This is the outline for this session.

The objectives of this session are:
1. Understand the circumstances that cause systemic and cardiovascular toxicity in the daily clinical practice of regional anesthesia.
2. Understand the management of systemic and cardiovascular toxicity of local anesthetics.
3. Cite methods for avoiding local anesthetic neural toxicity.

When properly given, local anesthetics are generally free of side effects. However, systemic or localized toxicity occurs with accidental intravascular injection or by injecting excessive doses (especially intrathecally). Additionally, other adverse effects occur with certain agents, e.g., allergic reactions to the amino-esters, and methemoglobinemia with benzocaine and with high doses of prilocaine.

Systemic toxicity affects the central nervous and the cardiovascular systems. The central nervous system (CNS) is more susceptible to local anesthetic toxicity than is the cardiovascular system. The dose and blood level of local anesthetic that produce CNS toxicity is lower than the dose that causes circulatory collapse. Although local anesthetic cardiovascular toxicity occurs less frequently than CNS toxicity, it is more serious and more difficult to treat.

The initial symptoms of CNS toxicity include feelings of lightheadedness and dizziness followed by visual and auditory disturbances such as difficulty in focusing and tinnitus. Other subjective CNS symptoms are disorientation and feelings of drowsiness. Objective signs of CNS toxicity are excitatory in nature. They include shivering, muscular twitching and tremors initially involving muscles of the face and distal parts of the extremities. Later, tonic-clonic convulsions occur.

If a sufficiently large dose or a rapid intravenous injection of local anesthetic is given, the initial signs of CNS excitation are followed rapidly by CNS depression. Ultimately, seizure activity ceases and respiratory depression is followed by respiratory arrest. In some patients, CNS depression occurs without the preceding excitatory phase, particularly if other CNS depressant drugs were given.
Classically, CNS excitation is believed to be due to local anesthetic blockade of inhibitory pathways in the cerebral cortex. The blockade of inhibitory pathways dis-inhibits facilitator neurons, resulting in convulsions, owing to unopposed excitatory nerve activity. Further increases in the dose of local anesthetic causes inhibition of both inhibitory and facilitator pathways resulting in CNS depression. This graphic shows what I have observed clinically. With lidocaine, there is more excitation (upper left) before the seizure (upper right) than with the more potent agents like etidocaine, where there is little excitation (lower left) and the seizure occurs abruptly (lower right).¹

A recent study of cultured inhibitory synapses found that although increasing concentrations of lidocaine reduced inhibitory synaptic transmission they also caused a depolarization and general excitation of both presynaptic and postsynaptic neurons. This graphic shows the increased excitation of the presynaptic cell owing to increasing concentrations of lidocaine. The implication is that lidocaine’s side effects, such as convulsion, seizure, and hyperventilation, may result from such changes in general neuronal excitability.²

There is a correlation between local anesthetic potency and CNS toxicity.³ For example, in cats, the convulsive dose of procaine is approximately seven times the convulsive dose of bupivacaine and procaine is approximately 8 times less potent than bupivacaine. A similar study in dogs indicates that the relative CNS toxicity of bupivacaine, etidocaine, and lidocaine is 4:2:1. This is similar also to their relative local anesthetic potencies.⁴ Intravenous infusion studies in human volunteers show a similar relationship between the intrinsic anesthetic potency and the dosage that causes CNS symptoms.⁵,⁶

The rate of injection and therefore the rapidity that toxic blood levels are reached alters the toxicity of local anesthetics. For example, when etidocaine is infused into human volunteers at the rate of 10 mg/ml, CNS symptoms occur when the venous blood level reaches 3.0 µg/ml (mean dose = 236 mg). Increasing the infusion rate to 20 mg/ml causes CNS symptoms when the venous blood level is only 2.0 µg/ml (mean dose = 161 mg).⁷
Local Anesthetic Toxicity
Rate of Injection
- Slow rates of injection are less likely to result in systemic toxicity
- Intermittent injections, at slow rates will lessen further the likelihood of systemic toxicity
- These two steps, in my opinion, are better than a test dose of local anesthetic with epinephrine as tracer

Because rapid rates of injection result in CNS excitation more quickly than slower injections, we should use slow rates of injection when large doses of local anesthetics are administered. Intermittent and slow injections are preferred, as they are associated with less toxicity.

