Pruritis in Palliative Care

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Overview of Lecture

• Describe the prevalence of pruritis in palliative care
• Briefly cover the presumed pathophysiology
• Discuss treatment options
Prevalence

- “General” palliative care – 6%
- “Incurable Cancer” – 5 - 24%
  - By medical record 5%, std interview 5%, questionnaire 19%
- End-stage Renal Failure (ESRD) – 55 - 80%
- End-stage Liver Disease / Cholestasis – 20-25%
  - 100% in primary biliary cirrhosis (PBC)
- Hematologic
  - Polycythemia rubra vera – 50%
  - Hodgkin’s Lymphoma – 30%
- Skin conditions - Variable
- Other - Variable
  - Opioids – 1%
Pathophysiology

• Neuroanatomy
  • Nerve endings found in dermo-epidermal junction (superficial layers of skin – more superficial than pain)
    • Clustered into “itch points” groups
  • Mostly C-fibre, transmitted similar to pain (but felt to be distinct)
  • Scratching stimulates A-delta sensory fibres which temporarily blocks the sensation
  • Molecular mediators - numerous
Pathophysiology

• Itch mediators
  • Histamine
  • Serotonin
  • Endogenous opioids
  • Proteases, bradykinin, cytokines
• Receptors
  • ‘General’ receptors (H1, 5-HT2, 5-HT3, mu)
  • Newly discovered (IL-31, GRPR, H4) - ?more itch specific
End-Stage Renal Failure

- Reaction to chronic renal failure (not usually acute)
  - Incidence up to 80% in long-term dialysis patients.
- Etiology:
  - Dry skin
  - Secondary hyperparathyrodisim
  - Abnormal mast cell proliferation in skin after hemodialysis
  - Increased plasma histamine, serotonin, Mg, PO4, Al
  - Accumulation of “pruritogenic metabolites”
Cholestasis

- Often associated with skin changes (post-inflammatory hyperpigmentation, sparing mid-back)
- No real correlation with bile acid levels and intensity of pruritis
  - However, lowering plasma bile acids with cholestyramine appears to help.
- Theories:
  - Accumulation of pruritogenic intermediary in bile acid synthesis
  - Bile salt toxicity to cells $\rightarrow$ release of unidentified pruritogen
  - Pruritogenic endogenous opioid accumulation due to hepatocyte secretory failure
Lymphoproliferative disorders

- Uncertain etiology
- Platelet serotonin +/− prostaglandins
- Histamine
  - Increased basophils in many lymphoproliferative diseases
- Auto-immune response to lymphoid cells → release pruritogens
Opioids

- Rare (< 1%) in systemic administration
- More common (20-90%) in spinal administration (such as IT)
- Opioids cause release of histamine from mast cells
  - Not felt to be the mechanism
- Stimulation of serotoninergic pathways
- In spinal → antagonism of glycine and GABA
Treatment

- Prevent boredom, anxiety, dry skin, heat
- Treat skin infections appropriately
- Discontinue drugs that may cause pruritis
- Eliminate common skin allergens
- Apply cold application
- Provide medicated baths
- Apply topical medications
Treatment

- Topical
  - Methol/camphor, capsaicin, tacrolimus, pramoxine, lidocaine
- Antihistamines
- Serotonin modulators
  - SSRI (paroxetine, sertraline), mirtazapine
  - Ondansetron
- Opioid antagonists
- Antiepileptics (gabapentin, pregabalin)
- Rifampicin
- Thalidomide
- Cholestyramine
- Leukotriene antagonists
- EPO
- Charcoal
Treatment - Topical

• Emollients in general (most patients have dry skin)
• Cooling sensation - Menthol 1-3%
  • Modest improvement in pruritis (no RCTs)
• Burning sensation - Capsaicin 0.025-0.5%
  • Modest improvement in pruritis (4 RCTs)
• Anaesthetic – pramoxin
  • Good improvement in pruritis (-61% in single RCT)
• UV Therapy (UVB)
  • Modest benefit, requires maintenance therapy, involved
Treatment - Antihistamines

- Hydroxyzine, Benedryl etc.
  - Ineffective (except in urticaria or rhinoconjunctivitis)
  - Sedative effect may reduce scratching / help with sleep.
Treatment - Serotonin

