Granuloma: Inflammatory Catheter Tip Mass as a Result of Intrathecal Drug Delivery

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Napa Pain Institute

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Welcome to Our Practice

At Napa Pain Institute, our mission is to help patients and contribute to health and wellness, through integrated clinical practice, research, and education.

The needs of our patients come first. We offer a "patient-centered" approach, tailored to each patient's needs, and provide access to a multidisciplinary team of specialists, educational materials, and the latest medical research.

Napa Pain Institute is a leader in pain care research and education. Our partnerships with NeuroVations, a nationally recognized organization, allow us to offer unique educational opportunities and a new understanding of pain and treatment strategies.

Napa Pain Institute is here to help.
### Eric Grigsby, MD - Disclosures

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### Granuloma

- History of Intrathecal Opiate Infusion
- Recognition of Granuloma
- Pathophysiology
- Mitigation
- Management
The History of Intrathecal Opiate Infusion

Studies on the direct spinal action of narcotics in the production of analgesia in the rat

Yaksh, Tony L.; Rudy, Thomas A.

ABSTRACT: In rats implanted with chronic catheters in the spinal subarachnoid space... Intrathecal injections of morphine sulfate (I sulfate) [64-31-3] produced a dose-dependent elevation in the nociceptive threshold as defined by tail flick, hot plate, paw pinch and shock titration tests.

The relative potency ranking for the narcotics tested was fentanyl [437-38-7] > L-methadone-HCl [5967-73-7] > meperidine-HCl [50-13-5], codeine [76-57-3] and ethylmorphine [76-58-4] showed a marginal degree of activity. Thus, the behaviorally defined analgesia observed after the systemic administration of narcotics is in part mediated by the pharmacol. action of these compds. on the spinal cord.

Journal of Pharmacology and Experimental Therapeutics (1977), 202(2), 411-28
FIRST STUDIES OF SPINALLY ADMINISTRED MORPHINE IN MAN

Pain relief by intrathecally applied morphine in man.

8 patients with pain due to genitourinary malignancies were randomized to either IT saline alone or IT saline +morphine, 0.5-1.0mgs. All patients reported complete pain relief with morphine lasting from 16-24 hours.

Wang JK, Nauss LA, Thomas JE. Anesthesiology. 1979 Feb;50(2):149-51

Epidural morphine in treatment of pain.

Epidural injections of a 2 mg morphine were given to 10 patients with severe acute or chronic pain. All cases had considerable amelioration of pain, which commenced within 2-3 min, reached a peak in 10-15 min, and was effective for 6-24 h. It is suggested that the morphine reached the subarachnoid space and produced its effect by direct action on the specific opiate receptors in the substantia gelatinosa of the posterior-horn cells of the spinal cord.


Early Recognition that Intrathecal Morphine Might Have Unintended Consequences
High Doses of Spinal Morphine Produce a Nonopiate Receptormediated Hyperesthesia: Clinical and Theoretic Implications

TL Yaksh, GJ Harty et al.

In rats with chronically implanted intrathecal catheters, high concentrations of morphine yielded a reliable and striking syndrome of pain behavior that involved intermittent bouts of biting and scratching at the dermatomes innervated by levels of the spinal cord proximal to the catheter tip. In addition, during intervals between bouts of agitation, the animals displayed a clear, marked hyperesthesia where an otherwise innocuous stimuli (brush stroke) evoked significant signs of discomfort and consequent aggressive behavior.

Anesthesiology 1986;64(5)

Recognition of Inflammatory Mass or Granuloma
Recognition of a Mass at the Tip of the Catheter: 1991

The first case of a catheter-tip inflammatory mass (granuloma) associated with IT morphine infusion for the treatment of chronic intractable pain was reported by North et al in 1991.


Coffey et al 2002

- Survey of the Literature and Medtronic Pos-market Surveillance with FDA
- 41 patients morphine and dilaudid
- Widely variable doses but seem related to dose and concentration
- Mechanism may be opioid induced mast cell degranulation

Coffey et al, Inflammatory Mass Lesions Associated with Intrathecal Drug Infusion Catheters: Report and Observations on 41 Patients, Neurosurgery, 2002;50;78-76.
The Pump Manufacturer Publishes More Surveillance Data

Medtronic, Inc. has noted an increase in reported cases of inflammatory mass associated with intrathecal drug delivery from **0.1 percent reported to date in 2001 to 0.5 percent reported to date in 2007**. The actual incidence is likely to be higher than stated due to under-reporting, but the extent of under-reporting is currently unknown. To date, there have been no reported deaths associated with this issue.

From Medtronic Inc., March 2008

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Symptoms Occurring in >2% of Granulomas

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<tr>
<th>Symptom</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased therapeutic response</td>
<td>150</td>
<td>33.50%</td>
</tr>
<tr>
<td>Pain</td>
<td>146</td>
<td>32.60%</td>
</tr>
<tr>
<td>Neurological deficit/dysfunction</td>
<td>78</td>
<td>17.40%</td>
</tr>
<tr>
<td>Unknown</td>
<td>74</td>
<td>16.50%</td>
</tr>
<tr>
<td>Paralysis/paraplegia/paresis</td>
<td>67</td>
<td>15.00%</td>
</tr>
<tr>
<td>Weakness/muscle weakness</td>
<td>62</td>
<td>13.80%</td>
</tr>
<tr>
<td>Numbness</td>
<td>43</td>
<td>9.60%</td>
</tr>
<tr>
<td>Incontinence</td>
<td>32</td>
<td>7.10%</td>
</tr>
<tr>
<td>Ambulation difficulties</td>
<td>12</td>
<td>2.70%</td>
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From Medtronic Inc., March 2008
Incidence of Inflammatory Mass

