Outline for Pharmacology of Local Anesthetics.

The objectives of this session are:
1. Become familiar with the sodium channel and its interaction with local anesthetics.
2. Become familiar with the physical and chemical properties of local anesthetics that are responsible for onset, potency and duration.

This slide is a micrograph of a nerve coursing over skeletal muscle. By applying a local anesthetic to this nerve, the anesthesiologist can produce anesthesia or analgesia by blocking the afferent impulses and prevent them from reaching the central nervous system. Additionally, the efferent impulses are also blocked, which produces muscle relaxation. Hence “regional anesthesia” can be produced that avoids many undesirable hemodynamic and central nervous system (nausea/vomiting/respiratory depression/loss of airway reflexes and protection/etc.) alterations.

Owing to the semi-permeable nature of the membrane and an active Na+/K+ ATP driven pump, which generates concentration gradients across the membrane for Na+ and K+, the normal resting nerve has a negatively charged interior (around -70 to -90 mV resting potential, which is close to the K+ equilibrium potential). The extra-cellular fluid is high in Na+ and low in K+. Conversely, the intra-cellular fluid is low in Na+ but high in K+.

By applying a depolarizing current the resting membrane potential becomes more positive (less negative) due to the influx of Na+ (increased sodium conductance) until the threshold potential is reached, where an “all-or-none” action potential is generated. During the action potential, Na+ conductance increases further and the membrane potential rises to the sodium equilibrium potential (around +40 mV). The membrane potential is then returned towards normal by a decline in the Na+ conductance (less Na+ enters the cell) and an increase in K+ conductance (when more K+ leaves the cell than Na+ enters).
This slide demonstrates the reversibility of local anesthetic action. Starting from the back of the slide (CONTROL), the compound action potential has an amplitude of approximately 40 mV. The compound action potential of the entire nerve is the sum total of all of the individual fiber generated action potentials. When the local anesthetic is applied (DRUG), the compound action potential declines, in direct proportion to the number of individual fibers that are blocked by the local anesthetic, until all of the fibers are block (around 22 min). The washout out (WASH) of the local anesthetic results in the return of the compound action potential towards pre-block levels. We will see in the lecture on toxicity of local anesthetics that under certain circumstances the machinery that produces the action potential can be permanently wrecked and this results in irreversible conduction blockade.

This slide shows the sequence of events in the attachment of the local anesthetic to the nerve’s receptor site. At physiological pH, local anesthetics exist as an uncharged base (B) or as the charged cation (BH+). Both are important to conduction blockade.

In order for a molecule to diffuse across barriers, it is best if it is uncharged. Thus, the uncharged base diffuses across the epineurium, which is the connective tissue that encases the individual nerve fibers that make up a nerve bundle. It then diffuses across the nerve membrane itself to enter the axoplasm.

The pH of the sub-epineurial fluid and the axoplasm is less than that of the extracellular fluid. Hence the equilibrium shifts from B + H+ to BH+ and some of the uncharged base is converted to the cation (BH+) as the base penetrates deeper into the nerve.

Studies in giant axons, where the axoplasm can be removed and the interior of the nerve perfused with base or cation, show that it is the cation (BH+) that produces conduction block. Thus the base (B) is important for getting the local anesthetic to the target (receptor site), but it is the cation (BH+) that produces the block.

The voltage-gated Na channels are membrane proteins responsible for the generation of action potentials in excitable membranes. In mammalian cells, the Na channel family contains one large α subunit and one or two smaller β auxiliary subunits (β1, β2, not shown). The α− subunit primary sequence contains four homologous domains (D1–D4), each with six transmembrane segments (S1–S6). Current structural models suggest that the Na channel is organized as a pseudotetramer with the S6 segments possibly lining the internal vestibule of the pore.

The +S4+ segment is believed to be the voltage sensitive segment, which is responsible for the voltage sensitivity of the sodium channel blockade.

The arrows indicate the putative BTX (batrachotoxin) binding site and the putative LA (local anesthetic) binding site at segment D1-S6, D3-S6, and D4-S6. The role of D2-S6 in BTX and LA action is unknown as labeled by a question mark. P designates the pore region within the S5-S6 extracellular linker.1
The upper portion of this slide shows that the four domains of the sodium channel contains six alpha helix segments. The structure within the membrane is shown below. The segments are folded upon themselves and form a structure that makes up the pore of the channel, which is the space bounded by segments 5 and 6. Segment 4 is voltage sensitive and is believed to be responsible for “opening the gate” in response to membrane depolarization.

The sodium channel allows for the selective flow of Na+ from outside to inside of the cell Na channels and it can exist in at least 3 native conformations: resting, open (activated), and inactivated. During an AP, the Na channels open, Na ions flow into the cell depolarizing the cell. In milliseconds, Na channels inactivate and Na current ceases. The efflux of potassium ions restores the resting potential. The sodium-potassium ATP pump, which pumps the Na from inside to outside of the cell in exchange for potassium maintains the proper ionic gradients across the cell membrane.

While this figure is not exactly accurate, the sodium channel is composed of four domains, which are made up of six segments each. Note the following:

- The pore is selective for Na ions (selectivity filter)
- The S4 segment is voltage sensitive. Depolarization causes conformational changes in the pore, which promotes the influx of Na ions.
- The tetrodotoxin (TTX) receptors are on the extracellular surface. TTX is only effective when applied to the external membrane.
- The inactivation gate is on the internal surface of the membrane. Local anesthetics gain access to the pore when the channel is activated (internal surface gate is open).

This is probably a more accurate depiction of the Na channel. The four domains are folded onto themselves and the pore is lined only by segments 5 and 6, (not all six segments as is shown in the previous slide).
The figure on the left shows a “resting sodium channel.” In this conformation, the proteins that make up the pore are selectively excluding (filtering) the Na+ ions and preventing them to flowing down their concentration.

