Intrathecal Therapy

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Precision Pain Management

Disclosure

Speaker Bureaus:
- Purdue
- Eli Lilly
- Medtronic

Learning Objectives

- Indications for Intrathecal Therapy
- Pharmacokinetics of Intrathecal Meds
- Cancer vs. Non-Cancer Pain
Indications and Theory of Intrathecal Analgesia

- Pain
  - Intractable
  - Uncontrolled with oral agents
  - Significant side effects with oral agents

- The intrathecal route
  - Bypasses the blood brain barrier
  - Compared to the epidural route
    - Higher rates of satisfactory pain relief
    - Lower rates of treatment failures
    - Lower rates of technical complications


Pain Management: A More Flexible Approach

- Different timeframes
- Multiple therapies at once
- Different starting points

Intrathecal Therapy for Pain: Patient Selection

- Objective evidence of pathology
- Failure to achieve adequate results from oral opioid therapy
- Inability to tolerate the side effects of oral opioids
- Psychological evaluation

Trial Procedure

- Final step in patient selection: patient’s response to the opioid during a screening test
- Several Methods of Trial
  - Single bolus
  - Multiple injections
  - Continuous infusion
- Patients who experience 50% or greater pain relief, generally are candidates for permanent implant

Pharmacological Considerations

- Receptors for the agents have to be at the spinal level
- Drug considerations
  - Lipid solubility
  - Density and baricity
  - Bolus vs. continuous
  - Location of catheter/receptors
Mechanism of Action--IT

- CSF ~ ISF
- Most receptors are in the substantia gelatinosa 1-2 mm from surface of dorsal horn
- Hydrophilic > Hydrophobic
  - Longer ½ life
  - Deeper penetration
  - Smaller volume of distribution
  - Rostral spread

Pharmacokinetics - Lipophilicity

- Moderately hydrophilic agents (such as morphine, baclofen or clonidine) → concentration gradient in the CNS whereby the cisternal CSF drug concentration is 1/3 to 1/7 that in the lumbar CSF
- Much lower supratentorial effects
Morphine

- Receptors in the substantia gelatinosa
- Only FDA approved opioid for ITP
- IT MSO₄ → a higher concentration in the cerebrospinal fluid (CSF) compared to epidural administration
  - Lower volume of distribution (70 ml)
  - Lower vascular absorption


Reduce Dose – Reduce Side Effects

- 1 mg intrathecal morphine = 300 mg oral morphine


IT MSO₄ -- Myth

- Administration of low doses of intrathecal opiates will eliminate the problems associated with high oral or parenteral doses
- Similar to oral opioids, problems with tolerance, pruritus, sedation and respiratory depression occur with intrathecal administration especially in patients with chronic benign pain
Unique IT Opioid Side Effects

- Pruritus: IT>>oral or parenteral
- Intrathecal granuloma (at the tip of intrathecal catheters) is a serious complication that can occur with chronic intrathecal opioid infusions
- Opioid-induced hyperalgesia
  - R/O granuloma
- Peripheral edema
- Hypogonadotrophic hypogonadism, central hypocorticism and growth hormone deficiency

Paice J et al., Pain Symptom Manage 11, 1996

IT Opioid Dose Escalation

Cancer Pain

Table 2. Reduction in Pain and Drug Toxicity from Baseline to 4 Weeks

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Baseline</th>
<th>Baseline at 4 Weeks</th>
<th>Reduction at 4 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>78</td>
<td>6.8 ± 3.6</td>
<td>1.0 ± 1.5</td>
<td>5.8 ± 3.1</td>
</tr>
<tr>
<td>EDD</td>
<td>78</td>
<td>7.2 ± 4.0</td>
<td>3.2 ± 3.4</td>
<td>4.0 ± 3.4</td>
</tr>
</tbody>
</table>

Cancer-Related Pain Studies: Limited by Survival

- Of the 119 patients implanted, 15 made it to 13 months

IT Granuloma

- Typical histopathology:
  - Macrophages, neutrophils and monocytes
  - Necrotic center
  - No evidence of infectious process
- Granulation tissue

