Neuropathic Pain
Peripheral Neuropathy Workshop
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RPAH
Pain Management Centre
Alliance For Improving the MANAGEMENT of PAIN 2014
CLASSIFICATION OF NEUROPATHY

- Disease process involving cranial or peripheral nerve
- Sensory, motor and / or autonomic fibres

- **Mononeuropathy**
  - single nerve

- **Mononeuritis multiplex**
  - multiple discrete nerves

- **Polyneuropathy**
  - generalised and symmetrical

- **Polyradiculopathy**
SYMPTOMATIC POLYNEUROPATHY

• Most common form of PN
  – Stocking sensory loss + distal weakness
  – Loss of ankle jerks
    • other reflexes lost with severe axonal loss (earlier in demyelination)

• Metabolic - diabetes, uraemia
• Nutritional - B12, thiamine (B6) deficiency
• Toxic – alcohol, drugs (statins, chemotherapy), metals (Pb)
• Connective tissue disorders, vasculitis
• Malignancy, paraprotein, amyloid
• Hereditary (HMSAN, HSN) and infection (HIV, Lyme)
MONONEUROPATHIES

- Sensory loss and weakness in territory of individual nerve
  - Entrapment compression
    - median nerve at the wrist
    - ulnar nerve at the elbow
    - common peroneal nerve at the fibular head
- Trauma
- Diabetes
- Leprosy and Sarcoid
- Vasculitis
- Hereditary sensitivity to pressure palsies
- Multifocal motor neuropathies
CASE 1 - HISTORY

- 64 yo man

- NIDDM Dx 2002 - HbA1c 8.8%
  - Diamicron MR

- 5 month history of increasing paraesthesia and numbness of both feet
  - walking on “cotton – wool”
  - unsteady when walks
  - no pain
CASE 1 - EXAMINATION

- Wide based gait
- Reduced sensation in stocking distribution to mid-shin
- Absent vibration sense to ankles
- Absent ankle reflexes
- Reduced knee reflexes
CASE 1 - DIAGNOSIS?

- Diabetic Peripheral Neuropathy

- International Consensus Meeting defined diabetic peripheral neuropathy as:
  “the presence of symptoms and / or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes”
CASE 1–FURTHER INVESTIGATIONS?
INVESTIGATIONS - ELECTROPHYSIOLOGY

• Study of function of nerves and muscle
  – Considered an extension of the clinical exam
  – Performed by experienced physician

• Uses
  – peripheral nerve dysfunction
  – large fibre peripheral neuropathy
  – radiculopathies
  – plexopathies
STUDIES

• Sensory
  – Median / Ulnar / Sural

• Motor
  – Median- APB / Ulnar – ADM
  – Peroneal-EDB / Tibial-AHB

• F waves
  – Median / Ulnar / Tibial / Peroneal
SENSORY NERVE CONDUCTION STUDIES

• Stimulate and record from nerve

• Sensory action potential amplitude
  – normal if lesion proximal to dorsal root ganglion as axon remains intact with proximal lesions - nerve root compression

• Sensory conduction velocity
  – need only record from a single point
MOTOR NERVE CONDUCTION STUDIES

- Stimulate nerve and record compound muscle action potential amplitude (CMAP) from muscle

- CMAP from proximal and distal sites
  - conduction block

- Distal motor latency

- Latency from 2 sites gives motor conduction velocity
NORMAL RESULTS

• **Upper limb**
  – Median DML <4.0ms / Ulnar DML <3.0ms
  – SNAP >5uV
  – CMAP >5mV
  – Conduction velocities >50m/s

• **Lower limb**
  – Peroneal and Tibial DML <6.0ms
  – Sural SNAP >5uV
  – Peroneal CMAP >2mV / Tibial CMAP >5mV
  – Conduction velocities >40m/s
• Moderate - severe generalised sensori-motor peripheral neuropathy
  – Absent sural sensory response
  – Marked reduction peroneal and tibial motor amplitudes (0.5mV)
  – Slowing of peroneal and tibial motor conduction velocities (36 m/s)
AXONAL LOSS

- If mild, NCS normal, esp. if only involving small fibres
- Absent or low amplitude SNAP’s
- Low amplitude CMAP’s
- Slowing of motor and sensory CV’s
  - low but >40ms in UL
  - low but >32ms in LL
    - fast conducting fibres survive even when 75% of axons have died
DEMYELINATION

- Normal SNAP’s
- Prolongation of DML’s (>50% normal)
- Normal CMAP’s distal to block
- Reduced CMAP’s proximal to block

- Slowed motor CV across block
  - <80% if CMAP amplitude >80% ie UL <40m/s
  - <70% if CMAP amplitude <80%

- Absent or prolonged F waves
### OTHER INVESTIGATIONS – PATHOLOGY ??

