Chapter

Current Local Anesthetic Applications in Regional Anesthesia

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Abstract

Complete anesthesia is often described using terminology that pertains to the pharmacodynamic effects of the medications administered. This vocabulary often includes akinesia, analgesia, amnesia and hypnosis. Local anesthesia is more specific and represents the administration of an amide or ester local anesthetic, to affect analgesia, at or around the site of administration. Anesthesiologists employ a breadth of different clinical techniques that utilize local anesthetic medications. These techniques include topical, mucosal, endotracheal, intravenous, peripheral nerve block, epidural, and intrathecal (spinal) administration. Unique to the fields of anesthesiology and pain medicine, however, is the administration of epidural and intrathecal local anesthetic. Together, these routes are jointly referred to as neuraxial anesthesia and are often utilized to facilitate surgical intervention, labor analgesia, or pain therapy. The history of neuraxial local anesthetic administration is rich and intriguing. The anatomy of the spinal cord and surrounding structures is complex and pertinent to the pharmacologic discussion of neuraxial local anesthetic administration. The pharmacodynamic and pharmacokinetic interactions of local anesthetics, when administered via the neuraxial route, are unique and worthy of continued investigation. Much has been studied, but there is still more to be discovered. These topics will be the focus of our discussion.

Keywords: anesthetics, local, anesthesia, conduction, pharmacology, administration and dosage pharmacokinetics, drug-related side effects and adverse reactions, injections, spinal, injections, epidural, epidural space, analgesia, epidural, anesthesia, epidural, ropivacaine, bupivacaine, lidocaine, chloroprocaine

1. Introduction

Anesthesia is often described using terminology that references the pharmacodynamic effects of a medication. This terminology often includes akinesia (loss or impairment of voluntary movement), analgesia (insensibility to pain), amnesia (loss of memory) and hypnosis (any of various conditions that resemble sleep). Local anesthesia is more specific and represents the administration of a medication, typically an amide or ester local anesthetic, to affect analgesia, and possibly akinesia, at or around the site of administration. Anesthesiologists employ a breadth of different clinical techniques that utilize local anesthetic medications. These techniques include topical, mucosal, endotracheal, intravenous, peripheral

nerve block, epidural, and intrathecal (spinal) administration. Unique to the fields of anesthesiology and pain medicine, however, is the administration of local anesthetics via the epidural and intrathecal routes. Together, these routes are jointly referred to as neuraxial anesthesia and are often utilized to facilitate surgical intervention, labor analgesia, or pain therapy. Much has been studied, but there is still more to be discovered. These topics will be the focus of our discussion.

2. Neuraxial anesthesia

2.1 Basic anatomy

To understand the pharmacokinetic, pharmacodynamic, and pharmacotherapeutic activity of local anesthetics in this region, one needs a thorough understanding of neuraxial anatomy. The term neuraxis refers to the axial unpaired portion of the central nervous system. Of great importance to the discussion of neuraxial anesthesia is the spinal cord, nerve roots, and the meninges and vertebral bodies that house and protect them.

2.1.1 Membranes

The spinal cord is surrounded by three protective membranes which delineate potential and actual neuraxial spaces. Listed from outermost to innermost, these membranes are termed meninges and refer to the dura mater, the arachnoid mater and the pia mater. The pia mater directly envelops the spinal cord (**Figure 1**). Epidural refers to the potential space between the ligamentum flavum and the outer surface of the dura mater. Subdural refers to a potential space between the dura mater and the arachnoid mater. The term intrathecal refers to the thecal sac or the dura mater enclosure of the cerebrospinal fluid-filled sub-arachnoid (i.e., sub-arachnoid mater) space. This space remains outside of the pia mater. These spaces are surrounded by the bony architecture created by the vertebrae.

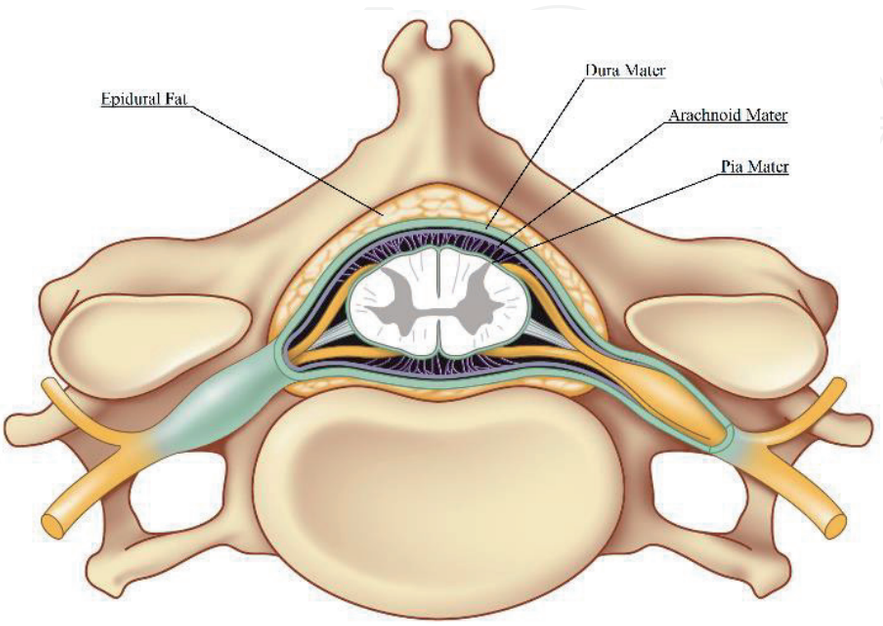

Figure 1.
Meninges—protective membranes of the spinal cord.

2.1.2 Bones and ligaments

The vertebral column protects the spinal cord and provides support for standing and walking. The vertebral column is easily recognized by its three curvatures (cervical lordosis, thoracic kyphosis, and lumbar lordosis) and five sections, to include the cervical, thoracic, lumbar, sacral and coccygeal regions. Each region consists of seven, twelve, five, five, and four vertebrae respectively for a total of 33. Each vertebra consists of two components: a vertebral body and the remaining vertebral arch. The vertebral arch is composed of several components to include laminae, pedicles, spinous, and transverse processes (**Figure 2**). Access to the epidural and intrathecal space for neuraxial local anesthetic administration is obtained via the spaces between each vertebra. Variation in bony structure between lumbar, thoracic, and cervical vertebrae will dictate the approach to these specific regions (e.g., the greater downward angle of the thoracic spinous processes necessitates a steeper midline approach). Between each of the vertebra are several ligaments that are also typically traversed when administering neuraxial local anesthetics. From superficial to deep are the supraspinous ligament, interspinous ligament, and the ligamentum flavum (named for its yellow pigmentation). The interspinous ligament is affixed to the inferior and superior aspect of the spinous processes. The supraspinous ligament attaches to the tips of the vertebral spinous processes (**Figure 3**) and runs from the level of C7 to the sacrum.

2.1.3 Vasculature/adipose tissue

The epidural space contains several anatomic structures and tissues to include vasculature, nerve roots, and adipose tissue. The internal vertebral venous plexus, also known as the epidural venous plexus, assists with vertebral venous drainage and serves as an alternate conduit for venous return in the setting of compromised caval blood flow. The plexus consists of two larger anterior longitudinal veins, located in the anterior aspect of the spinal canal, and two smaller posterior longitudinal veins. These veins are connected by transverse veins, completing the plexus. The longitudinal veins are located more posteriorly at the level of the cervical and lumbar vertebrae, and more posterolaterally at the level of the thorax [1]. The plexus is surrounded by epidural adipose tissue. Combined with reported

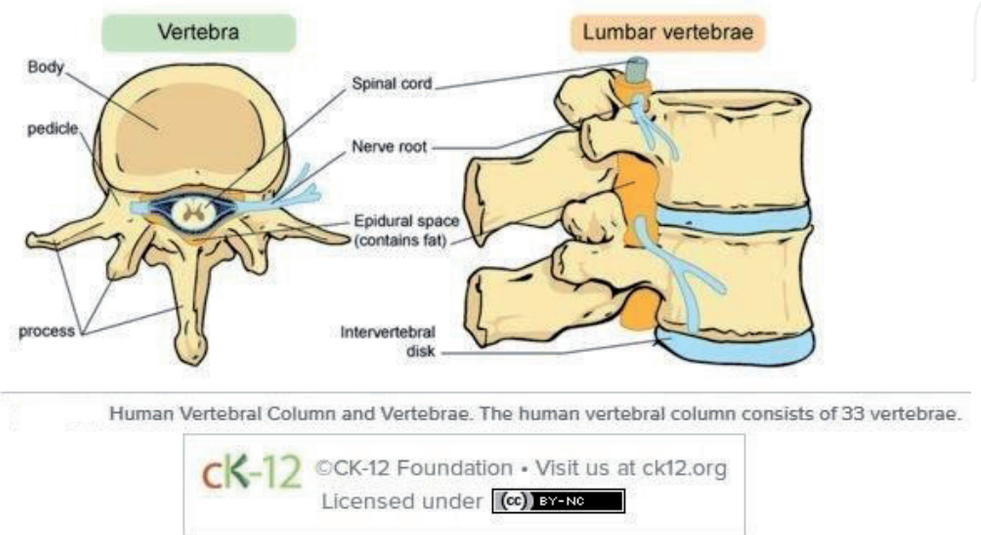

Figure 2.
Human vertebral column and vertebrae. The human vertebral column consists of 33 vertebrae.

