THE NORTHERN HOSPITAL

NALOXONE

"The Bather" oil on canvas, 1928, Pablo Picasso, Metropolitan Museum of Modern Art.

On his knees, and with his chin level with the top of the table, Stephen watched the male mantis step cautiously towards the female mantis.

She was a fine strapping green specimen, and she stood upright on her four back legs, her front pair dangling devoutly; from time to time a tremor caused her heavy body to oscillate over the suspending limbs, and each time the brown male shot back. He advanced lengthways, with his body parallel to the table top, his long toothed, predatory front legs stretching out tentatively and his antennae trained forwards: even in this strong light Stephen could see the curious inner glow of his big oval eyes.

The female deliberately turned her head through forty-five degrees, as though looking at him. "Is this recognition?', asked Stephen., raising his magnifying glass to detect some possible movement in her feelers. "Consent?"

The brown male certainly thought it was, and in three strides he was upon her; his legs gripped her wing covers; his antennae found hers and began to stroke them. Apart from a vibratory, well sprung quiver at the additional weight, she made no apparent response, no resistance; and in a little while the strong orthopterous copulation began. Stephen set his watch and noted down the time in a book, open upon the floor.

Minutes passed. The male shifted his hold a little. The female moved her triangular head, pivoting it slightly from left to right. Through his glass Stephen could see her sideways jaws open and close; then there was a blur of movement so rapid that for all his care and extreme attention he could not follow them, and the male's head was off, clamped there, under the crook of her green praying arms. She bit into it, and the eye's glow went out; on her back the headless male continued to copulate rather more strongly than before, all his inhibitions having been removed. "Ah", said Stephen with intense satisfaction, and noted down the time again.

Ten minutes later the female took off three pieces of her mate's long thorax, above the upper coaxial joint, and ate them with every appearance of appetite, dropping crumbs of chitinous shell in front of her. The male copulated on, still firmly anchored by his back legs.

"There you are cried Jack". "I have been waiting for you this quarter of an hour".

"Oh", said Stephen starting up. "I beg your pardon. I beg your pardon. I know what importance you attach to punctuality - most concerned. I had put my watch back to the beginning of the copulation," he said, very gently covering the mantis and her dinner with a hollow ventilated box. "I am with you now".

"No you aren't", said Jack. "Not in those infamous half-boots. Why do you have them soled with lead anyhow?"

At any other time he would have received a very sharp reply to this, but it was clear to Stephen that he had not spent a pleasant afternoon with the admiral; and all he said, as

he changed into his shoes, was, "You do not need a head, nor even a heart to be all a female can require".

Patrick O'Brian, "Master and Commander", 1970.

Following the Great War, Pablo Picasso enthusiastically embraced the new genre of Surrealism, but he did so in his own unique way. In his "Bather" of 1928 we see his arresting vision of a topless female bather sitting on a sun-drenched beach against the backdrop of a stunning Santorini like turquoise - blue sea. The work could certainly be called surreal, but it also contains vestiges of his pre-war period of Cubism in the sharp almost geometric lines of his figure. The true Surrealists, heavily influenced by Sigmund Freud, were preoccupied, indeed obsessed, with depicting the deepest levels of the subconscious mind. It is sometimes difficult to make any sense of Picasso's enigmatic works. He was a very great lover of women, but do we see in his "Bather" of 1928, some subconscious insecurities? The woman, at one level appears quite alluring, yet at the same time the startling praying mantis type head and stick like limbs suggest a certain perilous danger. What does it all mean? Should he approach, or should he retreat? We are left very uncertain!

Perhaps the eminent Dr Stephen Maturin, in his insightful observations upon Natural History, provides us with a glimpse into the Freudian subconscious of some females regarding their attitude towards the male of the species.....they are useful for just one thing!

The useful opioid antagonist, naloxone has been advocated for a range of toxic syndromes other than opioid toxicity, including for clonidine, benzodiazepines, alcohol, and even sodium valproate toxicity. Yet there is no consistent rationale at all as to why this very specific agent should be of any use in these diverse non-opioid syndromes. We may therefore take a lesson, from the male of the praying mantis species - it is indeed useful...but only for one thing!