The figure on the right shows an “activated sodium channel.” There has been a change in the conformation of the protein structure owing to depolarization that now allows for flow of Na+ ions down their concentration gradient (from outside to inside the cell).

One portion of the channel determines its ion selectivity. Another portion of the channel serves as a gate that can open and close. The gate is controlled by a voltage sensor, which responds to the level of the membrane potential. The membrane potential is designated at the left of the figure by the net excess of positive and negative changes. Finally, an inactivation gate is shown. This limits the period of time the channel remains open, despite steady stimulation.

The solid gray portion of the figure shows the voltage sensor. The voltage sensor is a transmembrane alpha helix with fixed positive charges.

At a typical resting membrane potential (for example, -70 mV) the channel is closed. Then should any factor depolarize the membrane potential sufficiently (for example, to -50 mV), the voltage sensor moves outward and the gate opens.

Source:http://courses.washington.edu/conj/membrane/nachan.htm

Local anesthetics gain access to the pore via the intracellular side of the membrane when the Na channel is in the open or active state. Once inside the pore the cationic local anesthetic alters the Na channel in such a way that the flow of Na ions is stopped.

Additionally, some of the non-charged local anesthetic can gain access to the Na+ channel via the lipid bi-layer. Permanently non-charged benzoicaine probably works this way.
Many compounds can inhibit the sodium channel. Toxins, calcium channel blockers, \( \alpha_2 \)-adrenergic agonists, volatile general anesthetics, and meperidine can also inhibit Na channels.\(^2,3\)

To summarize, the sequence of local anesthetic block consists of diffusion of the non-charged local anesthetic base through the nerve sheath, and lipid bilayer, and into the Na\(^+\) channel (blockade), which prevents the flow of Na\(^+\) ions into the cell (decreased sodium conductance). This leads to a decrease in electrical depolarization, failure to achieve threshold, and a failure to propagate an action potential that culminates in conduction blockade.

Local anesthetics consist of an aromatic ring and an amine, separated by a hydrocarbon chain.

There are two types of local anesthetics based on the hydrocarbon chain linkage:
- Esters have [-CO-O-] linkage
- Amides have [-HN-CO-] linkage

Ropivacaine and levobupivacaine are single (S-) optical isomers. Other LAs are racemic mixtures or have no asymmetric carbons (see below).

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Cocaine (not shown), procaine, chloroprocaine, and tetracaine are the prominent local anesthetics of the local anesthetic ester group. They consist of an aromatic portion (left end), an ester link (center box) and a tertiary amine group (right end).

Procaine is the basic structure of this group. Chloroprocaine is procaine with the addition of a chloride molecule attached to the aromatic ring (arrow).

Tetracaine results from the substitution of butyl group for a hydrogen (left box), and the replacement of procaine’s ethyl groups with methyl groups (right box).

For simplicity, I show the amide local anesthetics as consisting of two types: “bupivacaine analogues” and “lidocaine analogues” (see next slide).

Bupivacaine analogues have the basic local anesthetic structure of an aromatic portion (left end), an aminoamide link and a tertiary amine group (right end).

Note that these compounds differ only by the aliphatic group attached to the tertiary amine. Mepivacaine has a methyl group, ropivacaine has a propyl group (I don’t know why they didn’t call it propivacaine), and bupivacaine has a butyl group.

All of these compounds have an isomeric carbon atom (just to the right of the link next to the tertiary amine group). Because of this, these compounds exist as enantiomers. Thus, a solution of these compounds is racemic and consists of “R” and “S” isomers depending on their ability to rotate polarized light.

We’ll see later that S isomers appear to be less toxic than R isomers.

Ropivacaine and levobupivacaine are solutions that contain only S isomers.

Mepivacaine and bupivacaine are racemic mixtures of R and S isomers.

Prilocaine and etidocaine are lidocaine analogues. They differ from lidocaine as follows:

Prilocaine has a methyl group attached to the carbon adjacent to the amino amide link (box) and the tertiary amine on the right has a hydrogen only in place of one of lidocaine’s ethyl groups and a propyl group instead of lidocaine’s second ethyl group.

Etidocaine has an ethyl group attached to the carbon adjacent to the amino amide link (box) and the tertiary amine on the right has a propyl group instead of one of lidocaine’s ethyl groups.

Clinically and in terms of its block properties, prilocaine is very similar to lidocaine.

On the other hand, etidocaine, is one of the fastest onset and longest acting anesthetics, presumably owing to all of the additional carbon atoms attached to the right of the amino amide link.
For convenience, local anesthetics can be classified as to potency and duration.\(^{4,6}\)

Low potency anesthetics are generally of shorter duration than are the more potent local anesthetics (see below).

The two agents of low potency and short duration are procaine, and chloroprocaine. Both are esters and they have a relative potency of 1 on an arbitrary scale of 1 - 6. Chloroprocaine is fast in onset in spite of its high pKa, probably because it is usually used in a 3% concentration. These agents have a duration of 30 - 90 minutes.

Lidocaine, mepivacaine and prilocaine are agents of intermediate potency and duration. All are amide local anesthetics and all have a relatively rapid onset owing to intermediate range pKa’s. Depending on the site and the amount injected, their duration of action ranges from 90 - 240 minutes.

The high potency and long duration local anesthetics are shown in this table. Ropivacaine has a relative potency of 4 in comparison to the other agents, which have a relative potency of 6.

Ropivacaine, bupivacaine, and levobupivacaine have an intermediate onset.

Tetracaine is slow in onset owing to its high pKa and because it is used in relatively low concentrations.

Etidocaine on the other hand has a fast onset, which is believed to be due to its extremely high lipid solubility.

This table illustrates the so-called “rule of Is.” It is a crutch that helps in recalling which local anesthetics are amides or esters. Local anesthetics whose name contains two “Is” are amides and those with only one I are esters. (Sanjay Datta is responsible for this rule)
Amides v. Esters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AMIDES</th>
<th>ESTERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stability</td>
<td>Stable</td>
<td>Unstable</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Liver</td>
<td>Plasma</td>
</tr>
<tr>
<td>Allergy</td>
<td>Rare</td>
<td>More common</td>
</tr>
</tbody>
</table>

Amides differ from esters in three important ways:

- Stability
- Metabolism
- Allergy

Amides are more stable in solution than are esters.

