THE NORTHERN HOSPITAL

TAPENTADOL

"The Corinthian Maid", oil on canvas, c. 1782-5, Joseph Wright of Derby.

"...if only there remained some imperfect image...the hateful departure, cruel as it was, would be less painful..."

Charles Perrault, Architect to Louis XIV.

Enough and more than enough has now been said about painting. It may be suitable to append to these remarks something about the plastic art. It was through the service of that same earth that modelling portraits from clay was first invented by Butades, a potter

of Sicyon, at Corinth. He did this owing to his daughter, who was in love with a young man, and she, when he was going aboard, drew in outline on the wall the shadow of his face thrown by a lamp. Her father pressed clay on this and made a relief, which he hardened by exposure to fire with the rest of his pottery; and it is said that his likeness was preserved in the Shrine of the Nymphs, until the destruction of Corinth by Mummius.

Pliny the Elder, "The Natural Histories", Bk XXXV; 153.
77-79 A.D

Sometime in the Seventh century B.C in Corinth, a tile maker by the name of Butades of Sicyon found himself greatly concerned for the wellbeing of his beloved daughter. She seemed most depressed. Normally so full of joy and life, she had lately been distant and distracted, she even, most uncharacteristically, had been arguing with her mother and brothers. She had taken to bed and refused to see her friends, even to eat or to drink. Her father did not know what was wrong, and so he simply tried to cheer her up with bunches of flowers and sweet smelling perfumes which she adored. But nothing seem to work. He decided to confront her and ask her why she was so withdrawn, and why she was being so abrupt with her mother and her five brothers; it really was most out of character. She broke down in tears and told her father that she was madly in love with a young man, whom she had been secretly seeing for some months, and now the young man, who was a soldier had been called up by the city of Corinth to go with the army to a far distant land. She tearfully confided that she might never see him again.

At first her father was outraged. "But you are only seventeen years old! How can you be in love you silly girl! And why wasn't I consulted over this young man. Does he come from a good family? And, by Zeus, what sort of a profession is soldiering! Wait till I tell your mother!".

But she simply screamed back at her father through rageful tears, "Well what does it all matter now! He may be killed in some battle in a foreign land and I will never see him again!"

Her uncontrolled sobbing upset her father - he recalled times long ago of his own first love - at age seventeen. His heart softened. "What can I do to help you", he quietly whispered.

"Nothing father, nothing. He is going with the army and there is nothing I, you or anyone can do to stop him".

Her father decided to leave her to herself for a while, but before he left her room he noticed the silhouette of a handsome male figure that had been scratched into the wall by an iron stylet.

"What is the on the wall?", her father asked.

"Forgive me father, but he has been in my room! When he was sleeping I noticed that he cast a most beautiful shadow in the candle light on the wall. I wanted to keep his image forever, so while he slept I traced out the outline of his shadow with this iron stylet. That

way even when he is far away, a part of him will still be with me forever! I know it's silly....I'm sorry I damaged the wall, father".

"Never mind - its only a wall", her father sighed.

The years went by and the young man never returned. Butades' daughter was inconsolable. Then one day Butades had an idea. He made many enquiries as to the character and appearance of the young man and the more that he heard the more impressed, and saddened he became for his daughter. When he had developed a mental image of the young man in his mind he went to his daughter's room one evening at stared at the silhouette she had made of him - for many hours - day after day. He then set to work. Butades was the most skilled clay worker in all of Corinth, in fact he was the most skilled in all Greece. He supplied all of Greece with the most exquisite roofing tiles - but now he would use his skills in a completely new way. He would fashion a likeness in clay of his daughter's young lover, based upon what he had learnt of the young man and the template of the candle-lit silhouette his daughter had outlined of him whilst he slept in her room, years ago. When he had finished he led his daughter into the courtyard and showed her his work. His daughter, gasped, and almost fainted to the floor. The image in clay was so lifelike that for a brief moment she imagined that her lover had returned to her! Years later Butades' daughter married the apprentice of her father and she had a long and happy life and had many children of her own. But she always kept the clay sculpture made by her father of her first love, the soldier, who never returned.

