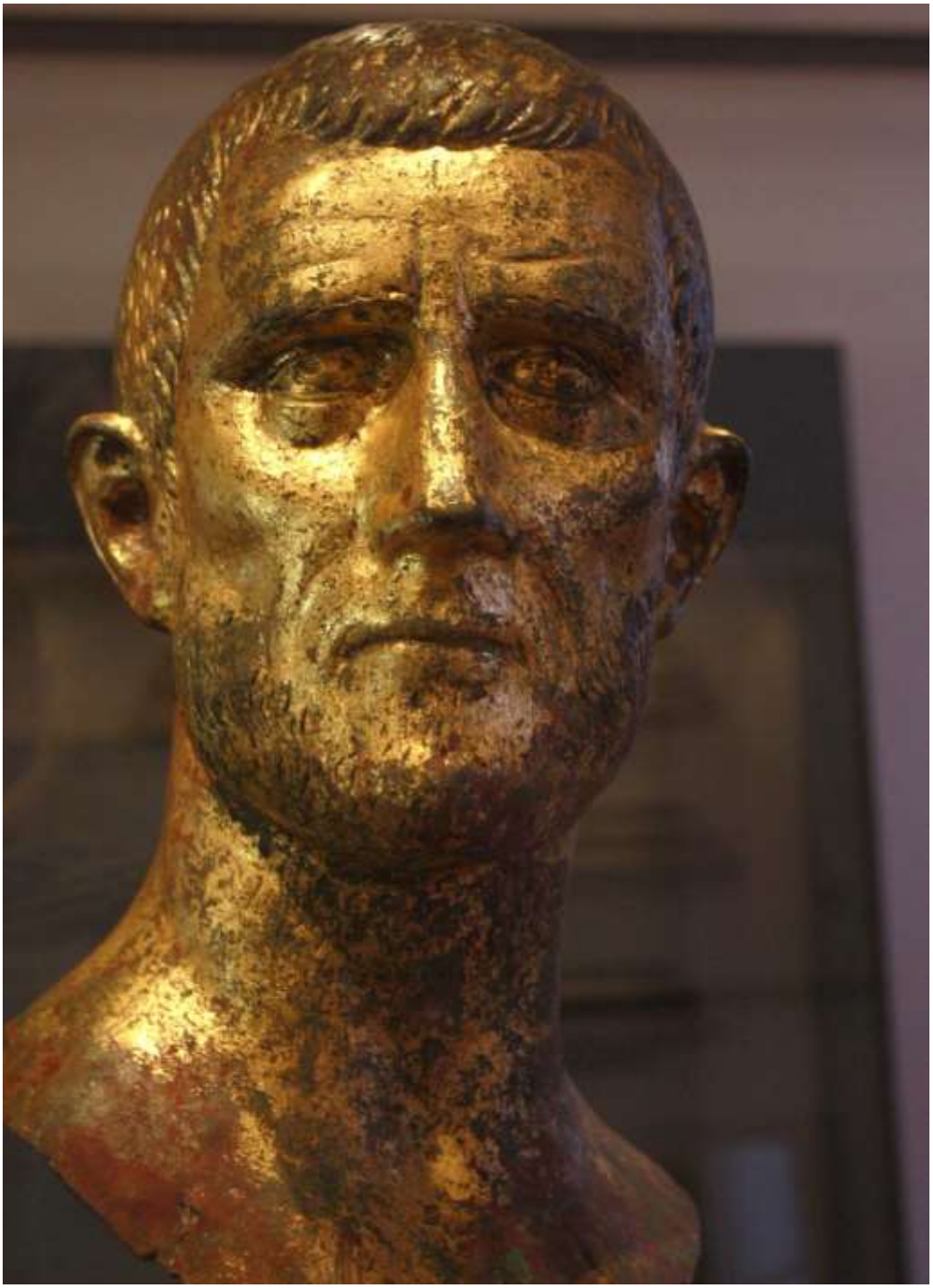
THE NORTHERN HOSPITAL

# ALFENTANIL



*Claudius II Gothicus, Bronze, c.268-70 AD, Museo Santa Giulia, Brescia.*

*One of two magnificent bronze busts of the mid - Third century Emperor, Claudius II Gothicus, that were discovered as part of a stunning hidden cache of bronzes beneath the Capitoline temple in Brescia in 1826. They were possibly hastily buried in anticipation of a barbarian attack on the town in the 4th or 5th century AD. The bronzes now reside in the Santa Giulia Archaeological Museum in Brescia, Italy.*

