Spinal Analgesia
(Neuraxial analgesia in humans)

Paul Farquhar-Smith
The Royal Marsden NHS Foundation Trust

And other humanoid species
Neuraxial analgesia
# Cancer pain

## ADDITIONAL ANALGESIC MEASURES

<table>
<thead>
<tr>
<th>Additional Analgesic Measures</th>
<th>Final Follow Up (Mean 66 Days Post Admission)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>14%</td>
</tr>
<tr>
<td>Hormonal therapy</td>
<td>16%</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>24%</td>
</tr>
<tr>
<td>Surgery</td>
<td>7%</td>
</tr>
<tr>
<td>Anaesthetic nerve block</td>
<td>8%</td>
</tr>
<tr>
<td>Neurolytic nerve block</td>
<td>2%</td>
</tr>
<tr>
<td>Neuroablative surgery</td>
<td>1%</td>
</tr>
<tr>
<td>Psychotherapy</td>
<td>3%</td>
</tr>
</tbody>
</table>

Good pain relief in 76%

Zech, 1995
New adaptation of the analgesic ladder

- Targeted drug delivery
- Percutaneous techniques
- Neurosurgical procedures
- Neurostimulation

- Strong opioids

- Weak opioids

- Nonopioid analgesics
  - NSAIDS

NSAIDS = Nonsteroidal anti-inflammatory drugs
Rational for neuraxial techniques:

Rational for neuraxial techniques:

Wang et al 2003

Song and Marvizon 2003
Neuraxial anatomy
Dorsolateral view of thoracic vertebrae and ligaments (the vertebral arch of the upper vertebra has been removed)

- Pedicle (cut)
- Posterior longitudinal ligament
- Intervertebral disc
- Facet joint
- Lateral costotransverse ligament
- Interspinous ligament
- Supraspinous ligament
- Spinous process

Anterior view of thoracic vertebrae (bodies removed from upper two)

- Ligamentum flavum
- Posterior longitudinal ligament
- Nucleus pulposus
- Annulus fibrosus
- Intervertebral disc
- Superior costotransverse ligament
- Radiate ligament
- Anterior longitudinal ligament
Transverse section of an intervertebral disc showing the subarachnoid space

- Supraspinous ligament
- Interspinous ligament
- Ligamentum flavum
- Facet
- Cauda equina
- Venous plexus and fat in epidural space
- Dural sac
- Subarachnoid space
- Cartilage plate
- Annulus fibrosus

Lateral view of lumbar vertebra excluding interspinous and supraspinous ligaments

- Posterior longitudinal ligament
- Ligamentum flavum
(a) Cross section view of vertebral column

(b) Longitudinal section of vertebral column

(c) Oblique view

(d) Posterior view
Virtual 3D Model of the Lumbar Spine

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Radio Listeners in Panic, Taking War Drama as Fact

Many Flee Homes to Escape ‘Gas Raid From Mars’—Phone Calls Swamp Police at Broadcast of Wells Fantasy

A wave of mass hysteria seized thousands of radio listeners throughout the nation between 8:15 and 9:30 o’clock last night when a broadcast of a dramatization of H. G. Wells’s fantasy, “The War of the Worlds,” led thousands to believe that an interplanetary conflict had started with invading Martians spreading wide death and destruction in New Jersey and New York, and ruins, stations here and in other cities of the United States and Canada seeking advice on protective measures against the raids.

The program was produced by Mr. Welles and the Mercury Theatre on the Air over station WABC and the Columbia Broadcasting System’s coast-to-coast network, from 8 to 9 o’clock.

The radio play, as presented, was to simulate a regular radio new...
The epidural space

- Variable dimension
  - Posterior space 5mm lumbar, less in thoracic and cervical (if any!) and less fat
  - DOS similar

- Patchy ligamentum flavum

- Preferential flow through intervertebral foramina (?)

- Older – greater spread

- Compartments
  - Dura-periosteum/fibrosis
  - Unilateral placement often not unilateral block (!)
Epidural space in cancer

- Site of metastasis
- Radiculopathy
- Spinal cord compression
- Refractory pain
- Interruption of epidural flow
- Paraplegia with epidural (?)
Neuraxial pharmacodynamics (in brief)
Neuraxial medication

- Lower dose opioid required (c. 10:1-100:1)
  - Failure if not opioid sensitive
  - Choice: onset, duration, lipophilicity, spinal action
    - Morphine, fentanyl, diamorphine, (oxycodone)

- Addition of LA for opioid sparing (synergism) (but more adverse effect potential)