Pliny the Elder in the First century A.D recorded that the glory of ancient Greece's sculpture, which would not be equalled until the Sixteenth century A.D, had its deep origins in a certain tile maker by the name of Butades, who lived in Corinth in the Seventh century B.C. Clay sculptures had of course existed before the time of Butades, but it was Butades who formed the first true likeness of a real living human being. Butades's image of his daughter's lover was so famous it was preserved by the city of Corinth up until 146 B.C, when it was finally lost when the city was attacked and subdued by Rome. Before Butades, all sculpture was of abstract and generic deities or spirits or animals, but not of real people. Butades, legend has it, was the inventor of portraiture, by sculpture.

In the modern world of medicine astonishing inventions are now made daily. Unlike long centuries past, the world now advances by the exponential function. In the field of analgesia in modern medicine the latest invention is the dual action analgesic agent Tapentadol. Like clay modelling this is not a new invention, the dual action agent tramadol preceded it - but, like the portraiture of Butades, it can be said that it is at least a significant advance when it comes to serotonergic side effects.

TAPENTADOL

Introduction

Tapentadol *(ta-PEN-ta-dol)* is a novel opioid analgesic agent that is structurally similar to tramadol and like tramadol has a dual mechanism of action.

Its two anti-nociceptive actions are:

1. Central μ-opioid receptor agonist.

2. Noradrenaline reuptake inhibitor.

Compared to tramadol:

1. It has a stronger μ-opioid receptor agonist effect:

    - In general its potency is said to be between that of tramadol and morphine, with an analgesic efficacy comparable to that of oxycodone.

2. It has only **weak** inhibition of serotonin reuptake:

    - Hence does not have the same potential for adverse serotonergic side effects.

A sustained-release formulation of tapentadol has been approved in Australia for use in moderate to severe chronic pain unresponsive to non-narcotic analgesia.

It is indicated for the management of moderate to severe chronic pain that is unresponsive to simple analgesics.

The main toxic effects of tapentadol are CNS and respiratory depression, which may be lethal.

Comparison with Tramadol:

Main Tapentadol advantages over Tramadol:

1. Lack of cytochrome P450 drug interactions

2. Lower risk of seizures (no listed risk of idiopathic seizures in the FDA labeling)

3. Lower risk of serotonin syndrome

4. Better analgesia due to stronger binding affinity for μ-opioid receptors

5. Earlier onset of action

5. No individual variation in drug response:

- Note that tramadol is a **prodrug,** i.e it must be metabolized in the body to its active form, (**O-desmethyltramadol**).

  The metabolic pathway is via the cytochrome **P450-2D6** enzyme.

  This pathway is *absent* in approximately 10% of Caucasians and approximately 2% of Asians. **These patients will therefore have a reduced effect with respect to the analgesia obtained from tramadol.**

6. Lesser incidence of nausea and vomiting

Main Tramadol advantages over Tapentadol:

1. Lower risk of respiratory depression
2. Less abuse potential
3. Lees of a problem in patients with asthma, hypercarbia, and paralytic ileus
4. Inexpensive and there is a wide availability of generic formulations

As for all opioids its specific antidote for the μ effects is naloxone.

See also separate Documents on:

- **Opioid Overdose, (Toxicology Folder)**
- **Heroin Overdose, (Toxicology Folder)**
- **Opioid Toxidrome**
- **Opiate Withdrawal, (Toxicology Folder)**
- **Naloxone, (Drugs Folder)**

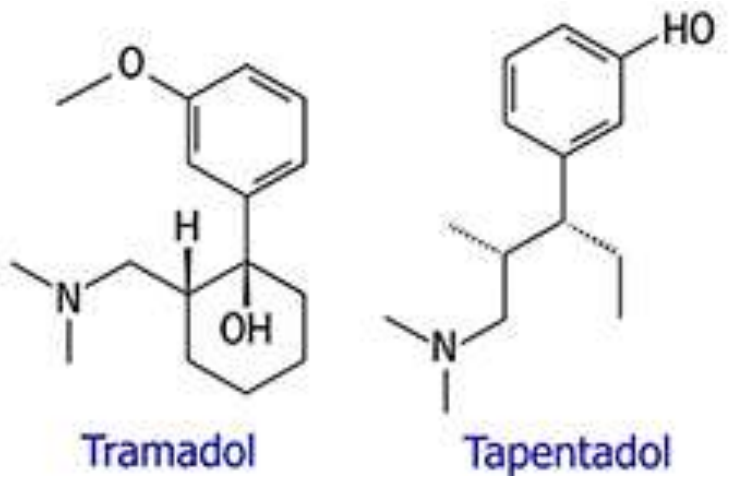
History

Tapentadol was approved by the US FDA on the 20th in 2008, by the TGA of Australia in 2010 and by the MHRA of the UK in 2011.

