Local Anesthetics

Contents of a Local Anesthetic Cartridge

- Local Anesthetic
  - Esters
  - Amides
- Vasoconstrictor
- Preservative
  - Sodium Metabisulfite
- Sodium Chloride and Sterile Water
Local Anesthetics

• Esters
  - Benzocaine
  - Chloroprocaine (Nesacaine)
  - Cocaine
  - Procaine (Novocaine)
  - Proparacaine
  - Tetracaine (Pontocaine)

• Amides
  - Articaine (Septocaine)
  - Bupivacaine (Marcaine)
  - Etidocaine (Duranest)
  - Lidocaine (Xylocaine)
  - Mepivacaine (Carbocaine)
  - Prilocaine (Citanest)
  - Ropivicaine

Systemic side effects

• Local anesthetic
  - CNS excitation
    • seizures
    • depression
  - CV excitation
    • arrhythmias

• Vasoconstrictor
  - Increase heart rate
  - Increase blood pressure
Interactions with Local Anesthesia

- Patients treated for ADD/ADHD
- Patients treated for narcolepsy
- Patients treated for obesity
- Patients treated for depression
- Patients treated for enuresis
- Stimulants
- Antidepressants
- Antipsychotics
- Beta-Blockers
- Monoamine Oxidase Inhibitors (MAOIs)

Facts and Comparisons (Articaine/epinephrine)

- **Vasoconstrictor toxicity:** Articaine/epinephrine contains epinephrine, a vasoconstrictor that can cause local or systemic toxicity and should be used cautiously. Local toxicity may include ischemic injury or necrosis, which may be related to vascular spasm. Use articaine/epinephrine with caution in patients during or following the administration of potent general anesthetic agents because cardiac arrhythmias may occur under such conditions. Patients with peripheral vascular disease and those with hypertensive vascular disease may exhibit exaggerated vasoconstrictor response.

  The American Heart Association has made the following recommendation regarding the use of local anesthetics with vasoconstrictors in patients with ischemic heart disease: "Vasoconstrictor agents should be used in local anesthesia solutions during dental practice only when it is clear that the procedure will be shortened or the analgesia rendered more profound. When a vasoconstrictor is indicated, extreme care should be taken to avoid intravascular injection. The minimum possible amount of vasoconstrictor should be used."
**Vasoconstrictor**

- Decrease systemic absorption
  - decrease systemic side effects
  - decrease systemic uptake and metabolism
  - Increase duration of action
- Decrease bleeding

**Distribution and Activity of Receptors**

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<td>α, β2</td>
<td>Vasoconstriction, Vasodilation</td>
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Vasoconstrictors

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<tr>
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<td>1/20</td>
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</tr>
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Vasoconstrictors available in local anesthetics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dilution</th>
<th>Maximum Cartridges for Healthy</th>
<th>Maximum Cartridges for Cardiac</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levonordefrin</td>
<td>1/20,000</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Levarterenol</td>
<td>1/30,000</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>1/50,000</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1:100,000</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>1:200,000</td>
<td>20</td>
<td>4</td>
</tr>
</tbody>
</table>
Psychostimulants for ADD/ADHD and Narcolepsy

- Methylphenidate
  - IR or chewable
    - Ritalin, Methylin
  - ER, SR
    - Ritalin LA, SR, Metadate, Methylin ER, Metadate CD
  - Concerta®
    - Coated with immediate release
    - contains an osmotic pump providing gradual release over 10 hours
    - produces slightly ascending serum concentrations
      - Daytrana TD (9 hr)
  - Dexamethasone phosphate (IR, ER)
    - Focalin (10 hr)

- Amphetamines
  - Dextroamphetamine
    - Dexedrine Spansules®, Dextrostat
  - Amphetamine/dextroamphetamine
    - (Adderall, Adderall XR)
  - Lisdexamfetamine Dimesylate
    - (Vyvanse®) (13 hr)
  - Pemoline (Cylert®)
  - Analeptics
    - Caffeine
    - Modafinil
      - Provigil

Patients using prescription appetite suppressants

- Benzphetamine
  - Didrex
- Mazindol
  - Mazanor, Sanorex
- Phendimetrazine
  - Bontril, Plegine, Adipost, Dital, Dyrexan-OD, Melfiat-105, Prelu-2, Rexigen Forte
- Phentermine
  - Fastin, Zantrel, Ionamin, Adipex-P, Obe-Nix 30
- Sibutramine
  - Meridia
Sympathomimetic Agents