Much has been said about what constitutes the ideal “test dose” for epidural local anesthetics injections, and epinephrine (5 ug/ml) is widely employed as a “tracer” to increase the heart rate if intravascular injection occurs. However the safest approach might be to use slow and intermittent injections while monitoring the patient for signs of CNS toxicity.

The acid base status effects the CNS toxicity of local anesthetic. In cats, the convulsive threshold of various local anesthetics is related to the arterial pCO2. For example, increasing the pCO2 from 25 - 40 torr to 65 - 81 torr decreases the convulsive threshold of procaine, mepivacaine, prilocaine, lidocaine, and bupivacaine by approximately 50%. Decreasing the arterial pH also decreases the convulsive threshold of these agents. In fact, the pH is probably more important than the pCO2 in terms of the CNS toxicity of local anesthetics. Respiratory acidosis (increased pCO2, decreased pH) decreases the convulsive threshold of local anesthetics. However, compensated metabolic alkalosis (increased pCO2, increased pH) does not decrease the convulsive threshold as much as the increased pCO2 owing to respiratory acidosis.

This potentiation effect of acidosis and/or hypercarbia may be due to several factors. Hypercarbia increases cerebral blood flow. Therefore, more local anesthetic is delivered to the brain. Additionally, hypercarbia may increase the diffusion of CO2 across the nerve membrane, causing intracellular pH to fall. Intracellular acidosis promotes the conversion of the base form of the local anesthetic to the cationic (active) form. Since the cation does not diffuse across the nerve membrane, ionic trapping occurs, increasing CNS toxicity of the local anesthetic.

Hypercarbia and/or acidosis also decrease the binding of local anesthetics by plasma protein. Therefore, elevating the pCO2 or decreasing the pH increases the proportion of free drug available for diffusion into the brain. On the other hand, acidosis increases the cationic form of the local anesthetic and this should decrease diffusion into the nerve.
Local anesthetics depress the mechanical activity of cardiac muscle. All local anesthetics exert a dose-dependent negative inotropic action in isolated cardiac tissue, which is proportional to their potency. Thus, the more potent local anesthetics depress cardiac contractility at lower concentrations than the less potent drugs.

Studies in intact dogs in which a strain gauge arch was sutured to the right ventricle show that all local anesthetic agents are negative inotropes. As in the isolated cardiac tissue studies, there is a relationship between the potency of local anesthetics and their myocardial depressant effect.

The mechanism by which local anesthetics depress myocardial contractility is not precisely known, but it may involve an interaction with calcium. Both procaine and tetracaine increase the release of calcium from skeletal muscle. The relative potency of tetracaine and procaine in terms of their ability to increase the rate of calcium efflux from sartorius muscle is proportional to their local anesthetic potency. Displacement of calcium from cardiac muscle should result in a decrease in myocardial contractility. However, studies with isolated guinea pig hearts show that increasing the extracellular calcium concentration does not reverse the negative inotropic action of bupivacaine or lidocaine.

In general, the sequence of cardiovascular events observed following a progressive increase in local anesthetic dosage can be summarized as follows: at doses of local anesthetic agents that produce nontoxic blood levels, either a slight increase or no change in blood pressure occurs. The slight increase in blood pressure is probably related to (a) an increase in cardiac output and heart rate which is believed due to an enhancement of sympathetic activity and (b) a direct vasoconstriction of certain peripheral vascular beds. Blood levels of local anesthetic agents approaching toxic concentrations cause hypotension as a result of peripheral vasodilation resulting from a direct relaxant effect on peripheral vascular smooth muscle. A further elevation of local anesthetic blood levels produces a decreased myocardial contractility, which results in a fall in cardiac output. This combination of reduced peripheral vascular resistance and cardiac output leads to profound hypotension. Finally, at lethal blood levels of local anesthetic agents, cardiovascular collapse ensues due to massive peripheral vasodilation, marked reduction in myocardial contractility, and slowed heart rate, which ultimately results in cardiac arrest.

This graphic shows the effect of local anesthetic toxicity prior to severe cardiodepressant effects.