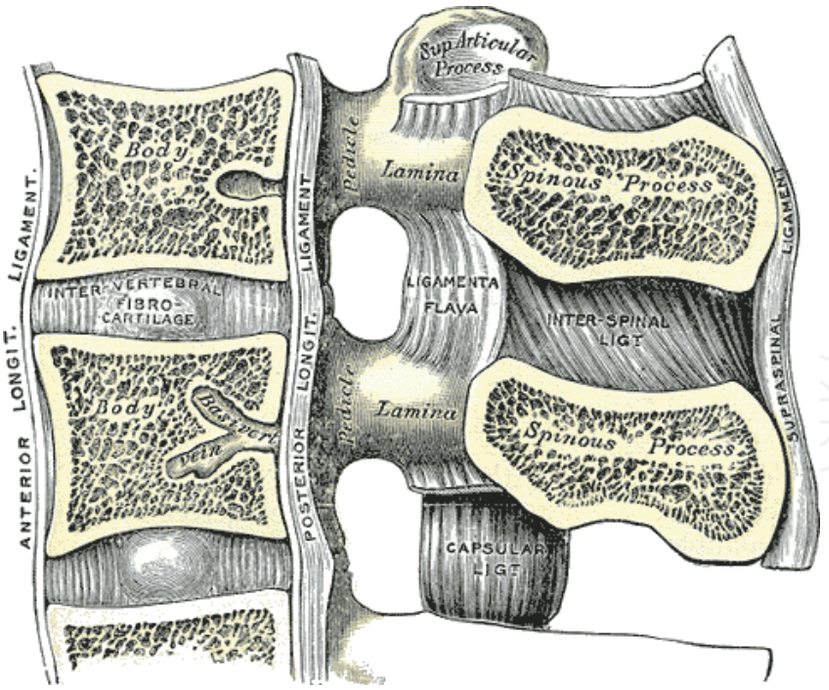

Figure 3.
Spinal ligaments—this file is licensed under the Creative Commons Public Domain Mark 1.0—https://commons.wikimedia.org/wiki/File:Gray301.png.

disruptions in the posterior fusions of the left and right ligamentum flavum, the adipose tissue and vasculature serve to provide variation in the construct of this potential space when expanded by local anesthetic.

2.2 Intrathecal administration

2.2.1 History of spinal anesthesia

Various local anesthetics have been investigated for surgical anesthesia (**Table 1**). These are divided into two primary categories of local anesthetics (i.e., esters and amides). Initial studies began with the investigation of the spinal effects of esters such as cocaine. This was followed by investigation of amylocaine (no longer utilized in clinical practice), procaine (also known as Novocain), dibucaine and tetracaine. Of note, amylocaine was first synthesized circa 1903 and is referenced as the first synthetic local anesthetic to be utilized in spinal anesthesia [2]. This was followed by the synthesis of procaine (circa 1904) with subsequent early twentieth-century investigation into its intrathecal administration. Procaine likely found greater clinical application as a result of the presumed systemic effects (to include physical dependence) and presumed neurotoxic effects of spinal cocaine administration [3]. Of note, however, is the side effect profile of procaine, which commonly includes nausea, vasomotor paralysis, and a greater risk for anaphylaxis associated with its metabolite para-aminobenzoic acid (PABA) [3, 4]. The period of 1930 through the early 1940s saw the discovery and intrathecal employment of longer acting local anesthetics (i.e., dibucaine and tetracaine). In 1930, Jones described his experiences with the administration of dibucaine (also known as cinchocaine or nupercaine) [5, 6]. With a shorter duration of action compared to dibucaine, a more favorable ratio of sensory to motor fiber blockade, less sympathetic blockade than procaine, and less perceived toxicity, initial studies into the administration of tetracaine showed significant promise [7, 8]. In 1945, lidocaine (originally called Xylocaine as it is a xylidine derivative) was initially administered as a spinal anesthetic. As a

Esters	
	Cocaine
	Amylocaine
	Procaine
	Tetracaine
	Chloroprocaine
Amides	
	Dibucaine
	Lidocaine
	Mepivacaine
	Prilocaine
	Bupivacaine
	Articaine
	Ropivacaine
	Levobupivacaine

Table 1.
Local anesthetics for spinal anesthesia.

short-acting amide local anesthetic, its pharmacologic profile was deemed ideal for short to moderate duration operative procedures [9]. Subsequently, in 1946, procaine was used to synthesize chloroprocaine. Initial reports for the use of chloroprocaine for spinal anesthesia were positive [10], and chloroprocaine was approved for spinal anesthesia by the United States Food and Drug Administration in 1955. With rapid ester hydrolysis neutralizing the effects of chloroprocaine, it became the local anesthetic of choice for the fastest onset and fastest resolution of spinal blockade. The rapid ester hydrolysis also created an environment in which almost twice the amount of chloroprocaine could be administered, compared to procaine, without toxicity. The improved safety profile also likely contributed to the popularity of this medication [10]. Despite investigations into other spinally administered local anesthetics, these three local anesthetics (i.e., chloroprocaine, lidocaine, and tetracaine) would find widespread use for short duration, moderate duration, and long duration operative procedures for the next half of a century. Shortly after the approval of chloroprocaine, mepivacaine (1956) [11] and prilocaine (1965) [12] would see their first usage in spinal anesthesia. These two medications, both xylidine derivatives as well, demonstrate similar potency when compared to lidocaine [9]. With subsequent studies demonstrating a risk for the development of transient neurologic symptoms associated with intrathecal lidocaine administration, it would seem that mepivacaine and prilocaine are currently undergoing further investigation and may serve as alternatives to lidocaine for ambulatory or surgical procedures of short to moderate duration [13–15]. The mid-1960s discovery, synthesis, and spinal administration of bupivacaine, an intermediate to long-acting amide local anesthetic, resulted in widespread popular clinical application [16, 17]. When evidence surfaced regarding the potential for racemic bupivacaine toxicity, two (S)-enantiomers of bupivacaine were researched and scrutinized for spinal anesthesia administration. Initial studies utilizing spinal ropivacaine (S-enantiomer of bupivacaine) were conducted in the early 1990s [18–20]. Additional studies regarding the other pure (S)-enantiomer of bupivacaine, levobupivacaine, were initiated in 1999 [21–23]. Intrathecal administration of both levobupivacaine and ropivacaine continue.

2.2.2 Pharmacokinetics of intrathecal local anesthetic administration

The exact mechanism and site of action of local anesthetics in the intrathecal space are not clear. Some evidence suggest that local anesthetics work to directly inhibit Na^+ and K^+ ion channel conduction at the peripheral dorsal nerve root and the spinal cord within the thecal sac [9, 24]. For this to occur, the local anesthetic must be absorbed by the neuron and bind to an intracellular site on the Na^+/K^+ ion channels. This may only occur when the channels are seen in a conformation associated with depolarization. Thus, the activity of local anesthetics is referred to as "use-dependent" activity [25, 26]. Understandably, there are a minimum number of axonal Na^+/K^+ channels which must depolarize to continue the propagation of the neuronal impulse. The term "conduction safety" has been utilized to refer to the overabundance of summation action potential necessary at the axonal regional level to facilitate continued propagation of this impulse. Due to the decreased conduction safety at the telodendron of the axon, as compared to the trunk, it is believed that the local anesthetic blockade has a greater effect in this region [27]. Recognizing the complexity of the neurophysiology of pain, this view of an isolated Na^+/K^+ channel mechanism may be too simplistic [24]. Primary, secondary, and tertiary synaptic activity occurs as sensory input is transmitted from the peripheral nervous system to the central nervous system and ultimately to the primary sensory cortex of the brain. It is widely recognized that neuronal transmission relies on both excitatory and inhibitory post-synaptic potentials for inter-neuronal transmission. Liu et al. summarized the current understanding of the research, which considers a multitude of potential sites for the activity of spinally administered local anesthetics, to include neuronal transmission at the level of the dorsal and anterior horn of the spinal cord [9]. It has been postulated that there may be a role for calcium ion channel manipulation (low voltage and high voltage L-type calcium channels) in this region [28]. Furthermore, it has been proposed that local anesthetics administered in the intrathecal space may contribute to the inhibition of substance P activity at the level of the dorsal root ganglion and the dorsal horn of the spinal cord [29]. Local anesthetics may also contribute to γ-aminobutyric acid inhibitory potentiation resulting in the inhibition of sensory transmission [30].

Even more fascinating is the discussion and research regarding alteration in electrical "coding" by disruption or alteration in "after-potentials" or "after-oscillations." This begins with interruption in neuronal transmission by an incomplete local anesthetic neuronal blockade due to sub-blocking concentrations of local anesthetic. Inhibition of sequential firing, or the depolarization of specific neurons, or disruption of weighted telodendron discharge patterns on a single neuron may contribute to changes in temporal excitability patterns sufficient to disrupt sensory input [27].

The extent of clinical activity depends upon several pharmacokinetic factors which can modify the overall visible clinical effects of the local anesthetic. By report, there are over 25 different factors, some theoretical, which can affect the spread and distribution of local anesthetics within the neuraxis [31]. Patient characteristics include age, height, intra-abdominal pressure, patient position, CSF currents, and CSF volume. Local anesthetic characteristics include potency, dosage, baricity, lipid solubility, degree of protein binding, and the log of the acid dissociation constant (i.e., the pK_a). These local anesthetic characteristics further determine the amount of local anesthetic absorption (neuronal, myelin, adipose, or vasculature) and will ultimately contribute to the observed clinical effect.

2.2.2.1 Cerebrospinal fluid

The intrathecal route of local anesthetic administration is unique in that it bypasses first pass metabolism by the liver and mechanically penetrates the blood-brain

barrier. This deposition into the cerebrospinal fluid generates unique pharmacokinetic considerations. As Greene et al. states, "Uptake of local anesthetic injected into the CSF determines which neuronal functions are affected, elimination from the CSF determines the duration, and distribution within the CSF determines the extent of altered neuronal function" [31]. A discussion of CSF is therefore critical.

Cerebrospinal fluid is maintained within the ventricular system of the brain, to include the cisterns and the intracranial subarachnoid space, as well as the spinal subarachnoid space (i.e., the thecal sac). There is approximately 150 ml of cerebrospinal fluid in the healthy, adult patient. CSF is continuously produced by the choroid plexus, and absorbed via arachnoid villi, at a rate of ~20 ml/h with 400–600 ml of CSF generated daily [32]. Decreased CSF volume at the time of injection increases the concentration of local anesthetic in the administered region and influences the clinical effect. Conditions which increase intra-abdominal pressure, and redistribute CSF, will mimic CSF volume depletion (i.e., obesity, pregnancy, etc.), amplify CSF oscillation, and potentially modify the effects of the local anesthetic as well [33].

