

VERAPAMIL



“The Vestal”, oil on canvas, c. 1882-83 Lord Frederick Leighton. Leighton House Museum, Kensington & Chelsea, London.

Originally there were four virgins who served the goddess Vesta. They were chosen by the king in accordance with the regulations which Numa established. Because of the numerous sacred duties which they perform, their number was increased to six, and six it has remained up to our own time. The virgins live in the sanctuary of the goddess, and none can be prevented from entering there in the day if he so wishes, but it is forbidden for any man to stay there at night.

The priestesses remain pure and unmarried for 30 years, offering sacrifices, and performing other religious rituals in the first ten years, and for the second ten years they perform them, and during the remaining ten years they must teach them to their successors. When the 30 years have been completed, nothing prohibits those who want to from putting aside their headbands and other insignia of their service and getting married. But only a few have done that, and their lives for their remaining years were neither enviable nor very happy. Therefore, taking what has happened to those unhappy few as a warning, the rest of the virgins remain in service to the goddess until their deaths, at which time another virgin is appointed by the priests to take the place of the one who has died.

They receive many splendid honours from the city, and therefore they do not want children or marriage. And anyway, there are heavy penalties for misbehaviour. Misdeeds are investigated and punished by priests according to the law. They whip those who have committed some lesser offence, but those who have lost their virginity are sentenced to a shameful and pitiful death. While they are still alive they are carried in a funeral procession. Their friends and relatives join the procession and mourn for them as though for someone deceased. They are taken as far as the Colline gate, and then interred alive in an underground cell which has been built within the walls of the gate. They are dressed in funeral clothes but they receive no monument or funeral offering or any of the other rites which are customary at funerals.

There are said to be many clues which indicate that a priestess who is performing a holy ritual is no longer a virgin, but the principle clue is that the fire goes out, something which the Romans fear more than all catastrophes, since they believe that whatever was the cause of the fire going out, it warns of the destruction of the city. They reintroduce the fire with many rituals of atonement.

*Dionysius of Halicarnassus,
The Roman Antiquities 2.67,
Late First Century B.C*

The tradition of the Vestal Virgins who dedicated their lives to the goddess Vesta in order to protect the city, is as old as the legendary founding, under Romulus and Remus, of Rome itself. Although the Romans, sacrificed goods and animals to the gods, they never had a tradition of human sacrifice as some other ancient cultures did. They did have one harsh ritual however the sacrifice of the virginity of six of the city's young women. These women held a very high and very respected place in Roman society, they were after all charged with the city's protection by the appeasement of the gods through their services to the goddess Vesta. Although they led a protected and extremely privileged life, this honour came at a substantial cost - they were to remain virgins for 30 years, so they could not

have their own children or marry. Whilst true that they were free to marry after their time of service, in the context of the times, they were “old” women by the time they were 45 years of age, and their fertility was doubtful as was their continued life span much beyond this age. Although living a life of privilege and luxury there always remained the threat of disastrous consequences if they did not strictly adhere the rules.

Plutarch in his history of Rome’s second king, Numa (10.3-7) painted an even more brutal picture for those who strayed than did the classic description recorded by Dionysius of Halicarnassus. He wrote:

“Numa bestowed great privileges upon them among which was the right to make a will while their father was alive, and to conduct other affairs without living under the control of a guardian...When they go out they are preceded by the lictors, and if they accidentally come across someone being led to execution he is not killed. But the virgin must swear an oath that the meeting was not deliberate and was by chance and not by design. One who passes under the litter on which they are carried is put to death.

The virgin’s punishment for other offences is being beaten. The Chief Priest administers the punishment when the offender is naked in a dark room with a curtain hung across it. But the one who has violated her vow of chastity is buried alive by the so-called Colline gate. In this place there is a ridge of earth inside the city that extends some distance. It is a mound or “choma” in the Latin language. There they construct an underground room, not large and having a way to get down from above. In it is placed a couch with coverings laid over it, a burning lamp and some small tokens of the necessities of life, such as bread, water in a bowl, milk, and olive oil. This is as if they would acquit themselves of the charge of destroying by hunger a body that had been consecrated to the greatest of holy rites.

