THE TREATMENT OF PAIN

Quo vadis?

THE PHARMACOLOGICAL MANAGEMENT OF PAIN

• Definition of pain
• Classification of pain
• Is the management of pain a function of the type of pain experienced?
• Pharmacology of opiates and opioids
• Non-opioid analgesics
• Acute versus chronic pain
• New developments

PAIN...

...is whatever the experiencing person says it is, existing whenever he/she says it does

(Nursing manual)

CLASSIFICATION OF PAIN

Acute
Post-operative, fracture, gunshot wound...

Chronic
Pain that lasts continuously or intermittently for 3 months or more

Main characteristics of different pain types

Acute
(seconds to minutes; activation of NS/WDR neurones proportional to the intensity of the stimulus)

Tissue injury
(minutes to days; sensitization of terminals at injury sites and delayed spinal sensitization)

Nerve injury
(days, months...?; changes in supply of trophic factors, sprouting and abnormal innervation, transynaptic degeneration)

Types of pain

■ Nociceptive (mechanical, thermal, electrical...)
■ Inflammatory (ischaemia, infection...)
■ Neuropathic pain (maladaptive plasticity)
Pain mechanisms - caveats

- Same mechanism – different pain
- Same pain – different mechanisms
- Changes can occur concomitantly at multiple levels (sensitisation of nociceptors, changes in neuronal excitability, upregulation of genes, structural alterations, neuronal loss)

---

Differential management of pain

Nociceptive
- Opioids
- Muscle spasm
- Muscle relaxants
- Nerve compression
- Steroids
- Opioids
- Nerve blocks
- Deafferentation
- Antidepressants
- Anticonvulsants
- Nerve blocks

Use of general principles (example “the analgesic ladder”) but no absolute rules

---

Pain ascending projections

Dorsal horn local circuits

---

Treatment strategy – cancer pain
Pain management – drug classes

NON-OPIOID MEDICATION

NSAIDs
- Paracetamol - well-tolerated, analgesic, antipyretic
- Aspirin - analgesic, antiinflammatory
- Ibuprofen, ketoprofen, COX-2 inhibitors...
- Nausea and gastrointestinal bleeding can be produced by any NSAIDs

Rheumatoid arthritis, osteoarthritis, osteoporosis, post-operative pain

Anticoagulant drugs (phenprocoumon, warfarin, sodium valproate)

Chronic pain following nerve injury, trigeminal neuralgia

Triacyclic antidepressants (amitryptiline)

Neuropathic pain, post-stroke pain, cancer pain...

Clonidine

Cancer pain

ENDOGENOUS OPIOID SYSTEMS

Main types of families and ligands
- PROOPiomelanocortin
- PROENkephalin
- PRODYNorphin

Characteristics: co-release and co-transmission, relative receptor selectivity

Receptors
- Mu (μ1 and μ2)
- Delta (δ1, δ2)
- Kappa (κ1, κ2, κ3)

Inflammatory mechanisms

COX-2 and the arachidonic acid cascade

The formation of prostaglandins and thromboxanes

Pain hypersensitivity, inflammation and COX-2

EFFECTS OF OPIOIDS

Central nervous system
- Analgesia
- Respiratory depression
- Drowsiness/lethargy
- Euphoria/Dysphoria
- Miosis
- Nausea and vomiting

Cardiovascular system
- Hypotension

Gastrointestinal system
- Delayed gastric emptying
- Decreased biliary and pancreatic secretions

Urinary urgency
- Itching
Practical aspects of opioid use

- Morphine (importance of titration, active metabolite)
- Heroin (high solubility compared to morphine; drug of choice in cachexia)
- Dextromoramide (active sublingually)
- Methadone (half-life increases on repeated dosing)
- Meptazinol (less respiratory depression?)
- Pethidine (poor oral bioavailability)

Caveats: respiratory depression, potentiation of the effect on blood pressure of benzodiazepines and phenothiazines, dysphoric effects with pentazocine, toxicity of norpethidine, accumulation of M6G if renal function is impaired

What is the risk of tolerance and addiction to opioids?

Tolerance

In the context of chronic pain there is very little risk of tolerance. Predictions made on the basis of animal and volunteer studies do not reflect the conditions of clinical use.

Addiction

Among 12,000 patients who received at least one strong opioid preparation, there were only 4 cases of addiction in patients without a history of drug abuse. The dependence was major in one instance (Porter and Jick, 1980).