2.2.2.2 Absorption, mechanism, onset and duration of action of spinal local anesthetics

The uptake or absorption of local anesthetic into the vasculature also limits the distribution and clinical effects of spinal anesthesia. As vascular absorption is greatest in the epidural space, and the meninges are permeable to local anesthetic, a concentration gradient is established between the spinal cord, intrathecal space, and the epidural space [34]. While there is little intrathecal vascular absorption, some local anesthetic may penetrate the pia mater and be absorbed by vasculature in the spinal cord directly. It is also believed that a more efficient mechanism is vascular absorption via the increased surface area in the perivascular space (where blood vessels perforate the pia mater) [24, 34]. Of additional interest is consideration of the effects that local anesthetics have on spinal vasculature. Bupivacaine and ropivacaine have been shown to decrease spinal blood flow, whereas tetracaine and lidocaine have been shown to increase spinal blood flow [35, 36].

With regard to absorption, local anesthetic must be in an electrically neutral configuration (i.e., as an uncharged hydrophobic form of the medication) to penetrate neuronal tissue. This concept necessitates further discussion of acid dissociation. Becker and Reed provide a summary for reference [37]. In order to maintain stability in solution, local anesthetics are formulated as a hydrochloride salt creating a quaternary amine formulation that is electrically charged to enable water solubility (hydrophilic). The local anesthetic must, therefore, revert to the uncharged lipophilic (hydrophobic) tertiary amine form for neuronal penetration (i.e., the electrically neutral form). The more a local anesthetic dissociates and releases hydrogen ions at the body's physiologically neutral pH of 7.4, the more local anesthetic will remain in the tertiary form and the greater the neuronal absorption (**Figure 4**). Understanding the resting pH of the medication is useful, as is understanding hydrogen ion dissociation. The dissociation equilibrium between hydrogen ions and the deprotonated local anesthetic constitutes the equilibrium that determines the K_a (acid dissociation constant) of the drug. It is expressed as a ratio of hydrogen ion dissociation at equilibrium by the following equation:

$$K_a = \frac{[B][H+]}{BH+} \quad (1)$$

K_a values are typically very small (i.e., 1×10^{-3}), making comparison and manipulation more challenging. However, the inverse logarithmic value of the K_a can be utilized to express pK_a. These pK_a values represent the log of the K_a

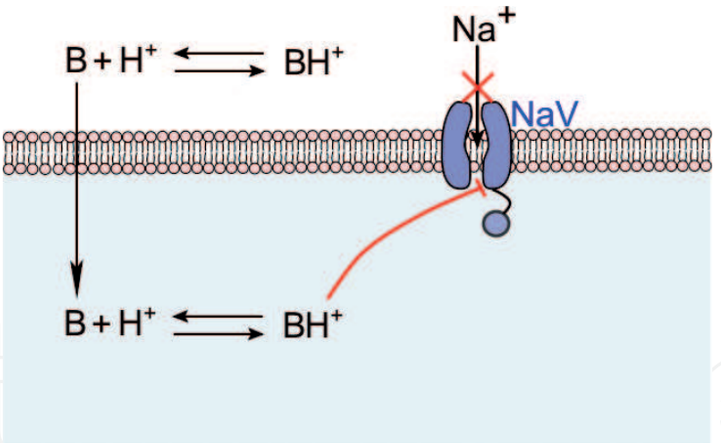

Figure 4.
Mechanism of action of local anesthetics—this file is licensed under the Creative Commons Attribution-Share Alike 3.0 Unported license. https://commons.wikimedia.org/wiki/File:LA_andNaV.svg.

(acid dissociation constant), or the pH at which 50% of the drug is in the protonated electrically charged hydrophilic quaternary amine form, and 50% is in the uncharged, lipophilic tertiary amine form. Values range from 7.6 ➔ ~9.0, meaning that no local anesthetics reach complete equilibrium within the body's normal pH range of 7.35–7.45. The pK_a values for mepivacaine (~7.6), prilocaine (~7.9) and lidocaine (~7.9) most closely approximate physiologic pH, suggesting that their neuronal absorption occurs more quickly, leading to faster onset of clinical symptoms. The pK_a values of bupivacaine (~8.1) and ropivacaine (~8.1) have a somewhat slower onset of clinical effect [37].

In addition to neuronal and vascular absorption, the lipid absorption of a local anesthetic also plays a role in the time of onset—the greater the lipid solubility, the faster the myelin/neuronal penetration. As reported by Becker and Reed, however, this appears only to be true in vitro. They hypothesize that the higher lipid solubility "may impede dispersion throughout tissue fluids." When applied in vivo, the lipid solubility appears to promote adipose tissue absorption over neuronal absorption leading to a delayed onset of clinical effect [37]. This helps to explain the clinically observed pharmacologic effects of long-acting local anesthetics (i.e., bupivacaine/ropivacaine/tetracaine) versus shorter-acting local anesthetics such as lidocaine and mepivacaine. Lidocaine and mepivacaine have a much faster onset of action compared to bupivacaine and ropivacaine when administered intrathecally (despite the increased lipid solubility of bupivacaine/ropivacaine).

The pharmacokinetic variable that appears to have the greatest influence on the duration of action is the degree of intrathecal protein binding. Clement et al. demonstrated that the non-protein bound or unbound fraction of intrathecal bupivacaine is lower than lidocaine. Because bupivacaine has a higher degree of protein binding, it has a longer observed clinical effect [38].

2.2.3 Pharmacodynamics of intrathecal local anesthetic administration

The nature of the surgical procedure, or site of pain origination, will dictate pursuit of a specific distribution of anesthesia. The distributed effect of intrathecal local anesthetic administration is often measured via perceived differences in sensation of temperature or sharp tactile stimulation. Each spinal nerve provides a specific anatomic distribution of sensation, or dermatome, which may be measured. In addition to the desired clinical sensory blockade, pharmacodynamic effects may be seen throughout several organ systems to include the cardiovascular, respiratory, gastrointestinal, renal, and immune systems.

2.2.3.1 Cardiovascular

Undoubtedly, the spinal administration of local anesthesia can result in hypotension. This is largely believed to be secondary to a sympathetic nervous system blockade in the region of the pre-ganglionic neuron prior to its synapse on the sympathetic chain ganglion. This blockade results in vascular dilation, which produces a decrease in systemic vascular resistance (SVR) (venous > arterial). This decrease in SVR, and the associated decrease in preload, may stimulate a reflexive baroreceptor response increasing the heart rate to maintain cardiac output. However, it has been well reported that patients may also experience a different type of cardiac reflex known as the Reverse Bainbridge (atrial), or Bezold-Jarisch reflex (ventricular). These reflexes stem from the recognition of a decreased preload to either the atria or ventricle, which results in reflexive bradycardia to slow the heart and allow for increased filling time. This ultimately results in a lower cardiac output.

Additionally, the distribution of local anesthetic can block cardiac accelerator fibers which stem from thoracic sympathetic ganglia T1-T4, further preventing the reflexive cardiac baroreceptor response. Due to the complexity of these interacting variables, changes to cardiac output with spinal anesthesia are also variable. Ultimately, spinal anesthesia often results in a decrease in mean arterial pressure (MAP), though this is not necessarily true for pre-eclamptic patients with non-sympathetically mediated elevations in blood pressure. When untreated, depressed cardiovascular effects may result in decreased cerebral perfusion, nausea/vomiting, and cardiovascular collapse.

2.2.3.2 Respiratory

In 1991, Steinbrook et al. investigated the effects of spinal lidocaine and bupivacaine on resting pulmonary function in eleven volunteers. They identified a slight decrease in end-tidal CO_2 (34 mmHg ➔ 31 mmHg) with an inverse age correlation (i.e., younger patients had a greater drop in end-tidal CO_2). They reported the absence of significant change in tidal volume, respiratory rate, and minute ventilation, hypothesizing instead an increase in dead space ventilation associated with spinal administration. They further comment on the paralysis of abdominal musculature leading to an increase in chest wall compliance and a decrease in mechanical work of breathing. It is interesting to note their comments regarding increased chest wall compliance and increased respiratory frequency variation [39]. Of note, they also allude to spinal level deafferentation of the chest wall receptors, but make no specific reference to intercostal involvement.

2.2.3.3 Renal

It is well recognized that the kidney receives direct sympathetic innervation from renal sympathetic nerve fibers derived from the sympathetic chain ganglia. In addition, the kidney auto-regulates its blood flow utilizing humoral/endocrine factors released as a result of changes sensed in the macula densa. It is believed that this mechanism functions both interdependently and independently from sympathetic function, enabling the preservation of renal blood flow in the absence of sympathetic directive. As described by Smith et al. [40], "It is possible to assume that the renal vascular bed acquires autonomy de novo only as a consequence of denervation, but in view of the rapidity and smoothness of anesthetic denervation any such assumption seems quite superfluous." It is now understood that there is little effect on overall renal function as a result of spinal or epidural sympathetic blockade from local anesthetic administration. Glomerular filtration and renal blood flow are recognized to only decrease slightly in direct relation to decreases in mean arterial pressure associated with the sympathetic blockade [40–42].

2.2.3.4 Digestive

Sympathetic nervous system blockade as a consequence of spinal local anesthetic administration leads to unimpeded parasympathetic nervous system activity and gastrointestinal hyperactivity. Hypotension encountered as a result of spinal local anesthesia may lead to gastrointestinal ischemia and the release of emetogenic substances such as serotonin. Furthermore, hypotension may lead to hypoperfusion of the area postrema of the medulla (brain stem—known chemoreceptor trigger zone for vomiting) resulting in increased serotonin release. The combination of these factors may contribute to intraoperative/postoperative nausea and vomiting. It is also important to recognize that hypotension associated with spinal local anesthetic administration may result in hypoperfusion of the liver. Because hepatic blood flow is not auto-regulated, this low perfusion pressure may result in impairment of metabolic functions to include subsequent drug metabolism [43].