- Incidence of Symptomatic Inflammatory Mass
  - 0.4 – 1% (Deer, Grigsby, et al, 2007 Consensus Statement)
  - 0.49% (Medtronic...Updated Information, 2008)

- Incidence of Asymptomatic Inflammatory Mass
  - MRI Screening of 208 patients, 6 granulomas found
  - 3% of implanted pumps (Deer, et al, 2004)

Napa Pain Institute

- Clinic History
  - 4 Inflammatory Masses diagnosed in 20 years
  - > 10,000 patient years of IT opiate infusion
  - Refill every 2 months since inception
  - Catheter tip typical location
  - Polyanalgesia typical of clinical practice and published guidelines
What is it? What Causes it? What Do We Know from Pre-clinical Models and Patients?

Dog Model of IT Morphine

- Increase in cisternal CSF protein
- Increase in CSF White Blood Cells
- Normal CSF Glucose
- Non-infectious
- Increase in Cytokines IL1 beta, TNF alpha
- Increase in iNOS, eNOS Reactivity

Mast Cell Degranulation: Mechanism or Association?

- Dog Model
- Morphine increased histamine concentration in CSF by 100%, Hydromorphone by 75%
- Lumbar Catheters in Place
- Dural Mast Cell Degranulation in Lumbar Region but not Cervical Suggesting Local Action


Histology of Granuloma

- 3 Patients
- Resection of Inflammatory Mass
- Histology:
  - Central Necrotic Debris
  - Inflammatory Hypervascular Tissue
  - Apparently Derived from the Arachnoid Layer

Pathophysiology of Granuloma


Courtesy Of Dr. Phil Kim
Medications Associated with Inflammatory Mass in Clinical Practice

- Monotherapy
  - Morphine
  - Dilaudid
  - Tramadol
  - Sufentanil

- In Combination Therapy
  - Clonidine
  - Ziconotide
  - Baclofen
  - Bupivacaine

Medications Not Associated with Inflammatory Mass Used as First in Pump Monotherapy

- Ziconotide
- Fentanyl
- Clonidine
- Bupivacaine
- Baclofen
Baclofen

Deer et al described two inflammatory mass cases associated with IT Baclofen. In both cases there was MRI evidence of mass at the catheter tip. However, the same authors report that there is controversy regarding whether baclofen causes inflammatory mass.

Take home message: No confirmed IM with Baclofen

Mitigation of Granuloma Formation

Screening and Surveillance
What do We Currently Believe?

- Granulomas Occur in a Dose Dependent Manner with Intrathecal Opiates
- Morphine Seems to be the Most Troublesome
- Association between Dose, Yearly Increase in Dose, Duration of Infusion
- Pre-clinical Data Support Concentration as a Factor, Inconclusive in Clinical Practice
- Impact of Flow Rate Unclear
- Impact of Catheter Tip Location Unclear
- Effect of Clonidine Unclear

2007 Polyanalgesic Consensus Panel Guidelines

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<tr>
<th>Drug</th>
<th>Max Concentration</th>
<th>Max Daily Dose</th>
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<tr>
<td>Morphine</td>
<td>20 mg/mL</td>
<td>15 mg</td>
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<tr>
<td>Hydromorphone</td>
<td>10 mg/mL</td>
<td>4 mg</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>2 mg/mL</td>
<td>No known</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>50 mg/mL</td>
<td>No known</td>
</tr>
<tr>
<td>Bupivaine</td>
<td>40 mg/mL</td>
<td>30 mg</td>
</tr>
<tr>
<td>Clonidine</td>
<td>2 mg/mL</td>
<td>1.0 mg</td>
</tr>
<tr>
<td>Ziconotide</td>
<td>100 μg/mL</td>
<td>19.2 μg (Pl)</td>
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Surveillance

- Frequent office re-evaluations
  - Decrease in Analgesia
  - New radicular symptoms in a dermatome c/w catheter tip
  - Other New Neurologic Symptoms

- Side port access and myelogram “protocol”

Imaging Surveillance
Time Interval or Symptom Based?

- Screening imaging evaluations
  - MRI
  - CT myelogram
Granuloma Mitigation
Polyanalgesic Consensus Panel
2007

- Lowest Possible Dose
- Bolus Dosing Regimen
- Catheter Tip Below the Conus
- Non-opioid Adjuvants to Reduce Opioid Dose
- Intrathecal Ziconotide

Inflammatory Mass Mitigation

- Canine Study

- Conclusions: Intermittent bolus delivery of morphine (1, 2 or 4 boluses per day) produced a marked reduction (>50%) in the incidence of IM formation relative to continuous infusion...

Management of a Granuloma

• Stop infusion into the granuloma
• Surgical decompression and resection if progressive neurological deficit
• Place the catheter tip below the conus if possible

Future Directions

• Infusion Method
• Dosing parameters
• Non-opioid molecules/agents
• Anti-histamines
• Anti-Inflammatory Agents
Targeted Drug Delivery for Pain and Neurologic Disease
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San Francisco, California

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