Amides are metabolized in the liver and excreted in the urine.

Esters are hydrolyzed in the plasma by pseudocholinesterase.

Allergy is extremely uncommon and rarely occurs with amides, but more common with esters. For example, procaine is converted to para-amino-benzoic acid (PABA). PABA is known to produce skin sensitivity reactions.

It is generally accepted that the potency of local anesthetics parallels their solubility in lipids. This is reasonable because the nerve membrane consists mostly of a matrix of lipids arranged in a bi-layer. The bi-layer is composed of polar heads (balls) located on outer and inner membrane surfaces and hydrophobic tails (sticks) that make up the center of the membrane.

The most lipid soluble local anesthetics gain easy access to the bi-layer and are able to cross the lipid membrane to gain access to the intracellular sodium channel pore.

The most lipid soluble agents (tetraacaine and etidocaine) are the most potent and have the lowest ED<sub>50</sub> (concentration required for 50% block)

The amino-esters are more potent than the amino-amides (most leftward curve).

The authors of this study speculate that the amino-esters may interact with a greater number receptor sites and this may explain their inherently greater potency.\(^7,8\)
In addition to the lipid bi-layer the nerve plasma membrane contains protein ion channels. In terms of neuronal conduction blockade, the Na+ channel is most critical. Classically the duration of local anesthetic action has been attributed to protein binding. This is consistent with the mechanism of action of local anesthetics a (see above) that postulate that the local anesthetic “binds” to the protein channel. Hence it is not a great leap to suggest that protein binding is important for duration of action because the local anesthetics which have the greatest protein binding also demonstrate the longest duration of action.4

Butterworth2 has challenged this concept:

“It is a misconception that the duration of regional anesthesia directly relates to LA protein binding. Protein binding refers to the mode by which drugs are transported in blood. More lipid-soluble LAs are relatively water-insoluble and, therefore, highly protein-bound in blood. More lipid soluble LAs are less readily removed by the blood stream from nerve membranes, and they are more slowly "washed out" from isolated nerves in vitro. The longer duration of LA action associates with increased lipid solubility, increased protein binding in blood, and with increased potency. It is mechanistically logical to associate duration with lipid solubility. The extent and duration of anesthesia can be correlated with local anesthetic content of nerves in animal experiments.”

This graph shows the classical dogma that the duration of brachial block relates to the ability of local anesthetics to bind to proteins.5

This graph shows that bupivacaine, tetracaine, and etidocaine, the local anesthetics of greatest lipid solubility (abscissa), are also the local anesthetic that are most highly protein bound (ordinate). Thus both lipid solubility and protein binding might result in prolonging the duration of local anesthetic action.9
Onset of local anesthesia is related to the non-ionized base moiety (B) and therefore to the local anesthetic’s pKa (dissociation constant). The non-ionized base is the moiety that is capable of penetrating the hydrophobic lipid bi-layer of the nerve membrane. On the other hand, the hydrophilic (lipophobic) cation (BH+) poorly penetrates the lipid by-layer.

This relationship is defined by the Henderson-Hasslebach equation:

$$\text{pH} = \text{pKa} + \log \left[ \frac{\text{base}}{\text{cation}} \right]$$

When the ratio of base to cation is 1 (the log of 1 is zero), the pH = pKa. Stated another way, when the pH = pKa, the concentration of base equals the concentration of cation.

For example, the pKa of lidocaine is 7.8. Therefore, the following holds true about the change in base and cation concentrations with change in pH:

<table>
<thead>
<tr>
<th>pH</th>
<th>[base]/[acid]</th>
<th>Conc. Base</th>
<th>Conc. Cation</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.0</td>
<td>0.0158</td>
<td>0.015</td>
<td>0.985</td>
</tr>
<tr>
<td>7.0</td>
<td>0.1584</td>
<td>0.136</td>
<td>0.864</td>
</tr>
<tr>
<td>7.4</td>
<td>0.3981</td>
<td>0.285</td>
<td>0.715</td>
</tr>
<tr>
<td>7.8</td>
<td>1.0000</td>
<td>0.500</td>
<td>0.500</td>
</tr>
<tr>
<td>8.0</td>
<td>1.5849</td>
<td>0.613</td>
<td>0.387</td>
</tr>
</tbody>
</table>

Note: For each incremental increase in pH, there is a ten-fold increase in the base concentration.

This graph shows that small changes in pKa cause large changes in the concentration of base at physiological pH (7.4).

<table>
<thead>
<tr>
<th>Local anesthetic</th>
<th>pKa</th>
<th>% base</th>
<th>Onset (min.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine</td>
<td>7.8</td>
<td>37</td>
<td>4</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>8.1</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>Tetracaine</td>
<td>8.6</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>Procaine</td>
<td>8.9</td>
<td>2</td>
<td>22</td>
</tr>
</tbody>
</table>

An exception to this rule is chloroprocaine, which has a high pKa (8.7), but a very fast onset.
This slide shows that when the injected volume is constant, an increase in the concentration of local anesthetic increases the degree of sensory anesthesia and the amount of motor block also increases.

However, as shown here, the ability to dissociate sensory from motor anesthesia is better with bupivacaine than with etidocaine. Even with low and intermediate concentrations of etidocaine, the amount of motor block in relation to sensory block is too great. Furthermore, with etidocaine it is nearly impossible to produce adequate analgesia without significant motor blockade. Thus etidocaine, which if used at all these days, is best used for orthopedic operations where profound motor block would be an advantage. Another advantage of etidocaine mentioned elsewhere is its rapid onset.

Bupivacaine shows great separation of sensory and motor anesthesia, especially at low concentration, which makes it an ideal agent for labor and postoperative analgesia where analgesia without motor block is desired.

