THE NORTHERN HOSPITAL

PETHIDINE

John Brown, daguerreotype, 1856

On Sunday evening, October 16 1859, the radical abolitionist John Brown led five blacks and thirteen whites into Harper's Ferry, Virginia. He brought along a wagonload of guns to arm the slaves he was sure would rally to him. Once they had, he planned to lead then southward along the crest of the Appalachians and destroy slavery.

Brown was an inept businessman who had failed twenty times in six states and defaulted on his debts, yet he believed himself God's agent on Earth.

In 1856, at Pottawatomie Creek in Kansas, he and his sons, had hacked five pro-slavery men to death with broadswords, all in the name of defeating Satan and his legions.

Brown and his men quietly seized the armory, arsenal, and engine house, and took up hostages, including George Washington's great grand nephew. After that, nothing went right. The first person killed was the town baggage master, a free black.

The slaves did not rise up, angry townspeople did.

The first of Brown's followers to fall was Dangerfield Newby, a former slave. Someone in the crowd cut off his ears as souvenirs.

On Tuesday morning federal troops arrived from Washington, led by a U.S army colonel named Robert E. Lee. Lee's men stormed the engine house, and nine more of Brown's men were killed, including two of his sons. Brown, severely wounded, was turned over to Virginia to be tried for treason.

"In firing his gun, John Brown has merely told what time of day it is. It is high noon…thank God"
(William Lloyd Garrison)

"An undivided South says, let him hang"
(Albany, Georgia Patriot)

Virginia found Brown guilty and sentenced him to death. Amoung the troops at the scene of his hanging were cadets from the Virginia Military Institute, led by an eccentric professor, Thomas J. Jackson. Also there, was a private in the Richmond Grays, a young actor named John Wilkes Booth.

December 2, 1859 - Old John Brown has been executed for treason against the state. We cannot object, even though he agreed with us in thinking slavery wrong. That cannot excuse violence, bloodshed, and treason. It could avail him nothing that he might think himself right".
(Abraham Lincoln).

Ralph Waldo Emerson likened Brown to Christ.

Nathaniel Hawthorne declared, "No man ever more justly hanged".

And Herman Melville called him "The meteor of the war"

Brown had said nothing from the gallows. But he did hand one of his guards a note;

"I John Brown am now quite certain that the crimes of this guilty land will never be purged away but with blood".

"His zeal in the cause of freedom was infinitely superior to mine. Mine was as the taper light, his as the burning Sun. If I could live for the slave, John Brown could die for him"
(Frederick Douglas)

"John Brown…John Brown….very important person in history. Important though for only one episode. Failure in everything in life, expect he becomes the single most important factor, in my opinion, in bringing on the war. The militia system in the South which had been a joke before this, before then, becomes a viable instrument, as the Southern militias begin to take a true form and the South begins to worry about Northerners agitating blacks to murder them in their beds".
(Historian , Ed Bearss)

It was the beginning of the Confederate Army.

"The feeling amoung the Southern members for the dissolution of the Union is becoming more general. Men are now beginning to talk of it seriously, who twelve months ago hardly permitted themselves to think of it. The crisis is not far ahead"
(Alexander Stephens)

Ken Burns', "The Civil War", 1990.

In the decade leading up to the Civil War the issue of slavery in America was on everyone's mind. With the expansion of the new nation to the west following victory in the war with Mexico new states were being added to the Union. Whether or not these states would be free or have slavery had become a burning issue. Slavery had been long dead in the North, but in the South it still very much flourished. Should new states such as Kansas and Nebraska become slave states the power and influence of the South as a whole would increase. The South was determined that the new states would be slave states, the North was just as determined that they would not be. Tensions rose steadily, the issue crystallized as one of "States rights". Accordingly a comprise was reached whereby the new states were to decide for themselves, but both sides fought a bitter battle to gain influence over them. Increasingly the South came to see that their rights were being trampled on. Never strongly cohesive with the North, secession began to be talked about, and yet most in the both the North and the South agreed that secession would be madness. Then came John Brown and his raid on Harper's Ferry, and attitudes hardened over night.

John Brown believed that he had been given a mission by God to end slavery in America, even if this meant arming the slaves themselves. The nation was shocked and deeply divided over the raid at Harpers Ferry. The incident radicalized many Southerners who formed up militias to defend their "States rights". From these militias would develop the Confederate armies.