Then they place the one being punished on a litter, and covering her over from above, they fasten her down with cords so that not even a cry would be heard from underneath, and they then carry her through the Forum. They all stand in silence and escort it without uttering a word, with a terrible downcast look. There is no other spectacle more horrifying, nor does the city endure any day gloomier than this. When the litter is brought to the place the attendants untie the cords while the Pontifex Maximus makes some secret prayers, and lifting his hands to the gods before the necessary act, leads her out veiled and places her on the ladder leading down into the chamber. Then he himself turns away, along with the other priests. When she has gone down, the ladder is lifted out and the chamber is covered over with much earth, plied over it from above, so that the place is level with the rest of the mound. This is the way in which those who disregard their sacred virginity are punished”.

The drug verapamil has a long tradition of use within the ED. Once widely used for a quite a number of indications, its use today remains far more restricted as other more effective and safer agents have been developed. Yet it still retains a second line role for a few indications, though there are strict rules on its use, and like the Vestal Virgins the consequences of operating outside of these rules, can be very harsh indeed!

VERAPAMIL

Introduction

Verapamil is a *non-dihydropyridine* calcium ion influx inhibitor.

In the **Vaughan-Williams** classification of antiarrhythmic drugs it is classified as a **class IV agent**.

Its principle uses in the **Emergency Department** include:

- Reversion of supraventricular arrhythmias:
 - ♥ Principally in cases where adenosine is contraindicated.
- Rate control of rapid AF
- Rate control of rapid Atrial flutter

Verapamil has a number of important contraindications and drug interactions.

See also separate Documents on:

- **Calcium Channel Blocker Overdose (Toxicology Folder)**

Chemistry

Verapamil is a non-dihydropyridine calcium channel blocking agent.

Classification

In the **Vaughan-Williams** classification of antiarrhythmic drugs verapamil is classified as a **class IV agent**.

Calcium channel blockers themselves can be classified into two principle groups:

1. **Dihydropyridines:**

The dihydro-pyridines act mainly on **arteriolar smooth muscle** to reduce peripheral vascular resistance and BP.

They have *minimal* effect on myocardial cells.

Examples include:

- Amlodipine
- Felodipine

- Lercanidipine
- Nifedipine
- Nimodipine
- Clevidipine

2. **Non-dihydropyridines:**

Non-dihydropyridines: act primarily on **cardiac** and **arteriolar** smooth muscle.

They reduce cardiac contractility, heart rate and conduction, with verapamil having the greater effect.

Diltiazem has a greater effect on arteriolar smooth muscle than verapamil.

Examples include:

- **Verapamil**
- Diltiazem

Preparation

Preparations include:

Tablets:

- **Immediate release** tablets: 40 mg, 80 mg, 120 mg and 160 mg
- **Slow release** tablets: 160 mg (caps), 180 mg (tabs), 240 mg (tabs or caps)

Ampoules:

- 5 mg/ 2 mL ampoules.

Mechanism of Action

Verapamil is a an **L-type calcium channel** blocking agent.

It blocks the *inward* current of *calcium* into cells in:

- Vascular smooth muscle:

- ♥ By its action on coronary arteriolar smooth muscle to reduce vascular resistance and myocardial oxygen requirements, it can relieve angina symptoms.
- ♥ By its action on vascular arteriolar smooth muscle to reduce vascular resistance, it can lower blood pressure
- Myocardium:
 - ♥ Negative inotropic effects
- Cardiac conducting system:
 - ♥ Negative chronotropic effects

Pharmacokinetics

Absorption:

- Verapamil can be given orally or IV.

With the *immediate* release formulation, more than 90% of the orally administered dose of verapamil is absorbed, however because of rapid biotransformation of verapamil during its first pass through the portal circulation, ultimate bioavailability ranges from only 20 - 35 %.

