Mepivacaine has excellent diffusion properties through tissue, allowing block success despite less than optimal needle position.[59] It also produces intense motor block, which is desirable for a variety of surgical procedures such as shoulder surgery.[69] In the authors' practice, mepivacaine is the preferred local anaesthetic to re-establish surgical block via pre-existing CPNB catheters for patients requiring multiple operations. Low toxicity, rapid onset and dense motor block associated with mepivacaine make it attractive for this application.

3.2.3 Bupivacaine – pK_a 8.1

Bupivacaine, with an extensive history of successful use, is the long-acting local anaesthetic to which others are compared. While a bupivacaine block is long acting, it also has the longest latency to onset of block. Bupivacaine is noted for having a propensity for sensory block over motor block (differential sensitivity) at low concentrations.[70] Additionally, placental transfer of bupivacaine is limited by its high pK_a and lipid solubility, favouring its use in obstetric anaesthesia.[71] These factors, as well as the low cost of bupivacaine, compared with newer long-acting local anaesthetics, have established bupivacaine as the long-acting local anaesthetic of choice in many institutions. When long duration analgesia is required, the use of bupivacaine for low volume infiltration or spinal anaesthesia is well established.

Despite the popularity of bupivacaine for regional anaesthesia, its use for large volume techniques such as epidural or peripheral nerve anaesthesia is controversial, particularly after the first reports of prolonged resuscitation following accidental intravascular injection.[72] The recommended dosages of bupivacaine are the lowest of any of the amide local anaesthetics. In dogs, the electrophysiological disturbance and haemodynamic depression associated with bupivacaine was more pronounced and specific than other local anaesthetics at equipotent dosages.[60] Compared with other long-acting local anaesthetics, such as ropivacaine, bupivacaine has been found to be consistently more cardiotoxic in animals[73-75] and humans.[76,77] On the basis of the wealth of information concerning the toxicity of bupivacaine, researchers have concluded that safer long-acting local anaesthetic alternatives exist.[78,79] If patient safety was the only issue (other than cost, convenience or availability) involved in long-acting local anaesthetic selection, the use of less toxic options other than bupivacaine for large volume blocks would seem intuitive. This issue remains controversial.[80]

3.2.4 Ropivacaine – pK_a 8.2

Ropivacaine is chemically similar to both mepivacaine and bupivacaine, but is unique in being the first local anaesthetic marketed as a pure levorotatory stereoisomer rather than a racemic mixture (combination of levo- and dextrorotatory molecules). Levorotatory enantiomers of local anaesthetics are typically less toxic than dextrorotatory enantiomers.[81] Although less cardiac toxic than bupivacaine, concern has been raised that the decreased

potency of ropivacaine may offset any potential benefit of its use. Polley et al.[82] found ropivacaine to be 40% less potent than bupivacaine for labour analgesia; however, an editorial accompanying the article questions these results.[83] Other authors failed to find a difference in labour analgesia provided by bupivacaine or ropivacaine at 0.25% or 0.125% concentrations.[84,85] Both local anaesthetics provide similar postoperative epidural analgesia when combined with morphine following major abdominal surgery.[86] Ropivacaine has also been shown to compare favourably with bupivacaine when used intrathecally for caesarean delivery.[87] The motor block sparing properties associated with ropivacaine spinal and epidural analgesia may be an advantage over bupivacaine use.[87-89]

Ropivacaine potency does not appear to be a significant issue for PNBs. Authors comparing ropivacaine and bupivacaine at similar volumes and concentrations for femoral nerve block have found the local anaesthetics equally effective.[90,91] Both local anaesthetics are equally effective at blocking the lumbar plexus and sciatic nerve, although duration of analgesia was longer (ropivacaine 13 hours, bupivacaine 17 hours) with bupivacaine.[92] Similar results are found in comparative studies of ropivacaine and bupivacaine use in brachial plexus blocks.[93,94] Finally, both drugs are similarly efficacious for patient-controlled continuous brachial plexus block analgesia at home.[95]

Multiple studies have compared ropivacaine with mepivacaine for latency and duration of analgesia in PNB. While mepivacaine latency to surgical block is consistently shorter than ropivacaine, the significantly longer duration of postoperative analgesia associated with ropivacaine favours its use.[96-98]

On the basis of the available information to date, ropivacaine is the safest long-acting local anaesthetic.[99,100] In the authors' practice, ropivacaine is the long-acting local anaesthetic of choice because of its favourable safety profile and efficacy when used in a variety of regional anaesthesias (table II).

