Local anesthetics and steroids: Contraindications and complications – clinical update

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Conflict of Interest

- None
How Chronic Pain Killed My Husband

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By Meredith Lawrence, Guest Columnist


When Painkillers Kill

Prescription opioid painkillers are now the leading cause of fatal overdoses

https://www.aarp.org/health/drugs-supplements/info-11-2011/painkillers-dangerous-effects.html
Introduction: > 25 million adults (11.6%) in the US have chronic pain

Suicide has been increasing, 10th leading cause of death

Aim: To estimate the prevalence of chronic pain among suicide decedents and to characterize suicide decedents with and without chronic pain

Methods: Retrospective analysis of National Violent Death Reporting System (NVDRS) in US, data from 18 states about suicide decedents who died from 2003 to 2014:
- demographic characteristics
- mechanism of death
- toxicology results
- precipitating circumstances
- suicide planning and intent

Results: Of 123,181 suicide decedents 10,789 (8.8%) had evidence of chronic pain (the percentage increased from 7.4% to 10.2%)

53.6% of suicide decedents with chronic pain died of firearm-related injuries and 16.2% by opioid overdose

Conclusion: Chronic pain may be an important contributor to suicide

Access to quality, comprehensive pain care and adherence to clinical guidelines may help improve pain management and patient safety
Glucocorticoids

- Glucocorticoids - class of steroid hormones released by adrenal cortex (corticosteroids):
  - control metabolism including glycemia
  - immunomodulatory effects
  - anti-inflammatory effects

- Mechanisms of action: activate/ inactivate gene transcription related to inflammatory proteins and cytokines

- Pharmacokinetics: synthetic glucocorticoid molecules have higher affinity for steroid receptors (SR) in the cytoplasm than molecules of endogenous glucocorticoids and last longer at the injection site!
Injectable steroids for pain treatment

- 1940 Thorn GW - the first use of intraarticular corticosteroids
- 1951 Hollander JL established the practice of hydrocortisone injections in joints, bursa, tendon sheaths in various conditions (rheumatoid arthritis, osteoarthritis, bursitis, systemic lupus erythematosus and gout) for suppression of inflammatory symptoms

- Routine steroid injections to treat painful musculoskeletal conditions
- Local anesthetics (LAs) may be combined with steroids:
  - to provide immediate short-term pain relief
  - to increase the volume and the dispersion of the injectate
  - for diagnostic feedback by differentiating between local and referred pain

Steroids for local pain treatment - clinical indications

- **Articular diseases**
  - **Inflammatory arthritis:**
    - Rheumatoid arthritis (RA)
    - Gouty arthritis
    - Psoriatic arthritis
    - Osteoarthritis
- **Tendon disorders:**
  - Synovitis, bursitis, fasciitis, tendinitis
  - Tendinosis; Stenosing tenosynovitis - de Quervain; Trigger finger
  - Adhesive capsulitis of the shoulder (frozen shoulder)
  - Carpal tunnel syndrome
- **Other disorders:**
  - Myofascial trigger points
  - Rheumatoid nodules
  - Costochondritis
  - Lumboischialgia
  - Facet joint syndrome
  - Dupuytren's contracture
  - Ganglion cystis
  - Neuromas
### Injectable steroids for pain treatment - physical characteristics

<table>
<thead>
<tr>
<th>Steroids</th>
<th>Chemical structure</th>
<th>Physical characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylprednisolone acetate</td>
<td>Esters</td>
<td>Highly insoluble in water Form microcrystalline suspensions (particle aggregation) Slow release at the site of injection and longer duration of action</td>
</tr>
<tr>
<td>Triamcinolone acetate*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Betamethasone acetate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexamethasone sodium phosphate</td>
<td>Non-esters preparations</td>
<td>Freely soluble in water Clear preparations (nonparticulate) Quicker onset of effect (reduced duration of action) Higher potency than esters (less doses to achieve similar potency)</td>
</tr>
<tr>
<td>Betamethasone sodium phosphate</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*particle aggregation

