THE NORTHERN HOSPITAL

ATROPINE

"Le Manteau Légendaire", (The Legendary Coat), oil on canvas, Léon-François Comerre c. 1890.

"....For she was a woman of surpassing beauty, and at that time, when she was in the prime of her youth, she was most striking; she also possessed a most charming voice and knowledge of how to make herself agreeable to everyone. Being brilliant to look upon and to listen to, with the power to subjugate everyone, even a love-sated man already past his prime, she thought that it would be in keeping with her role to meet Caesar, and she reposed in her beauty all her claims to the throne. She asked therefore for admission

to his presence, and on obtaining permission adorned and beautified herself so as to appear before him in the most majestic and at the same time pity-inspiring guise. When she had perfected her schemes she entered the city (for she had been living outside of it), and by night without Ptolemy's knowledge went into the palace". (XLII.34).

... So Cleopatra, taking only Apollodorus the Sicilian from among her friends, embarked in a little skiff and landed at the palace when it was already getting dark; and as it was impossible to escape notice otherwise, she stretched herself at full length inside a bed-sack, while Apollodorus tied the bed-sack up with a cord and carried it indoors to Caesar. It was by this device of Cleopatra's, it is said, that Caesar was first captivated, for she showed herself to be a bold coquette..." (XLIX).

Cassius Dio, 2nd century A.D

"Judging by the proofs which she had had before this of the effect of her beauty upon Gaius Caesar and Gnaeus the son of Pompey; she had hopes that she would more easily bring Antony to her feet. For Caesar and Pompey had known her when she was still a girl and inexperienced in affairs, but she was going to visit Antony at the very time when women have the most brilliant beauty and are at the height of intellectual power"

Plutarch, Life of Antony (XXVII), 1st century A.D

The question of Cleopatra's beauty has held a fascination for millennia. Portrait coins are not flattering which has led some modern historians to question her beauty, however coins of this period are purely stylized - not representative of a true likeness at all. Most coins produced of leaders at this time were purely generic depictions that were mass produced to standardised formulae for centuries hardly deviating in style at all.

Ancient sources such as Cassius Dio however seem to be in no doubt whatsoever - in her youth Cleopatra was stunningly beautiful. Perhaps, they conceded though, that in her "older" age (read forty) her looks had faded somewhat. In any case whatever she may or may not have lost in her looks over the years - and this in any case is ultimately a purely subjective and culturally based opinion - she more than made up for in her experience, her striking intelligence, and her political acumen. In her childhood, after the death of her father Ptolemy XII, she shared the throne of Egypt with her brother Ptolemy XIII who was seven years older than her. As the children grew older it became clear that Cleopatra was far more intelligent and far more popular than her brother - whom she had married.

Ptolemy alarmed at his sister's increasing popularity had her exiled from court. But in 48 B.C Egypt was invaded by the Roman Republic under Julius Caesar who was in pursuit of Pompey during a Roman civil war. Cleopatra at the age of just 22 years schemed to win the affection of Caesar and use his power to regain her position at court. Legend has it that her servants hid her in a carpet and smuggled her into the palace were Caesar was staying as a guest of Ptolemy. When the servants unrolled this "gift" for Caesar - Cleopatra emerged. She had made herself irresistible with adornments and perfumes - some say that she presented herself stark naked. Caesar was 52 years old at the time - but was thunderstruck by the apparition of beauty before him. In short time he came to

realize that not only was Cleopatra a stunning beauty but that she also possessed an astonishing intelligence. Caesar was hopelessly captivated and soon the two became lovers, even though Caesar was married at the time. Caesar moved to have Cleopatra restored to the throne but this provoked a battle between supporters of Ptolemy and supporters of Cleopatra - but with Roman help Ptolemy was defeated and killed. His younger brother was proclaimed Ptolemy XIV - but under mysterious circumstances he suddenly died - it was rumoured that he had been poisoned with aconite at the hands of Cleopatra who now became sole Pharaoh of Egypt. Cleopatra accompanied Caesar back to Rome - however after Caesar was assassinated in 44 B.C she returned to Egypt - but not before seducing one of Rome's most powerful generals, Mark Antony, whom she took back to Egypt with her. She had convinced Mark Antony that together they could rule the known world. Mark Antony and Cleopatra seemed destined to become the first Roman Emperor and Empress, but Caesar's nephew Octavian challenged the authority of the upstart general and the foreign Queen.