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<thead>
<tr>
<th>Investigation</th>
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<td>FBC</td>
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<td>Vitamin B12</td>
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<td>EPG</td>
<td>IEPG</td>
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<tr>
<td>Anti-GM1</td>
<td>Anti-GQ1b</td>
<td>Anti-MAG</td>
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CASE 1 - INVESTIGATIONS

- Anaemia (Hb 94) with rouleaux formation ++
- ESR (89)
- Urea 22.8 Creatinine 310 HbA1c 6.0%
- Paraprotein 16g/L of IgG Kappa

- Subsequent Ix –
  - Urinary Bence Jones proteinuria
  - Bone marrow biopsy
    - Plasma cells >10%

- Dx: Multiple Myeloma
PN SYMPTOMS

- Numbness or reduced sensation
- Tingling or paraesthesia
- Neuropathic pain
  - burning sensation
  - sharp, shooting, lacinating pain
- Allodynia
  - pain to non-painful stimulus
- Hyperalgesia
  - increased pain to painful stimulus
TYPES OF PAIN

Nociceptive pain

Mixed pain (Both types of pain co-exist in many conditions)

Neuropathic pain
BURNING
CRAWLING
STABBING
SHOCKING
FREEZING
CASE 2 - HISTORY

- 45 year old lady

- 6 month history of:
  - Paraesthesia and tingling of both feet
  - Increased sensitivity to touch, esp. bed covers
  - Occasional burning sensation
  - Symptoms worse at night and wake her
  - Associated restless legs – 1 hour to get to sleep
CASE 2 - EXAMINATION

- Weight 60 kg
- Steady gait
- Increased sensitivity to touch to mid-shin
- Normal vibration sense and 10g microfilament
- Ankle reflexes present

- Sleep study
  - Mild restless legs

- Bloods including 2 hour glucose tolerance test
  - Normal
**CASE 2 - NERVE CONDUCTION STUDIES**

- NCS in India – Normal
- NCS at North Shore Hospital – Normal
- Repeat NCS - Normal
  - Sural sensory amplitude - 15-17uV
  - Peroneal motor amplitude - 7.0mV
  - Tibial motor amplitude - 11.0 mV
  - Sensory and motor conduction velocity >40m/s
CASE 2 - DIAGNOSIS?
SMALL FIBRE NEUROPATHY

- Pain in the absence of objective signs
- Normal conventional nerve conduction studies
  - measures large nerve fibre function
CASE 2 – OTHER INVESTIGATIONS

• Punch skin biopsies
  – 3mm punch, 10cm above lateral malleolus
  – Reduced intradermal nerve fibre density

• Quantitative sensory testing (QST)
  – Non-invasive assessment of sensory perception
  – Small nerves - pain and temperature
    • Cold and heat pain thresholds
  – Large nerves – vibration threshold
CASE 2 - SMALL FIBRE NEUROPATHY

• Had previously tried

  – Amitriptyline up to 50mg nocte
  – Gabapentin 600 mg tds
  – Tegretol CR 400mg twice a day
CASE 2 – FURTHER TREATMENT?

• Pregabalin
  – Increased dose to 150mg bd
  – Improved pain by 10-20%

• Burning feet persists
  – Extended to ankles, worse at night
  – Unable to continue to work

• Next Option ??????
**CASE 2 – FURTHER TREATMENT?**

- **Tramadol SR** up to 200 mg bd
  - Improved pain by 10-20%

- **Norspan patch**, up to 20 mg weekly
  - Improved pain by 10-20%
  - Ceased due to constipation

- **Oxycontin** up to 20 mg bd
  - Improved 10-20%
  - Constipation
  - Targin not considered as improvement minimal
CASE 2 - FURTHER TREATMENT ??

