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.

**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.

**Tramadol**

- (+)-tramadol
- (-)-tramadol

**Analgesic actions:**

- Weak μ-opioid effect (6000x < morphine)
- Serotonin reuptake inhibition
- Noradrenaline reuptake inhibition

- (+) M1

- CYP2D6: Stronger μ-opioid effect (700x > (±) tramadol)
- Inactive metabolites
- CYP3A4

**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
- (-)-tapentadol
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 noradrenaline, increasing the concentration in the synaptic cleft.
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 be 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

- 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

Comment on "Probable Tapentadol-Associated Serotonin Syndrome After Overdose"

- 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 – MORNRI activities reside in patent molecule
  • Phase II metabolism
  • Less likely to be subject to drug-drug interactions or genetic variation

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<thead>
<tr>
<th>(+) M1</th>
<th>(-) Tramadol</th>
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<tr>
<td>CYP2D6</td>
<td>CYP3A4</td>
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Inactive metabolites

CYP2D6 inhibitors

- Fluoxetine (strong)
- Paroxetine (strong)
- Aripiprazole (strong)
- Bupropion (strong)
- Quinidine/Quinine (strong)
- Duloxetine (moderate)
- Haloperidol (n/a)
- Levomepromazine (n/a)

CYP3A4 inhibitors

- Amlodipine (moderate)
- Clarithromycin (strong)
- Fluconazole (strong)
- Ketoconazole (strong)
- Grapefruit juice (moderate)
- Miconazole (moderate)

COCINE OR TRAMADOL

BEFORE METABOLISM

<table>
<thead>
<tr>
<th>(+) Tramadol</th>
<th>(-) Tramadol</th>
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<td>CYP2D6</td>
<td>CYP3A4</td>
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LITTLE OR NO PAIN RELIEF
Due to few or no active analgesic metabolites

PAIN RELIEF
Due to an expected level of active analgesic metabolites

INDUCED LEVELS OF SIDE-EFFECTS
Due to an excessive level of active analgesic metabolites
Clinical Efficacy

- Tapentadol: Tramadol 1:1.5 to 1:4 for depending on conversion rates in published literature
- 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

**References**

Oral tapentadol for cancer pain

- 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

Tramadol with or without paracetamol (acetaminophen) for cancer pain

- 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 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 (compared to 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 metabolised 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