Tapentadol and Cancer Pain

This is a promotional meeting, organised by Grünenthal. The views expressed are those of the speaker, and not necessarily those of Grünenthal.

Date of Prep: September 2017    UK/P17 0082

Dr Andrew Dickman
Consultant Pharmacist
Royal Liverpool Hospital

Declarations

• I declare that I am a consultant to Grünenthal Ltd. and have therefore been paid an honorarium to provide services, such as chairing and/or speaking, for the company

• Declarations: No conflicts of interest

Overview

• Brief History of Analgesia
• Pharmacology of Tapentadol
• Tapentadol vs Step 3 Opioids
• Tapentadol - Place in Therapy

Brief History of Analgesia

• Friedrich Sertürner 1805
• German pharmacist’s apprentice
• Isolated “principium somniferum”
• Later called it “morphinum” after Morpheus
• French translation - morphine

Brief History of Analgesia

• Historical significance - for the 1st time in history of pharmacy, active ingredient of a plant could be isolated, permitting consistency of dose
• Deaths due to overdose or lack of effect could now be avoided by exact dosing

Brief History of Analgesia

• 1763 - Edward Stone publishes a report detailing the benefits of willow bark in curing fever
• 1828 - Joseph Buchner, professor of pharmacy at Munich University, Germany, succeeds in extracting salicin from willow bark
• 1838 - Raffaele Piria isolated a different, more potent, compound from willow and called it salicylic acid
• 1852 - Chemical structure of salicylic acid discovered
• 1897 - Arthur Eichengrün (Bayer) acetylates salicylic acid, creating a pro-drug and patents process
• 1899 - Aspirin launched by Bayer
**Brief History of Analgesia**

- Significant advances in organic chemistry in 19th Century
- Basic product for artificial dyes was aniline, which is derived from black coal
- Coal tar, a waste product, was found to contain aniline
- Dye industry boomed
  - Bayer, Hoechst

### 1883 – Phenazone (Hoechst)

- Marketed as Antipyrin
- For the next 15-20 years Antipyrin was the most widely used drug in the world
- Described as the “mother” of modern antipyretics
- Not without risk - in some people it caused agranulocytosis

### 1886 – Acetanilide (Kalle)

- Found to possess analgesic as well as antipyretic properties......
- ......by accidental dispensing error!
- Marketed as Antifebrin
- Despite popularity, it caused methaemoglobinemia
- Use continued in a few OTC preparations until 1971!
- Antifebrin was soon replaced by other, safer analogues

### 1887 – Acetophenetidin (Bayer)

- Marketed as Phenacetin®
- Popular for almost a century as an OTC remedy (often combined in tablets with caffeine and aspirin)
- Had to take large quantities (spoonfuls) for an effect
- Too much also led to methaemoglobinemia
- Heavy use linked to renal failure and renal tumours
- Eventually banned in the UK in 1980

### 1893 – N-acetyl-p-aminophenol (Bayer)

- To improve the tolerability of phenacetin, Bayer investigated a metabolite of phenacetin
- It appeared that (their) N-acetyl-p-aminophenol (due to impurities?) also caused methemoglobinemia
- Investigation of paracetamol was abandoned for over half a century
- Sterling (UK) - paracetamol free of methemoglobinemia and marketed it as Panadol® in 1955

### Pain in Palliative Care

- Pain is:
  
  -----whatever the experiencing person says it is, existing whenever he/she says it does-----

  McCaffrey 1985
**Pain in Palliative Care**

- Pain is:
  
  ....an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.

  International Association for the Study of Pain

**Pain in Palliative Care**

- Not all patients with cancer get pain
- Not all pains that patients with cancer complain of are due to cancer
- 60-90% of patients with advanced cancer will experience pain
- Pain is generally well controlled in about 85%

**Pain in Palliative Care**

- Modern hospice care in the UK can be credited to Dame Cicely Saunders
- Defined concept of "total pain"

**Tapentadol**

- Entered clinical practice in UK in May 2011
- Classed as a MOR-NRI
- Full μ-opioid agonist
- Activates α2-adrenoceptors (reuptake inhibition)
- No clinical effect on serotonergic pathways

**Tapentadol**

- Tapentadol MOR binding affinity 18 times lower than morphine
- Despite lower affinity, provides highly effective analgesia
- Analgesic potency approx 2.5x lower than morphine, 5x lower than oxycodone (for chronic pain)
- 100mg tapentadol = 40mg morphine = 20mg oxycodone
**Efficacy and safety of oral tapentadol extended release in Japanese and Korean patients with moderate to severe, chronic malignant tumour-related pain**

Inoizako K et al, Clin Drug Investig. 2014; 34(7):501-11

- Randomized, double-blind, active-controlled study of patients with moderate to severe, chronic malignant tumour-related pain
- No prior opioid

**Study endpoint**

- n=168
- n=172
- n=113
- n=123

**Discontinuation include**

1. Progressive disease 6.5% (11/168)
2. Adverse effects 7.1% (12/168)

3. Progressive disease 8.7% (15/172)
4. Adverse effects 8.1% (14/172)

**Notes**

- Tapentadol prolonged release is indicated for the management of severe chronic pain in adults, which can not adequately managed only with opioid and paracetamol.