Chemistry

Tapentadol is structurally similar to tramadol.

Tapentadol has an open-chain molecule, while tramadol has a 2-ring cyclic structure, resulting in distinct pharmacological properties



Classification of the Opioids [1]

Opioid analgesics may be:

- Pure agonists of specific opioid receptors (notably the mu receptor)
- Mixed agonist–antagonist drugs with opposing effects at distinct receptor subtypes
- Partial mu agonists.

The affinity of individual opioid analgesics for receptors varies

No ceiling effect to analgesia is found with the *pure* agonists, in contrast to the partial agonist and mixed agonist - antagonist opioids, which demonstrate a ceiling response above which an increase in dose does not produce any additional increase in effect.

Physiology

Opioid receptors are distributed widely in the:

- Brain
- Spinal cord
- Digestive tract.

The three principle opioid receptors are:

Receptor	Opioid class	Location	Possible Functions

Mu Subtypes include: μ_1, μ_2, μ_3	**Endorphins**	Brain: The highest concentration is found in the limbic system. Spinal cord Peripheral sensory neurons GIT	Analgesia/ physical dependence Respiratory depression/ miosis/ Euphoria/ reduced GIT motility/ physical dependence Possible vasodilation
Kappa Subtypes include: κ_1, κ_2, κ_3	**Dynorphins**	Brain: Spinal cord Peripheral sensory neurons	Analgesia/ convulsant effects/ dysphoria/respiratory depression/ reduced GIT motility
Delta Subtypes include: δ_1, δ_2	**Enkephalins**	Brain: Peripheral sensory neurons	Analgesia, (less than mu)

The endogenous opioids include:

- Dynorphins
- Enkephalins
- Endorphins
- Endomorphins
- Nociceptin.

Preparations

Tapentadol has immediate release and slow release formulations. The **slow release** formulation is available in Australia.

Slow release tablets:

- 50 mg, 110 mg, 150 mg, 200 mg, 250 mg.

Mechanism of Action

Tapentadol's two anti-nociceptive actions are:

1. Central μ-opioid receptor agonist.

2. Noradrenaline reuptake inhibitor.

Pharmacodynamics

Analgesia begins within 30 minutes of oral administration, and duration of action is for 4 - 6 hours

Pharmacokinetics

Absorption:

- Tapentadol is administered orally
- The slow release tablets should be swallowed whole, and not crushed or chewed.
- Bioavailability after single dose administration of the slow release preparation is approximately 30% due to extensive first-pass metabolism.

Distribution

- Tapentadol is widely distributed throughout the body.
- The serum protein binding is low at about 20%.
- It is unknown if tapentadol can cross the human placenta.
- It is unknown of tapentadol is excreted into human breast milk.

Metabolism and excretion:

- Tapentadol is extensively metabolised in the liver, mainly by glucuronidation, and to a lesser extent by CYP2C9 and CYP2C19, so drug interactions mediated through cytochrome P450 are unlikely.

  Most of the metabolites are excreted in the urine and the terminal half-life is four hours.

  There are no active metabolites.

- Elimination half-life is around 4 -5 hours.

Indications

The *immediate release* form of tapentadol is indicated for moderate to severe pain.

The *slow-release* form of tapentadol is indicated for the management of moderate to severe chronic pain that is unresponsive to non-opioid analgesia.

Contra-indications/precautions

1. Respiratory:

   Use with caution in patients at risk of respiratory depression:

   The following are relative contraindications:

   - Severe obstructive airways disease
   - Those at risk of upper airways obstruction
   - Obstructive sleep apnea

2. CNS:

   - Patients with a depressed conscious state.

3. CVS:

   - Hypotensive patients, (relative); titrate with caution.

4. Renal impairment:

   - The manufacturer does not recommend use if Cr Cl is <30 mL/minute (lack of data).