The initial increases in HR, MAP, and CO are due to CNS stimulation and seizure activity. Once the infusion is stopped and seizure activity ceases, HR and MAP return to normal but CO shows a late decline.
This graphic shows the hemodynamic changes that occur in sheep, when lidocaine is infused to the point of cardiovascular collapse. The dotted line shows the lidocaine blood concentration, the dashed line the heart rate and the hashed area the pulse pressure (upper line systolic, lower line diastolic pressures). The lidocaine infusion is begun at 1.9 mg/kg/min and continued as indicated by the black line (above). There is an initial decline in HR, then an increase along with BP increase with seizure activity (between arrowheads). At this point the infusion is stopped and the blood level declines. The infusion is then increased to 2.1 mg/kg/min. A second seizure occurs, and as the infusion continues cardiovascular collapse ensues. We will refer later to the CC:CNS ratio, which is the blood level that causes cardiovascular collapse divided by the blood level that causes seizure. In this experiment, that would be 45/15 = 3.

This graphic shows cardiac arrest owing to lidocaine.
Note the decline in ABP.
Note that there are no arrhythmias, only a decrease in R amplitude with progressive widening of the QRS and bradycardia. At the point of cardiac arrest resuscitation is relatively easy.

This graphic shows cardiac arrest owing to bupivacaine.
Note the decline in ABP.
Note that there is little decrease in R amplitude and no bradycardia. Instead there is a sudden ventricular tachycardia and fibrillation. Resuscitation from cardiac arrest is difficult.

This graphic shows “bupivacaine polymorphic ventricular tachycardia.” This is also referred to as “torsades de pointes” (a twisting of the points). It appears to the observer that it is VT alternating with VFib. It is not VFib. What we are observing is rotation of the QRS axis. The portion that appears to be VFib is actually VT but the QRS axis is “into and out off” the plane of the slide. The portion that appears as VT has an axis that is perpendicular to what appears to be the VFib axis. Because torsades de pointes is responsive to Mg2+, magnesium has been tried in the treatment in this arrhythmia owing to bupivacaine toxicity.
Qualitative differences exist between the electrophysiologic effects of the various agents. Bupivacaine depresses the rapid phase of depolarization (Vmax) in Purkinje fibers and ventricular muscle cells to a greater extent than lidocaine.\textsuperscript{17}

Increasing stimulation frequency (number of beats) causes a deepening of the block owing to local anesthetics (frequency dependent conduction blockade).

Compared to lidocaine, the rate of recovery from steady-state block is slower in bupivacaine treated papillary muscles. This slow rate of recovery results in an incomplete restoration of Vmax between action potentials, particularly at high heart rates. In contrast, recovery from lidocaine is complete, even at rapid heart rates. The different effects of lidocaine and bupivacaine are believed to be responsible for the antiarrhythmic activity of lidocaine and the arrhythmogenic potential of bupivacaine. Studies comparing ropivacaine to lidocaine and bupivacaine show ropivacaine to be intermediate in suppressing Vmax and recovery from steady-state block.\textsuperscript{18} Lidocaine is said to be fast in and fast out, while bupivacaine is fast in but slow out.

In summary, the rate of recovery of sodium channels is rapid with lidocaine and slow with bupivacaine, making resuscitation from a lidocaine overdose easier than from a bupivacaine overdose.

Electrophysiologic studies in intact dogs and in man corroborate the findings observed in isolated cardiac tissue. As the dose and blood levels of lidocaine increase, so, too, do the conduction times through various parts of the heart. This is reflected in the electrocardiogram as an increase in the PR interval and QRS duration. Extremely high concentrations of local anesthetics depress spontaneous pacemaker activity in the sinus node resulting in sinus bradycardia and sinus arrest.

To summarize the cardiovascular events of local anesthetic overdose, initially there is hypertension and tachycardia owing to the CNS excitation. This is followed by negative inotropy, decrease cardiac output, mild to moderate hypotension, peripheral vasodilation, then profound hypotension, and bradycardia.

The primary cardiac electrophysiologic effect of local anesthetics is a decrease in the maximum rate of depolarization, which is believed to be due to a decrease in sodium conductance in the fast sodium channels. The action potential duration and the effective refractory period are also decreased by local anesthetics. However, the ratio of the effective refractory period to the action potential duration is increased in Purkinje fibers and in ventricular muscle cells. This predisposes the patient to re-entry type arrhythmias.