- Others
  - Clonidine, ketamine
Bioavailability

- Affinity for receptors
- Ability to reach receptor
- Diffusion through neural tissue
- Movement through membranes
  - Lipid solubility
  - pKa
  - Molecular weight
  - Protein binding
Epidural/intrathecal Opioids

- Hydrophilic
  - Slow onset
  - Long duration
  - Duration increased by adrenaline

- Hydrophobic
  - Quick onset
  - Short duration
  - Spinal effect?
  - Duration may be reduced with adrenaline
Epidural Space

Lipid soluble

meninges

Epidural Space

CSF

White

Grey
Epidural Space

CSF

Lipid soluble

meninges

Epidural Space

CSF

Lipid soluble

meninges
Ascending opioid action
Ropivacaine 0.1% and fentanyl 2mcg/ml (adrenaline 2mcg/ml)
Neuraxial approach in cancer pain: evidence
Epidural steroid injection

- Most data in non-malignant pain
- Strong evidence for short-term benefit, moderate for long-term, if signs of radiculopathy (Boswell et al. 2005).
- Bone cancer radiculopathy
  - Tumour involvement
  - Vertebral invasion
  - Vertebral collapse
- Limited evidence for degenerative spinal stenosis
## Efficacy of epidural opioids

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study, n</th>
<th>Opioid</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kalso et al 29</td>
<td>RCT, 10</td>
<td>Morphine</td>
<td>Equal analgesia to s.c. Lower dose</td>
</tr>
<tr>
<td>Vainio and Tigerstedt 30</td>
<td>Prospective uncontrolled</td>
<td>Morphine</td>
<td>Equal analgesia to oral Less side effects</td>
</tr>
<tr>
<td>Crawford et al 33</td>
<td>Prospective uncontrolled, 105</td>
<td>Mostly morphine (Some buprenorphine)</td>
<td>67% satisfactory pain relief No serious side effects</td>
</tr>
<tr>
<td>Driessen et al 34</td>
<td>Prospective uncontrolled, 32</td>
<td>Morphine</td>
<td>All significant pain relief 3x increase morphine in first 3 weeks</td>
</tr>
<tr>
<td>Samuelsson et al 35</td>
<td>Prospective uncontrolled, 146</td>
<td>Morphine</td>
<td>83% some analgesic response 19% stopped because of increasing pain</td>
</tr>
<tr>
<td>Shir et al 36</td>
<td>Prospective uncontrolled, 70</td>
<td>Methadone</td>
<td>80% good pain control No serious side effects</td>
</tr>
<tr>
<td>Hassenbusch et al 32</td>
<td>Prospective uncontrolled, 69</td>
<td>Morphine</td>
<td>Decrease in systemic morphine by 80%</td>
</tr>
<tr>
<td>Waterman et al 31</td>
<td>Prospective uncontrolled, 33</td>
<td>Morphine</td>
<td>80% excellent/good pain relief</td>
</tr>
</tbody>
</table>
### Efficacy of Intrathecal Opioids

<table>
<thead>
<tr>
<th>Study</th>
<th>Study type, n</th>
<th>Outcome</th>
</tr>
</thead>
</table>
| Rauck et al $^{41}$    | Prospective uncontrolled, 119 | 91% >50% reduction in pain at 4 months  
Less opioid side effects                                                  |
| Onofrio and Yaksh $^{25}$ | Prospective uncontrolled, 53 | 64% excellent/good pain relief  
2.5x increase spinal dose at 16 weeks                                         |
| Gestin et al $^{42}$   | Retrospective, uncontrolled, 50| 50% good pain relief  
50% fair                                                                        |
| Sallerin-Caute et al $^{43}$ | Retrospective uncontrolled, 159 | 80% excellent/good pain relief  
2-3x increase in dose at 3 months                                               |
| Penn and Paice $^{44}$ | Retrospective uncontrolled, 35 | 80% good/excellent pain relief                                                   |
| Paice et al $^{45}$    | Multicentre survey, 133        | 95% excellent/good pain relief  
2x increase dose at 3 months                                                     |
| Devulder et al $^{46}$ | Retrospective uncontrolled, 33 | 80% good pain relief                                                             |
| Schultheiss et al $^{47}$ | Prospective uncontrolled, 79 | 96% excellent or good pain relief                                               |
| Follett et al $^{48}$  | Retrospective uncontrolled, 35 | 77% good pain relief                                                            |
| Madrid et al $^{49}$   | Retrospective uncontrolled 35  | 78% excellent/good pain relief                                                  |
| Brazenor $^{50}$       | Retrospective uncontrolled, 26 | 88% excellent/good pain relief                                                  |
Evidence for intrathecal efficacy

- 202 patients with
  - refractory cancer pain (VAS>5 receiving equivalent 200mg morphine)
  - comprehensive medical management (CMM) or CMM plus implanted intrathecal opioid.

