Review – Polyanalgesic Consensus 2007

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Article review

- Polyanalgesic Consensus Conference 2007
- Published in Neuromodulation Vol 10, No 4, 2007 pp 300-328
- Authors Timothy Deer et al
Summary

- Background
- Methods
- Discussion of content
- Comparing algorithms with previous consensus documents
- Conclusions
Background

- Follows on from 2 previous consensus conferences 2000 and 2003
  - Literature review
  - survey of the panelists
  - panel discussion of above
  - “guidelines for rational use”
- Specifically denies being a “standard of care”
Aims of conference

- Review previous conclusions
- Evaluate current guidelines
- Review responses of fellow peers (other panelists)
- Review data re analgesic drugs
- Formulate consensus opinions on critical issues
- Modify and update IT analgesic algorithm
- Identify areas promising for further research
- Disseminate the consensus opinions through the literature
Methods

- The Authors
  - All practising in the field
- The literature
  - 188 articles (2000-2006)
- Level of evidence
  - Generally accepted to be low level; Case series etc some Controlled studies. The opinion of the panelists was also taken into account.
Methods - continued

- Structure of review
  - Individual drug review of preclinical and clinical evidence
  - Review of other administration issues such as drug stability, compounding, catheter placement, ethics for end of life care etc
  - Algorithm for medications 1\textsuperscript{st} line, 2\textsuperscript{nd} line etc
2003 Algorithm

Morphine \leftrightarrow Hydromorphone

Morphine (or Hydromorphone) + Bupivacaine

Morphine (or Hydromorphone) + Clonidine

Morphine (or Hydromorphone) + Bupivacaine + Clonidine

Fentanyl, Sufentanil, Midazolam, Baclofen

Neostigmine, Adenosine, Ketorolac

Ropivacaine, Meperidine, Gabapentin, Buprenorphine, Octreotide, other **
Individual drug review - morphine

- Preclinical
  - Amlodipine
  - Intact adenosine receptors
  - IT IL 1 antagonists improve morphine analgesia and block hyperalgesia, allodynia and tolerance
  - Catheter tip masses shown to be dependent on concentration of solution
  - Stability shown of solution of morphine, clonidine and bupivacaine in a synchromed pump
Morphine

- Clinical

- Further case series reported with positive results

- A case of slow onset chronic respiratory depression was reported on 14 mg morphine per day in 41 yr old male

- Raphaels study of comparing IT with SCS for patients with LBP without prior surgery showed improved quality of life with IT and a nonsignificant trend to improve pain relief
Hydromorphone

- Preclinical
- More lipophylic than morphine
- Less tendency to produce granulomas
- Stability documented
Hydromorphone

- **Clinical**
  - 1:5 ratio equianalgesic
  - Less tendency to produce nausea, pruritus and sedation in patients intolerant to morphine
  - Oedema same as morphine long term
- Fentanyl

  - Preclinical
    - More lipophylic than morphine
    - Less differential in potency intrathecally than systemic
      - ED 50 for hotplate test was 2.4 mcg fentanyl and 4.2 mcg for morphine
    - Stability long term has not been documented

  - Clinical
    - No much evidence quoted for long term use
- **Sufentanyl**
  - Preclinical studies suggest less tolerance than morphine
  - Clinically little evidence presented

- **Methadone**
  - Clinical study has shown some benefit in opioid resistant pain in 1 study in 13 / 24 patients treated

- **Pethidine**
  - Prospective study of 10 cancer pain patients found improvements in neuropathic pain. Plasma levels of pethidine and norpethidine increased rapidly after 3 weeks of treatment
Bupivacaine

- **Preclinical** data shows LA damaging dorsal and ventral roots
- Bupivacaine safer than Lignocaine
- Stable in 0.75% solution in a pump alone and with Morphine and Clonidine
- **Clinical** data RCT showed 8mg per day didn't help
- Case reports of spinal cord compression from mass of precipitate
Ropivacaine

- No chronic pain data
Clonidine

- Preclinical
  - Reverses hyperalgesia in animal studies
  - Hydromorphone / clonidine mixtures have been found to be stable

- Clinical
  - Single case of depression, insomnia and night terrors apparently related to IT clonidine
Ketamine

- Preclinical
  - S+ ketamine was suggested to be less neurotoxic
  - Studies show neurotoxicity histologically
  - Currently not recommended
- Clinically
  - Has been reported for cancer pain with benefit
Adenosine

- Preclinical
  - Not analgesic in acute pain
  - Antagonises opioid analgesia
  - But ...A1 adenosine receptors block hyperalgesia
  - Long term administration causes hypersensitivity in animals
  - Appears to have opposing effects
Adenosine