Ultimately, cardiovascular collapse ensues.
In 1979, Albright reported a number of the cardiotoxic reactions owing to bupivacaine in pregnant patients.\(^\text{19}\)

As a consequence of these reports, the FDA convened a panel of experts to review these bupivacaine toxicity cases. There were a total of 14 non-obstetric and 35 obstetric cases (grand total of 49). Nearly half of these patients died indicating the difficulty associated with resuscitating the patients. While some patients received excessive doses, some patients were affected by as little as 50 mg of bupivacaine. A majority of the obstetric patients received 0.75% bupivacaine. The panel was concerned that the pregnant patient may be more susceptible to bupivacaine than non-pregnant patients. As a result, the 0.75% bupivacaine solution is not recommended for obstetric anesthesia in the U.S.A. Fortunately bupivacaine was not removed from the market.

Studies in pregnant and non-pregnant sheep show that the CC/CNS dosage ratio (see above) for bupivacaine decreases from 3.7 ± 0.5 in non-pregnant sheep to 2.7 ± 0.4 in pregnant animals.\(^\text{20}\) Nevertheless, there was little difference in the CC/CNS blood level ratio, which varied from 1.6 ± 0.1 in non-pregnant animals to 1.4 ± 0.1 in pregnant ewes. However, the blood level of bupivacaine when circulatory collapse occurred was lower in pregnant animals.

When the study in the previous slide was repeated, the same group found that pregnancy did not enhance bupivacaine’s or ropivacaine’s cardiotoxicity (bupiv ii and ropiv ii).\(^\text{21}\) Also, there was no difference in the myocardial uptake of bupivacaine in pregnant and non-pregnant sheep at the time of cardiovascular collapse. Thus, if the pregnant sheep is more susceptible to the cardiotoxic effects of bupivacaine, it apparently is not due to myocardial uptake of drug.
In a more recent study, the doses of bupivacaine, ropivacaine, and levobupivacaine required to produce convulsions were lower in pregnant than nonpregnant animals. However, there were no significant differences between pregnant and nonpregnant ewes in the dose required to produce hypotension, apnea, and circulatory collapse. The dose and serum concentration at each toxic manifestation was lowest for bupivacaine, intermediate for levobupivacaine, and highest for ropivacaine in both pregnant and nonpregnant animals. There were no significant differences between pregnant and nonpregnant ewes in total and free serum drug concentrations, except that at circulatory collapse, these were higher in pregnant animals. In conclusion, pregnancy increases the risk of convulsions but not of more advanced manifestations of local anesthetic toxicity.

Recall that ropivacaine and levobupivacaine are the S-(levo)-isomers, which are less cardiotoxic than the R-(dextro) isomer, which is present in bupivacaine solutions.

These results indicate that the systemic toxicity of ropivacaine is not enhanced by ovine pregnancy but neither is that of bupivacaine. In a previous study, lethal doses and plasma concentrations of bupivacaine were lower in pregnant than non-pregnant ewes. The reason for the discrepancy is unclear but may be due to lack of blinding and smaller sample size in the earlier study.

It is difficult to resuscitate patients from bupivacaine cardiac toxicity. Studies in acidotic and hypoxic sheep confirm that cardiac resuscitation is difficult following bupivacaine toxicity. Studies in bupivacaine toxic cats and dogs show that resuscitation is possible but requires large doses of epinephrine and atropine. In addition, bretylium but not lidocaine reverses the cardiodepressant effects of bupivacaine and raised the ventricular tachycardia threshold. Older studies in rats suggest that norepinephrine and epinephrine (agents with beta 1- and alpha 1-receptor activity) may be the best drugs to treat asystole caused by bupivacaine. Pretreatment of dogs with magnesium and rats with clonidine reduce the cardiac toxicity of intravenous bupivacaine.

Weinberg recently reviewed the treatment of local anesthetic cardiac toxicity. The three factors, which appear most important are an early response, airway, breathing and circulation (the ABCs), and institution of the ACLS protocols.
In his review, Weinberg suggests using amiodarone, instead of bretylium (which is no longer supported as an effective ACLS agent), and he points out that epinephrine may itself be arrhythmogenic.\textsuperscript{28}

It seems logical (watch out for backfiring logic) and some have suggested that lidocaine (by competition for the sodium channel) might be effective in the treatment of bupivacaine arrhythmias. On the other hand, lidocaine could be additive to the toxic effects of bupivacaine. The data are mixed on this use of lidocaine.

For vasopressor support, vasopressin 40 U, which is now in the ACLS protocol may be preferable to epinephrine because epinephrine itself can cause arrhythmias.

