THE NORTHERN HOSPITAL

ADENOSINE

"The Rock of Doom", (from the Perseus Series), oil on canvas, 1885-88, Sir Edward Burne-Jones.

Further along the coast is the region of Samaria, the free town Ascalon, Ashdod, the two towns named Iamnea, one of them inland; and the Phoenician city of Joppa (present day Jaffa in Israel) This is said to have existed before the flood; it is situated on a hill, and in front of it is a rock on which they point out marks made by the chains with which Andromeda was fettered: here there is a cult of the legendary goddess Ceto.

Pliny the Elder, "The Natural Histories", Bk V; 69
77-79 A.D

In Sir Edward Burne-Jones's stunning "Perseus" series, we are told the story of Perseus' rescue of Andromeda, who was chained to the "Rock of Doom", to await her fate with the sea monster, the fearful Kraken. The work invokes one of natures' most primally hard wired emotions - an ancient evolutionary physiology, that imparts to sentient creatures a sense of "impending doom" – presumably as a result of eons of natural selection conveying a survival advantage to the species Homo Sapiens.

Quite interestingly this primal sense of doom can be induced pharmacologically by the rapid intravenous bolus injection of the naturally occurring purine nucleoside, adenosine. An important aspect in the administration of this drug will therefore be strong reassurance that this reaction is natural, short lived, and not harmful despite the sometimes intense sensation of doom it can elicit. In Sir Edwards' work the "Rock of Doom", we see Perseus, giving heroic reassurance to a terrified Andromeda, before he prepares to take on the Kraken!

Pliny the Elder in the First Century A.D described a local Phoenician cult that worshiped Ceto, a goddess of sea-monsters, and held that a rock off the coast of Jaffa ("Andromeda's Rock" seen above) was were Andromeda was chained to await her fate.

ADENOSINE

Introduction

Adenosine is a naturally occurring purine nucleoside.

It can be administered as a rapid intravenous bolus for the acute termination of re-entrant supraventricular tachyarrhythmias.

An unpleasant feeling of "impending doom" is often experienced with this drug. Although very uncomfortable to some patients, it is not harmful. Patients should be strongly reassured that the reaction is "normal", and not be feared.

It is an extremely safe drug when used appropriately, and extremely effective.

It has a number of important advantages over many other antiarrhythmic agents, including:

- A very short half-life, (seconds) - therefore any adverse reactions will be short lived.
- Its safety in VT
- Its relative safety in the hypotensive patient

History

Adenosine was introduced into clinical practice in the early 1990s, when it replaced verapamil as the preferred first line drug for the treatment of SVT.

Chemistry

Adenosine is a naturally occurring **purine nucleoside.**

It is widely found in nature and plays a critical role in many biochemical processes, most importantly as an energy transfer molecule in the form of adenosine triphosphate (ATP).

Classification

Adenosine is used clinically as an antiarrhythmic agent, but does not fit into the original 4 class classification designed by Vaughan- Williams

Some now classify adenosine (along with digoxin) as a "class V" antiarrhythmic agent.

Preparation

Adenosine as:

Ampoules:

- 6 mg/ 2ml

Mechanism of Action

The effects of adenosine are mediated by via its interaction with specific G-protein coupled **adenosine receptors.**

Adenosine activates acetylcholine sensitive K+ current in the atrium and sinus and A-V nodes, resulting in shortening of action potential duration, hyperpolarization and slowing of normal automaticity.

Adenosine also inhibits the electrophysiological effects of increased intracellular cyclic AMP that occur with sympathetic stimulation.

Because adenosine thereby reduces calcium currents it can be antiarrhythmic by increasing A-V nodal refractoriness.

Inhibition of action:

Methylxanthines such as theophylline and caffeine block adenosine receptors and so increased doses may be required in patients taking these agents.

Enhancement of action:

The effects of adenosine are enhanced in patients who are taking dipyridamole, which is an adenosine uptake inhibitor.

Carbamazepine can increase the degree of heart block.

Pharmacodynamics

Administration of an IV bolus of adenosine in humans results in transitory:

1. Slowing of the sinus rate
2. Slowing of AV nodal conduction velocity
3. Increase in AV nodal refractoriness
4. Peripheral and coronary vasodilation.
    - Continuous infusions result in hypotension.

Adenosine has a **very rapid onset** of action, at around just **10 seconds.**

It also has a **very short duration** of action, also of around just **10 seconds.**

Pharmacokinetics

Absorption:

- Adenosine must be administered by **rapid IV bolus.**

  It is a unique drug in that it requires rapid IV bolus to be effective.

  Slow administration results in the drug's rapid elimination even before its arrival at the heart!