American Journal of Roentgenology 2007; 189: W375-W381

Timothy Deek, MD • Elliot S. Krane, MD • Samuel J. Hansenbusch, MD, PhD • Allen Burton, MD • David Caraway, MD • Stuart Dupen, MD • James Eisenach, MD • Michael Edel, MD • Eric Grigson, MD • Philip Kim, MD • Robert Levy, MD, PhD • Cladstone McDonell, MD • Nagi Merkhi, MD • Sunil Parvati, MD • Joshua Prager, MD • Richard Rau, MD • Michael Sainson, MD • Todd German, MD • Peter Stains, MD • Michael Stanton-Hicks, MD • Lisa Stens, MD • K. Dean Willis, MD • William Witt, MD • Kenneth Follett MD, PhD • Marc Hunteos, MD • Leong Liem, MD • James Rathmele, MD • Mark Wallace, MD • Eric Burcher, MD • Michael Cusack, MD • Anne Ver Zijl, MD

2007 POLYANALGESIC ALGORITHM FOR INTRatheCAL THERAPIES

Line #1: (a) morphine ↔ (b) hydromorphone ↔ (c) ziconotide

Line #2: (d) tianeptine (e) morphine/hydromorphone ↔ (f) ziconotide/morphine/hydromorphone + butylscopolamine/denipine

Line #3: (g) dextromethorphan ↔ (h) morphine/hydromorphone/tianeptine + butylscopolamine/denipine + butylscopolamine/denipine + ziconotide

Line #4: (i) substan (j) substan + butylscopolamine/denipine + ziconotide

Line #5: (k) levocabazine, buprenorphine, rizosdil, imipramine, ketorolac

Line #6: Experimental Drugs
galapentin, desvenlafaxine, doxepin, Nevipam, Verona, XEN, ZOL 168
### Dose Recommendations

TABLE 1: Concentrations and Doses of Intrathecal Agents Recommended by the Polyneuropathic Consensus Panelists, 2007

<table>
<thead>
<tr>
<th>Drug</th>
<th>Maximum concentration</th>
<th>Maximum dose/days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>20 mg/mL</td>
<td>15 mg</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>16 mg/mL</td>
<td>4 mg</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>2 mg/mL</td>
<td>No known upper limit</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>50 μg/mL, but available for compounding</td>
<td>No known upper limit</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>40 mg/mL</td>
<td>30 mg</td>
</tr>
<tr>
<td>Ketamine</td>
<td>2 mg/mL</td>
<td>1.0 mg</td>
</tr>
<tr>
<td>Scopolide</td>
<td>100 μg/mL</td>
<td>100 μg, (see recommendations)</td>
</tr>
</tbody>
</table>

### Predictive Value of Trialing

#### Table: Predictive Value of Trialing

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>86</td>
</tr>
<tr>
<td># Males</td>
<td>33</td>
</tr>
<tr>
<td># Females</td>
<td>53</td>
</tr>
<tr>
<td>Average age</td>
<td>57 years</td>
</tr>
<tr>
<td>Age range</td>
<td>21 – 84 years</td>
</tr>
<tr>
<td>Average follow-up</td>
<td>18 months</td>
</tr>
<tr>
<td>Range of follow-up</td>
<td>6 - 48 months</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Low</th>
<th>Standard</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>0.25 mg</td>
<td>0.50 mg</td>
<td>1.00 mg</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>0.0625 mg</td>
<td>0.125 mg</td>
<td>0.25 mg</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>2.5 mcg</td>
<td>5.0 mcg</td>
<td>10 mcg</td>
</tr>
</tbody>
</table>

### Predictive Value of Trialing

[Graph showing predictive value of trialing]
Gender

Age

Influence of age on the effect of reference analgesics in rats (mechanical threshold)
Influence of age on the effect of reference analgesics in rats (thermal threshold)

Age-Dependent Morphine Tolerance Development in the Rat


Age as an Outcome Factor?