Drugs which are contraindicated include:
- Calcium channel blockers
- Phenytoin
- Bretylium

Other methods for resuscitation include lipid infusions (including propofol) or insulin/glucose/potassium (I/G/K) infusion and these are currently under investigation.\textsuperscript{29,30}

Lipid infusion provides mitochondrial substrate, improves survival and increase the dose required for toxicity in rats. The lipids may sequester the highly lipid soluble bupivacaine in blood, making less bupivacaine available to inhibit the cardiovascular system.

I/G/K may restore K$^+$ gradients for repolarization and help restore ATP stores.
Now the question is this? Are the new levo-local anesthetics (ropivacaine and levobupivacaine) really any safer than racemic bupivacaine? If one thinks only of obstetrical anesthesia, or postoperative pain management, the answer might be, “it doesn’t really matter because the infusion concentrations we use are so low.” Also, most elective cesarean sections are done with spinal anesthesia and emergent cesarean sections done with epidural anesthesia are initiated with rapid acting agents such as chloroprocaine or lidocaine.

However, peripheral nerve blocks, which require large doses that approach toxic limits are another story. There have been three case reports and an editorial after ropivacaine caused cardiac arrest in patients having, posterior lumbar plexus, interscalene, or lower extremity block.31-34 All patients were resuscitated without sequelae. In these instances where a long acting local anesthetic is desirable, then ropivacaine and levobupivacaine make sense and they are probably worth the added expense that these drugs command.

Plain ropivacaine and levobupivacaine (25 mg) solutions are unsuitable for use as intravenous test doses during regional anesthesia because CNS symptoms are insufficient. When using ropivacaine or levobupivacaine for regional anesthesia, for test dose purposes, Owen, et al recommend the addition of epinephrine to the local anesthetic solution or the use of a separate agent with more predictable CNS characteristics.35

A unique side effect of prilocaine is methemoglobinemia.36,37 There is a dose-response relationship between the dose of epidural prilocaine and the degree of methemoglobinemia. The development of clinically significant methemoglobinemia requires injecting more than 600 mg of prilocaine. The formation of methemoglobinemia is related to prilocaine’s chemical structure. Prilocaine lacks a methyl group in the benzene ring. Hepatic metabolism of prilocaine produces o-toluidine, which oxidizes hemoglobin to methemoglobin.

Topical benzocaine is also associated with methemoglobinemia.38 Methemoglobinemia caused by prilocaine or benzocaine is spontaneously reversible, or it can be treated with intravenous methylene blue (1 mg/kg).

The amino-esters such as procaine are derivatives of the allergen para-amino-benzoic-acid (PABA). Consequently, the amino-esters sometimes cause allergic reactions. Intradermal injections of amino-esters and amino-amides in patients with and without a history of local anesthetic allergy caused positive skin reactions in 25 of 60 patients without history of allergy.39,40 In all cases, the intradermal reactions occurred with amino-esters but not with amino-amides. Eight of eleven patients with a history of local anesthetic allergy developed a positive skin reaction to amino-esters, but not to amino-amides. In these studies, no subject developed anaphylaxis.
Amide Local Anesthetic Allergy

- Amides cause less than 1% of all local anesthetic allergies
- Prilocaine
  - orthotoluidine → met-hemoglobinemia
  - Oxidation of hemoglobin
  - Low oxygen saturation
  - Requires dose > 600 mg
  - Treatment is 1 mg/kg of methylene blue

With the exception of prilocaine’s ability to cause met-hemoglobinemia (not an allergy), allergic reactions to the amino-amides are extremely rare. It has been said, that true amide allergy is probably reportable.

Although the amino-amides do not usually cause allergic reactions, amino-amide solutions may contain the preservative, methylparaben, which is structurally similar to para-amino-benzoic-acid (PABA). Because patients injected intradermally with amide local anesthetic that contains methylparaben develop a positive skin reaction, it may appear that the skin reaction is due to the amino-amide when in fact it is due to the methylparaben.

Treatment of local anesthetic allergy is the same as the treatment of any allergy and consists of the ABCs (watch for airway edema, and bronchospasm), and epinephrine (I find that 0.3 mg epinephrine, sc works well for bronchospasm). If anaphylaxis should develop, the additional treatments are fluids, H1 and H2 receptor blockers and steroids.

This table shows reports of cauda equina syndrome resulting from regional anesthesia. The local anesthetic agents involved are procaine, tetracaine, chloroprocaine, and lidocaine.