*"Under the deplorable reigns of Valerian and Gallienus, the Empire was oppressed and almost destroyed by the soldiers, the tyrants and the barbarians. It was saved by a series of great princes, who derived their obscure origin from the martial provinces of Illyricum. Within a period of about thirty years, Claudius, Aurelian, Probus, Diocletian and his colleagues, triumphed over the foreign and domestic enemies of the state, re-established the military discipline, the strength of the frontiers, and deserved the glorious title of Restorers of the Roman world. The removal of an effeminate tyrant made way for a succession of heroes. The indignation of the people imputed all their calamites to Gallienus, and the far greater part were, indeed, the consequence of his dissolute manners and careless administration...*

*The obscurity which covered the origin of Claudius, though it was afterwards embellished by some flattering fictions, sufficiently betrays the meanness of his birth. We can only discover that he was a native of one of the provinces bordering on the Danube. The Senate and People already considered him an excellent officer, equal to the most important trusts, and censured the inattention of Valerian, who suffered him to remain in the subordinate station of a tribune....*

*We still possess an original letter addressed by Claudius to the Senate and People.... "Conscript fathers", says the Emperor, "know that three hundred and twenty thousand Goths have invaded the Roman territory. If I vanquish them, your gratitude will reward my services. Should I fall, remember that I am the successor of Gallienus..."*

*...The melancholy firmness of this epistle announces a hero careless of his fate, conscious of his danger, but still deriving a well-grounded hope from the resources of his own mind. The event surpassed his own expectations and those of the world. By the most signal victories he delivered the empire from this host of barbarians, and was distinguished by posterity under the glorious appellation of Claudius Gothicus...*

*During the course of a rigorous winter, in which they were besieged by the Emperor's troops, famine and pestilence, desertion and the sword, continually diminished the imprisoned multitude. On the return of spring nothing appeared in arms except a hardy and desperate band, the remnant of that mighty host which had embarked at the mouth of the Dniester.*

*The pestilence which swept away such numbers of the barbarians at length proved fatal to their conqueror. After a short but glorious reign of two years, Claudius expired at Sirmium, amidst the tears and acclamations of his subjects".*

*Edward Gibbon, "The History of the Decline and Fall of the Roman Empire", volume 1, 1776.*

*In the year 235 A.D, the young Emperor Severus Alexander was murdered by the battle hardened troops of the most dangerous sector of the Roman frontier, the Danube. The situation had become so desperate on the frozen northern frontier, that the troops no longer trusted the fate of the Empire to a young and seemingly effeminate Emperor. Only a solder and great leader would do. The year 235 A.D marked a watershed year for Imperial Rome. After two centuries marked by brilliant Emperors that had made Imperial Rome great, the tide had finally turned. The teaming Germanic hordes of the far north could no longer be restrained behind the Rhine and the Danube, the great natural northern boundaries of the Empire that had been set by Augustus Caesar in 9 A.D. After the murder of Severus, a Roman general Maximinus, shockingly of barbarian descent, was declared Emperor by the troops of the*

*Danubian provinces. For the next half a century the Empire would enter a period some historians refer to as Imperial Rome's "Dark Ages". The years 235 AD to 285 AD represent years of crises for the Empire, relatively little is known about this period when compared to the Severan age that preceded it and the age of Diocletian that followed it. They were desperate years beset by northern barbarian incursions on an unprecedented scale. The very authority of the Emperor in Rome was increasingly questioned. Troops of local sectors began to declare their own generals as Emperor, having lost confidence in the ability of single man in Rome being able to lead to lead an Empire as large as the Roman Empire had become. During these years no less than sixty individuals would attempt to claim the purple. All but a handful would meet their ends in violence. Succession was largely determined by the assassination of one's predecessor. Eventually the Empire split into three - seemingly for good. In the West, Postumus ruled over Gaul, Spain and Britain, while Queen Zenobia ruled over the Eastern provinces. In Rome and the central provinces a succession of Emperors ruled, each for little more than a year or two, before relative stability was achieved under Valerian and his son Gallienus. But this stability came at a price, the shameful division of the Empire into three distinct entities. In 268 A.D Gallienus was murdered and everything changed. A series of brilliant Emperor - Generals, would, over the next thirty years, bring about the defeat and expulsion of the marauding barbarian hordes, and would crush all internal dissent. By 285 AD the Roman Empire would be reunited and resurrected to its former glory for another two centuries.*