2.2.3.5 Immune

Regarding the anti-inflammatory and immunomodulatory effects of local anesthetics, Cassuto et al. wrote that it is well recognized that the innate and adaptive immune systems contribute to the destruction of foreign substances and tissue repair following injury. The immune cells involved in these processes include neutrophils, macrophages, monocytes, mast cells, T-cells, and B-cells. These cells must undergo chemotactic targeting to the area of injury, adhere to blood vessel walls, traverse the blood vessel wall into the tissue, engulf the offending agent, and destroy it. Local anesthetics have been thought to interfere with every step of this process. They inhibit leukocyte adherence to the vascular endothelium by possibly interrupting interactions between leukocyte cell membrane integrins and their receptors (cellular adhesion molecules—CAMs) expressed on the vascular endothelium. Similarly, they inhibit the trans-endothelial migration and motility of leukocytes and may interfere with the "priming" of leukocytes, preventing their full pathogen-destroying capability by decreasing their free radical production. It has been suggested that local anesthetics further interrupt the normal cellular actomyosin filament activity resulting in disruption of the ability of the leukocyte to modulate the cell membrane to engulf the offending agent for lysosomal destruction. Furthermore, local anesthetics are responsible for a dose-dependent decrease in the release of lysosomal enzymes [44, 45].

Of additional interest are the anti-inflammatory properties of local anesthetics that are believed to stem from their inhibition of arachidonic acid derivative synthesis, their release of histamine, and their attenuation of cytokine release (i.e., IL-1, IL-6, IL-8, TNF-alpha, etc.). Inhibition of phospholipase A2 synthesis prevents arachidonic acid cleavage; inhibition of prostaglandin E1/E2 synthesis has been attributed to a potential reduction in inflammatory pain; inhibition of thromboxane A2 synthesis results in decreased platelet aggregation; and inhibition of leukotriene B4 synthesis has been implicated in the reduction of capillary hyper-permeability, resulting in decreased edema formation due to inflammatory plasma extravasation. Based on this aggregate model of cell membrane interference (i.e., ion channel inhibition, cell membrane protein cleavage, cell membrane receptor binding and inhibition, cell membrane actomyosin function disruption, etc.) researchers have targeted investigation of specific local anesthetics for their antibacterial and antiviral effects [44, 46].

2.2.3.6 Factors which effect intrathecal spread

Several factors are considered relevant to the intrathecal spread of local anesthetic. These factors may be divided into three categories: factors specific to the

local anesthetic solution, factors specific to the patient, and factors specific to the procedure itself. All of these have been described in an article by Hocking and Wildsmith which may be referenced for additional information [47].

With regard to the local anesthetic solution, the degree of intrathecal spread is related to the baricity, temperature, viscosity, and dosage of local anesthetic administered. Baricity is the ratio of substance density to CSF density. As such, there are hyperbaric, hypobaric or isobaric (i.e., denser than cerebrospinal fluid, less dense than cerebrospinal fluid, or similar density to cerebrospinal fluid) formulations of local anesthetic solution. Upon injection, baricity affects the caudal versus cephalad spread of solution within the CSF. Baricity, in combination with patient positioning, will ultimately determine the spread and distribution of local anesthetic within the thecal sac. Temperature also affects the density of a local anesthetic solution such that a refrigerated or warmed solution may possess a baricity different from its manufactured specification. Investigations evaluating the additional effect of local anesthetic solution viscosity on intrathecal spread suggest that increased viscosity is associated with increased local anesthetic distribution within the intrathecal space [48]. Finally, there is a relationship between dosage, volume, and concentration. Recognizably, changes in any of these variables influence the others as they pertain to the specific mixture of a local anesthetic solution prepared for administration. Though several studies have been performed to evaluate these factors, dosage seems to have the most significant impact on the intrathecal spread of local anesthetic.

In discussing patient factors, patient height, position, and age all contribute to the spread of intrathecal local anesthetic. Though it may affect spread, gross height is not a reliable characteristic for determination of local anesthetic dosing. Hartwell et al. demonstrated a correlation between vertebral column length and the level of local anesthetic sensory blockade. As a surrogate for height, the authors suggest the use of vertebral column length instead. This recommendation is based on the recognition that there may be patient height differences attributed to differences in extremity length, which have no reference value with regard to thecal sac dimensions or cerebrospinal fluid volume. Regarding thecal sac characteristics, it is recognized that the vertebral column curvatures (and thus variations in thecal sac positioning) influence the intrathecal spread of local anesthetic. The interplay between lumbar lordosis, thoracic kyphosis, and baricity helps to explain the largely "dependent" thoracic distribution of hyperbaric local anesthetic solutions after intrathecal injection and positioning of a patient in the supine position. With regard to baricity, it was demonstrated that the density of CSF varies between patients. CSF in women is less dense than in men. It is less dense in pregnant women than in non-pregnant women and is less dense in pre-menopausal women than in post-menopausal women. This fact has unique importance in that a significant portion of surgeries performed under spinal anesthesia are cesarean sections in pre-menopausal, pregnant women who can be expected to have decreased CSF density. It has been further demonstrated that extremes of age can impact the spread of intrathecal local anesthetic. Veering et al. reported on the increasing length of time required for the maximum upper level of analgesia to be seen with advancing age. This was associated with an inverse onset of motor blockade relationship such that a faster onset of motor blockade was seen with advancing age. Furthermore, the time to peak plasma concentration of local anesthetic was increased, and the total plasma clearance decreased with advancing age [49–52].

Finally, procedural components may have an impact on the distribution of local anesthetic. It is known that the initial pressure generated by the injection of local anesthetic creates waves within the CSF. It was previously believed that generation of additional fluid waves, via a technique known as barbotage, would facilitate greater spread. Several investigations have demonstrated that barbotage does not affect the

ultimate height of the sensory blockade. It may, however, slightly decrease the time to achieve maximum sensory and motor blockade, though this may be of limited clinical value [53–55]. Regarding injection speed and pressure itself, studies have been mixed. It would seem that utilizing increasing speed, and pressure of injection potentially facilitates a greater spread of isobaric local anesthetic with diminishing effects seen with hyperbaric local anesthetic [47, 56]. Lastly, the needle orientation and approach (midline versus paramedian) to the neuraxis may alter local anesthetic distribution. James et al. demonstrated a faster onset of T4 block when the Sprotte needle was inserted with the side eye facing cephalad [57]. Urmey et al., similar to Neigh et al., also reported a higher dermatomal distribution when the side aperture of the needle was oriented in a cephalad manner [58, 59]. To the contrary, Masse et al. reported that the orientation of the aperture of the Whitacre needle did not influence the cephalad spread of hyperbaric bupivacaine in parturients [60]. Stienstra et al. demonstrated that a paramedian approach with steep angle (70–100 degrees from level) was also associated with a greater cephalad sensory blockade [61].

2.2.4 Adverse effects

2.2.4.1 Local anesthetic systemic toxicity

Each local anesthetic has a unique pharmacokinetic profile. This profile dictates the potential for adverse events that may be seen with local anesthetic administration. One of the most concerning adverse effects is local anesthetic systemic toxicity (LAST). Inadvertent vascular administration or changes in vascular absorption may result in a constellation of symptoms, dependent upon the rate of increase in serum concentration and the injection location. Symptoms are typically classified into two groups: central nervous system or cardiovascular. Central nervous system (CNS) symptoms may include dizziness, perioral numbness, tinnitus, metallic taste, agitation, seizures, and coma. Cardiovascular (CV) symptoms, usually seen with increasing serum concentrations, may include dysrhythmias (i.e., tachycardia, bradycardia, and ventricular ectopy), myocardial depression, hypotension, and asystole. It is important to note, however, that CNS symptoms may not be noted prior to the onset of cardiovascular collapse. The potential for local anesthetic toxicity may be conceptualized using a metric estimation of the ratio of CV toxic dose: CNS toxic dose. This ratio is lower (i.e., more potential for cardiac toxicity) for amide anesthetics such as ropivacaine and bupivacaine (with bupivacaine having the lowest ratio and greatest potential for toxicity). This is due in part to its lipid solubility, greater protein binding, and hepatic metabolism [62, 63]. An exact mechanism for LAST has yet to be fully elucidated, but it has been suggested that the ultimate cause is likely a combination of $Na^+/K^+/Ca^{2+}$ ion channel blockade (resulting in myocardial depression) in conjunction with metabotropic intracellular effects. These intracellular effects include a potential mitochondrial translocase inhibition, which may prevent the movement of the acyl portion of fats and ketones into the inner mitochondria for energy processing. This substrate reduction may create a synergistic depression of cardiac function as a consequence of the myocardial reliance on mitochondrial oxidation of fatty acids and ketones for energy [63].

It is important to recognize that certain pathophysiologic states will also affect the toxicity of local anesthetics. These include renal dysfunction, cardiac dysfunction, and hepatic dysfunction. In patients with renal dysfunction, a greater volume of distribution and greater alpha-1 glycoprotein binding would portend a lower free fraction serum concentration. However, there is often a hyperdynamic circulation associated with diminished elimination of the agent leading to a variable serum concentration and recommendations for reduced dosages [63]. Patients with severe heart failure

experience a decreased intravascular uptake portending a lower serum concentration. However, they often experience diminished renal and hepatic perfusion leading to a decreased rate of metabolism and elimination necessitating recommendations for reduced dosages as well. Finally, severe hepatic disease, with its associated decreased hepatic metabolism, necessitates decreased local anesthetic administration to offset the delayed metabolism and elimination of the local anesthetic from the body [63].

Regardless of the manifestation, the key to successful treatment is early consideration of the diagnosis. The development and widespread distribution of lipid emulsion has improved the survival of such cases via a mechanism that includes a combination of reduced tissue binding and improved energetic-metabolic effects. Since the first report of a patient saved by lipid rescue in 2006 [64] case reports and clinical experience have continued to add to the body of evidence suggesting its efficacy.