Opioid use – the challenge of side effects in terminal care

- Nausea and vomiting (possible tolerance, anti-emetics, change of mode of administration)
- Delirium (opioid substitution, benzodiazepines, antipsychotics)
- Myoclonus (dose reduction, benzodiazepines)
- Sedation (methylphenidate)

Opioid use – the challenge of side effects in terminal care

- Switching between routes of administration (transdermal fentanyl)
- Opioid rotation – special case of methadone (tolerance?)

Opioid use – the challenge of difference in sensitivity between patients

- COMT inactivates catecholamines in the CNS
- Polymorphism Val158Met leads to up to 4-fold increase in enzyme activity
- Met/Met leads to the highest response to pain
- Val/Val: the highest requirement for morphine

Variable sensitivity to morphine as a function of the Val vs. Met genotype variations

<table>
<thead>
<tr>
<th></th>
<th>Val/Val</th>
<th>Val/Met</th>
<th>Met/Met</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=44</td>
<td>n=96</td>
<td>n=67</td>
</tr>
<tr>
<td>Morphine dose (mg/24 h)</td>
<td>155 (162)</td>
<td>117 (100)</td>
<td>95 (99)</td>
</tr>
<tr>
<td>Morphine serum (nmol/l)</td>
<td>119 (159)</td>
<td>86 (88)</td>
<td>79 (72)</td>
</tr>
<tr>
<td>M6G serum (nmol/l)</td>
<td>711 (992)</td>
<td>506 (493)</td>
<td>440 (484)</td>
</tr>
<tr>
<td>M6G serum (nmol/l)</td>
<td>569 (443)</td>
<td>2812 (2209)</td>
<td>2586 (2707)</td>
</tr>
</tbody>
</table>

All numbers are mean (SD). No statistically significant differences were observed for the other observations (P=0.06 for differences in M6G conc.; P=0.14 for differences in morphine conc.).

* Post hoc Mann–Whitney test; P=0.025.

Val/Val and Met/Met genotype groups.
Opioid use – can individual sensitivity be predicted?

- The mu opioid receptor (Opmr1 gene) is essential in the addictive and analgesic effects of opiates
- More than 100 polymorphisms have been identified in the gene
- This may explain the variations in minimal effective analgesic concentrations (MEAC) for the same opiate in different patients

(Ikeda et al., 2005)

New developments in the treatment of visceral pain

Referred pain in angina pectoris

Role of the dorsal columns in visceral pain

Therapeutic targets for new analgesics to treat visceral pain

- Neurokinin antagonists (NK1, NK2, NK3)
- 5-HT receptor antagonists (5-HT3 antagonists and 5-HT4 partial antagonists)
- Opioid kappa receptor antagonists
- Bradykinin receptor antagonists (B1 and B2)

Challenges of neuropathic pain
Pain management – disease or pain types
Current treatments – example of polypharmacy approach in neuropathy
- TCA
- SSRI
- Anticonvulsants
- Gabapentin
- Local anaesthetics
- Capsaicin
- Ketamine, dextromethorphan
- Baclofen
- Opioids

Anticonvulsant drugs
- Lamotrigine
- Gabapentin

Antidepressant drugs
- Rapid onset compared to antidepressant effects
- Mechanism of action (5-HT and Nad, sodium channel blockade, alpha-adrenergic blockade, NMDA receptor antagonism?)
- TCA more effective than SSRI

Gabapentin
- Inhibitor of calcium channels (alpha2-delta)
- Inhibition of N-type calcium channels
- Modulator of glutamatergic synapses?
- Activation of GABA metabotropic receptors
- Up-regulation of T-type channels?
- Possibility of using it as pre-emptive medication
- Combination therapy: e.g. rofecoxib
- Pregabalin – similar profile
The case of venlafaxine

- 5-HT and noradrenaline reuptake inhibitor
- Active metabolites (e.g., R-o-desmethylvenlafaxine)
- At steady-state (dose-dependent): 5-HT then noradrenaline