The agent pethidine was at the turn of the century executed for treason. It was originally developed by Big Pharma amidst great promises that it would fight the curse of addiction. We cannot object, even though Big Pharma agreed with us in thinking addiction wrong - but it availed Big Pharma nothing in using dubious methods for the cause!

PETHIDINE

Introduction

Pethidine (also known outside of Australia as **meperidine**) is a fully synthetic, intermediate acting, opioid analgesic.

Its effects are generally similar to those of morphine, *despite* its unrelated chemical structure.

By the 1970s, pethidine was the most widely used opioid for acute severe pain, and was widely used for chronic pain.

Its popularity was due to its supposed advantages over morphine, which were said to include a better safety profile, less potential for addiction and was reportedly superior for the treatment of pain associated with biliary spasm and renal colic due to its anticholinergic effects.

Subsequent clinical experience in the decades that followed demonstrated all of these supposed advantages to be myths.

Further, it became apparent that pethidine had significant *disadvantages* when compared to morphine, which included:

1. A toxic metabolite - norpethidine - which has a **neuroexcitatory effect**, potentially leading to **seizures**.

2. Potential for **serotonin syndrome**, especially when used in combination with other serotonergic agents.

3. A *very high* potential for strong **addiction**.

Because pethidine possessed no true advantages over morphine, and had some significant disadvantages compared to morphine, its use is now discouraged. Use in **Emergency Departments declined** in the mid to late 2000s, and today its use is rare.

Despite its disadvantages, it nonetheless is a potent and efficacious opioid analgesic, which may retain some *limited* indications, for *short term* use including:

1. Genuine *severe allergic* reaction to morphine / fentanyl:

    - Though IV oxycodone is an alternative, if available.

2. Critical shortage of supply of fentanyl / morphine:

    - As occurred nationwide in Australia, for fentanyl in 2017.

The specific antidote 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

Pethidine was first synthesized in by the German chemist **Otto Eisleb** in 1939 as a potential *anticholinergic agent*.

Its opioid properties were first recognized by **Otto Schaumann** while working for the German chemical and pharmaceutical company, IG Farben, (the same company that produced Zyklon B during the Second War, and that later developed the nerve gas, sarin).

Pethidine was the first *wholly synthetic* opioid developed.

It was very widely used in the last quarter of the Twentieth century, before falling out of favour in the early 2000s, when it became apparent that it was not superior to morphine, and it possessed significant adverse effects, over and above morphine.

Chemistry

Pethidine is a phenylpiperidine, and is a fully synthetic opioid.

Physiology

Opioid receptors are distributed widely in the:

1. Brain
2. Spinal cord
3. 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.

Classification

Opioids may be classified according to:

1. Derivation
2. Receptor activity

Opioid Derivation Classification:

1. **Natural Alkaloids of Opium:**

- Benzylisoquinolines:
  - ♥ Papaverine
  - ♥ Noscapine
- Phenanthrenes:
  - ♥ Morphine
  - ♥ Codeine
  - ♥ Thebaine

2. **Semi-synthetic Derivatives:**
   - Diacetylmorphine (heroin)
   - Hydromorphone
   - Oxymorphone
   - Hydrocodone
   - Oxycodone
3. **Fully Synthetic Derivatives:**
   - Morphinans:
     - ♥ Levorphanol
   - Benzmorphans:
     - ♥ Pentazocine
     - ♥ Phenazocine
     - ♥ Cyclazocine
   - Propionanilides:
     - ♥ Methadone
   - Phenylpiperidines:
     - ♥ **Pethidine**

- ♥ Fentanyl
- ♥ Remifentanil
- ♥ Alfentanil
- ♥ Sufentanil
- ♥ Carfentanyl

Opioid Receptor Activity Classification:

1. **Pure agonists**:

   These are pure agonists of specific opioid receptors (notably the mu receptor)

   There is no limiting ceiling effect with the *pure* agonists,

   Examples include:

   - Morphine
   - Fentanyl
   - **Pethidine**

2. **Mixed agonist - antagonists**:

   These have opposing effects at distinct receptor subtypes, i.e agonist activity at one receptor type and antagonist activity at another receptor type

   Examples include:

   - Nalorphine
   - Pentazocine

3. **Partial mu agonists**:

   These agents produce a less than maximal response and, therefore, have a lower *intrinsic* activity.

   The partial agonist (and mixed agonist - antagonist) opioids, demonstrate a ceiling response above which an increase in dose does not produce any additional increase in effect.

   Partial agonists are able to **antagonize** the effects of large doses of **full** agonists

Examples include:

- Buprenorphine

A fourth group can be described as **pure antagonists**, of which **naloxone** is an example.