- Clinical
  - Analgesia in humans with neuropathic pain with single doses
  - Not effective in post op pain study (hysterectomy)
Baclofen

- **Preclinical**
  - Gaba B agonist
  - Increases effect of SCS
  - Stable with clonidine for over 12 weeks
- **Clinical**
  - May assist SCS
  - Case report in PHN
  - Dangers of OD and withdrawal emphasised
  - Pruritus a sign of withdrawal
Other drugs

- Droperidol
  - Works epidurally in 1 study
- Gabapentin
  - Preclinical anti-allodynic and morphine sparing effects
- Ketorolac
  - Preclinical analgesic intrathecally
Midazolam

- **Preclinical**
  - Definitely analgesic
  - Controversial re clinical neurotoxicity potential
- **Clinical**
  - Use in chronic pain still restricted to case reports and small case series
Other drugs continued

- Neostigmine
  - Analgesic? by inhibition of c-fos expression
  - Still only given to humans as single dose – gives post op analgesia

- Octreotide
  - Couple of case reports
Ziconitide

- Now first line analgesic
- 5% of patients with cancer /HIV reported complete analgesia
- In noncancer pain 31% VAS decrease compared with 6% for placebo
- Interest in stability of combinations
  - most current drugs apparently reasonably stable with Ziconitide
Panel discussion

- Discussed
  - Pharmacokinetics
  - morphine HCL vs morphine sulphate,
  - drug mixtures
  - compounding standards,
  - equianalgesic conversion,
  - dangers of drug withdrawal,
  - catheter related issues,
  - hormonal adverse effects
  - trials,
  - patient monitoring and
  - granuloma formation

- Granuloma has been the topic of separate review, most drugs have caused it except fentanyl and sufentanil, clonidine may be protective, concentration of drug important
Panel discussion

- Importantly the different choices that apply to different individuals, (for example trialling midazolam, pethidine or ketamine at the end of life) were noted
2003 Algorithm
# 2007 Algorithm

## 2007 Polyanalgesic Algorithm for Intrathecal Therapies

<table>
<thead>
<tr>
<th>Line</th>
<th>Choices</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>(a) morphine ← (b) hydromorphone ← (c) ziconotide</td>
</tr>
<tr>
<td>#2</td>
<td>(d) fentanyl ← (e) morphine/hydromorphone + ziconotide ← (f) morphine/hydromorphone + bupivacaine/lonidine</td>
</tr>
<tr>
<td>#3</td>
<td>(d) lonidine ← (h) morphine/hydromorphone/fentanyl/bupivacaine +/lonidine + ziconotide</td>
</tr>
<tr>
<td>#4</td>
<td>(i) sufentanil ← (j) sufentanil + bupivacaine +/lonidine + ziconotide</td>
</tr>
<tr>
<td>#5</td>
<td>ropivacaine, buprenorphine, midazolam, meperidine, ketorolac</td>
</tr>
<tr>
<td>#6</td>
<td><strong>Experimental Drugs</strong></td>
</tr>
<tr>
<td></td>
<td>gabapentin, octreotide, conopeptide, Neostigmine, Adenosine, XEN2174, AM336, XEN, ZGX 160</td>
</tr>
</tbody>
</table>
Table 2
Recommended Maximum Intrathecal Dosages and Concentrations*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage (mg/day)</th>
<th>Concentration (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>15</td>
<td>80</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>10</td>
<td>80</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>20</td>
<td>38</td>
</tr>
<tr>
<td>Clonidine</td>
<td>1.0</td>
<td>2.0</td>
</tr>
</tbody>
</table>

*These values represent general recommendations and are dependent upon the specific patient and the clinical experience of the physician; thus, maximum dosage and/or concentration may vary from these values.

Table 1. Concentrations and Doses of Intrathecal Agents Recommended by the Polyanalgesic Consensus Panelists, 2007

<table>
<thead>
<tr>
<th>Drug</th>
<th>Maximum concentration</th>
<th>Maximum dose/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>20 mg/mL</td>
<td>15 mg</td>
</tr>
<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 upper limit</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>50 μg/mL (not 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>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 (Elan recommendations)</td>
</tr>
</tbody>
</table>
What do I take away from this?

- Hydromorphone rather than morphine
- Use low concentrations of opioids
- Use clonidine
- Baclofen good for spasm but probably worth a try as single agent for analgesic testing and ? With SCS
- Bupivacaine in higher doses for cancer pain but low dose no good
- Fentanyl and sufentanyl have never caused granulomas ....
- Pain medicine remains divided in terms of how to apply invasive therapies and who to – this was a technical article not a discussion of who should get treatment
Thankyou