Distribution:

- Adenosine very rapidly distributed to all virtually all cells
- The degree of protein binding is unknown
- It is unknown if adenosine is transferred across the human placenta
- It is unknown if adenosine is excreted into human breast milk.

Metabolism and excretion:

- Adenosine is eliminated with a half-life of **< 10 seconds.**
- It is eliminated by carrier-mediated uptake by most cells, including the vascular endothelium.
- Within cells it is then metabolized by adenosine deaminase.

Indications

In the absence of contraindications adenosine is first line therapy for the acute termination of re-entrant supraventricular tachyarrhythmias, (**SVT**).

It will not revert AF or atrial flutter, but will make the diagnosis more apparent by increasing the degree of A-V block and so can be very useful in this regard from a diagnostic point of view.

It is relatively safe to give in cases of VT and so it be a diagnostic aid for broad or narrow complex tachycardias in general.

If adenosine does not revert an SVT, the diagnosis of SVT may need to be reconsidered.

Adenosine is also used in some Radionuclide Perfusion Imaging protocols.

Contra-indications/precautions:

These include:

1. AF due to pre-excitation syndromes:

    - Adenosine is *absolutely* contraindicated in cases of AF (or atrial flutter) which is due to **pre-excitation syndromes**, due to its propensity to cause AV nodal block, and thus allowing unimpeded supraventricular transmission into the ventricles via aberrant pathways, with a consequent risk of the development of VT/ VF

2. Advanced heart block:

    - Adenosine is contraindicated in cases of second or third-degree heart block (without pacemaker) or sick sinus syndrome (without pacemaker).

3. Caution in patients with a predisposition to significant bronchospasm:

    - Asthma
    - COPD

    May cause bronchoconstriction lasting up to 30 minutes.

Pregnancy:

Adenosine is a class **B2** drug with respect to use in pregnancy:

Category B2 drugs 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 are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

There is limited information available describing the use of adenosine during pregnancy.

Intravenous administration of adenosine is unlikely to cause serious maternal or fetal harmful effects as the medicine has a short half-life and duration of action.

If adenosine is the medicine of choice, use the lowest effective dose for the shortest duration possible .

Breastfeeding:

Adenosine is safe to use in breastfeeding mothers.

Adenosine has a short half-life and duration of action. The medicine is also unlikely to be orally absorbed by breastfed infants.

Therefore, adenosine is considered safe to use during breastfeeding.

Adverse Effects

Adverse affects are relatively frequent, however are usually of a benign nature.

They include:

1. Transient bradycardias - even short periods of asystole

2. Transient sensations of **flushing** or **chest tightness**.

3. Transient psychic sensations, usually described as a sense of "**impending doom**".

    - This can be a very significant effect in some patients, and so it is important to strongly reassure patients, should this occur.

4. Bronchospasm in patients with asthma or COPD.

5. AF - this may occur if the SA and AV nodes are strongly inhibited.

    - This is important to recognize in patients who have **pre-excitation pathway** syndromes, where *further* adenosine could induce VT or VF.

Dosing

Adenosine is given by **rapid (i.e 1- 2 seconds) IV bolus** injection.

It is best given into a larger bore cannula placed with a large peripheral (e.g cubital fossa) vein.

Following the bolus injection, a bolus of 5 - 10 mls of normal saline is also given immediately following to ensure full delivery of the adenosine from the cannula.

All patients being adenosine should be on continuous ECG monitoring.

Many patients will experience intense feelings of impending doom with this agent.

It is important to explain to the patient (in *non-anxiety inducing terms*) that this reaction may be experienced before its administration and that it is a *normal* reaction of the drug. Should the reaction occur, strong reassurance is usually sufficient to allay patient anxiety.

Doses used are as follows:

- Adenosine is usually given as an initial **6 mg IV** bolus. It is given **rapidly** over **2 seconds.**

- If this is unsuccessful, then a second bolus of **12 mg** by rapid IV bolus injection can be given.

- If the 12 mg dose is ineffective (but well tolerated), then a further dose of **18 mg** may be given by rapid IV bolus injection.

Dose reductions:

The initial adenosine dose should be reduced to **3 mg**:

- In patients taking **dipyridamole** or carbamazepine.

- Patients with transplanted hearts, (due to denervation hypersensitivity).

- If being given by central venous access.

Dose increases:

Patients taking **methylxanthines**, (including those haven taken recent **caffeine**), will usually require increased doses to be effective.

One study has also shown that the ingestion of caffeine (an adenosine receptor blocker) within four hours significantly reduces the effectiveness of a 6 mg IV dose of adenosine. Higher doses of 12 mg will usually be required in these cases. [6]

Paediatric dosing:

Paediatric dosing is more complex.

The Australian Medicines Handbook recommends:

- *<1 month*, rapid IV bolus, initially 0.15 mg/kg

  Increase by 0.05 - 0.1 mg/kg every 1 - 2 minutes, if necessary.