This slide shows the effect of increasing doses of etidocaine (the same is true for all local anesthetics) on the onset of analgesia, the adequacy of the anesthesia and the anesthetic duration.

As the dose of etidocaine increases, the onset time decreases from 12 min. to 5 min, the adequacy of anesthesia increases from 40% to 100%, and the duration increases from 100 to 260 min.

The more local anesthetic injected, the faster it comes on, the better the block, and the longer it lasts. There is a limit, however to how much can and should be injected. The more that is injected, the greater is the likelihood of systemic toxicity.

With the exception of cocaine, all local anesthetics cause some vasodilatation (panel on the left). This results in the vascular absorption of the local anesthetic, which in addition to making less local anesthetic available for neural blockade increase the amount of local anesthetic that appears in the plasma. Increasing plasma concentrations increase the chance of the local anesthetic systemic toxic effects.

The center and right panels show that the addition of epinephrine to the local anesthetic produces vasoconstriction (arrows showing constricting of the veins both intra- and extra-neuronal). Hence, less local anesthetic is removed from the injection site making systemic toxicity less likely, and more local anesthetic enters the nerves improving and prolonging the neural blockade.

The effect of adding epinephrine on the duration of anesthesia relates to the block type.

Brachial block is increased from 50% for the lipid soluble agents like bupivacaine and etidocaine and nearly 100% for lidocaine, mepivacaine, and prilocaine.

On the other hand, the addition of epinephrine during epidural block prolongs lidocaine and mepivacaine anesthesia more than with prilocaine, bupivacaine and etidocaine. With epidural anesthesia, this is probably due to the greater vascularity of the epidural space, prilocaine’s ability to diffuse, and the greater amount of epidural fat to sequester bupivacaine and etidocaine.
This is a micrograph of a cross section through an area that is rich with nerve bundles. In addition to the nerves (N), the area consists of connective tissue (CT), which contains blood vessels (BV). When we do peripheral nerve blocks, we avoid injecting directly into the nerves to minimize the possibility of causing neural injury and we try to make our injection (Inj.) into the connective tissue near the nerves. In order for the block to develop completely, the local anesthetic must penetrate barriers such as the epineurium (E) and it must diffuse (arrows) to the center of the nerve bundles if complete block is to be achieved. The arrows show that the local anesthetic also diffuses into the blood vessels. This decreases the amount of local anesthetic available for neural blockade. Vasoconstriction minimizes the amount of local anesthetic absorption and it is the reason that epinephrine is added to local anesthetics.

Although local anesthetics are classified as agents of short, moderate, or long duration with slow or rapid onset, the type of anesthetic procedure performed affects these properties. In general, the most rapid onset but the shortest duration occurs with intrathecal or subcutaneous injections, while the slowest onset and the longest duration are seen with brachial plexus blocks. For example, spinal bupivacaine has an onset of approximately five minutes and a duration of approximately three to four hours. However, when bupivacaine is used for brachial plexus blockade, the onset time is 20 - 30 minutes and the duration averages ten hours. These differences in onset and duration are due in part to the anatomy of the injection site, the rate of vascular absorption, and the amount of drug used. In the case of spinal anesthesia, the absence of a sheath around the spinal nerves and the spinal cord, and the injection of the local anesthetic close to the target tissue is responsible for the rapid onset. On the other hand, the small amount of drug used for spinal anesthesia accounts for its short duration. In the case of brachial plexus blockade, the onset of anesthesia is slow because the local anesthetic is injected at some distance from the targeted nerves, and it must diffuse through various tissue barriers before reaching the nerves to be blocked. The long duration of brachial plexus blockade is probably due to decreased vascular absorption as well as the larger doses of drug routinely used for this anesthetic technique.

This graphic shows another example of how the site of injection affects onset and duration. In this example, 400 mg of lidocaine for brachial plexus block (40 ml of 1%) is compared to 400 mg for epidural anesthesia (20 ml of 2%) and 100 mg of bupivacaine for brachial block (40 ml of 0.25%) is compared to 100 mg (20 ml of 0.5%) for epidural anesthesia. When equal amounts of lidocaine or bupivacaine are used, the differences in onset and duration of epidural anesthesia v. brachial plexus block is likely due to the anatomy of the different sites and how they affect diffusion, and uptake and distribution of the local anesthetic.
AddingNaHCO₃toalocalanestheticispHadjustmentandnotcarbonation
ofthelocalanesthetic.Becauselidocainebaseispoorlysoluble,itis
preparedasaHClsalttoincreasetoolsolubility.Ontheotherhand,
carbonatedsaltsolutionsoflidocainearepreparedbybubblingCO₂through
awaterymulsionoflidocainebaseinthecold.Inthisway,acarbonated
saltsolutionoflidocaineloseswithoutadditionofHCl.Thissolution
hasapHof6.5(aboutthesameastheplainhydrochloridesolution)¹⁰
Unfortunately,carbonatedlocalanestheticsareonlycommerciallyavailable
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enhancesconductionblockadeisnotpreciselyknown,butfewer
possibilitiesexist:(1)carbondioxidemaybeadirectlocalanesthetic
effect,(2)theincreaseinCO₂insidethenervedecreasespHcausinglocal
anestheticcationtrapping,and(3)lossofCO₂asthevialisopenedincreases
thepHofthesolutionfrom6.5to>7.0makingmorefreebaseavailablefor
nervepenetration.Thefirsttwoofthesemechanismsarepredicatedonthe
rapiddiffusionofCO₂throughthenervemembraneeintotheaxoplasm.