NALOXONE

Introduction

Naloxone (trade name in Australia - "**Narcan**") is a pure opioid antagonist used for the reversal of the clinical effects of opioids.

It can be a life-saving antidote to opioid poisoning.

Naloxone is a well tolerated life-saving medicine with minimal/ no adverse effects, whose benefits outweigh any possible risks.

As such, on 1 February 2016, the Australian Therapeutic Goods Administration (TGA) made naloxone available (over the counter). [5]

This decision made Australia only the second country, after Italy (in 1995), to have naloxone formally available over the counter, although some individual states of the US also have this provision.

Take home naloxone programs are designed to help manage opioid overdose events in the prehospital setting.

These programs involve training potential overdose witnesses (typically opioid users, and their friends and families) in overdose response (including naloxone administration), and then prescribing and distributing naloxone to potential overdose victims for later use in an overdose situation.

Naloxone is on the World Health Organization's List of Essential Medicines, the most effective and safe medicines needed in a health system.

History

Jacob Fiszman (**Jack Fishman)** (1930 - 2013), was a Polish - American pharmaceutical researcher from Kraków. Along with **Mozes J. Lewenstein** developed naloxone in 1961.

It was approved for opioid overdose by the Food and Drug Administration in 1971.

Preparations

Ampoules:

- Naloxone 400 micrograms in 1 ml ampoule.

Pre-filled syringes:

- Naloxone 800 micrograms in 2 ml pre-filled syringe, ("minijet")
- Naloxone 2 mgs in 5 ml ampoule pre-filled syringe

Combination oral preparations:

Examples include:

- **Suboxone** (Buprenorphine and naloxone):

  Because of its marked first pass metabolism, naloxone administered orally or sublingually has no detectable pharmacological activity.

  However, when administered intravenously to opiate dependent persons, the presence of naloxone in Suboxone produces marked opiate antagonist effects and opiate withdrawal, thereby deterring illicit intravenous abuse.

- **Targin** (Oxycodone and naloxone):

  Naloxone in the targin formulation reduces local bowel function disorders such as constipation that typically arise during opioid analgesic treatment with e.g. oxycodone, due to its local competitive antagonism of the opioid receptor mediated oxycodone effect in the gut.

  Oral administration of naloxone is unlikely to result in clinically relevant **systemic** effects due to a pronounced first pass effect and its very low bioavailability via this route of administration (< 3%).

Mechanism of Action

Naloxone is a pure competitive antagonist at opioid receptors (mu, kappa and delta).

Pharmacodynamics

Naloxone reverses the clinical effects of opioids, including sedation, respiratory depression and so hypoxia due to these effects.

When naloxone is administered **IV,** the effects are usually apparent within **2 minutes**. The onset of action is only *slightly less rapid* when it is administered intramuscularly or subcutaneously. [6]

In general terms the duration of action is dependent upon the dose and route of administration (as well as the does and route of administration of the opioid), but it is usually in the region of 1 - 4 hours.

IM administration produces a **more prolonged effect** than intravenous administration.

Pharmacokinetics

Absorption:

- Naloxone can be given IV or IM or SC
- It may also be given in a nebulized form, as well as via an ETT.
- Naloxone has poor oral bioavailability, with virtually no systemic activity.

  It is however given orally as part of some specific combination medications such as suboxone and targin (see above)

Distribution:

- Following parenteral administration naloxone is rapidly distributed throughout the body.
- It is 50% protein bound.
- Naloxone crosses the human placenta.
- It is unknown whether naloxone is excreted into human breast milk.

Metabolism and excretion:

- It is metabolized in the liver
- It has a relatively short half-life of 60 - 90 minutes.

Indications

These include:

1. Reversal of CNS and respiratory depression caused by opioids, (either natural or synthetic).

   In *general* terms:

   - Respiratory rate < 8
   - Any hypoxia.
   - Significant GCS depression (<12)

2. Empirical treatment of coma though to be secondary to opioids

   - In addition to being potentially life - saving, a good response will be diagnostic (either wholly or in part) of an opioid cause for altered conscious state.

Contra-indications / Precautions

There are *no* absolute contraindications to naloxone.

A *relative* contraindication is its *unnecessary* use in opioid dependent patients who show mild toxicity only.