2.2.4.2 Neurotoxicity

Initial concerns regarding the administration of lidocaine for spinal anesthesia surfaced in the early 1990s. At that time, microcatheters were being employed for the continuous intrathecal administration of lidocaine. A case report in 1991 brought to light the potential for cauda equina syndrome associated with intrathecal lidocaine administration. This was believed to be a result of pooling of high concentration (5%) lidocaine inside the caudal dural sac [65]. Ongoing surveillance and reporting, however, indicated a continuum of symptoms. This was described at the time as Transient Radicular Irritation (TRI) associated with intrathecal bolus lidocaine administration for spinal anesthesia. These symptoms were later reclassified and have come to be better known as Transient Neurologic Symptoms (i.e., the occurrence of sensory radicular neuropathic pain in the absence of motor dysfunction that resolves within 72 h) [66]. Additional studies were performed to evaluate for contributing causes to include concentration, baricity, dosage, and adjuncts (i.e., epinephrine, dextrose, etc.). Furthermore, the occurrence of TNS with alternative local anesthetics, such as bupivacaine, mepivacaine, etc., have been investigated as well.

2.2.4.2.1 Reported incidence of neurotoxicity

According to data presented by Brull et al., the incidence of radiculopathy or neuropathy following contemporary spinal local anesthetic administration is believed to occur in 3.78 out of 10,000 spinal esthetics. They further report that the risk of cauda equina syndrome with spinal anesthesia is less frequent, occurring in ~0.11/10,000, and the risk of permanent neurologic injury is reportedly exceedingly rare [67].

2.2.4.2.2 Neurotoxicity mechanism

The exact mechanism for the occurrence of neurologic injury or production of transient neurologic symptoms is unknown. Recognizably, each local anesthetic has a different pharmacodynamic profile resulting in greater frequency (i.e., lidocaine) versus lesser frequency (i.e., bupivacaine) of neurologic symptoms believed to be secondary to neuronal insult. There has been a suggestion that neurologic symptoms following spinal local anesthetic administration may stem from the local vasoconstrictive properties of the local anesthetic [68]. It is understood that different local anesthetics have different vasoconstrictive effects and that these effects are also dose-dependent. High concentrations of local anesthetic result in vasodilation, whereas low concentrations have a more vasoconstrictive effect [68]. This vasoconstrictive effect at low dose may result in neuronal ischemia. Certainly, there is always the potential for mechanical trauma from the needle or intrafascicular

injection with increased intrafascicular administration pressures leading to neuronal ischemia and injury [65]. This, however, is rare. There is research that suggests the effects of local anesthetics are the result of their impact on intracellular metabolism, such as on the mitogen-activated protein kinase (MAPK) and caspase pathways. It is interesting to note the activation of different MAPK pathways with specific local anesthetics (i.e., tetracaine activates the c-Jun N-terminal kinase pathway versus lidocaine activation of the p38 MAPK pathway) [69]. Furthermore, use of lipoxygenase inhibitors seems to diminish the degree of neuronal apoptosis in response to lidocaine administration suggesting a potential role for inflammatory mediators in the generation of neurotoxicity [69]. Kan et al. further investigated an inflammatory component by demonstrating the ability to regulate levels of caspase-9 and matrix-metalloprotease-3 expression via preemptive incubation with subsequent inflammatory signaling pathway modification. This resulted in decreased apoptosis in response to in vitro neuronal lidocaine administration [70].

2.2.4.3 Other adverse effects

2.2.4.3.1 Hypotension

Hypotension after spinal local anesthetic administration is a well-known direct effect of sympathetic nervous system blockade with venous pooling of blood in the lower extremities. Defining hypotension is as challenging as determining treatment since the literature utilizes different definitions (i.e. <100 mmHg, <90 mmHg, <80% of baseline, etc.) [71]. Numerous studies have evaluated different methodologies for treating this hypotension. Definition and treatment are beyond the scope of this chapter.

2.2.4.3.2 Infectious complications

Historically, and anecdotally, spinal local anesthetic administration has a low reported incidence of infectious complications, and include, but are not limited to paraspinal abscesses, spinal/epidural abscesses, meningitis, arachnoiditis, and systemic inflammation with sepsis. In reviewing the literature for infectious complications, a very low correlating incidence was discovered. Moore and Bridenbaugh, after reviewing 52,112 spinal anesthetics, reported the occurrence of three central nervous system infections (i.e., 0.06 cases per 1000) [72]. In a more recent review, Horlocker et al. reported on the occurrence of two infectious complications out of 4767 consecutive spinal anesthetics which were reviewed (i.e., 0.4 cases per 1000). One case was a disc abscess and the other a paraspinal abscess. Both patients remained neurologically intact after appropriate treatment. Infections associated with spinal local anesthetic injection are infrequent and, as discussed previously, may be due in part to the concentration-dependent antibacterial effects of local anesthetic administration [73].

2.2.4.3.3 Vertebral canal hematoma

The etiology of vertebral canal hematoma after neuraxial local anesthetic administration appears multifactorial with patient-related (i.e., demographics, comorbidities, etc.), medication-related and procedural contributions [74]. Historical demographic data portrays a potential predisposition based upon age and gender [75]. The retrospectively reported incidence of vertebral canal hematoma varies widely and ranges from 1:3600 (seen in patients receiving a spinal local anesthetic for total knee arthroplasty), to 1:200,000 (as seen in obstetric patients receiving an epidural local anesthetic for labor analgesia) [74, 76, 77]. The report on the Third National Audit Project of the Royal College of Anesthetists further suggests a prospective

incidence of 8 vertebral canal hematomas in 707,425 (~ 1:88,000). Interestingly, 46% of these neuraxial blocks were spinals, and there were zero vertebral canal hematomas associated with spinal instrumentation. Recognizably, this complication portends a notably poor prognosis associated with persistent neurologic deficit [78].

2.2.4.3.4 Thermoregulatory disruption

Administration of spinal anesthesia is associated with a disruption in thermoregulation. The threshold for vasoconstriction and shivering in response to hypothermia becomes dysregulated. According to Kurz et al., the threshold for triggering a thermoregulatory response to hypothermia is decreased by ~0.5°C. Temperature is lost more quickly during the initial 30 min after spinal anesthesia (as a result of core-to-peripheral redistribution of heat) when compared to epidural local anesthetic administration. This is believed to be secondary to a lesser degree of autonomic thermal dysregulation in the lower extremities with epidural local anesthesia administration (i.e., failure to obtain a complete blockade with epidural versus spinal local anesthesia administration). This clinical effect garners greater importance when considering the detrimental effects of hypothermia (i.e., wound infection, coagulopathy, delayed arousal from anesthesia, etc.). Though beyond the scope of this chapter, yet still of clinical importance, is the potential additive effect of intrathecal opioid administration on the disruptive thermoregulatory effect of spinal local anesthetic administration [79–81].

2.2.4.3.5 Post-dural puncture headache

The term post-dural puncture headache often refers to a clinical constellation of symptoms seen after penetration of the dura mater. Symptoms include the presence of a transient, self-limited, positional, frontal-occipital headache traditionally believed to occur within 72 h of dural penetration. In addition, patients may complain of nausea (+/− vomiting), dizziness, tinnitus, neck stiffness, or photophobia. Studies indicate a significant association with specific types of needles used for spinal local anesthetic administration. Smaller gauge, pencil point needles (i.e., spinal needles) are less often associated with post-dural puncture headaches, as compared to larger gauge cutting needles (i.e., epidural needles). For this reason, post-dural puncture headache is less often associated with spinal local anesthetic administration, as compared to inadvertent puncture with epidural catheter placement. Historically, treatments focused on bed rest, hydration, caffeine, and analgesics to include acetaminophen and NSAIDs. These conservative treatments are not currently supported by evidence of efficacy. The sterile epidural injection of blood (i.e., an epidural blood patch), is recognized as traditional therapy and is effective in providing adequate pain relief in ~65–70% of patients. Optimally, in light of the challenges with treating post-dural puncture headaches, it is best to avoid inadvertent dural puncture. If inadvertent dural puncture occurs, techniques to minimize the likelihood of post-dural puncture headache should be considered [82].

2.2.4.3.6 Hearing loss

Hearing loss after neuraxial local anesthetic administration deserves special consideration. Some providers remain unaware of the potential for this type of transient, self-limited low-frequency sensorineural hearing loss. This type of hearing loss may be as prevalent as 10–50% of all spinal local anesthetic administrations (with such variable reported prevalence due to the limited degree of patient/clinician awareness). Interestingly, it seems the same risk factors for a post-dural

puncture headache apply in the setting of post-spinal local anesthesia hearing loss. According to Sprung et al., the subarachnoid space is contiguous with a small canal in the ear (i.e., the cochlear aqueduct) that transmits cerebrospinal fluid pressure to the inner ear. Sound waves are theorized to be transmitted through the fluid in the middle ear onto the basilar membrane. Changes in transmitted pressure to the middle ear are hypothesized to distort the interpretation of these sound waves through the basilar membrane. Decreases in cerebrospinal fluid pressure, as transmitted through the cochlear canal and into the fluid of the inner ear, is believed to be the mechanism by which patients suffer a loss of low-frequency sensorineural hearing after spinal anesthesia administration [83].

2.3 Epidural administration

2.3.1 Contents and structure of the epidural space

Transitioning to a discussion of epidural local anesthetic administration generates an opportunity for a brief discussion of the epidural anatomy to supplement the anatomy discussed at the beginning of the chapter.

2.3.1.1 Definition/surrounding bony construct

The epidural space is widest posteriorly in the midline and averages about 5 mm between the ligamentum flavum and the dura in the lumbar region. The boundaries of the epidural space are:

Above: the foramen magnum where the periosteal and spinal layers of the dura fuse

Below: the sacrococcygeal membrane

Anteriorly: the posterior longitudinal ligament covering the posterior aspect of the vertebral bodies and the intervertebral discs

Posteriorly: the anterior surfaces of the vertebral lamina and the ligamentum flavum

Laterally: the pedicles of the vertebrae and the intervertebral foramina [1, 84]

Interestingly, spinal nerve root cuffs are identified along the lateral aspect of the epidural space. These have previously been defined as "prolongations of the dura and arachnoid lamina" and are believed to enclose spinal nerve roots within this space. Previously referred to as "dural cuffs," it is now believed that the cuffs include not only the dura mater but the arachnoid mater as well, thus making this previous term inaccurate [85]. This construct may influence the spread of local anesthetic when administered via the epidural route.