Alkalinizationoflocalanestheticsolutionsisusedalsoquickentheonset
ofconductionblockade.Theadditionofsodiumbicarbonateincreases
the
ofthelocalanestheticsolution,invturnincreasingtheamountofdrugin
theunchargedbaseform.Thus,thelocalanestheticshoulddiffuseacross
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ofanesthesia.Indeed,someclinicalstudiesshowthattheadditionofsodium
bicarbonatetosolutionsoflidocaineorbupivacainespeedstheonsetof
brachialplexusorepiduralblockade.¹¹,¹²Inaddition,thedurationof
brachialplexusblockisprolongedaalsoincreasingthePHof
bupivacaine.¹³

Thisgraphicisasummaryoftheeventsthatarepostulatedtooccurwhen
NaHCO₃isaddedtoalocalanesthetic.Normally,localanestheticsolution
havearelativepH(4.5-6.5)andbecauseoftheirhighpKa,thereismore
poorlydiffusiblechargedLA~H⁺availablethantheneutralLA.Additionof
NaHCO₃(upperleft)producesH₂O,LAandCO₂.TheunchargedCO₂
andLArapidlydiffuseacrosstheplasmamembrane(lowerleft).Inside
theaxoplasm,CO₂picksupwatertoformcarbonicacid,whichliberatesa
H⁺thatreactswithLA(lowerright)toproduceLA~H⁺.Thisistheway
thelocalanestheticis“trapped”insidetheaxoplasmandisreferredtoas“ion
trapping”(upperright).
The purpose of this study by Ackerman, et al\textsuperscript{12} was to determine the effect of pCO\textsubscript{2} on the onset of epidural analgesia with chloroprocaine buffered to pH 7.7. They studied four groups consisting of ten patients each: C, control, commercial chloroprocaine (pH 4.35; pCO\textsubscript{2} = 11.8 ± 1.5 mmHg); B, chloroprocaine buffered with sodium bicarbonate (pH 7.7; pCO\textsubscript{2} = 113.0 ± 1.4 mmHg); T, chloroprocaine buffered with THAM (tromethamine) (pH 7.7; pCO\textsubscript{2} = 3.0 ± 0.3 mmHg), and BT, chloroprocaine buffered with sodium bicarbonate and tromethamine (pH 7.7; pCO\textsubscript{2} = 74.1 ± 1.0 mmHg).

The time to the onset of analgesia was significantly faster in Group B (2.7 ± 0.8 minute), while the onset of analgesia was significantly slower for Group T (5.4 ± 0.4 minute) than either Group C (4.2 ± 0.8 minute) or Group BT (3.4 ± 0.3 minute). Regression analysis revealed that the onset times of the buffered solutions were significantly related to pCO\textsubscript{2} (r\textsuperscript{2} = 0.81).

On the other hand, the duration of analgesia of Group T (55.7 ± 4.29 minute) and Group BT (47.5 ± 5.1 minute) were significantly longer than either Group C (27.0 ± 6.1 minute or Group B (26.2 ± 4.2 minute). Thus the onset of buffered epidural chloroprocaine was influenced by changes in pCO\textsubscript{2}, while the duration was affected by the choice of the alkalinizing agent.

The take home message is that while it is possible to decrease the onset of analgesia by buffering local anesthetics, it may come at the cost of shortening the duration of analgesia.

This study shows also that while buffering chloroprocaine with NaHCO\textsubscript{3} statistically significantly decreases the onset of epidural anesthesia, the actual gain (1.5-minute) is so small that the clinical usefulness of such a maneuver is questionable.
This study intended to determine the effect of adding sodium bicarbonate to lidocaine with and without epinephrine versus equivalent alkalinization by sodium hydroxide (NaOH) on onset, degree, and duration of peripheral nerve block.14

Part I examined alkalinization by sodium bicarbonate versus NaOH to pH 7.8 on 0.5% lidocaine, with and without epinephrine (1:100,000), prepared from crystalline salt.

Part II examined 0.5% and 1.0% commercial lidocaine solutions, with and without epinephrine, either unalkalinized or alkalinized with sodium bicarbonate or NaOH. With NaOH, pH was adjusted to 7.8, but with sodium bicarbonate, no pH adjustments were made to simulate clinical conditions.

In part I, addition of either NaOH or sodium bicarbonate to 0.5% lidocaine without epinephrine produced a faster onset than did unalkalinized lidocaine, without effecting degree or duration of block. In solutions with epinephrine there were no differences in onset, degree, or duration between lidocaine alkalinized with sodium bicarbonate versus NaOH.

In part II, addition of sodium bicarbonate or NaOH to 1.0% commercial lidocaine without epinephrine did not accelerate onset compared with the unalkalinized solution. However, adding sodium bicarbonate decreased the degree and duration of block by 25% and more than 50%, respectively, compared with lidocaine unalkalinized and alkalinized with NaOH. With epinephrine (not shown), sodium bicarbonate hastened onset without effecting degree and duration compared with the unalkalinized solution.

CONCLUSIONS: With 1% commercial lidocaine without epinephrine, sodium bicarbonate does not accelerate onset but decreases the degree and duration of block. However, in solutions with epinephrine, sodium bicarbonate hastens onset, without effecting degree or duration. [It is never as simple as it seems.]

In this study by DiFazio, et al.,11 a pH adjustment of lidocaine from 4.6 to 7.2 hastened the onset of epidural anesthesia only 2.5 minutes. This is intriguing, because this pH change results in a 332-fold increase in the amount of base present in solution at the higher pH. This is equivalent to doing epidural anesthesia with 455% lidocaine at pH 4.6! Why isn't the onset of anesthesia hastened more than it is? The answer may be that the effect of increasing the amount of base in solution on the onset of anesthesia has limits. Rud determined that, as the amount of lidocaine base increases, the concomitant speed of onset of nerve block is less than would be achieved with a linear relationship.15 It is possible that the concentrations of local anesthetics that we use clinically provide enough base (even at a low pH) so that the speed of onset is blunted because the increase in the amount of base due to the pH change occurs on the plateau (flat) portion of the curve.
Comparison of pH-Adjusted Solutions for Epidural Anesthesia

- The plain (no Epi) solution produces nearly the same effect as does the pH adjustment of the Epi containing solution.