Reports of bupivacaine cauda equina syndrome owing to spinal anesthesia have recently appeared, but the details are lacking.41

Neurologic injury owing to spinal anesthesia is relatively rare. One of the first clues that local anesthetics might be associate with nerve injury appeared in this study by Vandam and Dripps that dates back to 1955.42

In this study, there were seventy one sensory neurological symptoms and signs out of 8,460 patients who had 10,098 spinals.

In the overwhelming number of patients the numbness was restricted to the lumbar and sacral areas of the body.

It appears that the spinal anesthetic injected rather than the lumbar puncture played a nonspecific part in the development of the numbness.
In 1980 there were case reports of patients experiencing cauda equina syndrome after the accidental intrathecal injection of large amounts of chloroprocaine intended to be delivered epidurally.

These reports usual involved young pregnant women and the injuries were permanent in most cases. Animal studies regarding the neurotoxicity of chloroprocaine are contradictory. Paralysis occurred only in rabbits injected intrathecally with chloroprocaine solutions that contained sodium bisulfite. Pure solutions of chloroprocaine (no sodium bisulfite) did not cause paralysis. On the other hand, solutions of sodium bisulfite alone (no chloroprocaine) caused paralysis.

The etiology of the neural injury owing to chloroprocaine is believed by some to be due to the low pH and the antioxidant, sodium bisulfite, contained in chloroprocaine solutions. However there are other possible etiologies.

A detailed study in isolated rabbit vagus nerve investigated the neurotoxicity of the components of commercial chloroprocaine solutions. These solutions contain 2-3% chloroprocaine, 0.2% sodium bisulfite, and they have a pH around 3.0. Bathing isolated vagus nerves for 30 minutes with commercial 3% chloroprocaine results in irreversible conduction blockade. However, bathing the nerves with commercial 3% chloroprocaine buffered to pH 7.0 causes reversible conduction block. A 3% chloroprocaine solution with pH of 3.0 but without sodium bisulfite also causes reversible blockade. Bathing the nerves with a 0.2% sodium bisulfite solution at a pH of 3.0 causes irreversible conduction block whereas a 0.2% sodium bisulfite solution with a pH of 7.0 causes no conduction block. The results of these studies indicate that the combination of pH< 3.0 and 0.2% sodium bisulfite is responsible for the potential neurotoxicity of commercial chloroprocaine solutions. 2-3% chloroprocaine itself does not appear to be neurotoxic. However, a recent behavioral study in rats indicates that intrathecal chloroprocaine causes neural toxicity in the absence of bisulfite. In fact, Tanaguichi, et al found that nerve injury scores after administration of plain chloroprocaine were significantly greater than with chloroprocaine containing bisulfite, suggesting a protective effect of bisulfite.

As a result of these in vitro studies (but before the most recent findings of Tanaguichi, et al), the manufacturers of chloroprocaine removed the sodium bisulfite from the solution. Unfortunately, they substituted sodium ethylenediaminetetraacetic (EDTA). EDTA is a calcium chelating agent. It may be responsible for the reports of severe back pain after epidural anesthesia with the EDTA-containing chloroprocaine solution. The pain may be due to tetanic contractions of the back muscles owing to localized hypocalcemia from calcium sequestration. An alternative explanation is that the EDTA is neurotoxic, per se. In vivo rat experiments show that EDTA (in concentrations slightly higher than that present in the commercial chloroprocaine solution) is neurotoxic.
Tissue Toxicity
Cauda Equina Syndrome after Continuous Spinal Anesthesia

Rigler ML, Drasner K, Krejcie TC, et al
Anesthesia Analgesia 72:275-281;1991

There are reports of cases of cauda equina syndrome after continuous spinal anesthesia. 54,55

Cauda Equina Syndrome after Continuous Spinal Anesthesia

<table>
<thead>
<tr>
<th>Catheter Gauge</th>
<th>Drug</th>
<th>Number Injection (mg)</th>
<th>Total (mg)</th>
<th>Duration (months)</th>
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</thead>
<tbody>
<tr>
<td>28</td>
<td>Lidocaine</td>
<td>4</td>
<td>175</td>
<td>&gt;7</td>
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<tr>
<td>20</td>
<td>Tetracaine</td>
<td>5</td>
<td>37</td>
<td>&gt;31</td>
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All solutions Hyperbaric


Most, but not all, cases of cauda equina syndrome occurred with so-called microcatheters and large doses of 5% hyperbaric lidocaine. There are case reports of cauda equina syndrome that occurred after the accidental intrathecal injection of 2% lidocaine intended for epidural anesthesia. 56,57 These cases indicate that commonly used local anesthetics, while safe when used in appropriate amounts and in appropriate locations, can be neurotoxic under certain circumstances.