- Direct acting-directly stimulates receptor
  - epinephrine
  - norepinephrine
  - levonordefrin
  - isoproterenol
  - dopamine
  - methoxamine
  - phenylephrine

- Indirect-acting-releases norepinephrine from nerve terminal
  - Tyramine
  - Amphetamine
  - Methamphetamine

- Blocks reuptake of norepinephrine and dopamine
  - Methylphenidate
  - Amphetamine

- Mixed-acting-both direct and indirect actions
  - ephedrine

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<td>Peripheral Resistance</td>
<td>( \alpha )</td>
<td>Vasoconstriction</td>
</tr>
<tr>
<td></td>
<td>( \beta_2 )</td>
<td>Vasodilation</td>
</tr>
</tbody>
</table>
Vasoconstrictor Interactions with CNS Stimulants

- Additive CV and CNS stimulation with other sympathomimetic agents
  - CNS
    - Agitation
    - Seizure
  - CV
    - Increase HR, BP
- Decongestants
- Diet aids
- Psychostimulants
  - Methylphenidate
    - Ritalin®
    - Concerta®
  - Amphetamines
    - d-Amphetamine
    - Adderall®
    - Vyvanse®
- Bronchodilators
  - Albuterol®
  - Theophylline

Vasoconstrictors

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Vasoconstrictor

- Levonorgestrel
  - Greater effect on BP than HR
- Epinephrine
  - Similar effects on HR and BP

Antidepressants

- ADD/ADHD
  - Atomoxetine (Strattera®)
- Anxiety
  - Social Phobia
  - Panic Disorder
  - OCD
- Depression
- Enuresis
- Sleep Disorders
- Premenstrual Dysphoric Disorder
Anti-depressants in Top 200

- Selective Serotonin Reuptake Inhibitors (SSRIs)
  - Lexapro (Escitalopram) (9)
  - Sertraline (35,58)
  - Fluoxetine (43,114)
  - Citalopram (153,194)
  - Paroxetine (87)
- Serotonin update preneuronal
  - Trazodone (45,191)

- Serotonin/ Norepinephrine Reuptake Inhibitors
  - Tricyclics
    - Amitriptyline (149)
    - Effexor XR (Venlafaxine) (23)
    - Cymbalta (Duloxetine) (34)

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Vasoconstrictor Interactions with Antidepressants

- **Antidepressants**
  - Block reuptake of norepinephrine and/or serotonin

- **Interaction**
  - Increased and prolonged effects on receptors
  - Increased alpha and beta stimulation
    - increased heart rate
    - increased cardiac contractility
    - increased peripheral resistance

Interacting Antidepressants

**Tricyclic Antidepressants**
- **Tertiary Amines**
  - Amitriptyline (Elavil)
  - Clomipramine (Anafranil)
  - Doxepin (Adapin, Sinequan)
  - Imipramine (Tofranil)
  - Trimipramine (Surmontil)

- **Secondary Amines**
  - Amoxapine (Asendin)
  - Desipramine (Norpramin; Pertofrane)
  - Maprotiline (Ludiomil)
  - Nortriptylin (Aventyl; Pamelor)
  - Protriptylin (Vivactil)

**Tetracyclic**
- Maprotiline (Ludiomil)
- Mirtazapine (Remeron)

**Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)**
- Desvenlafaxine (Pristiq)
- Duloxetine (Cymbalta)
- Milnacipran (Savella)
- Venlafaxine (Effexor)

**Selective norepinephrine reuptake inhibitors**
- Atomoxetine (Strattera)
  - Most serious
Vasoconstrictors

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Levonordefrin – > effect on BP than HR, but both

Epinephrine
  – Effects on HR and BP
Antipsychotics in Top 200

- Seroquel (Quetiapine) (32)
- Risperdal (Risperidone) (116)
- Abilify (Aripiprazole) (117)
- Zyprexa (Olanzapine) (157)

Phenothiazine products

- Promethazine (137)
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Vasoconstrictor Interactions with Antipsychotics, Antiemetics and Alpha-adrenergic blockers

- blockade of alpha adrenergic receptors
  - orthostatic hypertension
  - reflex tachycardia
  - potentiation of antihypertensives

- predominance of beta adrenergic effects
  - increased heart rate
  - increased cardiac contractility
  - peripheral vasodilation
Interacting Antipsychotics and Antiemetics

- **Phenothiazines**
  - Chlorpromazine (Thorazine)
  - Fluphenazine (Prolixin)
  - Perphenazine (Trilafon)
  - Prochlorperazine (Compazine)
  - Promethazine (Phenergan)
  - Thioridazine (Mellaril)
  - Trifluoperazine (Stelazine)