Clinical use of injectable steroids

- Intraarticular steroid preparations (concentration and duration of action):
  - methylprednisolone acetate (Solu-Medrol) 40-80 mg/mL 8 days
  - triamcinolone acetonide (Kenalog) 10-40 mg/mL 14 days
  - triamcinolone hexacetonide (Aristospan) 20 mg/mL 21 days
  - betamethasone acetate (Betaject) 6 mg/mL 9 days
  - dexamethasone sodium phosphate (Decaject) 4 mg/mL 6 days

<table>
<thead>
<tr>
<th>JOINT SIZE</th>
<th>methylprednisolone acetate, mg</th>
<th>triamcinolone acetonide, mg</th>
<th>betamethasones, mL</th>
<th>dexamethasone sodium phosphate, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>LARGE</td>
<td>20-80</td>
<td>10-15</td>
<td>1-2</td>
<td>2-4</td>
</tr>
<tr>
<td>MEDIUM</td>
<td>10-40</td>
<td>5-10</td>
<td>0,5-1</td>
<td>2-3</td>
</tr>
<tr>
<td>SMALL</td>
<td>4-10</td>
<td>2,5-5</td>
<td>0,25-5</td>
<td>0,8-1</td>
</tr>
</tbody>
</table>
Contraindications to local injections of steroids

■ Absolute
- Periarticular infection – introduction of local infection into the joint
- Septic joint, sepsis, bacteremia – exacerbation of existing infections
- Intraarticular fracture – steroids inhibit bone healing
- Joint instability – worsening of joint instability (weakening of the capsule and ligaments, development of subchondral osteonecrosis)

■ Relative
- Juxta-articular osteoporosis – steroids could worsen bone density
- Coagulopathy (anticoagulants are not contraindication for aspiration or joint and soft tissue injections with narrow needles)
- Frequency of injection (safe frequency varies according to cartilage depth – up to three times in one year and one injection every six weeks)
### Adverse effects and complications of steroid local injections

| Adverse events | Systemic | Facial flushing  
Hyperglycemic effect (in patients with diabetes)  
Iatrogenic adrenal suppression  
Menstrual disturbances  
Neurotoxicity (preservatives)  
Embolisation by microcrystalline formulations - spinal cord /cerebral embolic infarction (transforaminal injections) |
|----------------|----------|----------------------------------------------------------|
| Local          |          | Postinjection flare (local increase of inflammation)  
Postinjection pain  
Subcutaneous atrophy  
Skin depigmentation  
Soft tissue calcifications |
| Potential complications | Local | Tendon rupture  
Articular hyaline cartilage damage (dexamethasone has no chondrocyte toxicity)  
Inhibit bone healing  
Septic arthritis  
Avascular necrosis (osteonecrosis) |
Complications of steroid intraarticular injections

Subchondral erosions and sclerosis in the femoral head in septic joint after intraarticular steroid therapy

Steroid-induced osteoporosis (GIOP)

Bacterial septic arthritis of the left shoulder following fluoroscopy-guided corticosteroid injection


- The expert panels in Germany reviewed 1528 cases of treatment errors relating to injections; in 278 cases complications arose after local steroid injections (intraarticular, paravertebral, intramuscular, other locations)

- The most common treatment errors:
  - delayed recognition of infection (24 cases)
  - patients were not informed of the risks (20 cases)
  - inadequate aseptic technique (18 cases)
  - injection at too short intervals (14 cases)
  - too superficial gluteal injection (14 cases)
  - lack of indication (13 cases)
  - errors of organization and documentation (6 cases)
  - excessive doses (4 cases)

- Conclusions
  - Injections must be performed in adherence to the manufacturer’s instructions
  - Intraarticular injections should be performed for aseptic inflammation
  - Aseptic technique should be strictly maintained
  - The indication and informed consent should be double-checked
Local anesthetics

- **AMINO ESTERS**
  - Hydrolyzed in plasma by pseudocholinesterase
  - Relatively unstable in solution
  - Allergic hypersensitivity reactions secondary to the breakdown product para-aminobenzoic acid