Venlafaxine in polyneuropathic pain

<table>
<thead>
<tr>
<th>Venlafaxine in polyneuropathic pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table 3: Effect of venlafaxine vs. placebo on percentage of patients with 50% or more improvement in pain intensity over 8 weeks.</td>
</tr>
<tr>
<td>Pain relief</td>
</tr>
<tr>
<td>Moderate</td>
</tr>
<tr>
<td>Severe</td>
</tr>
<tr>
<td>Pain-free</td>
</tr>
<tr>
<td>*Pain-free, *p &lt; 0.05</td>
</tr>
</tbody>
</table>

Atypical antidepressants - Bupropion

- Inhibitor of noradrenaline reuptake
- Weak inhibitor of dopamine reuptake
- NMDA receptor down-regulation

Bupropion in neuropathic pain

<table>
<thead>
<tr>
<th>Bupropion in neuropathic pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table 4: Comparison of global change in pain relief at weeks 4 and 12.</td>
</tr>
<tr>
<td>Treatment</td>
</tr>
<tr>
<td>Pain relief</td>
</tr>
<tr>
<td>Pain-free</td>
</tr>
<tr>
<td>*Pain-free, *p &lt; 0.001</td>
</tr>
</tbody>
</table>
Are there structural changes associated with chronic pain?

Definition of the PSD

- A proteinaceous “organelle” optimised for signal transduction (organisation of NMDA receptors, adhesion molecules, ion channels, trk receptors…)
- 30-40 nm thickness, several hundred nm wide and contains several hundred molecules
- Enrichment in the PSD95/SAP90 protein and other proteins with PDZ domains (modular protein domains of 90 aa that bind to C-terminal peptides)

NMDA receptor complex anchoring

- PSD-95/SAP90 (MAGUK superfamily of proteins); proteins with PDZ domains
- Also direct connection to the cytoskeleton (e.g. beta-actinin)
- Connection to SynGAP (a protein involved in spine and dendrite dynamics?)
- Connection to proteins such as Shank, Homer and ultimately link to mGluR
Structural changes and pain?

Knockdown of PSD-95/SAP90 delays the development of neuropathic pain in rats
Tao et al., Neuroreport, 12 (15) 3251-3255, 2001

Role of membrane-associated guanylate kinase proteins (MAGUK proteins) in pain?

Special cases – new prospects?

Trigeminal neuralgia

TRIGEMINAL NEURALGIA

Causes

Compression, distortion or stretching of the V root fibres by a branch of the anterior or posterior inferior cerebellar artery

TRIGEMINAL NEURALGIA

TREATMENT

Pharmacological
Carbamazepine
Baclofen
Phenytoin
Valproate
Clonazepam
Baclofen with carbamazepine

Management of pain - challenges

Case of the patient with trigeminal neuralgia that had tried: imipramine, doxepin, carbamazepine, valproic acid, baclofen, pethidine, lidocaine, capsaicin cream....
Other questions?

Processes that are still poorly understood

Role of co-expressed peptides in primary afferents?

Clearance of co-localised tachykinins in the striatum in vivo

Management of refractory pain

Evolution of medication used in a neuraxial approach

Outcome of neuraxial analgesia

Notes:
A  Pain score in the range 7 to 10 (i.e. severe pain range)
B  Opioid consumption expressed as mg/day oral morphine equivalents
Conclusion - Issues

- Dichotomy preclinical research and clinical application
- Rising pain prevalence – elderly population
- Management of terminal disease (intrinsic processes and iatrogenic pain)
- New targets? New models?
- New clinical strategies?
- A universal analgesic?

Management of pain in elderly patients

- Paracetamol (liver disease, drug interactions)
- NSAIDs (COX-2 inhibition preferrable in theory, but renal toxicity, hypertension, limb oedema)
- Opioids (titrated; constipation, sedation, impaired cognition, urinary retention)
- Various types of neuropathic pain (post-stroke or fall, TBI-type): gabapentin, TCAs, capsaicin cream, lidocaine patches…

Pharmacogenetics of analgesia and anaesthesia

- Morphine and M6G (A118G mu opioid receptor: reduced nausea and vomiting, sedation)
- Codeine (CYP2D6: slower conversion to morphine with reduction in analgesic effects but not adverse effects)
- Methadone (CYP2D6: slower metabolism, but not consistently)
- Paracetamol (CYP2E1: faster elimination rate)
- Celecoxib, ibuprofen, naproxen (CYP2C9: slower metabolism)
- Suxamethonium (butyrylcholinesterase: longer duration of action)
- Diazepam (CYP2C19: increased half-life and prolonged sedation)