Preparations

Pethidine hydrochloride as:

Ampoules:

- 50 mg/mL, 1 mL
- 50 mg/mL, 2 mL

Mechanism of Action

Opioids interact with one or more subtypes of opioid receptors (e.g. mu, kappa, delta) at supraspinal, spinal and peripheral sites to produce analgesia and a multitude of other effects.

Opioid mimic the effects of the endogenous opioids by activating opioid receptors in the central nervous system, peripheral nervous systems

Current potent opioid analgesics are mu agonists, although specific delta and kappa agonists may also produce analgesia.

Opioids act by: [1]

- Presynaptic inhibition of neurotransmitter release from C-fiber terminals.
- Postsynaptic inhibition of evoked activity in nociceptive pathways.
- Disinhibition of other circuits regulating nociceptive transmission.
- Supraspinal opioids increase descending inhibition of spinal nociceptive transmission

Pethidine is a pure **mu opioid agonist.**

Pharmacodynamics

Pethidine has:

1. Opioid effects

2. Anticholinergic effects

3. Some local anesthetic effects

After parenteral administration, pethidine 100 mg has comparable analgesic, euphoric and respiratory depressant effects to morphine 10 mg.

Pethidine has a **more rapid onset** of action (about **10 minutes** after IM administration) but a **shorter** duration of **analgesic effect** than does morphine.

Useful analgesia lasts between **2 - 4 hours**

Therapeutic effects of opioids in general include:

1. Analgesia

2. Sedation

3. Anxiolysis

4. Cough suppression:

    - Via a direct effect within the medulla of the brain stem.

      The depressant effect of pethidine on the cough reflex may be less than that of morphine at equianalgesic doses.

Additional effects of pethidine include:

1. Pethidine has spasmolytic as well as spasmogenic effects, and so may produce less constipation than morphine.

2. Atropine-like effects such as dry mouth and blurred vision have been reported with pethidine.

3. Corneal analgesia (after IV/IM administration) - can abolish corneal reflexes.

4. Unlike morphine there is no histamine release

Pharmacokinetics

Absorption:

- Pethidine is normally given **IV** or **IM**

  SC injection may cause local irritation and induration.

- Pethidine may also be taken orally, and although well absorbed from the gastrointestinal tract, it is considerably less effective orally than parenterally due to rapid first-pass metabolism, that limits bioavailability to around 50 %.

- In the past is was also administered intraspinally, for example, epidurally after Caesarean sections.

Distribution

- Pethidine has a volume of distribution of 4 L/kg

- Protein binding is variable at 65 - 80 %.

- Pethidine can cross the human placenta

- Pethidine is excreted into human breast milk.

Metabolism and excretion:

- Pethidine is mainly metabolised in the liver.

  Norpethidine, is a major demethylation metabolite, it is half as active as pethidine as an analgesic, but it is twice as active as a **pro-convulsive agent.**

  The elimination half-life of norpethidine is prolonged in patients with impaired renal function, persons over 60 years of age and neonates.

- The half life of pethidine is short, at around 3 hours, but is relatively long for norpethidine at around 24 - 48 hours.

Indications

Pethidine is **no longer** recommended as first-line treatment for acute pain in Emergency Departments. [6]

It should ***never*** be used for **recurrent** or **chronic** pain.

Pethidine was once widely used for the treatment of back pain and migraine, but it is now considered to be contraindicated for use in chronic conditions as its effect is only *short* lived and with repeated use it **commonly** led to addiction and drug-seeking behaviour

Despite its disadvantages, it nonetheless is a potent and efficacious opioid analgesic, which may retain some *limited* indications, for *short term* use including:

1. Genuine *severe allergic* reaction to morphine / fentanyl:

   - Though IV oxycodone is an alternative, if available.

2. Critical shortage of supply of fentanyl / morphine:

    - As occurred nationwide in Australia, for fentanyl in 2017.

Obstetric use:

Although not a marketed indication, epidural pethidine is occasionally used for analgesia in labour and more often for analgesia after caesarean section

Contra-indications/precautions

Pethidine as an **opioid** shares the same contraindications / precautions as all opioids in general and so include:

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, (relative contraindication):

    - Pethadine and its toxic metabolite **norpethidine** *accumulate* in renal impairment and have a longer half-lives which may result in adverse effects.

5. Hepatic impairment:

    - Use with *caution* in severe hepatic impairment (relative contraindication) - may cause excessive sedation or coma.