2.3.1.2 Adipose tissue

The contents of the spinal canal are cushioned in a packing of fat, through which injected solutions track while spreading to target receptors. This adipose tissue is richly vascularized [86, 87] yet lies mostly unattached in the spinal canal. In the region of nerve roots, collagen concentration increases and coalesces with the fat in the intervertebral foramina. Adipose tissue "competes" for its share of the drug, along with nervous tissue and vasculature, and is an important pharmacologic space and repository. Medications with high lipid solubility and/or lipoprotein binding tend to enter and remain in this tissue, depending on local blood flow, and can impact drug behavior in the epidural space profoundly. This competition with extraneural tissue then generates, when compared to spinal doses, a higher epidural medication dosage requirement [88].

2.3.1.3 Vasculature

Spinal arteries, epidural veins, and lymphatics are all co-inhabitors of this space. Spinal arteries derive from the vertebral, ascending cervical, deep cervical, intercostal, lumbar, and iliolumbar arteries. They lie chiefly in the lateral epidural space. Epidural veins arise from the internal vertebral venous plexus and drain both the spinal cord and the spinal canal. Lying mainly anterolaterally, they pass through the intervertebral foramina on their journey toward the vertebral, posterior intercostal, lumbar and lateral sacral veins. It is through this network that increased pressures (intra-abdominal and intrathoracic) are transmitted to the epidural space [84]. The lack of valves in this system results in the distention of these vessels and a consequent reduction in epidural space volume. The lymphatic network is located anteriorly to the intervertebral foramen and aid in the cleansing of the subarachnoid space, draining to the regional lymph nodes.

2.3.1.4 Rivulets

The interrelationship between the factors that influence epidural blockade and the clinical effect is surprisingly complex. Epidural analgesia is not a simple matter of spinal root or ganglion blockade, but rather is the end state of action at various sites after passage through multiple sites. Unique to epidural local anesthetic administration is the concept of rivulets. Hogan reported the spread of injected ink as "rivulets" through numerous small channels rather than as a unified advancing front [89]. Injection results in circumferential spread anteriorly and posteriorly around the thecal sac. Laterally, epidural solution extrudes beyond the intervertebral foramen following a parallel path along the paraspinous musculature fascial plane [89]. Hogan et al. also noted that the lateral spread of epidural solution sporadically encompassed the more proximal dorsal nerve root prior to the dorsal root ganglion in the "axilla" of the nerve root. This non-uniform distribution of solution, within the epidural space, may then correlate with clinical data suggesting that slow, not fast, injection rates (0.3–0.75 ml/s) result in the most effective spread of analgesia [89]. Undoubtedly, this variation in epidural space content combined with varying spread contributes to the somewhat unpredictable clinical effects seen with epidural local anesthetic administration.

2.3.2 Pharmacokinetics of epidural local anesthetic administration

2.3.2.1 Factors which affect epidural spread

As mentioned above, and contrary to the effects of intrathecal local anesthetic, the complex nature of epidural analgesia is suggested by the lack of relevance of physical factors affecting anatomical spread when compared to the clinically present segmental analgesia.

2.3.2.2 Absorption, potency, duration, onset

Local anesthetics stabilize excitable cell membranes and block sodium and potassium flux through the axonal membrane ion pores. The anesthetic profile and clinical characteristics of a local anesthetic depends on its lipid solubility, protein binding, and dissociation constant (pK_a). Lipid solubility is generally agreed to be the primary determinant of intrinsic anesthetic potency. Protein binding is the characteristic associated with duration of action of the agent since those that attach to protein components of nerve membranes are less likely to diffuse from the site of action to enter the systemic circulation. The pK_a of a compound, as discussed earlier

in detail and defined as the pH at which there is equilibrium between the ionized and unionized states of the molecule, impacts the rate of onset of clinical effect. This value is important for effective anesthesia because the uncharged form of the molecule is essential for epineural diffusion across lipid nerve sheaths and cell membranes. Conversely, only the charged form can dissociate in water and diffuse through cellular fluid and intracellular metabolism [90, 91].

2.3.2.3 Metabolism

The metabolic mechanism of local anesthetics depends on their chemical classification. Amide-type local anesthetics, including ropivacaine, are primarily metabolized by the hepatic esterase activity seen in the P450 system in the liver [92, 93]. Ester-type local anesthetics (procaine, benzocaine, tetracaine) are predominantly hydrolyzed by plasma pseudocholinesterase.

2.3.3 Pharmacodynamics of epidural local anesthetic administration

2.3.3.1 Measuring effects

A discussion of clinical effect should include a comment on the differential blockade. Independent of differences in nerve fiber size and resistance to blockade, local anesthetics have varied differential blockade characteristics. Even within a single agent, the differential blockade can vary. As an example, bupivacaine, one of the best agents at producing effective analgesia while sparing motor loss, loses its motor-sparing characteristics as the bupivacaine concentration is increased from 0.5 to 0.75%.

The mode of action of epidural analgesia is far from clear. Proposed sites of action have included: (1) mixed spinal nerves in the paravertebral space, (2) dorsal root ganglia, (3) spinal roots, and (4) the periphery of the spinal cord. Regardless, blockade of a nerve fiber varies based on the duration of exposure, the exposed length of the axon, the type and site of the axon, and the concentration of local anesthetic at the axonal membrane.

Tachyphylaxis describes the condition of acute tolerance to local anesthetic drugs, though its mechanism is not well understood. The relationship between the change of response and interval between injections is complicated. However, it is likely the interval between the disappearance of analgesia and the subsequently repeated injection of local anesthetic is primary. When it occurs, decreasing analgesic effectiveness is noted, including a decrease in the number of dermatomes blocked as well as a decrease in motor block, showing that all measurable components of anesthesia are affected. Simply, with repeated doses, fewer segments are anesthetized, the duration of action is decreased, and both motor and sensory blockade are less intense [94].

The response to epidural blockade includes both autonomic blockade as a result of sympathetic interruption and somatic pain blockade (similar to intrathecal injection of local anesthetic, but with a greater duration of time to achieve clinical effect). The sympathetic blockade has consequent effects on vascular beds, cardiac functioning, and other visceral structures as discussed previously. Somatic pain blockade provides for the potential of anatomic functional restoration secondary to pain responses. Both results can occur as a consequence of epidural blockade and may be utilized in the operating room, in the labor suite or the pain clinic.

3. Conclusions

In conclusion, the administration of local anesthetic via the intrathecal or epidural route possesses unique pharmacokinetic and pharmacodynamic properties. These

properties are influenced by the complex anatomy of bones, ligaments, membranes, vasculature, and adipose tissue. Understandably, the mechanism of action of local anesthetics is complex with primary Na^+ and K^+ ion channel activity. Additional involvement of Ca^{2+} ion channels, γ-aminobutyric acid, and substance P have been proposed.

Pharmacokinetic variables affecting the clinical picture associated with local anesthetic administration include the protein binding, lipid solubility, and pK_a. Spinal local anesthetic pharmacodynamic effects are variable and influenced by factors that are unique to the local anesthetic solution, factors that are unique to the patient, and factors that are associated with the method of local anesthetic administration. Epidural pharmacodynamic effects are characterized by a lack of relevance of physical factors affecting anatomical spread when compared to the clinically present segmental analgesia. Both spinal and epidural local anesthetic administration are associated with clinical effects that involve the cardiovascular, pulmonary, digestive, renal, and immune systems to varying degrees of significance. Local anesthetic toxicity affects the nervous system and cardiovascular system to varying degrees based on the properties of the individual local anesthetic (i.e., lipid solubility, CV: CNS toxicity ratio, etc.) and the toxic dosage administered. Regardless of the manifestations of toxicity, the key to successful treatment is early consideration of the diagnosis. The development and widespread distribution of lipid emulsion has improved survival and should be considered in all cases where local anesthetic toxicity is a concern.

Conflict of interest

The views expressed in the manuscript are those of the authors and do not reflect the official policy or position of the Department of the Navy, Department of Defense, or the U.S. Government.

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References

[1] Richardson J, Groen GJ. Applied epidural anatomy. Continuing Education in Anaesthesia Critical Care & Pain. 2005;**5**(3):98-100

[2] Barker AE. A report on clinical experiences with spinal analgesia in 100 cases, and some reflections on the procedure. British Medical Journal. 1907;**1**(2412):665-674

[3] Axelrod EH, Alexander GD, Brown M, Schork MA. Procaine spinal anesthesia: A pilot study of the incidence of transient neurologic symptoms. Journal of Clinical Anesthesia. 1998;**10**(5):404-409

[4] Johnson S. Cocaine to procaine: An unexpected history of local anaesthesia. Biomedical Journal of Scientific & Technical Research. 2018;**7**(2):1-4. DOI: 10.26717/BJSTR.2018.07.001467

[5] Jones WH. Percaine: A new regional and spinal analgesic, with special reference to high thoracic nerve root block and a new technique. Proceedings of the Royal Society of Medicine. 1930;**23**(7):919-928

[6] No authors listed. Dibucaine, cinchocaine, or nupercaine? CIBA's Trademarked long-acting amide local anesthetic. Anesthesiology. 2018;**128**(4):753. DOI: 10.1097/ALN.0000000000002165

[7] Lund PC, Rumball AC. Hypobaric pontocaine spinal anaesthesia; 1,640 consecutive cases. Anesthesiology. 1947;**8**(2):181-199

[8] Garth WL. Subarachnoid block with crystalline pontocaine. Anesthesiology. 1941;**2**(2):205-206

[9] Liu SS, McDonald SB. Current issues in spinal anesthesia. Anesthesiology. 2001;**94**(5):888-906

[10] Foldes FF, McNall PG. 2-Chloroprocaine: A new local anesthetic agent. Anesthesiology. 1952;**13**(3):287-296

