Review – Polyanalgesic Consensus 2007

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Article review

- Polyanalgesic Consensus Conference 2007
- Recommendations for the management of Pain by Intrathecal (Intraspinal) Drug Delivery: report of an Interdisciplinary Expert Panel 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
  - “guidlines 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

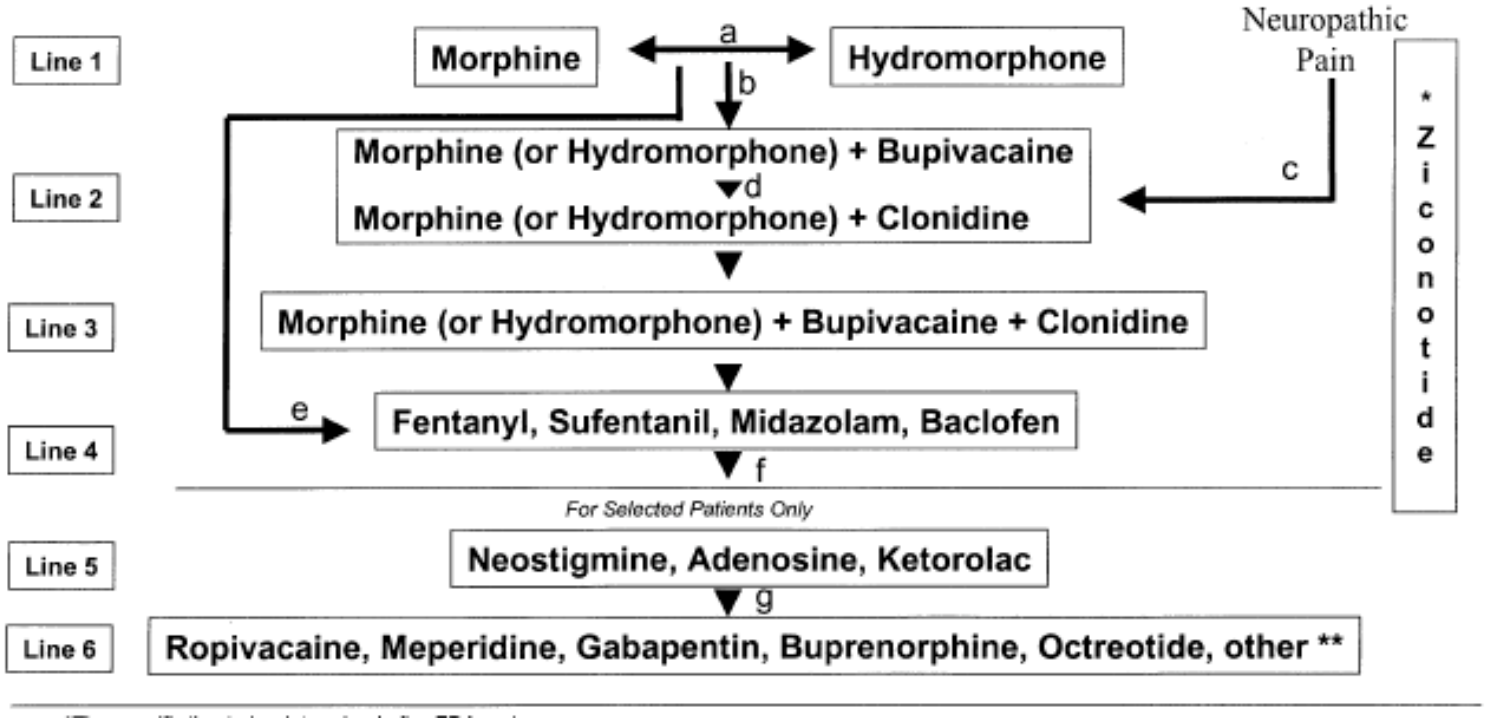
Methods

- 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 adminstration issues such as drug stability, compounding , catheter placement, ethics for end of life care etc
  - Algorithm for medications 1st line ,2nd line etc

2003 Algorithm



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 morpine ,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 tendancy to produce granulomas
- Stability documented

Hydromorphone

- **Clinical**
- 1:5 ratio equianalgesic
- Less tendancy 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