- **AMINO AMIDES**
  - Biotransformation by enzymes (liver)
  - Extremely stable in solution
  - Some preparations contain preservatives whose chemical structure is similar to PABA
  - True allergic reactions are rare

<table>
<thead>
<tr>
<th>Procaine</th>
<th>Ropivacaine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetracaine</td>
<td>Etidocaine</td>
</tr>
<tr>
<td>Chlorprocaine</td>
<td>Prilocaine</td>
</tr>
<tr>
<td>Levobupivacaine</td>
<td>Articaine</td>
</tr>
</tbody>
</table>

Amino-esters are derivatives of PABA which is known to be allergenic and may produce allergic reactions. Majority of reactions to LAs are non-allergic.
Functional characteristics of LAs

- **Dissociation constant pKa:** onset of action
  - greater fraction of neutral base forms - more rapid onset

- **Lipid solubility:** high lipid solubility - higher potency

- **Protein binding:**
  - low affinity to plasma proteins – free drug fraction increased - higher potential for systemic toxicity
    - Low: procaine, chloroprocaine
    - Intermediate: lidocaine, mepivacaine, prilocaine
    - High: bupivacaine, ropivacaine, etidocaine, tetracaine (longer duration of action)
  - local anesthetics with high affinity for protein binding remain bound to nerve membranes longer - increased duration of action.

- **Intrinsic vasoactive effects:**
  - vasodilators - greater vascular uptake from injection site into the central circulation - higher potential for systemic toxicity
Comparative physicochemical characteristics of LAs

<table>
<thead>
<tr>
<th>LA</th>
<th>RELATIVE POTENCY</th>
<th>PROTEIN BINDING, %</th>
<th>pK</th>
<th>LIPID SOLUBILITY</th>
<th>ONSET</th>
<th>DURATION OF ACTION, min</th>
<th>MAXIMAL SAFE DOSE, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procaine</td>
<td>1</td>
<td>5,8</td>
<td>8,9</td>
<td>1,7</td>
<td>Intermediate</td>
<td>30-60</td>
<td>500</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>2</td>
<td>55</td>
<td>7,8</td>
<td>25</td>
<td>Rapid</td>
<td>80-120</td>
<td>200</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>8</td>
<td>96</td>
<td>8,1</td>
<td>346</td>
<td>Slow</td>
<td>180-360</td>
<td>175</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>6</td>
<td>95</td>
<td>8,1</td>
<td>115</td>
<td>Intermediate</td>
<td>140-200</td>
<td>375</td>
</tr>
</tbody>
</table>
Biological mechanism of LA failure – inflammation

Local anesthesia may not be successful when LAs are administered in the region of inflamed tissue!

1. Local tissue acidosis (pH ↓) leading to a greater proportion of ionised hydrochloride form which diffuses poorly

<table>
<thead>
<tr>
<th>LA</th>
<th>% of total drug in base forms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pK</td>
</tr>
<tr>
<td>Benzocaine</td>
<td>3,5</td>
</tr>
<tr>
<td>Mepivacaine</td>
<td>7,6</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>7,9</td>
</tr>
<tr>
<td>Etidocaine</td>
<td>7,7</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>8,1</td>
</tr>
<tr>
<td>Tetracaine</td>
<td>8,6</td>
</tr>
<tr>
<td>Procaine</td>
<td>8,9</td>
</tr>
<tr>
<td>2-Chloroprocaine</td>
<td>9,1</td>
</tr>
</tbody>
</table>

2. Increased nerve excitability
3. Increased local blood flow and absorption from the site of action
Spread of LA after injection

Anesthetic

BH⁺ ↔ B + H⁺

Non specific tissue binding

Systemic tissue

Blood stream

Liver: hepatic metabolism

Excretion by kidney

Neural axonal blockade

Skin

Plasma concentration of LA Cp after peripheral block
The dose of LA

The absorption of LA from the site injected
  - Vasoactivity of the LA
  - Site vascularity: IV > tracheal > intercostal > paracervical > epidural > brachial plexus > sciatic > subcutaneous