  Maximum single dose 0.3 mg/kg.

- *1 month -1 year*, rapid IV bolus, initially 0.15 mg/kg

  Increase by 0.05 - 0.1 mg/kg every 1 - 2 minutes, if necessary.

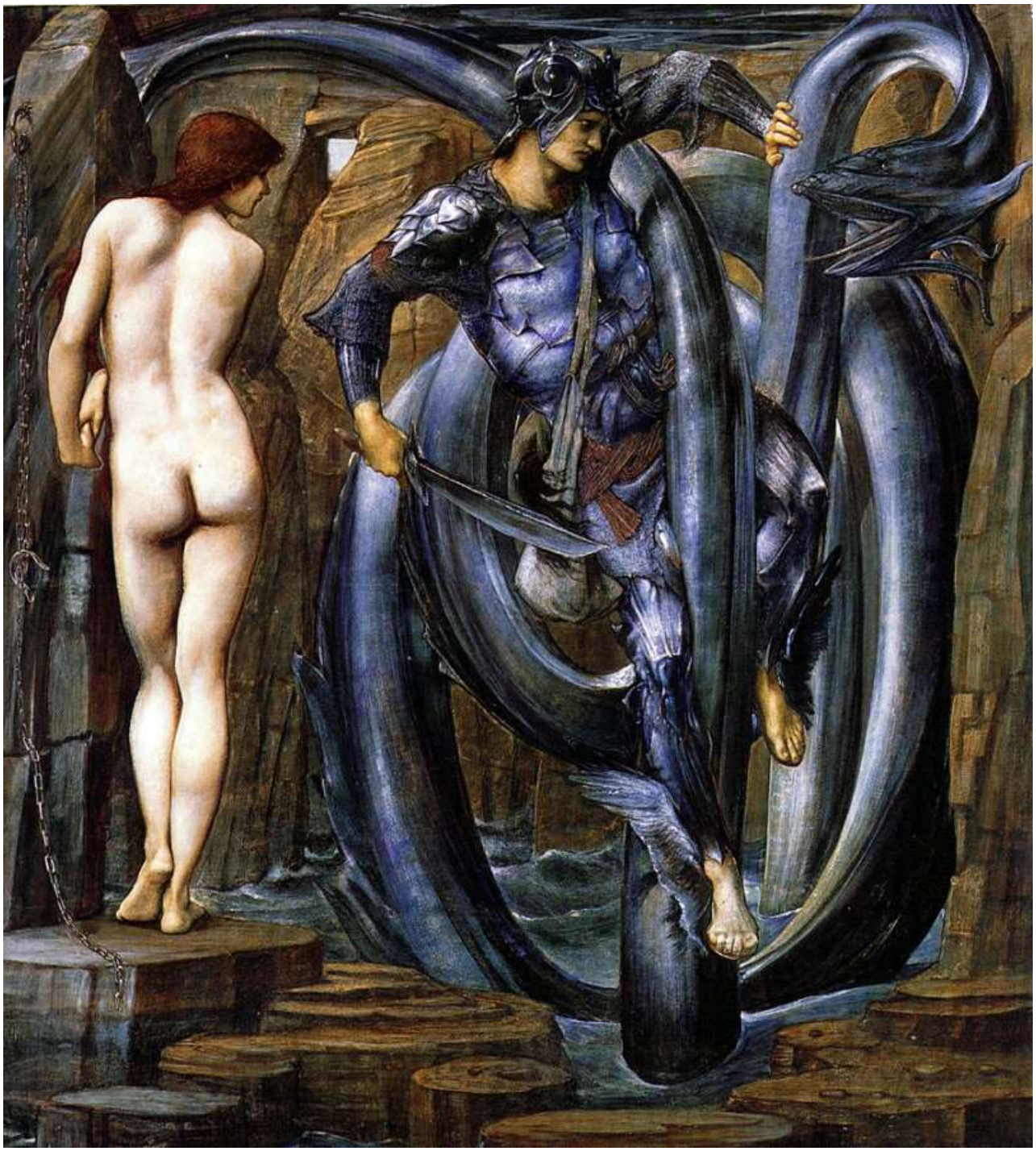
  Maximum single dose 0.5 mg/kg.

- *1–12 years*, rapid IV bolus, initially 0.1 mg/kg

Increase by 0.05 - 0.1 mg/kg every 1 - 2 minutes, if necessary.

Maximum single dose 0.5 mg/kg (dose not to exceed 12 mg).

Larger doses may be used after consultation with a paediatric cardiologist



"The Doom Fulfilled"(from the Perseus Series), oil on canvas, 1884-85, Sir Edward Burne - Jones.

Perseus does battle with the Kraken.

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