The ensuing titanic sea battle of Actium off the coast of western Greece in 31 B.C was one of the most decisive battles in history. Octavian's forces defeated those of Mark Antony and Cleopatra. Cleopatra on hearing of the suicide of her lover, killed herself by the agency of the bite of a deadly Nile Asp. Octavian now stood supreme in the Roman world, changed his name to Augustus Caesar, abolished the Republic and became the first Emperor of Rome. Cleopatra possessed beauty, intelligence, sexual magnetism, power and unimaginable wealth. It would prove a most powerful combination - indeed powerful enough to bring down the Roman Republic which had existed for over seven centuries. It was said that the old Roman Republic had only ever feared two people - Hannibal and Cleopatra.

Cleopatra used every device known to the ancient world to enhance her sexual appeal, amoung these was the application of extract of the henbane to her eyes. This plant contained powerful atropine like alkaloids which would greatly dilate her pupils making her eyes appear enormous and enchanting. This trick was not without risk however - whilst the cosmetic effect was dramatic, and no doubt assisted in her seduction of Caesar there was always the chance that paralysis of her ocular accommodation could have resulted in a disastrous tripping over - an undignified accident that would have somewhat detracted from her dramatic naked emergence from the carpet! Nevertheless Cleopatra was used to playing with fire, she accomplished her scheme to seduce Caesar with poise, balance and brilliance!!

Cartouche from the Temple of Horus at Edfu, First century B.C. The inscribed name reads "Cleopatra".

ATROPINE

Above: Flowers of the Deadly Nightshade, Atropa belladonna. Below: The brilliant iridescent blue fruit of the belladonna.

Introduction

Atropine is a **competitive muscarinic antagonist.**

It is used primarily in:

1. Brady-asystole rhythms in ACLS protocols
2. In various toxicological syndromes
3. Some ocular conditions, (topically).
4. Pre-anaesthetic medication to reduce salivary secretions and bronchial secretions.

See also separate documents on:

- **Organophosphate poisoning (in Toxicology folder)**
- **Topical Ocular Medications (in Drugs folder)**
- **Anticholinergic Toxidrome (in Toxicology folder).**

History

The plant alkaloid atropine has been known since classical times.

Atropine and the genus name for the deadly nightshade from which it is derived comes from the Greek "**Atropos**", who according to ancient Greek mythology was one of the of the three Goddesses of Fate. Clotho spun the thread of life, in effect creating a new life. Lachesis drew out this thread and allotted its length. **Atropos** cut the thread of life - it was she who determined the exact hour and manner in which a life would end.

Legend has it that Cleopatra would place drops derived from juices of the henbane into her eyes which would enormously dilate her pupils, thus enhancing the apparent size, and hence the beauty, of her eyes.

Italian Renaissance princesses, used juices from the Atropa belladonna (or beautiful lady) to enhance the appearances of their eyes. It was said that the notorious **Lucretia Borgia**, daughter of Pope Alexander VI was not averse to using the belladonna to poison her enemies.

In Paris of the late Belle Epoch, women of high society, would also enhance their allure, by use of the belladonna drops.

In 1831, the German pharmacist Heinrich F. G. Mein (1799-1864) succeeded in preparing atropine in pure crystalline form.

In 1867 Bezold and Bloebaum showed that atropine blocked the cardiac effects of vagal stimulation.

In 1872 Heidenhain found that it prevented salivary secretion produced by stimulation of the chorda tympani.

Atropine was first synthesized by German chemist Richard Willstätter in 1901.

Since then many semisynthetic derivatives of the belladonna alkaloids and a large number of synthetic muscarinic receptor antagonists have been developed for medical use.

Chemistry

Atropine (and **hyoscine),** are **naturally occurring belladonna plant alkaloids.**

One natural source is from the Atropa belladonna, commonly known as the deadly nightshade, a perennial herbaceous plant native to Europe, North Africa, and Western Asia.

Preparations

Ampoules:

- **Atropine sulfate: 0.6 mg/ml ampoules.**
- **Atropine sulfate: 1.2 mg/ml ampoules.**

Mechanism of Action

Atropine is a **competitive muscarinic antagonist**, both **peripherally** and **centrally.**

It acts by blocking the effects of acetylcholine at muscarinic cholinergic receptors, on smooth muscle, cardiac muscle, gland cells and peripheral ganglia, and within the CNS.