CCF IDDS Implants 2000-2006 → 171 Patients

Excluded
- 13 Malignancy
- 12 ITB
- 11 No opioids

→ 135 Patients
Indications for implant

1. Failed Back Surgery 51.9% (n=70)
2. CRPS 10.4% (n=14)
3. Spinal cord pathology 8.8% (n=12)
4. Other (including postherpetic neuropathy, lumbosacral neuritis, diabetic peripheral neuropathy, visceral pain syndromes) 28.9% (n=39)

Oral Opioid Dose

<table>
<thead>
<tr>
<th>Time in treatment (months post implant)</th>
<th>Oral opioid dose (morphine equivalent in mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time 0</td>
<td>0</td>
</tr>
<tr>
<td>3 m</td>
<td>20</td>
</tr>
<tr>
<td>6 m</td>
<td>40</td>
</tr>
<tr>
<td>12 m</td>
<td>60</td>
</tr>
<tr>
<td>&lt;50 yrs old</td>
<td>80</td>
</tr>
<tr>
<td>&gt;50 yrs old</td>
<td>100</td>
</tr>
</tbody>
</table>

IT Opioid Dose

<table>
<thead>
<tr>
<th>Treatment time (months from implant date)</th>
<th>Change in intrathecal opioid dose from baseline (as a % increase from implant date dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 m</td>
<td>*p&lt;0.05</td>
</tr>
<tr>
<td>6 m</td>
<td>*p&lt;0.001</td>
</tr>
<tr>
<td>12 m</td>
<td>*p&lt;0.05</td>
</tr>
<tr>
<td>&lt;50 yrs old</td>
<td></td>
</tr>
<tr>
<td>&gt;50 yrs old</td>
<td></td>
</tr>
</tbody>
</table>
Conclusions

- Judicial application of intrathecal infusion therapies can be helpful in the management of cancer and non-cancer related pain.
- Thorough understanding of the pharmacology and physiology is crucial to ensure optimal outcomes.
  - Age may be an important consideration in algorithmic management of patient with IDDS in non-cancer pain.

Intrathecal opioid administration through implanted devices
Modified infusion dose in the first year post implant

<table>
<thead>
<tr>
<th>Time from implant</th>
<th>&lt;50 yrs old</th>
<th>&gt;60 yrs old</th>
<th>&gt;50 yrs old</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implant</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3 m</td>
<td>50 ± 10</td>
<td>50 ± 10</td>
<td>50 ± 10</td>
</tr>
<tr>
<td>6 m</td>
<td>100 ± 20</td>
<td>100 ± 20</td>
<td>100 ± 20</td>
</tr>
<tr>
<td>12 m</td>
<td>150 ± 30</td>
<td>150 ± 30</td>
<td>150 ± 30</td>
</tr>
</tbody>
</table>

*Percentage of IT dose increase (in % vs the baseline, time 0 implant)
The effects of Bupivacaine coadministration with opioids on the rate of increase of IT opioids at the first year post implant.

The graph shows the effects of Bupivacaine coadministration with opioids on the rate of increase of IT opioids at the first year post implant. The x-axis represents the treatment group, and the y-axis shows the opioid dose increase from implant date (Δ in % of time 0). The bars indicate the opioid dose increase at 3 months, 6 months, and 12 months post implant. The asterisk indicates a p-value of 0.035. The treatments are labeled as IT OP (alone) and IT OP+B (with Bupivacaine).

The diagram illustrates the classification of pain as nociceptive or neuropathic, with different stages of pain severity such as mild, moderate, severe, and strong opioid requirements.

Consultants' estimates of prevalence of use of more invasive therapies:
- Nerve blocks
- Epidural and intrathecal
- Intravenous and subcutaneous drops
- Oral, transdermal, and intramuscular agents

Note: This figure depicts a hierarchy of pain management strategies from least invasive to most invasive therapies.
Cancer Pain

Pain

- Nociceptive
  - Visceral (e.g. pancreatic CA → back pain)
  - Musculoskeletal (e.g. bone CA/mets)
- Neuropathic (e.g. plexopathy from mets)
  - lesion of the nervous system

Neuropathic pain can occur in 60% of patients with cancer involving soft tissues, spine and pelvic cancer with sacral invasion

~50% of cancer patients experience a combination of pain types at the time of dx

Granuloma Formation

Typical histopathology*

- Macrophages
- Neutrophils
- Monocytes
- Necrotic center
- No evidence of infectious process

Signs of both acute and chronic process

Granulation tissue