This graphic shows that the onset of epidural analgesia (not anesthesia) is 5 minutes when an epinephrine solution (pH = 4.55) is used compared to 4 minutes for a solution that contains no epinephrine (pH = 6.35). Adjusting the pH to 7.2 further decreases the onset time to 2 minutes. While these time savings are statistically significant, they are not clinically important, especially when the amount of time required to find the NaHCO3, draw it up into a syringe, and mix it with the local anesthetic are taken into consideration.

There is a limit to the amount of sodium bicarbonate that can be added to local anesthetics, because high pH causes precipitation. Guidelines for adding sodium bicarbonate to the various local anesthetics are shown below. Another beneficial aspect of increasing the pH of local anesthetic solutions is that less pain is felt during intradermal or subcutaneous injection.

**SUGGESTED AMOUNTS OF NaHCO3 TO ADD TO LOCAL ANESTHETICS TO ADJUST pH**

<table>
<thead>
<tr>
<th>LOCAL ANESTHETIC</th>
<th>ml OF 4% NaHCO3 PER 20 ml OF LA</th>
<th>pH AFTER NaHCO3</th>
</tr>
</thead>
<tbody>
<tr>
<td>2% CHLOROPROCAINE</td>
<td>4</td>
<td>7.51</td>
</tr>
<tr>
<td>3% CHLOROPROCAINE</td>
<td>4</td>
<td>7.43</td>
</tr>
<tr>
<td>1% MEPIVACAINE</td>
<td>4</td>
<td>7.26</td>
</tr>
<tr>
<td>1.5% MEPIVACAINE</td>
<td>2</td>
<td>7.00</td>
</tr>
<tr>
<td>1% ETIDOCAINE</td>
<td>0.015</td>
<td>5.90</td>
</tr>
<tr>
<td>1% ETIDOCAINE (EPI)</td>
<td>0.1</td>
<td>5.73</td>
</tr>
<tr>
<td>1.5% ETIDOCAINE (EPI)</td>
<td>0.1</td>
<td>5.76</td>
</tr>
<tr>
<td>0.25% BUPIVACAINE</td>
<td>1</td>
<td>6.97</td>
</tr>
<tr>
<td>0.5% BUPIVACAINE</td>
<td>0.05</td>
<td>6.62</td>
</tr>
<tr>
<td>0.75% BUPIVACAINE</td>
<td>0.05</td>
<td>6.56</td>
</tr>
<tr>
<td>0.5% BUPIVACAINE (EPI)</td>
<td>0.3</td>
<td>6.37</td>
</tr>
<tr>
<td>0.75% BUPIVACAINE (EPI)</td>
<td>0.3</td>
<td>6.32</td>
</tr>
<tr>
<td>1% LIDOCAINE</td>
<td>4</td>
<td>7.43</td>
</tr>
<tr>
<td>1.5% LIDOCAINE</td>
<td>4</td>
<td>7.31</td>
</tr>
<tr>
<td>2% LIDOCAINE</td>
<td>4</td>
<td>7.24</td>
</tr>
<tr>
<td>1% LIDOCAINE (EPI)</td>
<td>4</td>
<td>7.21</td>
</tr>
<tr>
<td>1.5% LIDOCAINE (EPI)</td>
<td>4</td>
<td>7.16</td>
</tr>
<tr>
<td>2% LIDOCAINE (EPI)</td>
<td>4</td>
<td>7.08</td>
</tr>
</tbody>
</table>

(EPI) = Commercially prepared epinephrine solution
Local anesthetic solutions containing epinephrine have a pH of 4.5 to prevent oxidation of the epinephrine. Therefore, a larger increase in pH can be produced by adding sodium bicarbonate to these solutions compared to non-epinephrine containing solutions (pH = 6.5). As a result, solutions containing epinephrine show the greatest decrease in onset when their pH is adjusted with sodium bicarbonate.

An alternative to adjusting the pH with sodium bicarbonate is to add fresh epinephrine (5 µg/ml) to the plain local anesthetic just before injection. This produces an epinephrine containing solution with pH 6.5, without having to add sodium bicarbonate.

For each one pH value increase, the amount of non-charged local anesthetic (base) will increase ten fold. Thus adding 1 ml of NaHCO3 to 10 ml of lidocaine commercially prepared with epinephrine (pH = 4.5) will increase the pH of the solution to 6.5 and increase the non-charged base 100 fold. The same result can be achieved starting with a plain solution of lidocaine (pH = 6.5) and adding 1:1000 epinephrine (1 mg/ml) to it. Adding 0.05 ml epinephrine to each 10 ml of plain lidocaine will produce a lidocaine-epinephrine solution that has a pH of 6.5. The amount of non-charged local anesthetic will be the same whether NaHCO3 is added to a commercially prepared epinephrine solution or whether epinephrine is added to a plain lidocaine solution.

The popularity of using mixtures of local anesthetics for regional anesthesia has waxed and waned. The rationale for mixing local anesthetics is to compensate for the short duration of agents like chloroprocaine or lidocaine and the long latency of agents like tetracaine and bupivacaine. Mixtures of chloroprocaine and bupivacaine theoretically offer advantages of rapid onset and low systemic toxicity (chloroprocaine) and long duration (bupivacaine). Brachial plexus blockade with a mixture of chloroprocaine and bupivacaine results in quick onset and prolonged duration.

As shown in this graphic, the quick onset and prolong block seen with mixtures of chloroprocaine and bupivacaine in brachial block do not occur with epidural anesthesia. In epidural anesthesia, the duration of anesthesia with a mixture of chloroprocaine and bupivacaine is shorter than that owing to bupivacaine alone. Thus, the kind of regional anesthetic block influences whether or not mixtures of local anesthetics have the intended effect.
This graphic shows that if isolated nerves are allowed to recover from block with chloroprocaine or exposure to a metabolite of chloroprocaine and then blocked by bupivacaine, the time for 50% recovery of the bupivacaine block is decreased from 50 minutes to 22-25 minutes. The postulate is that a metabolite of chloroprocaine may inhibit the binding of bupivacaine to membrane receptor sites. Unfortunately a bupivacaine block, once established, can not be reversed by bathing the nerve in chloroprocaine or its metabolite.