6. Concomitant use with other central nervous system depressants, effects are synergistic

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.
- Risk of **norpethidine** toxicity is increased in the elderly.

8. Neonates and infants:

- Neonates and infants up to approximately 12 months are more susceptible to respiratory depression associated with opioid use. Start with a low dose and titrate to effect.

9. Known hypersensitivity to pethidine

10. Caution with serotonergic agents:

- In particular treatment with, or within 14 days of, a MAOI (including selegiline) is **contraindicated**

Pregnancy

Pethidine is classified as a category C class drug with respect to pregnancy.

Category C class drugs 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.

Nonetheless pethidine was/ is widely used in obstetrics.

Maternal use of pethidine has not been associated with an increased risk of congenital malformations.

However, **respiratory depression** in the neonate and **neonatal abstinence syndrome (NAS)** can occur following *regular* use of pethidine during the last trimester of pregnancy.

NAS symptoms include excessive crying, tremors, poor feeding, sleep duration changes and irritability.

Infants should be monitored for NAS symptoms and management should be provided accordingly, using both pharmacologic and non-pharmacologic management.

Pethidine is considered safe to use during pregnancy at the **lowest effective dose** for the **shortest duration possible**.

Breast feeding

Small amounts of pethidine are excreted into breast milk, but these amounts are unlikely to pose harmful effects in breastfed infants.

Pethidine is considered safe to use during breastfeeding at the lowest effective dose for the shortest duration possible.

However, observe the breastfed infant for potential adverse effects such as drowsiness, poor feeding and sleeping pattern changes.

Adverse Effects

Pethidine as an **opioid** shares the same adverse reactions as all opioids in general and so 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 - this is a particular adverse effect of **pethidine**.
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).
        - ♥ It is a very common reaction.
        - ♥ An antiemetic may be given prophylactically

- Decreased GIT motility
    - ♥ Delay in gastric emptying
    - ♥ Constipation, this is common with **prolonged** use.

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:
    - Minor local histamine release is common and benign.
    - Histamine induced hypotension - usually mild
    - True IgE mediated anaphylaxis is **very rare**

6. Urinary retention:
    - This may occasionally occur due to increased bladder sphincter tone, (anticholinergic effect of pethidine)

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 - *especially* with pethidine**
- **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 of morphine.
   - Tolerance can develop rapidly, particularly in intravenous drug users who use opioids in the absence of pain.

Additional adverse effects specific to pethidine include:

9. A toxic metabolite - **norpethidine**:

   This has which as a **neuroexcitatory effect**, which may lead to:

   - Agitation / irritability
   - Tremors / twitching
   - Myoclonus.
   - Confusion
   - **Seizures**

   Risk factors for the *accumulation* of **norpethidine** include:

   - Renal impairment
   - Age > 60 years
   - Neonates

10. Potential for **serotonin syndrome**, especially when used in combination with other serotonergic agents.

    - In particular treatment with, or within 14 days of, a MAOI (including selegiline) is **contraindicated**

Dosing

Usual adult dosing of pethidine is :

- **0.5 - 1 mg/ kg IM every 2 -3 hours as required**

- **0.25 - 0.5 mg /kg IV every 2 -3 hours as required**

Note however that, when given at this frequency the active and toxic metabolite norpethidine (half-life 24 - 48 hours) accumulates (particularly in renal failure).

Use lower doses in patients >70 years of age.

The suggested maximum total dose in young adults is **1000 mg in first 24 hours**, then **600 mg daily**; use for no longer than 24 - 36 hours, on account of norpethidine toxicity.

Obstetric analgesia:

IM, 50 -100 mg initially.

May be repeated after 1 - 3 hours; with a maximum 300 mg in 24 hours.

Avoid use within 2 hours of anticipated delivery.

Severe hepatic impairment:

Decrease dose by half to three-quarters.

Antidote:

Naloxone is the specific antidote for opioid toxicity/ overdose

Note that while naloxone reverses the sedating and respiratory depressant effects of pethidine, it does not reverse the neuroexcitatory effects of its metabolite, **norpethidine**, and may in fact exacerbate these side effects.

See also separate Document, Naloxone (in Drugs Folder).

Virginia found Brown guilty and sentenced him to death. Amoung the troops at the scene of his hanging were cadets from the Virginia Military Institute, led by an eccentric professor, Thomas J. Jackson. Also there, was a private in the Richmond Grays, a young actor named John Wilkes Booth.

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