Distribution:

- Approximately 90% is bound to plasma proteins.

Metabolism and excretion:

- Verapamil is mostly metabolized in the liver (less than 5% is excreted unchanged) by **cytochrome P450 - 3A4** (abbreviated **CYP- 3A4**).

CYP- 3A4 is a member of the cytochrome P450 family of oxidizing enzymes.

Pharmacodynamics

Dilatation of main coronary arteries and arterioles, with reduction in total systemic resistance (afterload) and blood pressure

Prolongs the effective refractory period within the AV-node and slows AV conduction in a rate related manner.

Normal sinus rhythm is usually not affected, but in patients with sick sinus syndrome, verapamil may interfere with sinus node impulse generation and may induce sinus arrest or sinoatrial block.

Indications

Principle indications in the **Emergency Department** include:

- Reversion of supraventricular arrhythmias in cases where adenosine is contraindicated.
- Rate control of rapid AF
- Rate control of rapid Atrial flutter

Other indications outside of the ED setting include:

- Chronic hypertension.
- Chronic stable angina pectoris:
 - ♥ Including Prinzmetal variant angina.
- Prophylaxis of cluster headache
- Frequent benign extrasystoles causing distressing symptoms.
- Prophylaxis for cluster headache.
- Prophylaxis for migraine headache.

Contraindications/ Precautions

These include:

1. Hypotension, (contraindicated)
 - In general terms, a systolic BP < 90 mm Hg.
2. Cardiogenic shock, (contraindicated)
3. Bradycardia, (contraindicated)
4. Sick sinus syndrome (contraindicated)
5. Conduction delays, (contraindicated)
 - Second or third degree atrioventricular block without pacemaker,
6. Significant LV failure, (contraindicated)

- Calcium channel blockers may further depress myocardial function in patients with systolic heart failure.

Verapamil and diltiazem are generally contraindicated (unless under specialist supervision); dihydropyridines may be used with caution.

7. AF in patients with an accessory bypass tract, (contraindicated).

- e.g. Wolff-Parkinson-White, Lown-Ganong-Levine syndromes

8. VT, (contraindicated)

9. **Calcium channel blocker and Beta Blocker** interaction:

- The combination of beta blocker and calcium channel blocker *frequently* causes conduction delay problems in the *elderly*, especially in the presence of *renal impairment*.
- Calcium antagonists of the verapamil type should **not** be given by intravenous administration to patients treated with beta-blockers

10. **Grapefruit juice** should be avoided:

- Grapefruit juice is a well documented **inhibitor of the CYP - 3A4 enzyme**, which is involved in the metabolism of many commonly prescribed drugs.

By inhibiting the CYP - 3A4 enzyme, it can result significantly increased levels of verapamil in the blood and result in toxicity.

11. Known hypersensitivity to verapamil hydrochloride.

12. Caution in liver impairment.

Pregnancy

Verapamil is classified as a class C drug with respect to pregnancy

Class 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.

Breast feeding

Compatible

Adverse Effects

In general the dihydropyridines have more pronounced vasodilatory effects than diltiazem and verapamil.

Verapamil, (and to a lesser extent, diltiazem), reduce cardiac contractility, heart rate and conduction.

The important adverse effects include:

1. Hypotension
2. Negative inotropy
2. Bradycardia
3. Conduction delays
4. Myasthenia-like neuromuscular disease:
 - Calcium channel blockers in general may increase risk of muscle weakness and respiratory depression (most case reports are with verapamil).

Less severely:

5. Peripheral edema, (though *dihydropyridines* more commonly cause peripheral oedema due to redistribution of extracellular fluid - rather than fluid retention)
 - Note that this does *not* respond to treatment with diuretics, which may put patient at risk of volume depletion.
6. Constipation

Dosing

Hypertension/ Angina:

Immediate release tablet, adult:

- Initially: **80 mg 2-3 times a day then adjusted according to response.**

Once stabilized daily dosing can be converted to a slow release preparation.