• Clonazepam commenced 0.25mg nocte
  – Improved pain, esp. burning – 80%
  – Improved sleep
  – Feels well
  – Back to work
PREDOMINANTLY SMALL FIBRE NEUROPATHIES

- Diabetes
- Alcohol
- Amyloid
- Paraproteineamia
- Malignancy
- Radiation
PHARMACOTHERAPY

• Generally involves use of anti-convulsants and / or anti-depressants

• “Even with the current generation of drugs, effective analgesia is achieved in less than half of this population” (Sindrup 1999)
NEUROPATHIC PAIN THERAPIES - 2014

- Carbamazepine (NNT to obtain 50% relief - 1.7)
- Valproate, Phenytoin, Gabapentin, Lamotrigine, Topiramate, Oxcarbazepine
- Pregabalin, Levetiracetam, Tiagabine
- Lacosamide (Vimpat), Zonisamide
- Clonazepam
- Amitriptyline, Nortriptyline, Imipramine
- Duloxetine
- Opioids – Tramadol, Buprenorphine, Oxycodone (Targin), Tapendatol, Morphine, Fentanyl, Hydromorphone
- Baclofen, Mexilitene, Clonidine
- Capsaicin cream, Lignocaine 5% Dermal patch
- N-methyl-D-aspartate (NMDA) blockers – Ketamine, Memantine
- Botulinum Toxin
- Vitamin B12
WHO ANALGESIC LADDER

Strong opioids (oxycodone, Targin, morphine, fentanyl)
for moderate-severe pain
 +/- non opioids +/- adjuvants

Persistent pain or increasing pain

Weak opioids (codeine, tramadol, buprenorphine, tapendatol)
for mild-moderate pain
 +/- non opioids +/- adjuvants (TCA, AED)

Persistent pain or increasing pain

Non-opioids (paracetamol, NSAID’s, COX-2)

Supervised

Symptoms
Severe
Mild
NNT’S FOR DIABETIC PERIPHERAL NEUROPATHY

- Tegretol  2.3  (CI 1.6-3.8)
- Amitriptyline  2.9  (CI 2.4 - 4)
- Gabapentin  3.8  (CI 3.5-5.7)
- Tramadol  3.8  (CI 2.8 to 6.3)
- Pregabalin  3.9 – 6.6

Cochrane report (2007)
- states that whilst Gabapentin is gaining popularity as a treatment for neuropathic pain, no clear advantage has been demonstrated over Tegretol
### NNH’s for Diabetic Peripheral Neuropathy

- **NNH** - major harm not statistically significant for any drug compared to placebo

- **NNH** for minor harm were:
  - Tegretol: 3.7 (CI 2.4-7.8)
  - Gabapentin: 2.5 (CI 2.0-3.2)
  - Amitriptyline: 3.7 (CI 2.9-5.2)
  - Pregabalin: 4 – 5.0
  - Opioids: 4.2 (CI 3.2-5.6)
  - Tramadol: 8.3 (CI 5.6-17) quick and slow
CASE 3 - HISTORY

• 54 yo man

• 3 day history of sudden onset R buttock pain radiating down right leg to ankle
  – Constant throbbing and BURNING with occasional shooting pain
  – Pain frequently waking him at night
  – Tried Ibuprofen and Voltaren with no relief

• Similar pain Nov 2008
  – CT disc bulge L4/5 with possible compression of right L5 nerve root

• Examination
  – Weakness right great toe dorsiflexion
  – Absent right ankle reflex
  – Reduced sensation lateral right leg
CASE 3 – DIAGNOSIS ??

- Dx – Right L5 radiculopathy
- Commenced Amitriptyline 10 mg nocte
- Changed Voltaren to Mobic 15 mg nocte
- Organised MRI lumbar spine
  - Large disc protrusion at L4/5 with compression of right L5 nerve root
CASE 3 - PROGRESS

- Sleeping better, but pain persisted
- GP added Oxycontin 10mg bd and Endone prn
- Increased Amitriptyline to 25 mg nocte
- Organised R peri-radicular block
- Pain free within 2 weeks
- Back to work and did not need block
WIND - UP

- Prolonged response to a noxious stimulus
  - dramatic increase in duration and magnitude of cell responses, but input into the spinal cord remains the same

- Activation of:
  - neurotransmitters (glutamate, substance P, NO)
  - receptors (NMDA)
  - inflammation and chemicals (neurotropin)
  - genes (Cfos)
KETAMINE

• Ketamine
  – non-competitive NMDA antagonist
  – use limited by due side effects (hallucinations)
  – lack of oral preparation (only IV, SC and spinal).