*The first Emperor - General to lead the military recovery after the dark ages of crises would be an Illyrian solider of obscure birth, Marcus Valerius Claudius, otherwise known to posterity as Claudius Gothicus. He was by all accounts a brilliant general. He annihilated a horde of invading Alemanni in Northern Italy, which gained him the title "Germanicus Maximus", but most impressive of all he defeated of horde of over three hundred thousand Goths, who had been rampaging throughout Thrace and Greece. This was the largest enemy tribe Rome would face until the time of the Emperor Valens, in 378 A.D. Though it would be left to his brilliant lieutenant and right hand man, Aurelian, who would succeed him as Emperor, to clear out the persisting remnants of this Gothic horde from the Empire, it would be Claudius who was remembered as the Emperor who saved Rome from the Goths in the mid-Third century A.D. In 270 AD Claudius was struck down by the plague, caught from the desperate remnants of the defeated Goths. Claudius reigned for barely two years, yet in that time he had brought the Empire from the brink of extinction and set it to the road of recovery that would be completed by Aurelian and his successors. Unlike most Emperors of this period, his death was genuinely mourned - by all - including the Senate, the People and this troops. His memory was so revered, the Senate deified him and erected a great golden statute of him in the Temple of Jupiter Optimums Maximus. A generation later, one of Rome's greatest ever Emperors, Constantine the Great would, to enhance his own prestige, claim spurious descent through his grandmother, from Claudius II Gothicus. In 1926 an incredible archaeological find at Brescia Italy unearthed a bronze bust believed to be that of Claudius. Images of Emperors from the period of the Imperial Dark Age are very rare compared to the number we have from earlier centuries, indeed for many we have no sculptured image at all. In the Claudius bronze we see a fleeting glimpse of the typical persona of these tough, war weary mid-Third century Emperors; closely cropped military haircut, short stubble beard, formidably grim.*

*We face many crises in the Emergency Department. Frequently we will be called on to perform painful duties. By our use of the opioid alfentanil, we recall the great Emperor Claudius Gothicus, saviour of Rome. Our allotted time will only be very brief - yet in that short time we have at our disposal a most powerful and effective agent!*

# ALFENTANIL

## Introduction

**Alfentanil** is a potent *synthetic* mu-opioid receptor agonist analgesic drug.

It is an analogue of the synthetic opioid *fentanyl*.

Compared to fentanyl, an equivalent dose of alfentanil has:

- A quicker onset of action
- A quicker time to maximal effect
- **A shorter duration of action**
- Around 1/10 the potency of fentanyl (on a *weight* basis)
- **Less cardiovascular instability**
- **Possibly more respiratory depression.**

Alfentanil is primarily used for:

- **Adjunctive analgesia during anaesthetics**
- **Stand alone sedation for short painful procedures in the Emergency Department.**

**See also separate Documents on:**

- **Opioid Overdose (Toxicology Folder)**
- **Naloxone (Drugs Folder).**

## History

Fentanyl was synthesized by the Belgian pharmacist, **Paul Janssen** in 1960. Janssen developed fentanyl by assaying analogues of the structurally related drug pethidine for opioid activity.

Following **Janssen's discovery**, many other **fentanyl analogues** were developed and introduced into medical practice, including **alfentanil, remifentanil** and **sufentanil.**

**Alfentanil** was developed at Janssen Pharmaceutica in 1976. It is a shorter acting derivative of fentanyl and is primarily used for analgesia *during anaesthesia.*

## 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**<br><br>Subtypes include:<br>$\mu_1$, $\mu_2$, $\mu_3$ | **Endorphins** | Brain: The highest concentration is found in the limbic system.<br><br>Spinal cord<br><br>Peripheral sensory neurons<br><br>GIT | Analgesia/ physical dependence<br><br>Respiratory depression/ miosis/ Euphoria/ reduced GIT motility/ physical dependence<br><br>Possible vasodilation |
| **Kappa**<br><br>Subtypes include:<br>$\kappa_1$, $\kappa_2$, $\kappa_3$ | **Dynorphins** | Brain:<br><br>Spinal cord<br><br>Peripheral sensory neurons | Analgesia/ convulsant effects/ dysphoria/respiratory depression/ reduced GIT motility |
| **Delta**<br><br>Subtypes include:<br>$\delta_1$, $\delta_2$ | **Enkephalins** | Brain:<br><br>Peripheral sensory neurons | Analgesia, (less than mu) |

The endogenous opioids include:

- Dynorphins
- Enkephalins
- Endorphins
- Endomorphins
- Nociceptin.

## Preparation

Ampoules:

- 1 mg / 2 mL
- 5 mg/10 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-fibre 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

Alfentanil is most active at the **mu receptors**.

## Pharmacodynamics

Alfentanil shares most of the actions of the opioid group.

**It has a short duration of action (around 10 minutes, after a single bolus dose of up to 10 micrograms/kg)**

It has 1/10 the potency of fentanyl (on a *weight* basis)

Therapeutic effects include:

1. Analgesia
2. Sedation
3. Anxiolysis
4. Induction of anaesthesia.

## Pharmacokinetics

*Absorption:*

- Alfentanil is administered IV, either by intermittent boluses or by continuous infusion.