Note that this case report includes one patient who developed cauda equina syndrome after continuous spinal anesthesia performed with 37 mg of tetracaine and a large bore (20 gauge) catheter.

In an effort to explain how these cases of cauda equina syndrome might have happened, Ron Hurley and I published a study in a spinal canal model. 58

Tissue Toxicity
Cauda Equina Syndrome and Continuous Spinal Anesthesia

DH Lambert and RJ Hurley
Anesthesia Analgesia 72:817-819;1991

This graphic shows the main results of our study. The study was performed in a plastic tube, which contained Ringer’s lactate solution and contoured to mimic the spinal canal of a patient in the supine position. 58

Panels A, B, and C: show the injection of 50 mg (1ml) hyperbaric lidocaine through a microcatheter.

Panel C shows the lidocaine pooled in sacral region.

Panels D, E, and F show the added effect of injecting additional 50 mg (1 ml) lidocaine.

Pooling occurs where cauda equina nerves would be located.

This graphic shows Lido running down tube.

Shows Microcatheter

Exposing those nerves to nearly undiluted 5% lidocaine.
This graphic shows another example of an experiment that is similar to the one above. The results of experiments such as these suggest that pooling of hyperbaric 5% lidocaine in the sacral region of the spinal canal could account for the cauda equina syndrome associated with lidocaine.

A study in isolated frog sciatic nerves, similar to the one described above for chloroprocaine, shows that some of the local anesthetics routinely used for spinal anesthesia cause irreversible or partially reversible conduction block.

The study consists of recording the block of the compound action potential amplitude after bathing the nerves for 15 minutes with the local anesthetic solutions (or components of the solution, e.g., dextrose), the washout of the drug for 2 - 3 hrs, and finally after soaking the nerves over night in Ringer's solution.

The results indicate that 5% lidocaine and 0.5% tetracaine caused irreversible block, while 1.5% lidocaine and 0.75% bupivacaine caused partially reversible block and 0.06% tetracaine caused total recovery.

Thus, we know from years of clinical practice that these local anesthetic solutions are safe for spinal anesthesia, when given as a single injection and in small doses. However, when they are injected through a spinal catheter and given repeatedly in large doses, they can displace the CSF, come directly in contact with the cauda equina nerves, and damage them.

Only three minutes of exposure to 5% lidocaine in 7.5% dextrose is enough to prevent any recovery of the action potential after washout.

This graphic shows the loss of recovery of the CAP as a function of lidocaine conc. in frog sciatic nerve. The LD50 is 45 mM, which is equivalent to 1% lidocaine.
The results obtained in frog sciatic nerve have been criticized because they were obtained in a non-mammalian preparation. However, similar results were obtained in mammalian (rabbit) vagus nerves.63

Sakura, et al using a rat intrathecal infusion behavioral model also obtained results similar to those gained in frog nerve.

In this study by Sakura and Drasner, tail-flick latency for the lidocaine group was significantly prolonged when compared with the bupivacaine, tetracaine, and saline groups.64

The results are similar to the frog nerve study except for tetracaine, which was as toxic as was lidocaine. In this graphic, the tetracaine actually appears protective. Oddly enough, however, this is what was seen in the frog nerve with very low concentrations of tetracaine.61

As shown in this graphic, the dextrose used to make spinal solutions hyperbaric does not appear to worsen the neurologic injury cause by lidocaine. Two experiments were performed. First, animals received a single intrathecal infusion of 5% lidocaine or 5% lidocaine with 7.5% glucose and sensory function was assessed using the tail-flick test. In the second experiment, rats were randomly divided into two groups to receive a 1-h intrathecal infusion of 5% lidocaine or 5% lidocaine with 7.5% glucose. In the first experiment, the two lidocaine solutions produced similar dose-dependent loss of sensory function. In the second experiment, the two solutions induced similar alterations in tail-flick latency. The presence of 7.5% glucose does not affect the potential of intrathecally administered 5% lidocaine to induce sensory impairment. These findings support for hypothesis that recent injuries after spinal anesthesia resulted from a direct neurotoxic effect of the local anesthetic.65
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