Another explanation for the shorter duration of bupivacaine when it is mixed with or given after chloroprocaine, relates to pH. Mixing a low pH solution like chloroprocaine (pH = 3.56) with bupivacaine (pH = 5.6) results in a mixture that has a pH of 3.6. This decreases the amount of non-ionized bupivacaine by 100 fold, lessening the amount of bupivacaine that penetrates the nerve and shortening its duration. In one study, the duration of bupivacaine blockade was unaffected by chloroprocaine when the pH of the mixture was increased from 3.6 to 5.6.

EMLA is a topical anesthetic primarily intended for use on intact skin. It is a mixture of crystalline 5% lidocaine and 5% prilocaine base, which becomes fluid at room temperature. A lowering of the melting points of the constituents, similar to that produced when crystalline salt and ice are mixed causes this. Other combinations of crystalline local anesthetics produce similar effects.

Because of the high concentration gradients of the bases of lidocaine and prilocaine in EMLA cream, it is useful for anesthetizing intact skin.

EMLA is intended for use in starting IVs in children, minor dermatological operations like split-thickness skin grafting and the treatment of certain skin disorders. Unfortunately, it takes a fair amount of time for EMLA to penetrate the cornified epithelium and it must be applied under an occlusive dressing, up to 60-90 minutes before the intended painful procedure is carried out.

Topical anesthesia may be produced also with a 4% tetracaine gel.

The spread of epidural or spinal anesthesia is greater in pregnant patients compared to nonpregnant patients. This graphic taken from Bromage’s Epidural Anesthesia text book shows that the dose of local anesthetic (ml per segment) is less in pregnant than in non-pregnant patients.

Now that women are having children in their fifties and sixties, more research will have to be done to see if this relationship still hold for these advanced year of child bearing. Furthermore, by extrapolation, it appears that centenarians should require little or no anesthesia. These two comments should not be taken seriously.
The decreased local anesthetic requirement in pregnancy is attributed to exaggerated spread brought about by mechanical factors. Dilated epidural veins supposedly decrease the diameter of the epidural and subarachnoid space resulting in more extensive longitudinal spread of local anesthetic solution.

Recent studies indicate that the increased local anesthetic sensitivity during pregnancy may be due to physiologic alterations. For example, the spread of epidural anesthesia is similar during the first trimester of pregnancy and at term. This indicates that mechanical factors alone cannot explain the enhanced spread of anesthesia.

A similar increased sensitivity to median nerve block with 1% lidocaine was observed in pregnant women (third trimester) compared to nonpregnant women. This also argues for an increased sensitivity to local anesthetic blockade seen with pregnancy, that is due to factors other than the venous engorgement and exaggerated spread suggested for epidural anesthesia.

Studies done in isolated sheathed vagus nerves reveal a more rapid onset and an increased sensitivity (lower minimum anesthetic concentration) to bupivacaine induced conduction blockade in nerves obtained from pregnant rabbits.
Furthermore, producing a “pseudo-pregnant” state in male animals could reproduce the decrease in minimum anesthetic concentration seen in nerves of pregnant v. non-pregnant animals. Male rabbits treated with progesterone showed a decrease in minimum local anesthetic concentration required for conduction blockade compared to untreated rabbits and those treated with the oil vehicle used to solubilize the progesterone given to the animals that were made “pseudo-pregnant.” The increased sensitivity to bupivacaine was similar to that seen in truly pregnant rabbits.28

Experiments with isolated desheathed nerves indicate that the enhanced neuronal sensitivity owing to pregnancy may be due to fewer diffusion barriers instead of an increased sensitivity of the nerve membrane. A and B desheathed nerve fibers from pregnant animals are actually more resistant to local anesthetic block than those from nonpregnant animals.29 Since sheathed nerve fibers are more sensitive to local anesthetics, this implies that pregnancy decreases the diffusion barriers that the local anesthetic must penetrate to reach the receptor sites in the nerve where the block occurs.

All in all, these results suggest that hormonal changes associated with pregnancy alter the basic responsiveness of the nerves to local anesthetics.30 Thus, the dosage for regional anesthetic procedures probably should be reduced during all stages of pregnancy.

Studies on peak plasma concentrations of a fixed dose of certain local anesthetics used in various blocks have been performed to a limited extent. This figure shows the order of peak concentrations for a number of amide-linked local anesthetics with the highest after intercostal block and higher after epidural than after brachial plexus block. The fact that all studies show that the highest peak concentrations occur after intercostal nerve block independent of the local anesthetic used is thought to be caused by the fact that several injections are made and the absorption area is large.31
Patient factors when large doses LA are given (cont.)

- Age
- Drugs

Local Anesthetic Pharmacokinetics, Metabolism, and Maximum Recommended Doses

- Uptake = absorption from the injection site
- Vascularity
- Tissue structure surrounding the injection site
- Addition of epinephrine
- Distribution (VDSS)
- Elimination is clearance of the drug
- Metabolism
- Excretion
- Elimination half-life (t1/2)

This graphic shows the important pharmacokinetic parameters of the amide-linked local anesthetics. The absorption of the local anesthetic into the circulation depends primarily on the vascularity of the site of deposition (injection) as well as on the structural composition of the surrounding tissues (e.g., presence of lipid).

Because of the huge interindividual and interblock variations and the fact that systemic toxicity of the amide-linked local anesthetics is caused by the un-bound (free) local anesthetic in plasma, the magnitude of a safe dose of the local anesthetic should not be based on the total plasma concentrations of the drug.

The volumes of drug distribution at steady state (Vdss) of local anesthetics occurs when uptake by less-perfused organs, together with simultaneous biotransformation, are matched by drug release from well-perfused organs. VDSS exceeds the total body volume because local anesthetics are more soluble in fat, liver, and brain and other organs than in water.