**Efficacy and safety of oral tapentadol extended release in Japanese and Korean patients with moderate to severe, chronic malignant tumour-related pain**

Inoizako K et al, Clin Drug Investig. 2014; 34(7):501-11

- This study included patients who:
  - were at least 20 years of age
  - had a diagnosis of any type of cancer
  - were experiencing chronic malignant tumour-related pain, with an average pain intensity score over the past 24 hours of at least 4 on a 11 point numerical rating scale (NRS; 0=no pain to 10=pain as bad as you can imagine) on the day of randomisation.

**Tapentadol**

- Tapentadol blocks the reuptake of NA that is released by the descending inhibitory pathway
- This potentiates the inhibitory effect of NA that would be achieved by a pure opioid alone
- Believed to be the basis for the observed intrinsic synergy of tapentadol
- May in turn be the basis of the high potency and efficacy of tapentadol
- Analgesia comparable to classical strong opioids, despite the moderate affinity for the MOR

**Figure**

- Pain signal transmitted through release of neurotransmitters
- Descending pathway reduces pain signal through release of noradrenaline/serotonin
- Tapentadol has both pre- and post-synaptic opioid inhibitory effects
- Tapentadol blocks the reuptake of NA that is released by the descending inhibitory pathway
- This potentiates the inhibitory effect of NA that would be achieved by a pure opioid alone
- Believed to be the basis for the observed intrinsic synergy of tapentadol
- May in turn be the basis of the high potency and efficacy of tapentadol
- Analgesia comparable to classical strong opioids, despite the moderate affinity for the MOR
Incidence of adverse effects was similar:
• tapentadol ER (87.5% [147/168])
• oxycodone CR (90.1% [155/172])

Incidence of GI adverse effects was lower in the tapentadol ER group (55.4% [93/168]) than in the oxycodone CR group (67.4% [116/172]).

Tapentadol MR (100 – 250 mg BD) is effective for the management of moderate to severe chronic malignant tumour-related pain and provides efficacy that is non-inferior to that of morphine MR (40 – 100 mg BD), but with an improved GI tolerability profile.
Tapentadol is no more and no less effective than oxycodone or morphine (low quality evidence)

No advantage of tapentadol over morphine or oxycodone in terms of serious adverse events

Based on a narrative review which included patients with moderate to severe oncological pain

Tapentadol is an effective, well-tolerated alternative for moderate or severe cancer pain

Few, typically mild, adverse reactions

Existing studies do not clearly show a superiority of tapentadol

More experience is required to draw valid generalisable conclusions

6 studies and one secondary analysis provided data regarding tapentadol used as a step-3 analgesic

Tapentadol was well tolerated and effective for the management of moderate-to-severe cancer pain

Reduced level of GI adverse effects may be a great advantage for cancer patients

Existing studies do not clearly show a superiority of tapentadol

More experience is required to draw valid generalisable conclusions

Tapentadol is accepted for restricted use within NHS Scotland and by the AWMSG

Available for the management of severe chronic pain in adults, which can be adequately managed only with opioid analgesics

Restricted to patients in whom morphine sulphate modified release has failed to provide adequate pain control or is not tolerated

Tapentadol SR—Place in Therapy

Indicated for the management of severe chronic pain in adults, which can be adequately managed only with opioid analgesics

Currently after a strong opioid has been tried

Issues of cross-titration?

Combination with other analgesics?*

First-line strong analgesic?

*Combination with other opioids may increase the risk of respiratory depression and/or sedation and impaired vigilance. Caution required when tapentadol combined with mixed mu-agonist/mu-antagonist or partial mu-agonist agonist, consult the Summary of Product Characteristics for further information
Case study

- 41 year lady
- Breast cancer survivor
- Received paclitaxel as part of chemotherapy regimen
- Presented to palliative care with classic symptoms of painful peripheral neuropathy
- Was in considerable distress

Case study

- Patient had already tried:
  - Tramadol (developed rash)
  - Amitriptyline (could not tolerate adverse effects)
  - Gabapentin ("spaced out")
  - Pregabalin ("spaced out")
- She refused to consider a strong opioid

Case study

- Week 1 – started duloxetine 30mg OD
- Week 2 – some response to duloxetine; dose increased to 60mg OD
- Week 3 – duloxetine discontinued due to rash; started nortriptyline 10mg ON
- Week 6 – nortriptyline titrated to 50mg ON, with moderate effect
- Week 7 – nortriptyline discontinued due to intolerance of daytime fatigue
- referral to chronic pain clinic
- Tapentadol 50mg BD commenced

Case study

- Week 8 – excellent response to treatment
  - mild nausea managed with metoclopramide 10mg TDS PRN
  - Tapentadol 100mg BD
- Week 10 – patient wanted to be discharged from palliative care