Outpatient Spinal Anesthesia: Is Chloroprocaine the Answer?

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I have no financial disclosures. I will be discussing off-label use local anesthetics.

“Local anesthetics are not neurotoxic when administered at recommended clinical concentrations”

Stoelting and Miller
Basics of Anesthesia, 2nd ed., 1984

Spinal Lidocaine: Neural Injury and TNS
Strategies to Reduce or Eliminate Risk

- Decrease Concentration
- Decrease Dose
- Avoid Glucose or Decrease its Concentration
- Avoid Epinephrine
Strategies to Reduce or Eliminate Risk

<table>
<thead>
<tr>
<th>Permanent Neurologic Deficits</th>
<th>Transient Neurologic Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease Concentration</td>
<td>↓</td>
</tr>
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<td>Avoid Epinephrine</td>
<td>↓↓</td>
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Spinal Lidocaine: Alternatives

- Low-Dose Bupivacaine
- Procaine
- Mepivacaine
- Prilocaine
- Chloroprocaine

Spinal Chloroprocaine: Back to the Future?

- Prilocaine
- Chloroprocaine


Smith KN, Kopacz DJ, McDonald SB: Spinal 2-Chloroprocaine: A Dose-Ranging Study and the Effect of Added Epinephrine.


Anesth Analg, January 2004
Persistent neurologic deficit and adhesive arachnoiditis following intrathecal 2-chloroprocaine injection

Reisner LS, Hochman BN, Plumer MH

Anesth Analg 1980; 59:452-454

Nesacaine Neurotoxicity: Chloro or Bisulfite? The Gissen Experiments

- 3% Nesacaine® (containing 0.2% bisulfite at pH 3) produced irreversible block.
- 3% Nesacaine® (buffered to pH 7.3) produced reversible block.
- Irreversible block with exposure to bisulfite without chloroprocaine, but only at a low pH.

“If we tear neurons from the mother tissue...then force them to lie naked and amputated on a hard plastic or glass surface in a sea of alien substances, how can we expect their behavior to tell us anything useful about the nervous system?”

Dennis Bray, 1991
Gissen Experiments: A Critical Analysis

- Experiments conducted on isolated segments of nerve in system devoid of normal physiologic processes.
- Model inherently unstable.
- Conduction failure is an imperfect surrogate endpoint.
- Nerves exposed to bath of undiluted bisulfite at pH equivalent to test solution.

Gissen Experiments (con’t)

- Activity of sulfite oxidase (protective enzyme catalyses oxidation of sulfites to less toxic sulfates) depressed in disrupted nerve at low pH and room temperature.

Tail-Flick Test
Tail-Flick Test
No Means No

**Sensory Impairment (%MPE)**

<table>
<thead>
<tr>
<th>Solution Administered</th>
<th>Chloroprocaine (Abbott)</th>
<th>Chloroprocaine (Astra)</th>
<th>Saline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100</td>
<td>60</td>
<td>0</td>
</tr>
</tbody>
</table>

* Taniguchi et al, Anesthesiology;2004:85-91

**Nerve Injury Score**

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</thead>
<tbody>
<tr>
<td></td>
<td>1.0</td>
<td>0.6</td>
<td>0.0</td>
</tr>
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</table>

* Taniguchi et al, Anesthesiology;2004:85-91

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**DAY OF RECKONING AT ASTRA**

Bildman, accused of sexual harassment, and three others are out

Most companies try to sweep scandals under the carpet. Not Astra, the giant Swedish drugmaker. Confronted by allegations in a May 13 BUSINESS WEEK cover story of widespread sexual harassment and other abuses at its Astra USA Inc. subsidiary, the company quickly suspended three top executives and launched an internal probe.

Just weeks later, on June 26, the parent company took decisive action: it announced that it had fired Astra USA President and CEO Ken Bildman without paying him any severance. Although Astra won't comment on specific sexual-harassment allegations, Carl-Gustaf Johansson, an Astra executive vice-president, says the investigation found that Bildman had "displayed inappropriate behavior, and company functions" and had "abused his power." Another suspended executive, George Roseman, also was shown the door, while a third, Edward Ananos, resigned. A senior executive in Sweden, Anders Lorm, was asked to resign for failing to report misconduct to superiors, Astra says.

Airing yet more dirty linen, Astra also disclosed that it believes Bildman used company funds to pay for about $2 million in personal expenses during the past decade. The bulk of the money supposedly came in the form of renovations done on three Bildman homes by Astra-paid contractors. Bildman allegedly also used company money to pay for lavish vacations and other personal expenses. The U.S. Attorney's office and...
“The fool sees what he believes; the wise man believes what he sees.”

Anonymous

“It doesn’t matter how beautiful your theory is, it doesn’t matter how smart you are. If it doesn’t agree with the experiment, it is wrong.”

Richard Feynman

[Graphs and charts showing sensory impairment and nerve injury scores with solutions administered.]