There will be a risk of withdrawal symptoms being induced, and/or aggressive agitation in some opioid dependent patients, making management in the ED problematic.

Adverse Reactions

In non-opioid dependent individuals naloxone is without adverse effects, even in large doses.

In opioid dependent individuals naloxone administration may result in significant **withdrawal symptoms.**

Pregnancy:

Buprenorphine is a category B1 drug with respect to pregnancy.

Category B1 drug are those drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.

There are limited published reports describing the use of naloxone in pregnancy, other than during labour. Naloxone crosses the placenta readily near term and fetal concentrations are higher than maternal levels due to lower protein binding in the neonate.

If naloxone therapy is indicated in the pregnant woman, it should never be withheld.

Breastfeeding:

Published information following the use of naloxone during breastfeeding has not been located.

Naloxone has a low molecular weight, which may pass into breast milk. However, due to the low oral bioavailability and negligible maternal serum levels after use, naloxone is unlikely to cause harm to the breastfed infant.

Naloxone is considered safe to use during breastfeeding, but monitor breastfed infants of opioid-dependent women for signs of withdrawal.

Dosing

Note that while naloxone may be life-saving it does not replace or negate the requirement for other supportive/ resuscitation treatments that may be required in any individual case.

IV / IM dosing:

In general terms:

- 400 micrograms IV or IM can be given initially.
- 100 micrograms IV or IM can be given to opioid dependent individuals to partially reverse opioid effects.
- Repeat doses can be given every 30-60 seconds as required, up to 2 mg. [2,3]

Patients given naloxone should be observed for at least 2 hours for possible re-sedation.

Larger doses may be required in cases of overdose of **partial opioid agonists**

Infusions:

Long acting opioids such as slow release morphine or methadone may require a **naloxone infusion.**

2 mg of naloxone in 100 mls of normal saline, will provide 100 micrograms in 5 mls. An infusion of 5-20 mls/hr can be commenced and then titrated according to effect.

Nebulized Naloxone:

Naloxone has also been shown to be effective in **nebulized** form. [4]

There are a number of advantages in this route of administration, including:

- When IV access is problematic
- Instead of administering multiple doses of naloxone for long-acting opiates, nebulized naloxone can provide a steady, low maintenance dose similar to an IV infusion but without the need for IV access.
- Nebulized naloxone in fact can be considered as a self-titrating medication! This is because as the patient awakens he/she will often pull off the nebulizing mask.

A disadvantage would include:

- Those patients who are particularly obtunded, where ventilatory effort is markedly depressed. Efficacy is less certain here, and parenteral therapy should be the first line treatment.

Commence with 1-2 mg naloxone made up to a volume of 4-5 mls with normal saline.

Therapeutic end points

In non-opioid dependent individuals naloxone can be given till the effects of opioids are fully reversed.

In opioid dependent individuals naloxone should be given sufficient to reverse dangerous CNS and respiratory depression, but full reversal of all symptoms is not necessary and may precipitate a withdrawal reaction.

The duration of action of naloxone induced withdrawal however is usually short (< 90 minutes)

Rebound Opioid Toxicity:

There is a possibility of rebound opioid toxicity due to the relatively short half-life of naloxone (mean, 60 min) compared with many opioids. Hence there is a need to monitor the patient and administer another dose of naloxone if required.

However, the evidence indicates that rebound toxicity is actually a rare (but not non-existent) phenomenon. [5]

Over the counter availability of Naloxone: [5]

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Take home naloxone programs are designed to help manage opioid overdose events in the prehospital setting. These programs involve training potential overdose witnesses (typically opioid users, and their friends and families) in overdose response (including naloxone administration), and then prescribing and distributing naloxone to potential overdose victims for later use in an overdose situation.

Training typically includes education on risk factors for opioid overdose, signs of opioid overdose, basic life support and overdose response, including resuscitation techniques, calling for an ambulance, administration of naloxone, and post-naloxone management.

To date, naloxone kits provided to trainees in Australian take-home naloxone programs have typically comprised between 2-5 minijets of naloxone 400 mg/mL plus intramuscular needles, swabs, gloves and instructional materials.

Jack Fishman, (1930 - 2013), date unknown, (Rockefeller University)

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