- Paroxetine
  - Palliative Care RCT (Zylicz 2003)*
  - Average Itch 5.2 vs 6.0 (-0.8), although 9/24 pts had > 50% improvement.
  - Starting dose 20mg → some N/V, otherwise well tolerated
- Mirtazapine
  - Palliative Care Case Report (Davis 2003)
  - Effective and well tolerated (15mg)
- Sertraline
  - ESRD Palliative Retrospective Review (Chan 2013)
  - Effective (NRS 2.5 vs 7.5 (-5.0)) and well tolerated
  - Slower to titrate than paroxetine

* Only heterogenous, representative palliative population study
Treatment - Serotonin

- Ondansetron (5-HT3 antagonist)
  - 4 RCTs, 3 ESRD, 1 cholestasis, all 8mg / day
  - 3 of 4 reported no advantage over placebo
Treatment – Opioid antagonist

- Naltrexone
  - Effective in uremic pruritis (Legroux-Crespel 2004, Peer 1996)
  - Effective in cholestatic pruritis (Wolfhagen 1997, Terg 2002)
  - Small studies
  - Only appropriate for patient not requiring opioids for pain control.
  - Usual dose 50mg/d
Treatment – Antiepileptics

• Gabapentin
  • Effective in uremic pruritis (Gunal 2004, Naini 2007)
    • Low dose (300-400mg after dialysis 3x weekly)
  • Not effective in cholestatic pruritis (Bergasa 2006)
  • Reasonably well tolerated

• Pregabalin
  • Randomized 14 week crossover in HD patients (Solak 2012)
  • 75mg pregabalin daily vs 300mg gabapentin after dialysis
  • Equally effective as gabapentin (VAS ~5.8 → 1.4)
  • Equally tolerated
Treatment – Others

- Rifampin (300-600mg / d)
  - Effective in cholestatic pruritis (Bachs 1989, Ghent 1988, Podesta 1991)
- Thalidomide
  - Effective in uremic pruritis (Silva 1994)
    - Overall -80% in pruritis, 2/3 of patients responded, not replicated
- Nalfurafine (kappa-receptor agonist)
  - Effective in uremic pruritis (Wikstrom 2005, Kumagi 2010)
- Cholestyramine (4 or 5g BID)
  - Somewhat effective in cholestatic and uremic pruritis (Duncan 1984, Silverberg 1977)
- Leukotriene antagonists (montelukast 10mg/d)
  - Somewhat effective in uremic pruritis (Nasrollahi 2007)
- EPO (36U/kg 3x weekly)
- Charcoal (6g/d)
  - Possibly effective in uremic pruritis (Pederson 1980)
- Oral cromolyn sodium (135mg TID)
  - Effective in uremic pruritis (Vessal 2010)
“Palliative” Pruritis

• Helpful:
  • Paroxetine reasonably effective
    • Start with lower doses (5-10mg QHS)
    • Effect usually seen 24-48 hrs

• Probably helpful:
  • Mirtazapine
  • ?Other SSRIs (sertraline studied in CKD)
Uremic/CKD Pruritis

• Helpful:
  • Naltrexone (but not appropriate if on opioids)
  • Gabapentin or Pregabalin (low dose, 300/75 2-3x per week)
  • Paroxetine
  • Nalfurafine (not available in Canada)

• Probably helpful:
  • Oral cromolyn sodium (100mg capsule TID, study was 135mg TID)
  • LRA (montelukast)
  • Thalidomide
  • Cholestyramine

• Not helpful:
  • Ondansetron
Cholestatic Pruritis

- Helpful:
  - Naltrexone (but not appropriate if on opioids)
  - Rifampin
- Probably helpful:
  - Sertraline (?other SSRIs)
- Not helpful:
  - Ondansetron
HIV Pruritis

- Very weak evidence base
- Indomethacin considered most effective oral medication
Topical treatments

- Evidence for topical treatments is low
- Probably helpful:
  - Menthol 1%
  - Capsaicin 0.025%
  - Pramoxine 1%
  - Calamine 3%
Summary

• Pruritis not the most common symptom, but very troubling.
• We don’t ask as often as we should.
• There are several effective medications options, although the evidence base is quite weak (most studies were very small)
• Avoid use of anti-histamines in general (may help with sleep)
• Don’t forget basic skin care/moisturizing tips
References


• Pruritis in Palliative Care. Seccareccia et al. CFP 57 (2011) 1010-1013

Questions?