[11] Dhuner KG, Egner B, Ekenstam BA, Oljelund O, Ulfendahl LR. Trials with carbocaine; a new local anaesthetic drug. British Journal of Anaesthesia. 1956;**28**(11):503-506

[12] Crankshaw TP. Citanest (prilocaine) in spinal analgesia. Acta Anaesthesiologica Scandinavica. Supplementum. 1965;**16**:287-290

[13] Liguori GA, Zayas VM, Chisholm MF. Transient neurologic symptoms after spinal anesthesia with mepivacaine and lidocaine. Anesthesiology. 1998;**88**(3):619-623

[14] Hampl KF, Heinzmann-Wiedmer S, Luginbuehl I, Harms C, Seeberger M, Schneider MC, et al. Transient neurologic symptoms after spinal anesthesia: A lower incidence with prilocaine and bupivacaine than with lidocaine. Anesthesiology. 1998;**88**(3):629-633

[15] Manassero A, Fanelli A. Prilocaine hydrochloride 2% hyperbaric solution for intrathecal injection: A clinical review. Local and Regional Anesthesia. 2017;**10**:15-24. DOI: 10.2147/LRA.S112756

[16] Ekblom L, Widman B. LAC-43 and tetracaine in spinal anaesthesia. A controlled clinical study. Acta Anaesthesiologica Scandinavica. Supplementum. 1966;**23**:419-425

[17] Lund PC, Cwik JC, Vallesteros F. Bupivacaine—A new long-acting local anesthetic agent. A preliminary clinical and laboratory report. Anesthesia and Analgesia. 1970;**49**(1):103-114

[18] van Kleef JW, Veering BT, Burm AG. Spinal anesthesia with ropivacaine: A double-blind study on the efficacy and safety of 0.5% and 0.75% solutions in patients undergoing minor lower limb surgery. Anesthesia and Analgesia. 1994;**78**(6):1125-1130

[19] Wahedi W, Nolte H, Klein P. Ropivacaine for spinal anesthesia. A dose-finding study. Der Anaesthesist. 1996;**45**(8):737-744. DOI: 10.1097/00000542-199801000-00025

[20] Gautier PE, De Kock M, Van Steenberge A, Poth N, Lahaye-Goffart B, Fanard L, et al. Intrathecal ropivacaine for ambulatory surgery. Anesthesiology. 1999;**91**(5):1239-1245. DOI: 10.1097/00000542-199911000-00013

[21] Burlacu CL, Buggy DJ. Update on local anesthetics: Focus on levobupivacaine. Therapeutics and Clinical Risk Management. 2008;**4**(2):381-392. DOI: 10.2147/tcrm.s1433

[22] Alley EA, Kopacz DJ, McDonald SB, Liu SS. Hyperbaric spinal levobupivacaine: A comparison to racemic bupivacaine in volunteers. Anesthesia and Analgesia. 2002;**94**(1):188-193

[23] Glaser C, Marhofer P, Zimpfer G, Heinz MT, Sitzwohl C, Kapral S, et al. Levobupivacaine versus racemic bupivacaine for spinal anesthesia. Anesthesia and Analgesia. 2002;**94**(1):194-198

[24] Olschewski A, Hempelmann G, Vogel W, Safronov BV. Blockade of Na+ and K+ currents by local anesthetics in the dorsal horn neurons of the spinal cord. Anesthesiology. 1998;**88**(1):172-179. DOI: 10.1097/00000542-199801000-00025

[25] Lirk P, Picardi S, Hollmann MW. Local anaesthetics: 10 essentials. European Journal of Anaesthesiology. 2014;**31**(11):575-585. DOI: 10.1097/EJA.0000000000000137

[26] Swadlow HA, Kocsis JD, Waxman SG. Modulation of impulse conduction along the axonal tree. Annual Review of Biophysics and Bioengineering. 1980;**9**:143-179

[27] Raymond SA. Subblocking concentrations of local anesthetics: Effects on impulse generation and conduction in single myelinated sciatic nerve axons in frog. Anesthesia and Analgesia. 1992;**75**(6):906-921. DOI: 10.1213/00000539-199212000-00008

[28] Sugiyama K, Muteki T. Local anesthetics depress the calcium current of rat sensory neurons in culture. Anesthesiology. 1994;**80**(6):1369-1378. DOI: 10.1097/00000542-199406000-00025

[29] Li YM, Wingrove DE, Too HP, Marnerakis M, Stimson ER, Strichartz GR, et al. Local anesthetics inhibit substance P binding and evoked increases in intracellular Ca2+. Anesthesiology. 1995;**82**(1):166-173. DOI: 10.1097/00000542-199501000-00021

[30] Nordmark J, Rydqvist B. Local anaesthetics potentiate GABA-mediated Cl- currents by inhibiting GABA uptake. Neuroreport. 1997;**8**(2):465-468

[31] Greene NM. Distribution of local anesthetic solutions within the subarachnoid space. Anesthesia and Analgesia. 1985;**64**(7):715-730

[32] Sakka L, Coll G, Chazal J. Anatomy and physiology of cerebrospinal fluid. European Annals of Otorhinolaryngology, Head and Neck Diseases. 2011;**128**(6):309-316. DOI: 10.1016/j.anorl.2011.03.002

[33] Higuchi H, Hirata J, Adachi Y, Kazama T. Influence of lumbosacral

cerebrospinal fluid density, velocity, and volume on extent and duration of plain bupivacaine spinal anesthesia. Anesthesiology. 2004;**100**(1):106-114. DOI: 10.1097/00000542-200401000-00019

[34] Greene NM. Uptake and elimination of local anesthetics during spinal anesthesia. Anesthesia and Analgesia. 1983;**62**(11):1013-1024

[35] Kozody R, Swartz J, Palahniuk RJ, Biehl DR, Wade JG. Spinal cord blood flow following sub-arachnoid lidocaine. Canadian Anaesthetists' Society Journal. 1985;**32**(5):472-478

[36] Kristensen JD, Karlsten R, Gordh T. Spinal cord blood flow after intrathecal injection of ropivacaine and bupivacaine with or without epinephrine in rats. Acta Anaesthesiologica Scandinavica. 1998;**42**(6):685-690

[37] Becker DE, Reed KL. Essentials of local anesthetic pharmacology. Anesthesia Progress. 2006l;**53**(3): 98-108. DOI: 10.2344/0003-3006(2006)53[98:EOLAP]2.0.CO;2

[38] Clement R, Malinovsky JM, Le Corre P, Dollo G, Chevanne F, Le Verge R. Cerebrospinal fluid bioavailability and pharmacokinetics of bupivacaine and lidocaine after intrathecal and epidural administrations in rabbits using microdialysis. The Journal of Pharmacology and Experimental Therapeutics. 1999;**289**(2):1015-1021

[39] Steinbrook RA, Concepcion M. Respiratory effects of spinal anesthesia: Resting ventilation and single-breath CO_2 response. Anesthesia and Analgesia. 1991;**72**(2):182-186

[40] Smith HW, Rovenstine EA, Goldring W, Chasis H, Ranges HA. The effects of spinal anesthesia on the circulation in normal, unoperated man with reference to the autonomy of the arterioles, and especially those of the renal circulation. The Journal of Clinical Investigation. 1939;**18**(3):319-341

[41] Mercatello A. Changes in renal function induced by anesthesia. Annales Françaises d'Anesthèsie et de Rèanimation. 1990;**9**(6):507-524

[42] Suleiman MY, Passannante AN, Onder RL, Greene-Helms WF, Perretta SG. Alteration of renal blood flow during epidural anesthesia in normal subjects. Anesthesia and Analgesia. 1997;**84**(5):1076-1080

[43] Borgeat A, Ekatodramis G, Schenker CA. Postoperative nausea and vomiting in regional anesthesia: A review. Anesthesiology. 2003;**98**(2):530-547

[44] Cassuto J, Sinclair R, Bonderovic M. Anti-inflammatory properties of local anesthetics and their present and potential clinical implications. Acta Anaesthesiologica Scandinavica. 2006;**50**(3):265-282

[45] Sasagawa S. Inhibitory effects of local anesthetics on migration, extracellular release of lysosomal enzyme, and superoxide anion production in human polymorphonuclear leukocytes. Immunopharmacology and Immunotoxicology. 1991;**13**(4):607-622

[46] Hodson M, Gajraj R, Scott NB. A comparison of the antibacterial activity of levobupivacaine vs. bupivacaine: An in vitro study with bacteria implicated in epidural infection. Anaesthesia. 1999;**54**(7):699-702. DOI: 10.1046/j.1365-2044.1999.00742.x

[47] Hocking G, Wildsmith JA. Intrathecal drug spread. British Journal of Anaesthesia. 2004;**93**(4):568-578. DOI: 10.1093/bja/aeh204

[48] Okutomi T, Nemoto M, Mishiba E, Goto F. Viscosity of diluent and sensory level of subarachnoid anaesthesia achieved with tetracaine. Canadian Journal of Anaesthesia. 1998;**45**(1): 84-86. DOI: 10.1007/BF03012001

[49] Hartwell BL, Aglio LS, Hauch MA, Datta S. Vertebral column length and spread of hyperbaric subarachnoid bupivacaine in the term parturient. Regional Anesthesia. 1991;**16**(1):17-19

[50] Danelli G, Zangrillo A, Nucera D, Giorgi E, Fanelli G, Senatore R, et al. The minimum effective dose of 0.5% hyperbaric spinal bupivacaine for cesarean section. Minerva Anestesiologica. 2001;**67**(7-8):573-577

[51] Veering BT, Burm AG, Spierdijk J. Spinal anaesthesia with hyperbaric bupivacaine. Effects of age on neural blockade and pharmacokinetics. British Journal of Anaesthesia. 1988;**60**(2):187-194. DOI: 10.1093/bja/60.2.187

[52] Richardson MG, Wissler RN. Density of lumbar cerebrospinal fluid in pregnant and nonpregnant humans. Anesthesiology. 1996;**85**(2):326-330. DOI: 10.1097/00000542-199608000-00014