The most important parameter is the elimination half-life (t1/2). It indicates how soon another dose or at which rate a continuous infusion of the local anesthetic can be administered safely. As a rule, 5 half-lives are required for a decline of the plasma concentration to near zero.

For example, bupivacaine is the most toxic of the currently used local anesthetics. It has an elimination half-life of about 3 hours. The administration of a second dose of bupivacaine (2 mg/kg) with epinephrine for intercostal nerve blocks after 6 hours, resulted in a peak plasma concentration that was 10% higher than the first one. In continuous inter-scalene brachial plexus block with an initial dose of 150 to 200 mg of 0.25% bupivacaine, an infusion at a rate of 6 to 10 mL/h, increased the total plasma concentration by about 20%, during the second postoperative day.31

Age, dysfunction of renal, hepatic, and cardiac systems, pregnancy and drug interactions all affect the dose requirements for LA blockade. In particular this refers to the higher doses necessary for major nerve blocks.

All of these conditions decrease the clearance of local anesthetics and a reduced dosage is indicated.

The reduced dosages associated with pregnancy are due to increased sensitivity, [possible] increased [cardiac] toxicity, and increased absorption (increased cardiac output causes increased perfusion of the injection site and this increases absorption) of local anesthetics.31

Many drugs inhibit the cytochrome P450 enzyme system that metabolize local anesthetics, which decrease clearance and elimination. Lesser amounts of local anesthetics should be injected when patients are receiving these enzyme inhibitors.31
The current recommendations of maximum local anesthetic doses in Finland, Germany, Japan, Sweden, and the United States are shown here. Such doses have usually been determined by extrapolating data obtained from laboratory animals to man, followed by clinical investigations in man using these extrapolated doses for peripheral nerve blocks and epidural block. Published case reports of systemic toxicity in patients are also referred to when recommendations have been given.

Resenberg, et al state that exact recommendations regarding *highest allowable doses of the local anesthetics* cannot be given. They suggest that anesthesiologists be guided by modern high-quality textbooks of regional anesthesia.

Adding epinephrine (2.5-5 ug/mL) to local anesthetic solutions is useful for reducing absorption. Because clearance is reduced by advanced age, renal, hepatic, and cardiac dysfunction, they recommend individualizing the dose of local anesthetic instead of relying on a standard milligram dose for a particular regional anesthetic block.

And, at no extra charge!

Determinants of the maternal uterine artery concentration (output to the fetus) of local anesthetic are: total dose, route of administration, epinephrine in solution, maternal metabolism and excretion, maternal protein binding, maternal pH and the pKa of the drug.

Determinants of the fetal umbilical artery concentration are: umbilical vein concentration (input), fetal pH, fetal protein binding, fetal tissue uptake, nonplacental elimination (fetal hepatic metabolism and renal excretion).

The transfer of drug from mother to fetus occurs at the placenta and in the intervillous space by Fick’s Law of passive diffusion. It is the free drug that is transferred because the local anesthetic bound to plasma proteins will not diffuse across the placenta.
Effect of differential protein binding by maternal and fetal blood

Maternal plasma | Fetal plasma
--- | ---
80% binding | 67% binding
- bound bound bound bound bound bound bound bound
- Free (20%) Free (35%) bound bound bound bound bound bound bound
- (4) + (1) (1) + (2)
5 molecules | 3 molecules

Effect of differential protein binding by maternal and fetal blood

Albumin, is plentiful, but has low affinity for local anesthetics. Globulins, are less plentiful but have high-affinity for local anesthetics. Alpha-1-acid glycoprotein (AAG) is the most reactive globulin. Fetal blood has 60% the albumin content of maternal plasma and 20% to 30% of the maternal AAG concentration. This limits the maternal-to-fetal transfer of local anesthetic. The more protein-bound the local anesthetic (e.g., bupivacaine), the more powerful is maternal trapping, and less local anesthetic enters the fetal circulation.

Only free (unbound) drug can cross the placental barrier. Free to cross in either direction, unbound local anesthetic equilibrates across the placenta. For a local anesthetic that is 80% bound to maternal plasma protein one unbound local anesthetic molecule in maternal plasma is free and four are plasma bound. If the fetal plasma binds half as many local anesthetic molecules (i.e., two) as maternal plasma then for each unbound local anesthetic molecule in fetal plasma, two will be plasma bound. Hence, the maternal plasma contains five local anesthetic molecules (one free, plus four bound) versus three molecules in fetal plasma (one free, plus two bound). The local anesthetic concentration in fetal blood is 60% of that in maternal blood (i.e., the fetal-maternal drug ratio = 0.6).

This hypothetical fetal-maternal gradient of 0.6 is quite close to that for: moderately bound local anesthetics such as lidocaine or mepivacaine. For high protein-bound bupivacaine and ropivacaine, the gradient is 0.3 to 0.4. At first glance this would make highly protein-bound local anesthetics a desirable choice for obstetric anesthesia, as less total drug crosses the placenta to reach the fetus. This is true in the short term but over time and with continuous infusion, the maternal-fetal gradient is overcome and mother and fetus plasma levels approach equilibrium.

Also worrisome is the fact that the fetus is less able to metabolize and clear local anesthetic than older children and adults. This image shows the effect of fetal acidemia on the ratio of the fetal artery to maternal artery lidocaine concentration during a continuous maternal infusion of lidocaine. The ratio is increased in the fetus during the acidemia owing to cationic trapping. As free lidocaine crosses the placenta, it is converted in the acidotic fetus to the charged moiety that can not back diffuse and the lidocaine becomes trapped in the fetus. Correction of the fetal pH reverses the ratio of free to charged local anesthetic, making more free lidocaine available for back diffuses down its concentration gradient into the mother. With elevation of the pH the fetal artery to maternal artery lidocaine concentration is restored to normal.
References