- **Benzisoxazoles**
  - Iloperidone (Fanapt)
  - Paliperidone (Invega)
  - Risperidone (Risperdal)
  - Zioprasidone (Geodon)

- **Benzisothiazols**
  - Lurasidone (Latuda)

- **Dibenzapines**
  - Asenapine (Saphris)
  - Clozapine (Clozaril, FazaClo)
  - Loxapine (Loxitane)
  - Olanzapine (Zyprexa)
  - Quetiapine (Seroquel)

- **Phenylbutylpiperadines**
  - Haloperidol (Haldol)
  - Pimozide (Orap)

- **Quinolinones**
  - Aripiprazone (Abilify)

- **Thioxanthene**
  - Thiothixene (Navane)

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Alpha Adrenergic Blockers

- **Alpha adrenergic blockers**
  - Clonidine (Catapres, Kapvay, Nexiclon)
  - Guanfacine (Intuniv, Tenex)

- **Alpha and Beta Adrenergic Blockers**
  - Carvedilol (Coreg)
  - Labetolol (Trandate, Normodyne)
Vasoconstrictors

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Vasoconstrictor

- Levonordefrin
  - No benefit, some CV effect
- Epinephrine
  - No benefit, greater CV effect
Beta-blockers

- Used to treat
  - Hypertension
  - Arrhythmias
  - Mitral Valve Prolapse
  - Migraine
  - Performance anxiety
    - Stage fright

- Beta-blockers
  - Atenolol (46, 81, 104)
  - Metoprolol tartrate (21, 27, 86)
  - Metoprolol succinate (51, 65)
  - Toprol-XL (Metoprolol) (165)

Beta-blockers

- Selective beta 1 antagonists
  - Acebutolol (Sectral)
  - Atenolol (Tenormin)
  - Betaxolol (Kerlone)
  - Bisoprolol (Zebeta)
  - Esmolol (Brevibloc)
  - Metoprolol (Lopressor)

- Non-selective beta antagonists
  - Carteolol (Cartrol)
  - Carvedilol (Coreg)
  - Nadolol (Corgard)
  - Penbutolol (Levatol)
  - Pindolol (Visken)
  - Propranolol (Inderal)
  - Sotalol (Betapace)
  - Timolol (Blocadren)
  - Labetalol (Trandate, Normodyne)
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Vasoconstrictor Interactions with Beta-blockers

- Blockade of beta 1 and beta 2 receptors
- Causes unopposed alpha peripheral vasoconstriction
- Initial hypertensive episode followed by bradycardia
Beta-blockers
Non-selective are greatest problem

- Selective beta 1 antagonists
  - Acebutolol (Sectral)
  - Atenolol (Tenormin)
  - Betaxolol (Kerlone)
  - Bisoprolol (Zebeta)
  - Esmolol (Brevibloc)
  - Metoprolol (Lopressor)

- Non-selective beta antagonists
  - Carteolol (Cartrol)
  - Carvedilol (Coreg)
  - Nadolol (Corgard)
  - Penbutolol (Levatol)
  - Pindolol (Visken)
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Vasoconstrictor

- Levonordefrin
  - Greater alpha adrenergic effects resulting in hypertension and reflex bradycardia
- Epinephrine
  - Predominance of alpha adrenergic effects resulting in hypertension and reflex bradycardia

Monoamine Oxidase Inhibitors (MAOIs)

- Social Phobia
- Panic Disorder
- Depression
- Parkinson's

- Antidepressants
  - Isocarboxazid (Marplan)
  - Phenelzine (Nardil)
  - Tranylcypromine (Parnate)
  - Selegiline (Emsam)
    - Transdermal 6, 9, 12 mg/24h
- Antiparkinson
  - Selegiline
    - Eldepryl 5 mg capsule
    - Zelapar 1.25 mg ODT
Vasoconstrictors and MAOIs

- MAOIs potentiate indirect or mixed-acting sympathomimetic substances
  - by inhibiting metabolism of MAO B
  - severe headache, hyperpyrexia, hypertension

- Interaction with direct-acting agents is minimal
  - selegiline inhibits MAO A and therefore is contraindicated with epinephrine and levonordefrin

Sympathomimetic Agents

- Direct acting-directly stimulates receptor
  - epinephrine
  - norepinephrine
  - levonordefrin
  - isoproterenol
  - dopamine
  - methoxamine
  - phenylephrine

- Indirect-acting-releases norepinephrine from nerve terminal
  - tyramine
  - amphetamine
  - methamphetamine