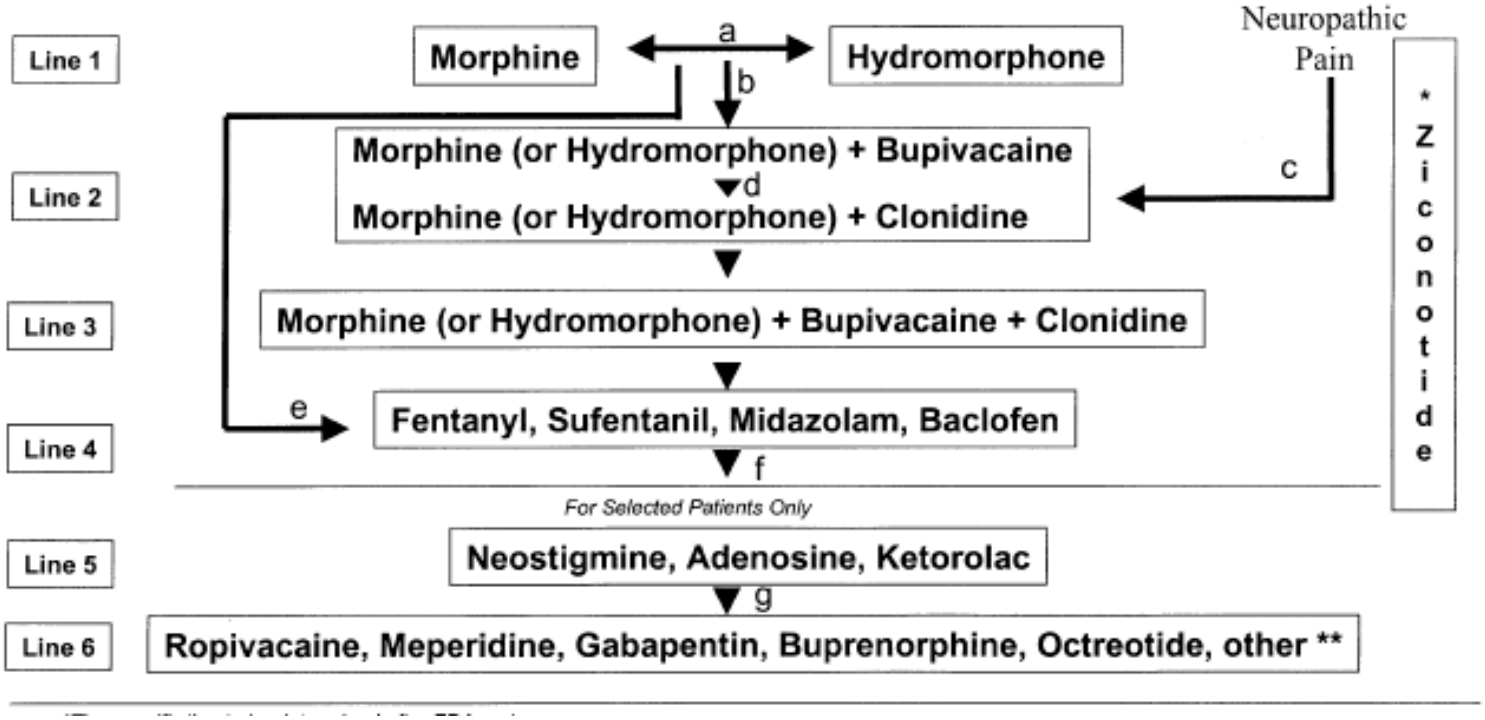
Panel discussion

- 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 sufentanyl, 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

Line #1:	**(a)** morphine	↔	**(b)** hydromorphone	↔	**(c)** ziconotide
Line #2:	**(d)** fentanyl	↔	**(e)** morphine/hydromorphone + ziconotide	↔	**(f)** morphine/hydromorphone + bupivacaine/clonidine
Line #3:	**(d)** clonidine	↔	**(h)** morphine/hydromorphone/fentanyl bupivacaine +/clonidine + ziconotide		
Line #4:	**(i)** sufentanil	↔	**(j)** sufentanil + bupivacaine +/clonidine + ziconotide		
Line #5:	**(k)** ropivacaine, buprenophine, midazolam meperidine, ketorolac				
Line #6:	***Experimental Drugs*** gabapentin, octreotide, conpeptide, Neostigmine, Adenosine, XEN2174, AM336, XEN, ZGX 160				

2003

Table 2
Recommended Maximum Intrathecal Dosages and Concentrations[a]

Drug	Dosage (mg/day)	Concentration (mg/mL)
Morphine	15	30
Hydromorphone	10	30
Bupivacaine	30	38
Clonidine	1.0	2.0

[a]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.

2007

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

Drug	Maximum concentration	Maximum dose/day
Morphine	20 mg/mL	15 mg
Hydromorphone	10 mg/mL	4 mg
Fentanyl	2 mg/mL	No known upper limit
Sufentanil	50 µg/mL (not available for compounding)	No known upper limit
Bupivacaine	40 mg/mL	30 mg
Clonidine	2 mg/mL	1.0 mg
Ziconotide	100 µg/mL	19.2 µg (Elan recommendations)

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