3.2.5 Levobupivacaine – pK_a 8.1

Recognition that levorotatory enantiomers of local anaesthetics are less toxic than racemic mixtures led to the development of levobupivacaine, the levorotatory enantiomer of bupivacaine. In isolated perfused guinea pig hearts, the dextrorotatory enantiomer of bupivacaine had a significantly greater tendency to delay atrioventricular conduction time and produce second-degree atrioventricular dissociation compared with levobupivacine.[101] Multiple different animal models consistently indicate that the order of toxicity is bupivacaine > levobupivacaine > ropivacaine.[75,102-104] The difference in toxicity between levobupivacaine and ropivacaine may be clinically insignificant if levobupivacaine is determined to be more potent and longer acting at lower dosages, as some animal and human studies suggest.[105-107] In human volunteers, levobupivacaine and ropivacaine produced similar CNS and cardiovascular effects at equipotent doses and infusion rates.[108] Levobupivacaine has been shown clinically to be equivalent to ropivacaine in terms of duration of analgesia and incidence of adverse effects with both intrathecal and epidural use.[86,109] It has also been used successfully for intravenous regional anaesthesia.[110] Compared with ropivacaine, levobupivacaine has been found equally efficacious for PNB and CPNB, although less levobupivacaine was required to maintain analgesia with continuous infusion.[106,111] Although evidence is mounting regarding the advantages of levobupivacaine compared with ropivacaine, further study is needed before a clear clinical improvement can be determined.

3.2.6 Other Agents

A number of other local anaesthetics (cocaine, benzocaine, etidocaine, prilocaine, dibucaine) have not been included in this discussion because issues of abuse, adverse effects, or limited/specialised

Table II. Standard adult ropivacaine dosages for single injection and continuous regional anaesthesia at Walter Reed Army Medical Center. Information is based on the authors' experience with ropivacaine[a] in a successful and busy regional anaesthesia practice

Regional anaesthesia technique	Adult single injection dose of ropivacaine	Continuous infusion of ropivacaine 0.2%	Patient-controlled bolus rate of ropivacaine 0.2%[b]	Notes
Interscalene	35–40mL of 0.5%	8–10mL	2mL bolus/20 min lockout	Often supplemented with an intercostal brachial nerve block
Supraclavicular	35–40mL of 0.5%	8–10mL	2mL bolus/20 min lockout	Shortest latency block of the brachial plexus
Infraclavicular	35–40mL of 0.5%	10–12mL	2mL bolus/20 min lockout	Catheter techniques less effective than supraclavicular catheters
Axillary	40mL of 0.5%	10–12mL	2mL bolus/20 min lockout	Catheter techniques less common
Paravertebral	3–5mL of 0.5% per level blocked	8–10mL	2mL bolus/20 min lockout	Catheters effective in thoracic region only
Lumbar plexus (posterior approach)	35–40mL of 0.5%	8–10mL	2mL bolus/20 min lockout	Epidural spread is a concern
Femoral	20–30mL of 0.5%	8–10mL	2mL bolus/20 min lockout	Catheter techniques less effective than lumbar plexus catheters
Sciatic (anterior or posterior approach)	20–30mL of 0.5%	8–10mL	2mL bolus/20 min lockout	Proximal approaches to the sciatic nerve preferable for catheters
Sciatic (lateral or popliteal approach)	35–40mL of 0.5%	10–12mL	2mL bolus/20 min lockout	Catheter techniques less common
Lumbar plexus or femoral + sciatic	50–60mL of 0.5% between both sites	5–10mL for both catheters	2mL bolus/20 min lockout on one catheter	Infusion rates divided between catheters based on distribution of patient's pain
Epidural	20–25mL of 0.5%	6–10mL	2mL bolus/20 min lockout	Opioids often added to infusions
Spinal	5–15mg of 1.0%	NA	NA	Opioids often added to injections

a Mepivacaine 1.5% can be used in place of ropivacaine at the volumes noted when a shorter duration block is desirable.

b Occasionally, 5mL bolus per 30-minute lockout is used in selected patients. Generally, total infusion (continuous plus bolus) >20mL/h are avoided.

NA = not applicable.

clinical application preclude their common usage for regional anaesthesia.

4. Regional Anaesthesia Adjuncts and Additives

The safe practice of regional anaesthesia assumes an awake, though possibly sedated, patient who can manifest early signs and symptoms of evolving CNS or cardiovascular local anaesthetic toxicity. Moderate sedation is used by many practitioners to reduce pain and anxiety that many patients perceive during regional anaesthesia procedures.[112] Although a variety of intravenous medications are available for sedation, midazolam, fentanyl and propofol are commonly used. Deep sedation or general anaesthesia is avoided since patient indicators of pending local anaesthetic toxicity are masked. Even moderate sedation with midazolam and fentanyl will degrade the subjective detection of intravenous lidocaine injection by patients.[113] The anaesthetist or anaesthesiologist must skillfully titrate sedation to strike a balance between patient comfort and safety during block placement.