5. Hepatic impairment:

   - Adjust the dose in moderate hepatic impairment. The manufacturer does not recommend use in severe hepatic impairment (lack of data).

6. Drug reactions:

   - CNS depressants:
     - ♥ Concomitant use with other central nervous system depressants, effects are synergistic.
   - MAOIs:

- ♥ As tapentadol increases noradrenaline, it should not be taken with monoamine oxidase inhibitors.

- ♥ Treatment with (or within 14 days of) an irreversible, nonselective MAOI is contraindicated.

- Serotonergic agents:

  - ♥ Drugs that may contribute to serotonin toxicity should be avoided with tapentadol, (although adverse reactions are thought to be less likely than is the case with tramadol).

7. Elderly:

   - Opioid dose requirement decreases progressively with age.

   - There is an increased risk of adverse effects including cognitive impairment, sedation, respiratory depression and falls.

   - Use lower initial doses and titrate cautiously to effect.

8. Known hypersensitivity to tapentadol

Pregnancy:

Tapentadol is a category C drug with respect to pregnancy.

Category C drug are those drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Specialised texts should be consulted for further details.

Reports describing the use of tapentadol during pregnancy have not been located.

Consider an alternative medicine during pregnancy if possible.

Breast feeding:

Reports describing the use of tapentadol during breastfeeding have not been located.

Consider an alternative medicine during breastfeeding.

Adverse Effects

Adverse effects include:

1. CNS:

   - Depressed conscious state, with attendant risk of airway compromise.

This is a principle cause of death in overdose/ toxicity.

- Euphoria/ dysphoria/ delirium/ hallucinations
- Occasionally there can be a lowering of seizure threshold, especially in those with convulsive disorders.

2. Respiratory depression/ arrest:

   - **This is a principle cause of death in overdose/ toxicity.**
   - **The risk is dose related and synergistic with other CNS depressants, including alcohol**

3. GIT:

   - Nausea and vomiting:
     - ♥ Nausea and vomiting is thought to occur via direct stimulation of the chemoreceptor trigger zone (CTZ).
     - ♥ Incidence appears to be *less* than is seen with oxycodone.
     - ♥ An antiemetic may be given prophylactically
   - Decreased GIT motility:
     - ♥ Possibly less so than seen with oxycodone.

4. CVS:

   - Hypotension:
     - ♥ Usually with larger doses, IV and rapid administration
     - ♥ Orthostatic hypotension in ambulatory patients.
   - Bradycardia:
     - ♥ Usually with larger doses, IV and rapid administration

5. Allergic reactions:

6. Urinary retention:

   - This may occasionally occur due to increased bladder sphincter tone.

7. Dependence/ addiction:

Addiction is a compulsive use to the detriment of physical and/or psychological and/or social function.

It can be physical and/or psychological:

Physical dependence:

- **This is common.**
- **Withdrawal symptoms** can occur if *chronic* treatment is stopped suddenly or an antagonist is given.

See also separate Document on Opiate Withdrawal Syndrome, (Toxicology Folder).

Psychological dependence:

- This is more common in those with a general history of substance abuse.

See also separate Document on Opiate Withdrawal

8. Tolerance:

- Tolerance (increasing dosage to achieve the same effect) may develop upon repeated administration.
- Tolerance can develop rapidly, particularly in intravenous drug users who use opioids in the absence of pain.

Dosing

Tapentadol 100 mg is comparable to oxycodone 15 mg. [3]

Immediate release:

- 50 mg - 100 mg 4- 6 hourly

Slow (or extended release):

- Start with 50 mg twice daily

  Increase dose by 50 mg twice daily every 3 days, according to response.

  The maximum daily dose is 500 mg.

Antidote:

Naloxone is the specific antidote for opioid toxicity/ overdose

See separate Document, Naloxone (in Drugs Folder).

References

1. Tapentadol in Australian Medicines Handbook Website, Accessed December 2015.

2. Tapentadol in MIMs, 1 November 2015.

3. Tapentadol, Aust Presc. vol 36 no. 3, 2013.

4. Tapentadol in RWH Pregnancy & Breastfeeding Guidelines, 20 June 2018.

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Reviewed November 2018.