Taniguchi et al, Anesthesiology;2004:85-91
The Evolving Saga of Local Anesthetic Neurotoxicity

**Good Stuff**
- Chloroprocaine
- Lidocaine

**Bad Stuff**
- Chloroprocaine
- Lidocaine

“All things are poison and nothing is without poison...The right dose differentiates a poison from a remedy.”

*Paracelsus, 1493-1541*

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CASE REPORTS

**Caudo-Epigastric Syndrome Following Intended Epidural Anesthesia**

Karen Bonner, MD; Maria L. Sosa, MD; Jennifer L. Soriano, MD;" "Sanchez, J. M., E., MD;" "Vasquez, R. E., M.D.

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**Solution Administered**

- 3% Chloroprocaine
- 2.5% Lidocaine

**Sensory Impairment (%MPE)**

**Solution Administered**

- Expt 1
- Expt 2
The Evolving Saga of Chloroprocaine and Bisulfite Neurotoxicity

**Good Stuff**
- Chloroprocaine
- Bisulfite
- Lidocaine

**Bad Stuff**
- Chloroprocaine
- Bisulfite
- Lidocaine

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**Spinal 2-Chloroprocaine: A Dose-Ranging Study and the Effect of Added Epinephrine**

Smith KN, Kopacz, DJ, McDonald SB

*Anesth Analg* 2004;98:81-88

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**“Flu-Like” Symptoms: Bisulfite Effect?**

<table>
<thead>
<tr>
<th>Solution Administered</th>
<th>Nerve Injury Score</th>
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<tbody>
<tr>
<td>3% Chloroprocaine</td>
<td>1.0</td>
</tr>
<tr>
<td>2.5% Lidocaine</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Expt 1

- Chloroprocaine
- Bisulfite
- Lidocaine

Expt 2

- Chloroprocaine
- Bisulfite
- Lidocaine

Chloro + Epinephrine 11/11

Chloroprocaine 0/18

Bisulfite dose: Epinephrine

0.2 ml X 0.9 mg/ml = 0.18 mg

Chloroprocaine (Epidural)

20 ml X 1.8 mg/ml = 36 mg

*Smith et al., Anesth Analg* 2004;98:81-88
The Evolving Saga of Chloroprocaine and Bisulfite Neurotoxicity

**Good Stuff**
- Chloroprocaine
- Bisulfite
- Lidocaine

**Bad Stuff**
- Chloroprocaine
- Bisulfite
- Lidocaine

“Anyone who isn't confused, doesn't really understand the situation.”

Edward R. Murrow (1908-1965)

Spinal Chloroprocaine Toxicity

- Whether bisulfite is neuroprotective or has inherent spinal toxicity in humans is unknown.
- Chloroprocaine, like all local anesthetics, has potential neurotoxicity if delivered at a high enough dose in the subarachnoid space.
- With respect to its spinal toxicity, chloroprocaine appears to be roughly equivalent to lidocaine on a mg for mg basis.
“The Food, Drug and Cosmetic Act does not limit the manner in which a physician may use an approved drug.”

*FDA Drug Bull. 1982; 12:4–5*

**Off-Label Use: Requirements**

Dear Christopher,

If physicians use a product for an indication not in the approved labeling, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects. We do not dictate what the records maintained should be or monitor doctors' for the completion of such records.

Best regards,
Center for Drug Evaluation and Research
Food and Drug Administration

This communication is consistent with 21CFR10.85(k) and constitutes an informal communication that represents our best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of the FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

Best regards,
Center for Drug Evaluation and Research
Food and Drug Administration

**Spinal Chloroprocaine Toxicity**

Is there “sound medical evidence” to support off-label use of spinal chloroprocaine?
If Nothing Goes Wrong, Is Everything All Right?

**Maximum Risk**

(95% Confidence) = 1 per \( n/3 \)

*for \( n > 30 \), within one percentage point of actual calculation

*Hanley and Lippman-Hand, JAMA 1983;249:1743-5*

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**Estimated Incidence for Spinal Chloroprocaine Neural Injury: Published Data**

900 Spinals Without Injury

Maximum Risk

(95% Confidence) = 1 per \( n/3 \)

= 1 per 900/3

= 1 per 300 or 0.3%

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**Estimated Incidence for Spinal Chloroprocaine Neural Injury: Unpublished Clinical Experience**

> 30,000 Spinals Without Injury

Maximum Risk

(95% Confidence) = 1 per \( n/3 \)

= 1 per 30,000/3

= 1 per 10,000 or 0.01%
Spinal Chloroprocaine Toxicity

Based on the foregoing, if you elect to use chloroprocaine for spinal anesthesia:

- Use a bisulfite-free formulation.
- Do not exceed 60 mg.
- Do not add epinephrine.
- OK to add fentanyl.

Repeat Injection after "Failed Spinal"

SUGGESTED GUIDELINES

- Attempt aspiration of CSF before and after injection.
- If CSF cannot be aspirated following injection, a "full" dose of anesthetic should not be considered unless exam reveals no evidence of block.
- If CSF is aspirated after injection, limit total dosage to maximum reasonable to administer as a single injection.