• Oral NMDA receptor antagonists
  – Dextromethorpan
  – Amantadine and Memantine
  – Dose required e.g. for Dextromethorpan,
    • as a cough suppressant 40-80mg
    • pain 400mg / day
**KETAMINE STUDY - RPAH**

- Determine whether ketamine provides short and long benefits:
  - Reduce pain levels
  - Reduce opioid requirements

- Retrospective chart review of 52 patients with chronic pain attending the RPAH Pain Clinic between 2007 and 2011
  - The assessment was based on the evaluation of a questionnaire performed over a telephone conversation
## AV. DAILY KETAMINE DOSE

<table>
<thead>
<tr>
<th>Description</th>
<th>Average daily ketamine infusion dose (mg)</th>
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<tbody>
<tr>
<td>Lowest</td>
<td>201</td>
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<tr>
<td>Highest</td>
<td>526</td>
</tr>
<tr>
<td>Sample Average</td>
<td>228</td>
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</tbody>
</table>

50ml Syringe
Ketamine 200mg +/- Lignocaine 2000mg (2x10x10% xylocaine)

Day 1 2ml/hr ie 8mg/hr or 192mg/day
Day 2 2.5ml/hr
Day 3 3ml/hr
Day 4 Double Ketamine (400mg) and reduce back to 2ml/hr
Chronic Lumbar Spinal Pain
41%

Other Chronic Neuropathic Pain Syndrome
3%

CRPS
13%

Migraine
8%

Trigiminal Neuralgia
8%

Idiopathic
5%

Radiculopathy
4%

Peripheral neuropathy secondary to diabetes
4%

Post herpetic neuralgia
3%

Fibromyalgia
2%

Other
9%

Other, including Metabolic Bone Disease, Phantom pain, Retinopathy, Pancreatitis, Visceral, MS, Mastocytosis, TMJD & Vulvodynia (each 1%)

Other Chronic Neuropathic Pain Syndrome
3%

Fibromyalgia
2%

Other
9%

Chronic Lumbar Spinal Pain
41%

PAIN LOCATION
VAS SCORES
BEFORE / AFTER KETAMINE

42/56 Improved

VAS before Ketamine (mean 6.38)

VAS after Ketamine (mean 4.60)
VAS SCORES (BEFORE / AFTER KETAMINE)

• Significant reduction in mean pain intensity by VAS:
  
• 6.38 before ketamine

• 4.60 after ketamine

• (p < 0.005)
## Equivalent Morphine Dose (Before / After Ketamine)

<table>
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<tr>
<th>Equivalent Morphine (mg)</th>
<th>Frequency</th>
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<tr>
<td>200-300</td>
<td>32</td>
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<tr>
<td>300-400</td>
<td>11</td>
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<tr>
<td>400-500</td>
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<tr>
<td>1500-1600</td>
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</table>

The diagram shows the frequency distribution of equivalent morphine doses before and after ketamine administration.
EQUIVALENT MORPHINE DOSE BEFORE / AFTER KETAMINE

- There was significant reduction in opioid dose at the end of ketamine infusion with the mean morphine equivalent dose:
  - 216 mg/day before ketamine
  - 89 mg/day after ketamine
  - \( p < 0.005 \)
KETAMINE SIDE EFFECTS

- Lightheadedness/Dizziness: 46%
- Headache: 12%
- Tired & Sedation: 25%
- Hallucinations: 12%
- UTI: 2%
- Double Vision: 2%
- Vivid dreams: 8%
FOLLOW-UP STUDY

• Prospective study to evaluate long-term efficacy of sub-lingual ketamine lozenges in reducing opioid dose after a 3-7 day ketamine infusion on another 48 patients

  – Oral or sub-lingual ketamine formulations are not currently commercially available in Australia. They have to be manufactured in hospital or compounding pharmacies

  – Studies have shown that the bioavailability of sub-lingual formulation is superior, 40% compared to 10-20% for the oral formulation

• Dose 50mg bd increasing if required to 100mg tds
KETAMINE INFUSION VS KETAMINE INFUSION + LOZENGES

Ketamine infusion & Lozenges after discharge 16%

Ketamine Infusion only 84%
EFFECT OF KETAMINE INFUSION

- Complete cessation of opioids: 6%
- No change in opioid or analgesic use: 61%
- Reduction in opioid use: 22%
- Increase in opioid use: 11%
- Complete cessation of opioids: 31%
- No change in opioid or analgesic use: 61%
- Increase in opioid use: 0%
- Reduction in opioid use: 8%
CASE 4 - HISTORY