- Intrathecal group better pain score, fewer side effects and increased survival (Smith et al 2005).
# Cochrane Cancer Pain

<table>
<thead>
<tr>
<th></th>
<th>Epidural</th>
<th>Subarachnoid</th>
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</thead>
<tbody>
<tr>
<td>Trials (no RCTs)</td>
<td>31</td>
<td>28</td>
</tr>
<tr>
<td>Patients</td>
<td>1343</td>
<td>722</td>
</tr>
<tr>
<td>Excellent pain relief</td>
<td>72%</td>
<td>62%</td>
</tr>
<tr>
<td>Confusion, respiratory depression, sedation</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Other opioid side effects</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

Ballantyne and Carwood 2005
QI points

- Very few controlled trials
- Most use morphine
- Little data in cancer patients of opioid/LA
- Tolerance
  - Over 16 weeks opioid dose increased by 250% (Onofrio et al 1990)
Morphine ↔ Hydromorphone

Morphine (or Hydromorphone) + Bupivacaine
Morphine (or Hydromorphone) + Clonidine

Morphine (or Hydromorphone) + Bupivacaine + Clonidine

Fentanyl, Sufentanil, Midazolam, Baclofen

For Selected Patients Only
Neostigmine, Adenosine, Ketorolac

Ropivacaine, Meperidine, Gabapentin, Buprenorphine, Octreotide, other **

*The specific line to be determined after FDA review
**Potential spinal analgesics: Methadone, Oxymorphone, NMDA antagonists

a. If side effects occur, switch to other opioid.
b. If maximum dosage is reached without adequate analgesia, add adjuvant medication (Line 2).
c. If patient has neuropathic pain, consider starting with opioid monotherapy (morphine or hydromorphone) or, in selected patients with pure or predominant neuropathic pain, consider opioid plus adjuvant medication (bupivacaine or clonidine), (Line 2).
d. Some of the panel advocated the use of bupivacaine first because of concern about clonidine-induced hypotension.
e. If side effects or lack of analgesia on second first-line opioid, may switch to fentanyl (Line 4).
f. There are limited preclinical data and limited clinical experience; therefore, caution in the use of these agents should be considered.
g. There are insufficient preclinical data and limited clinical experience; therefore, extreme caution in the use of these agents should be considered.
What do Palliative Care consultants think?

- ‘As required’ access to pain anaesthetist considered adequate by 71%
- More than 50% used pain specialist <4 times / year
- 25% had no joint consultation with anaesthetists
- All suggested role was for interventions
- <25% agreed role was prescribing pain medicines
- 8% palliative care patients require pain interventions
- Too few referrals
- Palliative care making judgement about block

*Linklater et al 2002*
What do Pain/Aphesthetic consultants think?

- Low referral rate from palliative care
- 31% <12 referrals per year
- Joint consultation rare but when happened associated with more referrals
- Only 25% anaesthetists have sessions in job plan for palliative care
- Under-referral
- Lack of resource allocation

Kay et al 2007
Pain services and palliative medicine – an integrated approach to pain management in the cancer patient

Tony O’Brien¹,²,³ and Christopher M Kane⁴

Abstract
The vast majority of cancer patients will experience pain during the course of their illness. Thankfully, in most instances, the consistent application of analgesic guidelines, tailored to the unique needs of each individual patient, will deliver a satisfactory outcome. These guidelines recommend the skilled use of analgesic medications, often in conjunction with a range of adjuvant therapies as may be required. Despite the consistent and rational application of such strategies, it is recognised that a small but significant proportion of cancer patients continue to experience more refractory pain. In addition, these patients may experience a plethora of unwanted dose-limiting side effects associated with their analgesic medication, sometimes even at low dose. All such patients with more complex and refractory pain syndromes require a more comprehensive review and many will require interventional therapy and/or adjuvant approaches. Unfortunately, the availability and accessibility of such services are variable. Even in circumstances in which palliative medicine and pain services co-exist in the same region, there may be poor integration between the two services. Each specialty area holds a unique set of skills and competencies, yet there is considerable overlap. Patient care and outcomes will be enhanced by establishing more formal relationships between these two specialty areas.
Case scans
November: Unilateral epidural