- Biotransformation, excretion

Uptake of local anesthetics based on different site of blockade

The site of injection plays an important role in toxicity!
Toxicity

<table>
<thead>
<tr>
<th>Category of LA toxic reactions</th>
<th>Local/ Systemic</th>
<th>Systemic</th>
<th>Localized</th>
</tr>
</thead>
</table>
| Allergic reactions            |                 | Cardiovascular system toxicity | Tissue toxicity:  
                                |                 | • neurotoxicity 
                                |             | • myotoxicity  |
| Central nervous system toxicity|                 |          |             |
| Methemoglobinemia             |                 |          |             |

The table shows categories the toxic effects of LAs.

In excessive doses, all LAs have the potential to produce toxicity in any type of tissue!
**Allergic reactions to LA**

- **Delayed contact allergy** (*delayed onset*, peak within 72h): localized dermatitis, swelling, mucosal inflammation at the site of injection – assess urgency of procedure:
  1. Elective or can be postponed – refer to patch testing
  2. Urgent:
     - LA associated with past reaction:
       - known – choose a different LA
       - not known - choose lidocaine
       - avoid LAs (if possible)

- **Immediate allergy** (*rapid onset*, <1h): pruritus, urticaria, angioedema, bronchospasm, hypotension
  1. Elective or can be postponed – refer to skin testing
  2. Urgent = the same procedure as for urgent delayed allergy

- **A true anaphylactic** allergy is extremely rare
A case report reported a middle-aged woman with documented history of anaphylactic reaction to lidocaine.

Allergist declined to test her for ester-type allergies because of previous anaphylactic reactions to amide type LA during testing.

The patient wanted to avoid GA. Dental treatment was performed under maxillary infiltration with anesthetic mixture of 1% diphenhydramine with 1:100,000 epinephrine.

This case emphasis that patients should be informed of alternative medications and forms of treatment.
Methemoglobinemia

- Prilocaine in high doses (600 mg)
- Metabolite O-toluidine is responsible for the oxidation of hemoglobin to methemoglobin → cyanosis
- The peak levels are directly related to the total dose and may not occur until 4-8 hours after administration
- Prilocaine should not be used in obstetrics!
- Spontaneously reversible or IV methylene blue
Local tissue toxicity

- **Neurotoxicity** - transient or long-term neurologic symptoms or permanent neural deficits
  - High concentrations / large volumes of LA
  - Chemical contamination of the LA solution
  - Preservative (sodium bisulfite) in LA solution
  - Neural ischemia produced by local pressure or hypotension
  - Intraneural injection and direct trauma from the needle

- **Myotoxicity** – reversible (muscle regeneration within 2 weeks)

- **Chondrocyte toxicity** – longer exposure to high concentrations (0.5% bupivacaine, formulations with epinephrine)
Local anesthetic systemic toxicity, LAST

- Life-threatening adverse event associated with the accidental intravascular injection of LA
- LAST events: immediately following injection (delayed presentation is rare)
- CNS toxicity = most common feature of LAST (68%–77%), primarily in the form of seizures
- LAST incidence: 3 per 10,000 peripheral nerve blocks PNBs\(^1\) / 0.03%, or 0.27 episodes per 1000 PNBs\(^2\)
- > 20,000 pts (>25,000 PNBs): 22 episodes of LAST, moderate signs of systemic toxicity (1 cardiac arrest)\(^3\):
  - 1:1000 LA technique without ultrasound vs. 1:1600 with ultrasound
  - *ultrasound guidance (UGRA) may improve safety because it is associated with a reduced risk of LAST*

\(^1\)El-Boghdadly K et al. Local Reg Anesth 2018;11:35-44
Risk factors for developing LAST

- **Drug**: CC/CNS ratio = “the ratio of drug dose required to cause cardiovascular collapse to the drug dose required to produce seizures” (low CC/CNS ratio - more cardiotoxic LA)
  - ropivacaine and levobupivacaine have higher CC/CNS ratios than racemic bupivacaine

- **Patient related**:
  - extreme of age (neonates and infants, elderly)
  - pregnancy
  - renal /cardiac /hepatic disease

- **Technique**:
  - LA infiltration techniques (20%)
  - central neuraxial block (epidural, caudal) (15%)
  - continuous infusion (13%)

El-Boghdadly K et al. Local Reg Anesth 2018;11:35-44
Systemic toxicity-sequence of events

Cascade of events beginning with CNS symptoms increasing in severity from excitation to seizure and coma. CNS excitation first causes tachycardia and hypertension, but subsequently, cardiac side-effects predominate and lead to CV collapse.