- 52yo Registered Nurse
  - Right TN Dx 1997
    - Lacinating pain in 2\textsuperscript{nd} and 3\textsuperscript{rd} division
  - Responded well to Tegretol and Epilim
    - Developed drug induced hepatitis
  - Microvascular decompression 1998
    - Pain free for next 4-5 years (normal facial sensation)

- Dec 2003, pain recurred
  - Commenced on Gabapentin – no response
  - 2\textsuperscript{nd} microvascular decompression Aug 2004
    - No evidence of vascular compression, nerve “pinched”
    - Pain free for 3 months then recurred
**CASE 4 - PROGRESS**

- R facial pain in all divisions of V nerve
  - Sharp, shooting, knife-like lasting for seconds
  - Attacks of pain brought on by touching face, chewing, talking, smiling, blinking, blowing nose
  - Increased sensitivity to touch over face

- Canberra hospital in Dec 2004
  - 5 day Lignocaine infusion revealed pain but recurred once infusion ceased

- Subsequently tried:
  - Endone, MS Contin, Baclofen, Mexilitine
  - Stereotactic radiotherapy in March 2005
CASE 4 - TREATMENT

- Initial Consultation:
  - Was on Gabapentin 600 mg and Lamotrigine 150 mg 6 times a day
- Admitted to RPAH in February 2006
  - Ketamine and Lignocaine infusion
    - Improved pain within 24 hours
  - Reduced Gabapentin and Lamotrigine within 3 days
    - 50% to 3 times a day
- Discharged home pain free
  - Ketamine lozenges 25 mg three times a day
CASE 4 – FOLLOW-UP

- Follow up March 2006 (4 weeks post)
  - Remained pain free and now able to touch face, rub cream, blow nose (unable to do for over 2 years)
    - Ceased Gabapentin and reduced Lamotrigine to 100mg tds
    - Feels less drowsy and has more energy
  - July 2006
    - Pain very well controlled – ceased Lamotrigine
      - Wearing make-up and no pain with wind blowing on face
  - December 2006 – (nearly 12 months post infusion)
    - Leading a completely normal life, without pain worry
      - Ketamine 25 mg three times a day only
CASE 4 – FOLLOW-UP

• November 2007
  - Reduced Keatamine to 25 mg twice a day and no episodes of pain

• December 2008
  - Ceased Ketamine Jan 2008
  - Accidentally hit face 2 months later – recurrence of pain
  - 4-5 episodes only in 6 months, lasting seconds when washes face in shower

• January 2012
  - Recurrence of pain with pain persisting despite recommencing Ketamine lozenges
  - Readmitted for Ketamine Infusion then lozenges
  - Pain free again – last review Jan 2014
STUDY SUMMARY

• The ketamine infusion was tolerated well with only 1 patient prematurely ceasing the infusion
  • 46% of patients experienced light-headness or dizziness, but did not need to discontinue the infusion

• Overall reduction in opioid use after Ketamine infusion was 39%
  • When Ketamine lozenges were given after the infusion, 31% were able to completely cease opioids compared to 6% without lozenges

• Reduction in pain (VAS) in 42/56 patients with only 5 patients noticing no change in the VAS by the end of the infusion
STUDY SUMMARY

• Provides strong evidence that a 3-7 day intravenous ketamine infusion has the potential to:
  – Reduce VAS
  – Reduce equivalent morphine doses in the short and long-term, even in chronic pain patients who have responded poorly to treatment in the past.
  – When Ketamine lozenges are given after the infusion, long-term benefits are sustained with reduced opioid use and pain control
CONCLUSION

• Neuropathic pain is common, under-reported, under-diagnosed and under-treated

• A simple, stepwise approach to diagnosis may help differentiate between neuropathic and nociceptive pain:
  
  – Listen to the patient’s pain description
  
  – Locate a potential nerve lesion/dysfunction, if possible
  
  – Look for neurological symptoms, such as sensory deficits
CONCLUSION

• Neuropathic pain responds poorly to conventional analgesia
  – First-line treatments include:
    • TCAs (amitriptyline)
    • Alpha 2-delta ligands (pregabalin)
    • SNRIs (duloxetine)
  – Second-line treatments include:
    • Opioids
CONCLUSION

• Pain can exist without objective signs
• Step-wise approach to medications
• Start small and increase slowly
• Use medications to maximum tolerated potential
• Combination therapy often required
  – different pain mechanisms

• Realistic goal is PAIN MANAGEMENT rather than resolution