The use of propofol and propofol with ketamine in the operating room following block placement for sedation are increasingly common.[114] Ease of titration and rapid recovery with minimal adverse effects have popularised these medications for sedation complementing the regional block. Remifentanil has also been successfully infused for regional anaesthesia sedation and compares favourably with propofol.[115]

Epinephrine (adrenaline) [1 : 200 000 or 1 : 400 000] is one of the most common local anaesthetic additives. It is combined with local anaesthetics to produce regional vasoconstriction, resulting in block prolongation and reduced plasma concentrations of local anaesthetic. Epinephrine added to local anaesthetics also serves as a marker of intravascular injection during single injection blocks. Accidental intravascular injection is indicated by observation of increased heart rate ≥10 beats per minute, increased systolic blood pressure ≥15mm Hg or decreased ECG T-wave amplitude depression ≥25% associated with as little as 10–15μg of intravascular epinephrine.[116] Epinephrine-containing local anaesthetic 'test dose' injections via epidural and peripheral nerve catheters with gentle aspiration is an accepted method to protect against intravascular placement.[117,118] On the basis of data from animal models, concerns that epinephrine-containing local anaesthetics may potentiate ischaemia following nerve injury or circulatory compromise have caused some physicians to reduce the dose of epinephrine (1 : 400 000) or limit its use to the test dose.[119]

A plethora of local anaesthetic additives have been used to enhance block duration and quality of analgesia. Multiple studies have shown the addition of opioids to intrathecal local anaesthetics prolongs sensory anaesthesia without prolonging recovery from ambulatory procedures.[120-122] The combination of local anaesthetics with opioids for epidural anaesthesia and analgesia is a common practice and has been shown to reduce local anaesthetic requirements in obstetric patients.[32,123] Despite the recognition of opioid receptors outside of the CNS,[124] the addition of opioids to peripheral nerve injections of local anaesthetics has not been successful in improving PNB characteristics.[125,126]

Clonidine is an α_2-adrenoceptor agonist that provides analgesia via a non-opioid receptor mechanism, and it has been shown to be effective in prolonging analgesia in spinal and epidural anaesthesia.[127-129] Some studies have also shown that clonidine is effective in enhancing PNBs;[130,131] however, other investigations have failed to find an effect with single injection axillary blocks using ropivacaine 0.75%[132] or when used with ropivacaine 0.2% for CPNB.[133] Further study is needed to define dose response and adverse effect profiles. Dexmedetomidine, another α_2-adrenoceptor agonist that is eight times more selective for the receptor than clonidine, has been combined with lidocaine to improve analgesia following intravenous regional anaesthesia.[134]

Neostigmine, a cholinesterase inhibitor that produces analgesia by inhibiting the breakdown of endogenous acetylcholine, has been shown to produce analgesia in humans when given intrathecally, but it is associated with significant nausea and vomiting in larger doses.[135,136] The drug has been added to local anaesthetics for obstetric epidural analgesia with less nausea and vomiting, but was not as effective as opioid additives[137] and was associated with mild sedation lasting several hours.[138] Neostigmine does not appear to enhance PNB.[139]

Ketamine is an NMDA receptor antagonist and has been used for epidural analgesia with success, but is not approved for this use in the US.[140,141] When added to ropivacaine for a brachial plexus block, ketamine did not significantly improve the block.[142]

The list of medications that have been used to improve regional anaesthesia continues to grow and includes drugs such as midazolam used intrathecally[143] and tramadol used for brachial plexus block.[144] These drugs as well as others have had varying success. These efforts are laudable since they have the potential to improve patient safety, enhance analgesia and expand the role of regional anaesthesia in perioperative management.

5. Future Possibilities

Regional anaesthesia is a dynamic and rapidly changing practice of medicine as researchers strive to improve its efficacy and safety. One area of active research involves efforts to greatly extend the duration of action of local anaesthetics to days rather than hours. Success in this area would prolong the benefits of local anaesthetic analgesia well into the recovery period, while reducing the need for difficult catheter procedures and expensive electronic pumps.

One approach toward this goal has been the encapsulation of local anaesthetic in liposomes that act as time-release capsules, greatly extending the duration of the block. In one study, intradermal bupivacaine 0.5% analgesia was extended from 1 hour to 19 hours when delivered in the liposomal form.[145] The addition of dexamethasone to the bupivacaine liposome capsules extended the analgesic effect between 1 and 7 days.[146]

Other researchers are exploring antidepressant drugs, known to block neuronal sodium channels, as possible long-acting alternatives to current local anaesthetics.[147] Still others are exploring novel methods to treat local anaesthetic toxicity, such as using lipid infusions to improve resuscitation of dogs from bupivacaine induced cardiac toxicity.[148]

6. Conclusion

This article has summarised the most common anaesthetics as well as the supporting literature defining their use in the practice of regional anaesthesia. Some of the controversies surrounding these medications have also been discussed. A thorough understanding of local anaesthetic and adjunct medication pharmacology is essential for the safe practice of regional anaesthesia. An investment in this knowledge by the anaesthetist or anaesthesiologist will result in a more satisfying regional anaesthesia practice for both physician and patient.

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