Controlled release tablet, adult:

- Initially 180 - 240 mg once daily, increasing if necessary to a maximum of 240 mg twice daily, (i.e. 480 mg / day in total).

Give daily doses > 240 mg in 2 doses.

SVT:

Verapamil:

- **Initially 4-5 mg over 2-3 minutes, then titrate at 1 mg/minute IV, up to a maximum of 15 mg.**¹

Always give IV injections slowly under continuous ECG and BP monitoring

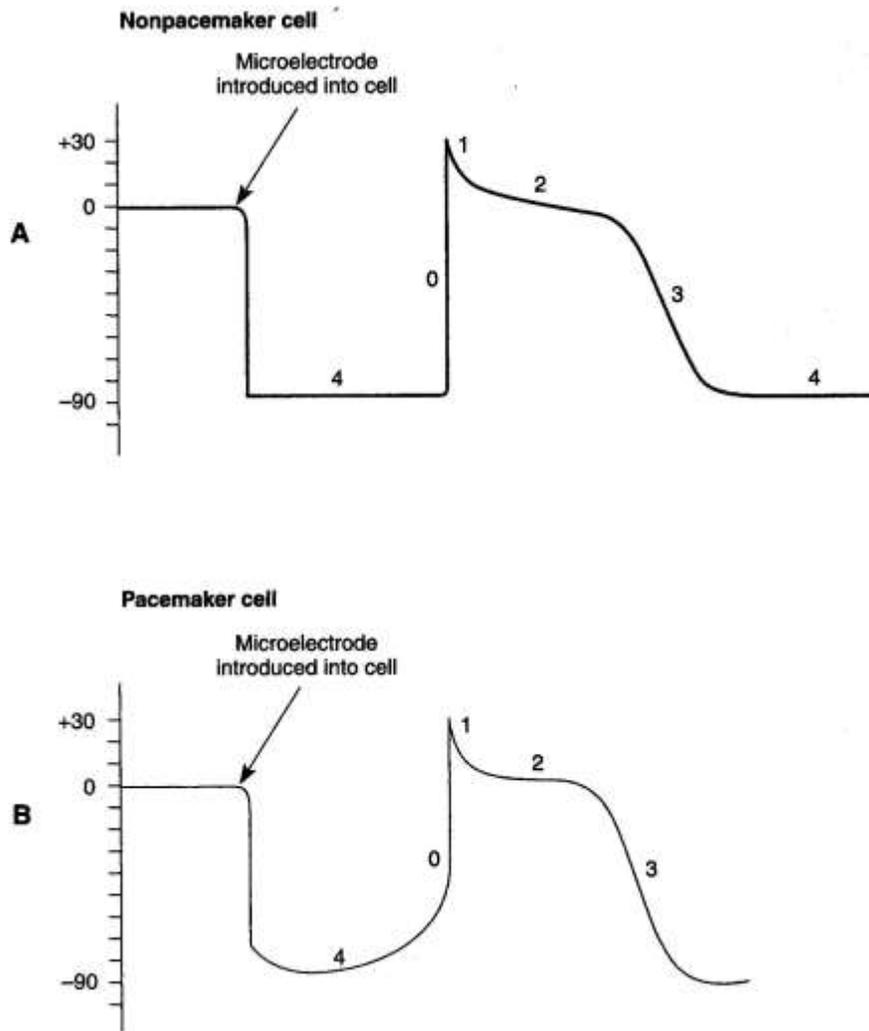
Excessively rapid IV administration may result in hypotension, bradycardia, heart block and asystole.

Rate control for AF/ Atrial flutter:

This may be achieved with IV dosing as above, but also more slowly via oral dosing in less urgent situations.

Appendix 1

Myocardial Action Potentials:



The pattern of action potentials from non-pacemaker cardiac cells and pacemaker cardiac cells.



“Portrait of a Vestal Virgin”, oil on canvas, c.1780-1785 Angelica Kauffmann, Museo Thyssen-Bornemisza, Madrid.

References

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