As with other antimuscarinic agents, the major action of atropine is a competitive or surmountable antagonism which can be overcome by increasing the concentration of acetylcholine at receptor sites of the effector organ (e.g. by using anticholinesterase agents which inhibit the enzymatic destruction of acetylcholine).

The receptors antagonized by atropine in therapeutic doses are primarily the **peripheral** structures that are stimulated or inhibited by muscarine (i.e. exocrine glands and smooth and cardiac muscle).

It does **not** act on **nicotinic** receptors.

Pharmacodynamics

Atropine has both peripheral and central actions.

Atropine has activity both on structures innervated by postganglionic cholinergic nerves and on smooth muscles which respond to endogenous acetylcholine but are not so innervated.

It **increases heart rate**, by reducing peripheral parasympathetic tone to the heart, as well as enhancing A-V nodal conduction.

Low doses of the drug may cause a paradoxical *decrease* in heart rate. This is thought to be due to a direct central nervous system (CNS) activity, that centrally stimulates the medulla and vagal nerve.

It reduces secretions, especially salivary and bronchial secretions, and also reduces perspiration, (and so may contribute to heatstroke type syndromes).

It has little effect on intestinal, biliary or pancreatic secretions since these secretions are principally controlled by hormonal rather than vagal mechanisms.

Atropine exerts a more potent and prolonged effect on the heart, intestine and bronchial muscle than hyoscine, but its action on the iris, ciliary body and certain secretory glands is weaker than that of hyoscine.

Atropine has an antispasmodic action on smooth muscle and diminishes gastric and intestinal motility.

Larger doses cause **prominent central excitation**, blocking the vagus nerve and resulting in **restlessness, irritability, disorientation, hallucinations or delirium.**

The duration of effect of atropine on the heart rate is reported to be up to **5 hours.**

Pharmacokinetics

Absorption:

- Atropine has poor oral bioavailability.
- It is given **IV** for immediate systemic effect.
- It is also well absorbed following IM administration, though it takes longer to act than the IV route. Peak plasma concentrations are reached within 30 minutes by the IM route.
- It can be given topically for local ocular effects.

Distribution:

- Atropine is **well distributed** throughout the body.
- Atropine can cross the blood-brain barrier
- Atropine can cross the human placenta
- Atropine is excreted into human breast milk in small quantities.

Metabolism and excretion:

- Atropine is metabolized by the liver.
- Half-life is 2 - 4 hours.

Indications

These include:

1. Bradyarrhythmias and asystole in ACLS protocols
2. Bradyarrhythmias in general where there is haemodynamic compromise.
    - Atropine is most effective for sinus node dysfunction or blocks occurring at the level of the atrioventricular (AV) node.
3. Toxicological indications:
    - Poisoning by drugs that impair A-V nodal conduction:
        - ♥ Digoxin.
        - ♥ Beta Blockers
        - ♥ Calcium channel blockers
    - Organophosphate poisoning:
        - ♥ Including in chemical warfare, as an antidote to powerful organophosphate nerve gas agents, such as Sarin, Soman, Tabun and VX.
    - Carbamate poisoning
4. In anesthesia:

- Pre-anaesthetic medication to reduce salivary secretions and bronchial secretions.

- Prevention of the muscarinic effects of neostigmine when this has been used to reverse non-depolarizing neuromuscular blockade.

5. Some ocular conditions.

Contra-indications/precautions:

Relative contra-indications include:

1. Closed angle glaucoma.

2. GIT obstruction

3. Obstructive uropathies.

4. Febrile patients or patients exposed to elevated ambient temperature, due to the risk of provoking hyperpyrexia and heat prostration.

5. Myasthenia gravis.

6. Atropine may cause increased anticholinergic activity when administered concomitantly with other anticholinergic drugs such as:

    - Phenothiazines, antispasmodics, anti-parkinsonian drugs, antiarrhythmics with anticholinergic activity (e.g. disopyramide and quinidine), some antihistamines, tricyclic antidepressants or butyrophenones.

Pregnancy

Atropine is a **class A** drug with respect to pregnancy.

Class A drugs are those which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.

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

Atropine crosses the placental barrier and may cause fetal tachycardia.

