Dr Andrew Dickman
Consultant Pharmacist
Royal Liverpool Hospital
Overview

• Brief History of Analgesia
• Tramadol
• Tapentadol
• Tramadol vs Tapentadol
• The Next Frontier
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

• Death 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 methaemaglobulinemia
- 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
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.
Tramadol

- Entered clinical practice in 1977
- Launched in UK in 1997
- Now one of the most widely prescribed drugs worldwide
- It has two chiral centres and is administered as a racemate of two enantiomers, (+)-tramadol and (-)-tramadol
Tramadol

• Pharmacology of tramadol is complex
• Ignorance causes the poor outcomes and adverse effects, not the drug
• Activates the μ-opioid receptor and inhibits NA & 5-HT reuptake
Analgesic actions:

- Weak µ-opioid effect (600× < morphine)
- Serotonin reuptake inhibition

CYP2D6

(+) Tramadol

(+ ) M1

Analgesic action:

- Stronger µ-opioid effect (700× > (±) tramadol)
- Noradrenaline reuptake inhibition

CYP3A4

(-) Tramadol
(±)tramadol

(+)M1

SP

Glut
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
Tapentadol

• Tapentadol also blocks the reuptake of NA that is released by activation of the descending inhibitory
• 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.
Differentiation of Tapentadol and Tramadol

- Chemical
- Pharmacodynamic
- Metabolic
- Clinical efficacy
- Abuse
- Summary
Organic Chemistry

• Physicochemical interactions between drug molecules and receptor sites are governed by functional groups

• There are >20
Chemical

• Many opioid analgesics share common structural elements
• Minor differences in structure can lead to major differences in pharmacological activity
Chemical

- Tramadol is a synthetic analogue of codeine
- Exists as a racemic mixture
- Active metabolites: M1 (and M5)

- 3D shape of tapentadol was rationally designed
- Pharmacodynamic and pharmacokinetic properties deliberate
- Exists as a single molecule, not racemic mixture
- No active metabolites
Pharmacodynamic

• Both drugs combine opioid and non-opioid pharmacology

• Tramadol analgesia derived from 3 discrete entities:
  - (+)M1 (affinity for MOR is 5.5x less than morphine)
  - (-) tramadol (NA reuptake inhibition)
  - (+) tramadol (5-HT reuptake inhibition)

• Tapentadol analgesia derived from single entity:
  - affinity of tapentadol for MOR (18x less than morphine)
  - NA reuptake inhibition but no clinically relevant effect on 5-HT
Pharmacodynamic

- Potency is defined as the dose of drug required to produce 50% of the drug's maximal effect
- Substantial potency difference between tramadol and tapentadol
- Tapentadol 2-5x more potent than tramadol
  - believed to due to better CNS penetration
  - although M1 is a more potent analgesic than tramadol, the metabolite has more difficulty passing into the CNS
  - tramadol requires metabolic activation – interpatient variation
## Serotonin Syndrome

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Anticholinergic poisoning</th>
<th>Neuroleptic malignant syndrome</th>
<th>Malignant hyperthermia</th>
<th>Opioid withdrawal</th>
<th>Serotonin syndrome</th>
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<td>Hyperactive bowel sounds</td>
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<td>Ocular clonus</td>
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</table>
Serotonin Syndrome

• The risk of serotonin syndrome is expected to be less with tapentadol than with tramadol
• No cases of serotonin syndrome reported in Phase 2/3 clinical studies (n=5791) as an AE
• No post-launch reported cases of serotonin syndrome in which tapentadol was the sole causative agent
Probable Tapentadol-Associated Serotonin Syndrome After Overdose

• Reports a possible case of tapentadol-induced serotonin syndrome after overdose
• 48-year-old male was found unresponsive after a witnessed overdose of medications including tapentadol
• Other medications that could be implicated in the patient's presentation included duloxetine and amitriptyline
• Tapentadol is a very weak serotonin reuptake inhibitor and is highly unlikely to cause significant serotonin toxicity

• Consistent with an opioid overdose followed by opioid withdrawal after a large dose of intramuscular naloxone was administered
Metabolic

• Tramadol - metabolism needed to achieve opioid analgesia
• Phase I metabolism (CYP2D6 and CYP3A4)
• Subject to genetic variation and drug-drug interactions

• Tapentadol – MORNR1 activities reside in patent molecule
• Phase II metabolism
• Less likely to be subject to drug-drug interactions or genetic variation
(+)-Tramadol

(+)-Tramadol
- CYP3A4
- Inactive metabolites
- (+) M1

(-)-M1

(-) Tramadol
- CYP3A4
- Inactive metabolites
- (-)-M1
CYP2D6 inhibitors

- Fluoxetine  (strong)
- Paroxetine  (strong)
- Abiraterone  (strong)
- Bupropion  (strong)
- Quinidine/Quinine  (strong)
- Duloxetine  (moderate)
- Haloperidol  (unclear)
- Levomepromazine  (unclear)
CYP3A4 inhibitors

- Amiodarone (moderate)
- Clarithromycin (strong)
- Fluconazole (moderate)
- Ketoconazole (strong)
- Grapefruit juice (moderate)
- Miconazole (moderate)
Clinical Efficacy

• Tapentadol:Tramadol 1:1.5 to 1:4 for depending on conversion rates in published literature\(^1\)

• Roughly corresponds to the potency difference between tapentadol and tramadol

• Assuming a conservative conversion rate of 1:2 between tapentadol and tramadol:
  - 250 mg tapentadol would correspond to 500 mg tramadol (exceeds max daily dose)