- Mixed-acting-both direct and indirect actions
  - ephedrine
### Local Anesthetics

<table>
<thead>
<tr>
<th>Tradename</th>
<th>Generic name</th>
<th>Available Conc</th>
<th>Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orabloc</td>
<td>Articaine</td>
<td>4% with 1:100,000 epi</td>
<td>1.7 ml</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4% with 1:200,000 epi</td>
<td></td>
</tr>
<tr>
<td>Marcaine</td>
<td>Bupivacaine</td>
<td>0.5% with 1:200,000 epi</td>
<td>1.8 ml</td>
</tr>
<tr>
<td>Sensorcaine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xylocaine</td>
<td>Lidocaine</td>
<td>2% with 1:50,000 epi</td>
<td>1.8 ml</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2% with 1:100,000 epi</td>
<td></td>
</tr>
<tr>
<td>Carbocaine</td>
<td>Mepivacaine</td>
<td>3% with 1:20,000 levonordefrin</td>
<td>1.8 ml</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citanest Plain</td>
<td>Prilocaine</td>
<td>4% with 1:200,000 epi</td>
<td>1.8 ml</td>
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<td>Citanest Forte</td>
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### Articaine

**JADA 2006; 137(11):1572-81**

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<tr>
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<th>1:100,000</th>
<th>1:200,000</th>
<th>0</th>
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<tbody>
<tr>
<td>Infiltration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onset</td>
<td>3.0 min</td>
<td>3.1 min</td>
<td>3.0 min</td>
</tr>
<tr>
<td>Duration</td>
<td>45.0 min</td>
<td>41.6 min</td>
<td>13.3 min</td>
</tr>
<tr>
<td>Subjective Anesthesia</td>
<td>98.4%</td>
<td>100%</td>
<td>93.5%</td>
</tr>
<tr>
<td>Block</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onset</td>
<td>4.7 min</td>
<td>4.2 min</td>
<td>4.3 min</td>
</tr>
<tr>
<td>Duration</td>
<td>51.2 min</td>
<td>61.8 min</td>
<td>49.7 min</td>
</tr>
<tr>
<td>Subjective Anesthesia</td>
<td>85.5%</td>
<td>87.3%</td>
<td>77.4%</td>
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Articaine
JADA 2006;137(11):1562-71

- Compared PK and CV effects
- 7 cartridges (11.9 ml) of the A/200 and A/100
- Administered over 7 minutes
  - Maxillary right first molar infiltration, maxillary left first molar infiltration, maxillary right first premolar infiltration, maxillary left first premolar infiltration, right inferior alveolar injection, left inferior alveolar injection, right long buccal infiltration (one-half) and left long buccal infiltration (one-half).
- CV:
  - mean SBP and HR at the 10 minute point were significantly higher with A/100
- PK
  - 22 min to maximum plasma concentration

Paresthesia after LA
JADA 2010;141(7):836-844

- FDA adverse event reports of paresthesias from 11/97 – 8/08.
- 248 cases
- 94.5% involved mandibular nerve block
- 4% prilocaine 7.3 X > expected
- 4% articaine 3.6 X > expected
- 89% tongue
### Local anesthetic effects with vasoconstrictors

<table>
<thead>
<tr>
<th></th>
<th>Anesthetic efficacy %</th>
<th>Duration of pulp anesthesia (min)</th>
<th>Duration of tissue anesthesia (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine 2%</td>
<td>38</td>
<td>6</td>
<td>60</td>
</tr>
<tr>
<td>+1/200,000 epi</td>
<td>97</td>
<td>35</td>
<td>155</td>
</tr>
<tr>
<td>+1/80,000 epi</td>
<td>97</td>
<td>63</td>
<td>193</td>
</tr>
<tr>
<td>Mepivacaine 2%</td>
<td>82</td>
<td>13</td>
<td>82</td>
</tr>
<tr>
<td>+1/200,000 epi</td>
<td>94</td>
<td>35</td>
<td>155</td>
</tr>
<tr>
<td>+1/100,000 epi</td>
<td>93</td>
<td>36</td>
<td>145</td>
</tr>
<tr>
<td>Mepivacaine 3%</td>
<td>91</td>
<td>17</td>
<td>103</td>
</tr>
</tbody>
</table>