  Other routes of administration *have not been evaluated.*

- Onset of action: [2]
  - ♥ The IV onset of action of alfentanil is at least twice as rapid than that of an equianalgesic doses of fentanyl
  - ♥ The maximal analgesic (and respiratory depressant) effect occurs within just **1-2 minutes.**

*Distribution*

- The Vd varies from 0.4 to 1.0 L/kg, which is approximately one-quarter to one-tenth that of fentanyl, indicating a limited distribution to the tissues.
- The small volume of distribution is also attributable to the limited liposolubility and strong plasma protein binding of the drug, (92 % mainly to $alpha_1$-acid glycoprotein).

*Metabolism and excretion:*

- Alfentanil is metabolised mainly in the liver with only 1% of the active substance being found unaltered in the urine.

## Indications

*Indications in the ED include:*

- **Adjunctive analgesia during anaesthetics for short duration procedures.**
- **Stand alone sedation for short painful procedures in the Emergency Department.**

*Indications outside the ED include:*

- **Adjunctive analgesia during anaesthetics for longer duration procedures, where it may be given as a continuous infusion.**

- In higher doses an induction agent, (although currently it is not generally used for this purpose).

## Contra-indications/precautions

Alfentanil, being an opioid, shares most of the contra-indications and precautions of this group of drugs:

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 apnoea

2. CNS:

   - Patients with a depressed conscious state.

3. CVS:

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

4. Hepatic impairment:

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

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

6. 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. 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 alfentanil, (rare).

*Pregnancy*

Fentanyl is classified as a **category C** Drug with respect to pregnancy.

Category C 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. [1]

*Breast Feeding:*

Compatible, in occasional doses

## Adverse Effects

Alfentanil, being an opioid, shares most of the adverse effects of this group of drugs:

Adverse effects include:

1. CNS:

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

  **This is a principal 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 principal cause of death in overdose/ toxicity.**

- **The risk is dose related and synergistic with other CNS depressants, including alcohol**

- Alfentanil may cause **stronger respiratory depression** than other synthetic opioids.

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

4. CVS:

- Hypotension:
  - ♥ Usually with larger doses, IV and rapid administration
  - ♥ Orthostatic hypotension in ambulatory patients.
  - ♥ Alfentanil tends to cause **fewer cardiovascular complications** than other synthetic opioids such as fentanyl and remifentanil.
- Bradycardia:
  - ♥ Usually with larger doses, IV and rapid administration

5. Allergic reactions:

- Uncommon.
  - ♥ Synthetic opioids are often used in those who have significant allergy to morphine.
  - ♥ Direct histamine release reactions is rare for synthetic opioids (as opposed to morphine where this is much more commonly seen).

6. Urinary retention:

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

7. Muscle rigidity:

- The incidence and severity of muscle rigidity is usually **dose related.** The higher the dose the more likely muscle rigidity will be.

## Dosing

*Spontaneously breathing patients for procedural sedation of short duration (< 10 minutes):*

The usual single **IV** bolus dose is around **5 - 7 micrograms/ kg slow IV-** so for an average **70 kg** adult, this is around **350 - 500 micrograms.**

Repeat doses of **2- 3 micrograms/kg IV** may be given 10 - 15 minutely as required, but patients must be closely monitored for apnoea.

**Doses of around 8 mcg/kg IV and above are much more likely to result in respiratory depression/ apnoea.**

*Anaesthetic induction:*

Higher doses can be given for **anaesthetic induction** or to **ventilated** patients.

For anaesthetic induction the dose range is: **10 - 20 mcg/ kg IV**

*Use in anaesthesia:*

Some **anaesthetists** may use alfentanil in higher doses **10 - 50 mcg/ kg IV** [5] or as an infusion for more prolonged effects in intubated and ventilated patients requiring operations of durations longer than 30 minutes.

Higher induction doses, will give longer durations of action but greater suppression of respiration, requiring ventilation.

**For procedures longer than one hour a continuous infusion may be given, (though in these situations morphine or fentanyl are usually given).**

**Lower doses are used if other anaesthetic agents are also being given**

*Antidote:*

**Naloxone is the specific antidote for opioid toxicity/ overdose**

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

*References*


1. Alfentanil in Australian Medicines Handbook, Accessed August 2014.

2. Alfentanil in MIMs, 1 October 2012.

3. James R. Miner et al. Alfentanil for Procedural Sedation in the Emergency Department. Ann Emerg Med. 2011; 57:117-121.

   doi:10.1016/j.annemergmed.2010.08.010

4. Rapifen Product Information - Janssen -Cilag, 15 September 2014

5. Alfentanil in Life in the Fast Lane Website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