60% of LAST cases follow the classical cascade, and there is interindividual variability in presentation!

Relationship between convulsive threshold dose and anesthetic potency of LA

As concentration of LA in systemic circulation increases various CNS and CVS signs appear

<table>
<thead>
<tr>
<th>LA</th>
<th>RELATIVE ANESTHETIC POTENCY</th>
<th>CONVULSIVE THRESHOLD DOSE (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROCAINE</td>
<td>LOW (1)</td>
<td>19,2</td>
</tr>
<tr>
<td>CHLOROPROCAINE</td>
<td>MODERATE (1)</td>
<td>22,8</td>
</tr>
<tr>
<td>LIDOCAINE</td>
<td>MODERATE (2)</td>
<td>6,4</td>
</tr>
<tr>
<td>MEPIVACAINE</td>
<td>MODERATE (2)</td>
<td>9,8</td>
</tr>
<tr>
<td>PRILOCAINE</td>
<td>MODERATE (2)</td>
<td>&gt;6</td>
</tr>
<tr>
<td>BUPIVACAINE</td>
<td>HIGH (8)</td>
<td>1,6</td>
</tr>
<tr>
<td>ETIDOCaine</td>
<td>HIGH (8)</td>
<td>3,4</td>
</tr>
<tr>
<td>TETRACAINE</td>
<td>HIGH (8)</td>
<td>2,5</td>
</tr>
</tbody>
</table>

Inverse relationship between the intrinsic anesthetic potency and the dosage required to induce CNS toxicity.
Cardiovascular system (CVS) toxicity

- CVS toxicity: dose and anesthetic potency
  - LA with high lipid-solubility, protein-binding and anesthetic potency are more cardiotoxic
    - Low concentrations: beneficial effect
    - High concentrations: refractory arrhythmias, cardiovascular collapse CC

- Relative potency for negative inotropic effect
  - Low: procaine, chloroprocaine
  - Intermediate: lidocaine, mepivacaine, prilocaine
  - High: etidocaine, bupivacaine, tetracaine

- Cardiac resuscitation is more difficult after bupivacaine–induced CC

- S forms of bupivacaine are less cardiotoxic than the R form
Management of LAST

- Early recognition of clinical symptoms and supportive treatment:
  - Stop injection, call for help
  - Maintenance of oxygenation and ventilation
  - Seizure control (antiepileptic drugs)
  - Manage arrhythmias, cardiovascular support:
    - ALS protocols, for CC: low dose epinephrine \( \leq 1 \text{ mcg/kg} \), avoid vasopressin, for arrhythmias - amiodarone as first line antiarrhythmic, avoid lidocaine and other sodium channels blockers, avoid beta-blockers and calcium channels blockers
    - Cardiac arrest – cardiopulmonary bypass if ILE and vasopressor therapy failed
  - Administer “Lipid rescue” 20% Intralipid Emulsion ILE

How to avoid complications?

- Careful patient selection and preoperative patient evaluation
- Complications could be avoided by limiting the total doses administered and using appropriate administration technique with incremental injection and testing doses
- Aseptic regional anesthesia technique
- Fluoroscopy, computed tomography imaging and ultrasound scans in invasive pain treatment
- Avoiding intraarticular corticosteroids before arthroplasty reduces risk of postoperative joint infection
- In transforaminal epidural steroid injections avoid the use of particulate corticosteroids and ropivacaine (vasoconstrictive properties)
- Close monitoring of well informed patient improves clinical outcomes and patient safety.