### Local Anesthetics

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Available Conc</th>
<th>Maximum Dose</th>
<th>Duration Maxillary Infiltration (min)</th>
<th>Duration Aveolar Block (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Articaine</td>
<td>4% with 1:100,000 epi</td>
<td>7 mg/kg</td>
<td>190</td>
<td>230</td>
</tr>
<tr>
<td></td>
<td>4% with 1:200,000 epi</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>0.5% with 1:200,000 epi</td>
<td>90 mg</td>
<td>340</td>
<td>440</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>2% with 1:50,000 epi</td>
<td>7 mg/kg (500 mg)</td>
<td>170</td>
<td>190</td>
</tr>
<tr>
<td></td>
<td>2% with 1:100,000 epi</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mepivacaine</td>
<td>3%</td>
<td>6.6 mg/kg (400 mg)</td>
<td>90</td>
<td>165</td>
</tr>
<tr>
<td></td>
<td>2% with 1:20,000 levonordefrin</td>
<td>6.6 mg/kg (400 mg)</td>
<td>130</td>
<td>185</td>
</tr>
<tr>
<td>Prilocaine</td>
<td>4%</td>
<td>8 mg/kg (600 mg)</td>
<td>105</td>
<td>190</td>
</tr>
<tr>
<td></td>
<td>4% with 1:200,000 epi</td>
<td>8 mg/kg (600 mg)</td>
<td>140</td>
<td></td>
</tr>
</tbody>
</table>
Phentolamine mesylate
Oraverse®

- MOA: alpha
  adrenergic blockade
  causes vasodilation,
  therefore reverses
  the effect of the
  vasoconstrictor (not
  the LA)
- This is same
  mechanism as
  interaction of
  antipsychotics and
  phenothiazine
  antiemetics
  interaction with
  vasoconstrictor in
  the LA

Phentolamine mesylate
Oraverse®

- 0.4 mg/1.7 ml cartridge
- JADA, 2008; 139:1080-93
  - Adolescents > 12 and adults
  - For restorative or scaling procedures
  - Lidocaine 2% w 1:100,000 epi
  - Articaine 4% w 1:100,000 epi
  - Prilocaine 4% w 1:200,000 epi
  - Mepivacaine 2% w 1:20,000 levonordefrin
  - Procedure completed w/in 60 min of LA administration
  - 1-2 cartridges Oraverse adm at same site
  - Reduced the median time to recovery in the lower lip by 85 min; upper lip by 83 min
  - w/in 1 hr 41% normal lower lip sensation v 7%; 59% v 12% for upper lip
  - Reduced median recovery time for tongue 65 min (52%)
Pediatric ADR to Local Anesthetics

**Soft Tissue Trauma**
- Decreased with sedation
- Decreased with bilateral LA
- Increased with unilateral LA
- Greatest in < 7 yo

**Paresthesias**
- Lidocaine > septocaine or prilocaine
- Trauma greatest in < 7 yo
- 40% at 3 h and 11% at 5 h
- 0% at 24 and 48 h

**Phentolamine mesylate**
*Oraverse®*

- 0.4 mg/1.7 ml cartridge
- JADA, 2008; 139(8):1095-104
- Children 6-11 yo
  - Reduced time to recovery by 75 min a 56% acceleration to normal sensation
- Bilateral Versus Unilateral Mandibular Block Anesthesia in a Pediatric Population
  - Postoperative soft tissue trauma
    - 18% (< 4 yo)
    - 16% (4-7 yo)
    - 13% (8-11 yo)
    - 7% (>12 yo)
Articaine

- Articaine is not contraindicated in patients with sulfa allergies; there is no cross-allergenicity between articaine's sulphur-bearing thiophene ring and sulfonamides.103

Type III

- Sulfonamide antibiotics
  - 25% of all drug-induced rashes
  - 75% of the most severe cutaneous reactions
  - Delayed onset, ~14 days from initiation of drug therapy
  - Sequence of ADRs (fever, skin rash, internal organ toxicity)
  - Reduced levels of C3 consistent with immune complex deposition as mechanism of renal disease
Sulfonamides

- Sulfonamide antibiotics
- Carbonic Anhydrase Inhibitors
- Celecoxib
- Loop Diuretics
- Thiazide Diuretics
- First and Second Generation Sulfonylureas

Sulfonamides

- Sulfamethoxazole
- Hydrochlorothiazide
- Glyburide
- Furosemide
Sulfonamides

Sulfamethoxazole

Acetazolamide

Celecoxib

PABA allergy

PABA and Procaine

PABA and sulfamethoxazole
Local Anesthetics that are PABA derivatives

- Benzocaine
- (Chlorprocaine)
- Dimethocaine
- Procaine
- (Tetracaine)

Sulfite anion    Na metabisulfite