• True equianalgesic ratio difficult to judge due to variation in effect of tramadol

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Tramadol with or without paracetamol (acetaminophen) for cancer pain
Wiffen PJ et al, Cochrane Database Syst Rev. 2017 May 16;5:CD012508

• Limited, very low quality, evidence from randomised controlled trials that tramadol produced pain relief in some adults with pain due to cancer
• Very low quality evidence that it is not as effective as morphine
• Place of tramadol in managing cancer pain is unclear
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.
Tapentadol for Cancer Pain Management: A Narrative Review

• 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
The role of tapentadol as a strong opioid in cancer pain management: a systematic and critical review


• 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
Drug misuse and dependence

UK guidelines on clinical management
Tapentadol abuse potential: a postmarketing evaluation using a sample of individuals evaluated for substance abuse treatment


• Sample of 113,914 individuals was examined for prevalence assessed for substance abuse treatment for abuse of tapentadol

• Tapentadol abuse was less likely to be abused than most of the examined Schedule II analgesics (comparators buprenorphine, fentanyl, hydrocodone, hydromorphone, morphine, oxycodone, oxymorphone, tramadol)
Summary

- Tapentadol is a single molecule; tramadol is a racemate
- Tapentadol has no analgesically active metabolites; tramadol has an active metabolite
- The main pathway of tapentadol metabolism is glucuronidation; tramadol is metabolized mainly via the CYP450 enzyme complex
- Tapentadol has substantially more CNS functional activity at MOR than does tramadol, about the same or more functional activity at NET, and substantially less functional activity at SERT
- The mechanisms of action of tapentadol reside in a single molecule; the mechanisms of action of tramadol reside in different molecules (enantiomers of the parent and M1 metabolite)
- Tapentadol is two to five times more potent than tramadol across a range of animal pain models. Likewise, clinically, tramadol is most effective for treating pains not requiring a strong opioid, whereas tapentadol is effective in treating pain requiring the efficacy level of strong opioids (e.g., oxycodone)
- Tramadol is CD3 POM, whereas tapentadol is CD2 POM
- Available evidence suggests that abuse of tapentadol is less likely than of tramadol
THE NEXT FRONTIER
Opioid Pharmacology

• Pharmacology – only progress within the last 30 years, despite widespread use
• Still much to learn
• Discovery of opioid receptors in 1973 led to hunt for endogenous ligand(s)
• Endogenous opioid peptides isolated in mid 1970s
Opioid Pharmacology

• Three types of receptor originally determined pharmacologically

\[
\begin{align*}
\mu & \text{ (mu)} \\
\delta & \text{ (delta)} \\
\kappa & \text{ (kappa)}
\end{align*}
\]

• \(\sigma\)-receptor no longer classed as an opioid receptor
Opioid Pharmacology

- 1992 - δ opioid receptor cloned
- Other opioid receptors μ and κ cloned soon after
- Orphan receptor with partial homology to μ, κ and δ opioid receptor discovered (ORL-1)
- BUT very low affinity for known opioid receptor ligands
- 1995 - Nociceptin/orphanin FQ peptide (NOFQ)
- ORL-1 now known as nociceptin/orphanin FQ peptide (NOP) receptor
Opioid Pharmacology

- Role of NOP in pain is complex
- Systemic administration of NOPr agonists may be effective analgesics
- Supraspinal administration reverses the effects of opioids manifesting as hyperalgesia
- NOP and opioid receptor agonists modulate pain and nociception via distinct yet related targets
Cebranopadol

• A potent NOP and m-opioid receptor agonist
Cebranopadol, a novel first-in-class analgesic drug candidate: efficacy, safety, tolerability in patients with cancer related chronic pain


- Randomized, multi-site, double-blind, double-dummy, active-controlled, parallel-group, multiple dose, non-inferiority trial
- 126 cebranopadol-naïve but opioid-experienced patients
- Primary endpoint: average daily use of rescue medication over the last 2 weeks of treatment in the maintenance phase
- Secondary endpoint: clinically relevant pain reduction over the last 2 weeks of the maintenance phase
**Enrollment (Pre-examinations)**

**Day -10 – Day -1**

**Prior opioid**

- Pain ≥5 points on 11-point NRS

**Titration Phase**

**Day 1 – Day 16**

- Cebranopadol
  - 200 - 1000 μg/day, QD
  - Morphine PR
    - 30 - 150 mg/day, BID

**Maintenance Phase**

**Day 17 – Day 44**

- Cebranopadol

- Morphine PR

**Follow up**

**Day 45 – Day 62**

- Follow-up
  - OR
    - Switch to open-label extension study with cebranopadol*
N = 132 Allocations

N = 1
Allocated to cebranopadol but not treated

N = 65
Subjects received cebranopadol

N = 24
Discontinuations
most frequent reasons: adverse event (N = 15), withdrawal of informed consent (N = 7)

N = 41
Trial completers

N = 61
Subjects received morphine PR

N = 5
Allocated to morphine PR but not treated

N = 16
Discontinuations
most frequent reasons: adverse event (N = 7), withdrawal of informed consent (N = 5)

N = 45
Trial completers
Cebranopadol, a novel first-in-class analgesic drug candidate: efficacy, safety, tolerability in patients with cancer related chronic pain


- Non-inferiority and superiority were demonstrated for cebranopadol vs. morphine for the primary endpoint
- For the secondary endpoint, non-inferiority could not be demonstrated
- Cebranopadol was safe and well-tolerated in the dose range tested