Opioid Resistant Pain

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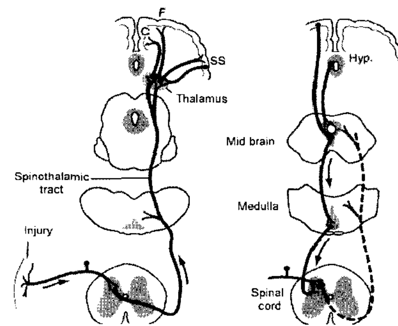
Pain

- Similar injuries is remarkably variable in different situations and individuals
- Athletes in play
- Soldiers in battle
- Complex physiological and emotional experience and not a simple sensation

Pain transmission and modulation system



Incidence of cancer pain

- Moderate and severe pain is experienced by 60% to 90% of advanced caner.
- Most cancer pain would be managed .
- Approximately 10% to 20% of cancer pain do not respond to strong opioid.

Opioid-resistant pain

- The pain responds to opioids but side-effects limit the dose of opioid
- The pain is unresponsive or partial to increasing doses of opioids
  - *Pseudo-opioid-resistant pain*
  - *True opioid-resistant pain*

What's pseudo-opioid-resistant pain?

- Persistent pain experience communicated by the patient or family after prescription and initiation of opioid therapy
- The pain experience needs to be properly assessed and communicated

Pseudo-opioid-resistant cancer pain

- *Misconceptions and knowledge deficit*
- *Lack of performance capabilities*

G.C.M. Evers. Support Care Cancer 1997;5:457-460

Misconceptions and knowledge deficit

- Misconceptions of primary goal of therapy as eradication of the cancer
- Fears about side effects and addiction
- Some opioid regimens are too complex for adequate understanding

Richard B Patt Cancer pain. Lippincott, Philadelphia, pp119-128

Lack of performance capabilities

- Not taking correct dose and frequency at least 30% of patients
- Reduced opioid intake due to vomiting, constipation

Lewis C, Linet MS. Am J Med 1983;74:673-678

True opioid-resistant cancer pain

- *Neuropathic pain*
- *Bone pain*
- *Raised intracranial pressure*
- *Intestinal colic*
- *Spiritual pain*

Neuropathic pain

- Arise from tumor invading peripheral or central nerve system
- Burning , tingling, electric shock-like
- Often severe
- Commonly accompanied by sensory loss and hypersensitivity to nonnoxious stimuli (allodynia, hyperalgesia)

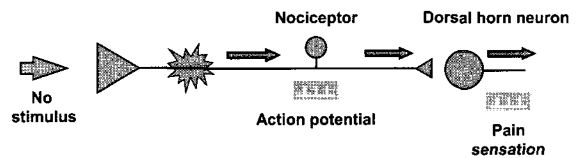
Evaluation of neuropathic pain

- Diagnosis is based primarily on history and findings on physical examination
- A loss of inhibitory mechanisms, peripheral and central sensitization is related to the pathogenesis of neuropathic pain

Ian Gilron et al. CMAJ. 2006;175(3):265-275

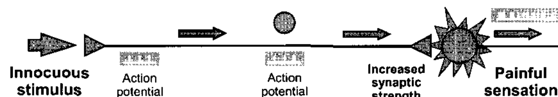
Pathophysiology of neuropathic pain (1)

Peripheral Sensitization



Pathophysiology of neuropathic pain (2)

Central Sensitization

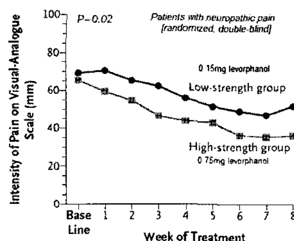


NMDA-receptor antagonist

- N-methyl-D-aspartate(NMDA) receptor is involved in the spinal neural circuitry that leads to a neuropathic pain
- NMDA-receptor antagonist
  - Dextromethorphan
  - Ketamine
  - Methadone
    - both opioid receptor agonist and NMDA receptor agonist

Treatment of neuropathic pain -opioid

- Effective in neuropathic pain include anti-convulsant drugs,antidepressants, and opioids



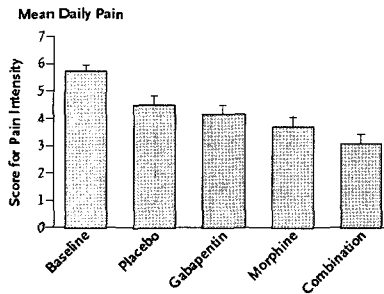
Michael C et al. N Engl J Med 2003 348(13);1223-1232

Anti-convulsant and depressants for neuropathic pain

- Tricyclic antidepressants ⇨ Principally by facilitation of descending inhibitory pain pathway
  - *amitriptylline, imipramine*
  - *Selective serotonin antagonist has less effect*
- Anticonvulsants for lancinating or electrical pain
  - *Gabapentin, Pregabalin*
    - Lethargy
    - Starting low and going slow
  - *Clonazepam*
  - *If one anticonvulsant is not effective , it's rational to try another*

Max MB et al. N Engl J Med 1992;326(19):1250-1256

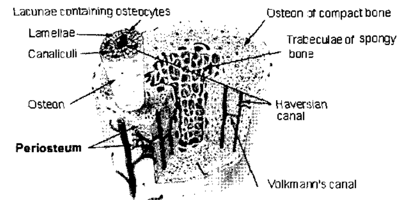
Treatment of neuropathic pain -single or combination drugs



Ian Gilron et al. N Engl J Med 2005 352(13);1324-1334

Malignant metastatic bone pain (1)

- Periosteum receives dense sensory and sympathetic innervation



Malignant metastatic bone pain (2)

- At its onset, pain can be intermittent, but rapidly progress into continuous pain
- Both associated with inflammation and neuropathic pain
- Once after established the chronic pain, nerve system undergoes a sensitization
  ⇨ Hyperalgesia , allodynia
  - Coughing, turning in bed

Clohisy DR, Mantyh PW. Cancer 2003;97(3):866

Treatment of bone cancer pain

- External beam radiation is most effective
  - About 90% get some pain relief
- Bisphosphate
  - Inhibition of osteoclast activity
  - Effective in providing some pain relief
- Radionuclides such as strontium
  - Take 3 months to have full effect
- Opioid , anticonvulsant, NSAID, corticosteroid

Wong R , Wiffen PJ. The Cochrane Library 2002:4

Other opioid resistant pain

- Headache due to cerebral edema
  ⇨ Dexamethasone
- Intestinal colic
  - Squeezing and perioidic nature
  - Hyoscin butylbromide (Buscopan®)
  - Corticosteroid may be helpful
  - Scopoamine or octreotide

Emotional pain

- Anxiety or depression are often associated with pain in cancer, and may be the cause, or result, of poor pain control
- Patients with higher anxiety and depression levels had higher cancer pain

Spiegel D, Sands S, Koopman C. Cancer 1994;74(9):2570-8
Ozalp G et al. Acta Anaesthesiol Scand. 2003 Jan;47(1):26-9