However, there are case reports of healthy pregnancy outcomes following maternal use.

Atropine is safe to use during pregnancy, but monitoring of maternal and fetal wellbeing is recommended if atropine is used immediately before delivery.

Systemic absorption of topical atropine preparations are expected to be minimal and unlikely to pose adverse effects in the developing fetus.

To further minimise systemic absorption, apply pressure against the inner corner of the eye (over the tear duct) for one to two minutes and blot away any excess drops.

Breast feeding:

Caution is advised in breastfeeding as there is insufficient data available.

Small amounts of atropine are thought to be excreted into breast milk and the effects can be highly variable.

Adverse effects have *not* been noted in breastfed infants following maternal use of atropine.

However, there is a theoretical risk that atropine may inhibit growth hormone secretion and oxytocin secretion, therefore resulting in the inhibition of lactation.

If atropine is the medicine of choice during breastfeeding, monitor the breastfed infant for adverse effects such as drying of secretions, temperature elevation and central nervous system disturbance.

Adverse Effects

Excessive atropine administration results in clinical features of anticholinergic poisoning:

Central anti-cholinergic neurological effects	**Peripheral muscarinic blockade**
Delirium/ agitation/ restlessness/ picking at imaginary objects in the air is characteristic.	**Mydriasis**/ blurred vision.
Fluctuating mental state.	**Tachycardia**
Visual hallucinations.	Dry mouth
Tremor.	Reduced sweating → hot dry skin
Myoclonic jerks.	**Hyperthermia**

Seizures, (uncommon)	GIT: reduced bowel sounds/ ileus.
Coma.	Urinary retention.

Dosing

Bradyarrhythmias / asystole: [1]

Adults:

- **Atropine 0.5 to 1.5 mg IV**
- **This can be repeated after 15 minutes if necessary, (maximum of 3.0 mg).**

Children:

- The usual paediatric dose is, **0.02 mg/kg** up to **0.5 mg IV bolus**.
- This may be repeated after 5 minutes if necessary up to a **maximum of 1 mg.**

Organophosphate Poisoning: [3.4]

This is the life saving antidote for organophosphorous poisoning.

Atropine in escalating doses is required to control the muscarinic cholinergic symptoms of organophosphorous poisoning.

Adults should initially receive 1.2 mg IV every 5 minutes until adequate atropinization is established.

Doses can be doubled every 5 minutes over the first few doses to gain quick control over toxicity. (Children 50 micrograms per kilogram).

A continuous infusion of atropine may be used.

In severe poisoning very large doses (up to 100 mg) may be required. *Anticipate this need and secure stocks early.*

For full description of the treatment of Organophosphate Poisonings, see Organophosphate Poisoning (in Toxicology folder)

Anaesthetic premedication:

Premedication:

- Adult: **IV/IM**, initially 0.3 - 0.6 mg.
- Child: **IV/IM**, initially 0.01- 0.02 mg/kg, (to 1.0 mg maximum).

Non-depolarizing muscle relaxant reversal with neostigmine:

Given to prevent neostigmine's muscarinic effects.

- Adult, **IV**, initially 0.6 - 1.2 mg
- Child, **IV**, initially 0.02 mg/kg (to 1.0 mg maximum).

Mydriatic and cycloplegic eye drops

Ophthalmological use for longer-acting mydriasis and cycloplegia in inflammatory conditions.

- **Atropine 1% eye drops, 1 drop.**

Peak effect:

- 30 to 40 minutes (mydriasis)
- 3 to 6 hours (cycloplegia)

Duration of action is **prolonged** at **10 - 15 days.**

Obv. ANT AVG III VIR R P C. Galley to the right with banners at the prow; Rev. LEG VI. Eagle (aquila) facing right between two legionary standards (signa). Reference: BMC 197, RSC 33, Sear 356.

Silver denarius issued by Mark Antony before the Battle of Actium, in 32 B.C. It was likely minted at Antony's winter headquarters in Patrae in Greece. Mark Antony used silver denarrii such as this to pay his legions and his fleet. Copper had been added reducing the silver content of these coins producing a cheaper alloy. As the value of these denarii had been debased they tended not to be hoarded but remained in constant circulation, explaining the much worn condition of most of them in modern day collections. The above example is a particularly fine one.

References

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