[53] Nightingale PJ. Barbotage and spinal anaesthesia. The effect of barbotage on the spread of analgesia during isobaric spinal anaesthesia. Anaesthesia. 1983;**38**(1):7-9

[54] Janik R, Dick W, Stanton-Hicks MD. Influence of barbotage on block characteristics during spinal anesthesia with hyperbaric tetracaine and bupivacaine. Regional Anesthesia. 1989;**14**(1):26-30

[55] Schroder W, Schwagmeier R, Schmidt A, Nolte H. The effect of barbotage on the sensory spread in spinal anesthesia using isobaric and hyperbaric 0.5% bupivacaine. Regional-Anaesthesie. 1990;**13**(7): 168-171

[56] Singh SI, Morley-Forster PK, Shamsah M, Butler R. Influence of injection rate of hyperbaric bupivacaine on spinal block in parturients: A randomized trial. Canadian Journal of Anaesthesia. 2007;**54**(4):290-295. DOI: 10.1007/BF03022774

[57] James KS, Stott SM, McGrady EM, Pearsall FJ, Frame WT, Russell D. Spinal anaesthesia for caesarean section: Effect of Sprotte needle orientation. British Journal of Anaesthesia. 1996;**77**(2): 150-152. DOI: 10.1093/bja/77.2.150

[58] Urmey WF, Stanton J, Bassin P, Sharrock NE. The direction of the Whitacre needle aperture affects the extent and duration of isobaric spinal anesthesia. Anesthesia and Analgesia. 1997;**84**(2):337-341. DOI: 10.1097/00000539-199702000-00017

[59] Neigh JL, Kane PB, Smith TC. Effects of speed and direction of injection on the level and duration of spinal anesthesia. Anesthesia and Analgesia. 1970;**49**(6):912-918

[60] Masse E, Drolet P, Girard M. Direction of injection does not affect the spread of spinal bupivacaine in parturients. Canadian Journal of Anaesthesia. 1997;**44**(8):816-819. DOI: 10.1007/BF03013156

[61] Stienstra R, van Poorten F, Kroon JW. Needle direction affects the sensory level of spinal anesthesia. Anesthesia and Analgesia. 1989;**68**(4):497-500

[62] El-Boghdadly K, Chin KJ. Local anesthetic systemic toxicity: Continuing professional development. Canadian Journal of Anaesthesia. 2016;**63**(3):330-349. DOI: 10.1007/s12630-015-0564-z

[63] Christie LE, Picard J, Weinberg GL. Local anaesthetic systemic toxicity. BJA

Education. 2014;**15**(3):136-142. DOI: 10.1093/bjaceaccp/mku027

[64] Rosenblatt MA, Abel M, Fischer GW, Itzkovich CJ, Eisenkraft JB. Successful use of a 20% lipid emulsion to resuscitate a patient after a presumed bupivacaine-related cardiac arrest. Anesthesiology. 2006;**105**(1):217-218. DOI: 10.1097/00000542-200607000-00033

[65] Verlinde M, Hollmann MW, Stevens MF, Hermanns H, Werdehausen R, Lirk P. Local anesthetic-induced neurotoxicity. International Journal of Molecular Sciences. 2016;**17**(3):339. DOI: 10.3390/ijms17030339

[66] Pollock JE. Neurotoxicity of intrathecal local anaesthetics and transient neurological symptoms. Best Practice & Research. Clinical Anaesthesiology. 2003;**17**(3):471-484

[67] Brull R, McCartney CJ, Chan VW, El-Beheiry H. Neurological complications after regional anesthesia: Contemporary estimates of risk. Anesthesia and Analgesia. 2007;**104**(4):965-974. DOI: 10.1213/01.ane.0000258740.17193.ec

[68] Lofstrom JB. 1991 Labat lecture. The effect of local anesthetics on the peripheral vasculature. Regional Anesthesia. 1992;**17**(1):1-11

[69] Haller I, Hausott B, Tomaselli B, Keller C, Klimaschewski L, Gerner P, et al. Neurotoxicity of lidocaine involves specific activation of the p38 mitogen-activated protein kinase, but not extracellular signal-regulated or c-Jun N-terminal kinases, and is mediated by arachidonic acid metabolites. Anesthesiology. 2006;**105**(5):1024-1033. DOI: 10.1097/00000542-200611000-00025

[70] Kan H, Wang Y, Wang D, Sun H, Zhou S, Wang H, et al. Cordycepin rescues lidocaine-induced neurotoxicity in dorsal root ganglion by interacting with inflammatory signaling pathway MMP3. European Journal of Pharmacology. 2018;**827**:88-93. DOI: 10.1016/j.ejphar.2018.01.049

[71] Klohr S, Roth R, Hofmann T, Rossaint R, Heesen M. Definitions of hypotension after spinal anaesthesia for caesarean section: Literature search and application to parturients. Acta Anaesthesiologica Scandinavica. 2010;**54**(8):909-921. DOI: 10.1111/j.1399-6576.2010.02239.x

[72] Moore DC, Bridenbaugh LD. Spinal (subarachnoid) block. A review of 11,574 cases. Journal of the American Medical Association. 1966;**195**(11):907-912

[73] Horlocker TT, McGregor DG, Matsushige DK, Schroeder DR, Besse JA. A retrospective review of 4767 consecutive spinal anesthetics: Central nervous system complications. Perioperative Outcomes Group. Anesthesia & Analgesia. 1997;**84**(3):578-584. DOI: 10.1097/00000539-199703000-00021

[74] Green L, Machin SJ. Managing anticoagulated patients during neuraxial anaesthesia. British Journal of Haematology. 2010;**149**(2):195-208. DOI: 10.1111/j.1365-2141.2010.08094.x

[75] Lagerkranser M. Neuraxial blocks and spinal haematoma: Review of 166 case reports published 1994-2015. Part 1: Demographics and risk-factors. Scandinavian Journal of Pain. 2017;**15**:118-129. DOI: 10.1016/j.sjpain.2016.11.008

[76] Moen V, Dahlgren N, Irestedt L. Severe neurological complications after central neuraxial blockades in Sweden 1990-1999. Anesthesiology. 2004;**101**(4):950-959. DOI: 10.1097/00000542-200410000-00021

[77] D'Angelo R, Smiley RM, Riley ET, Segal S. Serious complications related to obstetric anesthesia: The serious complication repository project of the Society for Obstetric Anesthesia and Perinatology. Anesthesiology. 2014;**120**(6):1505-1512. DOI: 10.1097/ALN.0000000000000253

[78] Cook TM, Counsell D, Wildsmith JA. Royal College of Anaesthetists Third National Audit Project. Major complications of central neuraxial block: Report on the Third National Audit Project of the Royal College of Anaesthetists. British Journal of Anaesthesia. 2009;**102**(2):179-190. DOI: 10.1093/bja/aen360

[79] Kurz A, Sessler DI, Schroeder M, Kurz M. Thermoregulatory response thresholds during spinal anesthesia. Anesthesia and Analgesia. 1993;**77**(4):721-726

[80] Joris J, Ozaki M, Sessler DI, Hardy AF, Lamy M, McGuire J, et al. Epidural anesthesia impairs both central and peripheral thermoregulatory control during general anesthesia. Anesthesiology. 1994;**80**(2):268-277. DOI: 10.1097/00000542-199402000-00006

[81] Saito T, Sessler DI, Fujita K, Ooi Y, Jeffrey R. Thermoregulatory effects of spinal and epidural anesthesia during cesarean delivery. Regional Anesthesia and Pain Medicine. 1998;**23**(4):418-423

[82] Kwak KH. Postdural puncture headache. Korean Journal of Anesthesiology. 2017;**70**(2):136-143. DOI: 10.4097/kjae.2017.70.2.136

[83] Sprung J, Bourke DL, Contreras MG, Warner ME, Findlay J. Perioperative hearing impairment. Anesthesiology. 2003;**98**(1):241-257

[84] Bromage PR. Epidural Analgesia. Philadelphia: Saunders; 1978

[85] Reina MA, Villanueva MC, Maches F, Carrera A, Lopez A, De Andres JA. The ultrastructure of the human spinal nerve root cuff in the lumbar spine. Anesthesia and Analgesia. 2008;**106**(1):339-344. DOI: 10.1213/01.ane.0000295803.31074.dc

[86] Tretjakoff D. Das epidurales Fettgewebe. Zeitschrift fur Anatomie und Entwicklungsgeschichte. 1926;**79**(1):101-111

[87] Ramsey HJ. Fat in the epidural space in young and adult cats. The American Journal of Anatomy. 1959;**104**:345-379

[88] Burm AG. Clinical pharmacokinetics of epidural and spinal anaesthesia. Clinical Pharmacokinetics. 1989;**16**(5):283-311

[89] Hogan Q. Distribution of solution in the epidural space: Examination by cryomicrotome section. Regional Anesthesia and Pain Medicine. 2002;**27**(2):150-156

[90] Erdemir HA, Soper LE, Sweet RB. Studies of factors affecting peridural anesthesia. Anesthesia and Analgesia. 1965;**44**(4):400-404

[91] Moore PA, Hersh EV. Local anesthetics: Pharmacology and toxicity. Dental Clinics of North America. 2010;**54**(4):587-599. DOI: 10.1016/j.cden.2010.06.015

[92] Covino BG. The pharmacology of local anesthetic agents. In: Stanley TH, Petty WC, editors. Anesthesiology, Developments in Critical Care Medicine and Anesthesiology. Vol. 11. Dordrecht: Springer; 1986

[93] Oda Y, Furuichi K, Tanaka K, Hiroi T, Imaoka S, Asada A, et al. Metabolism of a new local anesthetic, ropivacaine, by human hepatic cytochrome P450. Anesthesiology.

1995;**82**(1):214-220. DOI: 10.1097/00000542-199501000-00026

[94] Bromage PR, Pettigrew RT, Crowell DE. Tachyphylaxis in epidural analgesia: I. Augmentation and decay of local anesthesia. The Journal of Clinical Pharmacology and the Journal of New Drugs. 1969;**9**(1):30-38