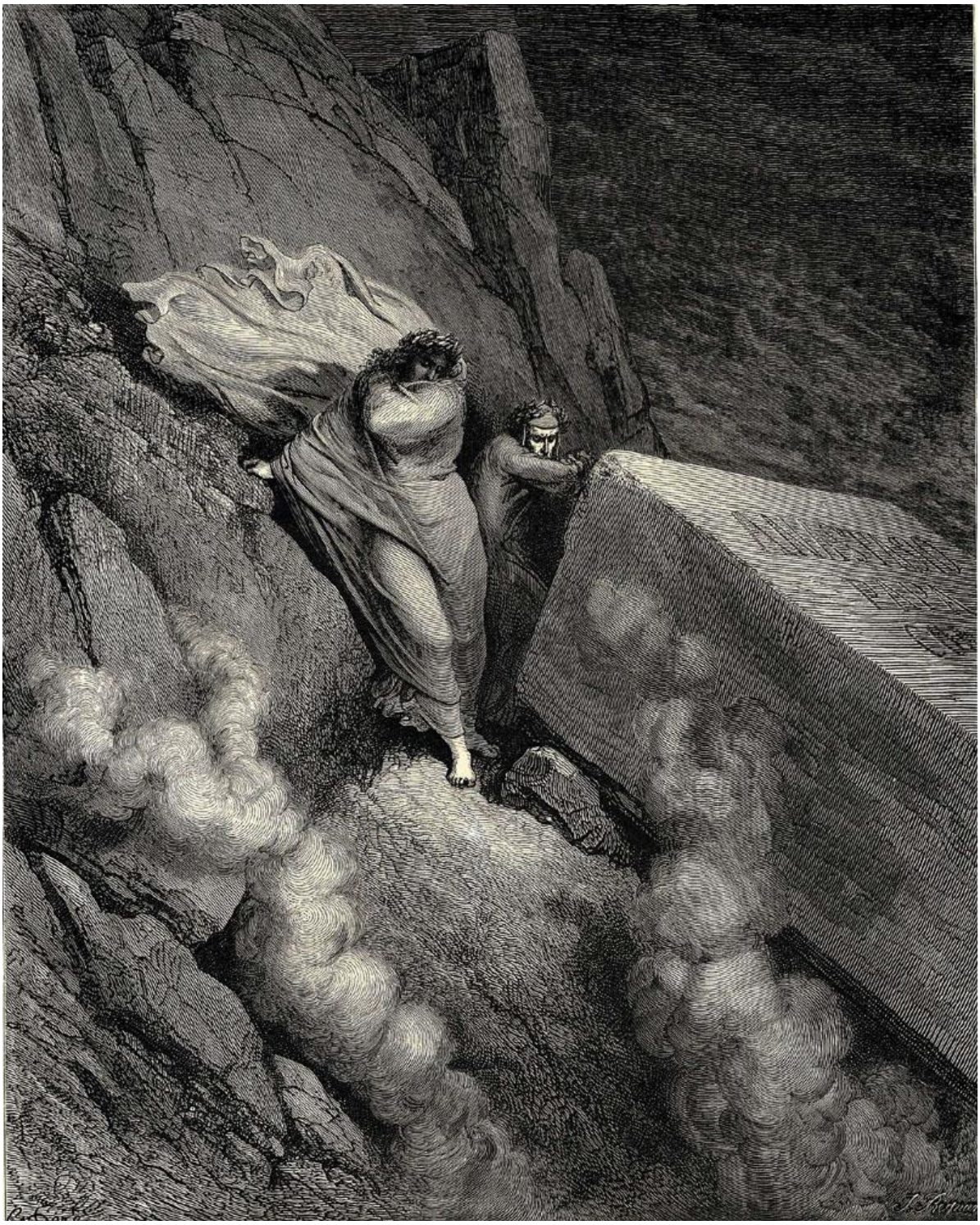
THE NORTHERN HOSPITAL

CARVEDILOL



"I hold Pope Anastasius...", woodcut print, 1867. Gustave Dore.

At the brink of a high bank formed
by broken boulders in a circle
we stopped above a still more grievous throng

Here, the unbearable foul stench
belched from the bottomless abyss
made us draw back behind the slab

of an imposing tomb, on which I saw inscribed
the words: "I hold Pope Anastasius:
Photinus drew him from the right and proper path"

"We must delay descending so our sense,
inured to that vile stench,
no longer heeds it...."

So spoke the master, I replied: "I know
you'll find a useful way to pass the time".
And he: "You'll see that is my plan".

"My son", he then began, "beneath these rocks
there are three circles, smaller, one below the other,
but otherwise like those you leave behind.

"All these are filled with souls condemned.
So that the sight alone may later be enough,
know how and why they are confined this way.

"Every evil dead despised in Heaven
has as its end injustice. Each such end
harms someone else through either force or fraud...

Dante Alighieri, The Inferno XI, 1-9 (1306-1317)

The early centuries of Christianity saw a great fluidity in beliefs and doctrines. A bewildering kaleidoscope of divisions and sects came and went as the new religion struggled to define itself. Differences in theological ideals created internecine conflict and tensions, in particular between the church authorities in Rome and those in Constantinople. One of the most contentious issues was that of "Monophysitism" versus "Dyophysitism", which led to the Acacian schism between the Eastern and Western Churches that lasted thirty-five years, from 484 - 519. The former doctrine decreed that Christ had but one combined "nature" - both human and divine, while the latter decreed that Christ had two separate human and divine "natures". The official doctrine held in Rome under the Popes was Dyophysitism, while in Constantinople Monophysitism held sway, under the Patriarchs.

Pope Felix III, dealt with the situation by excommunicating the Patriarch Acacius, which didn't particularly help matters. One of Felix's successors during the period of the schism, was Pope Anastasius II (496 - 498) who desperately tried to negotiate a compromise deal to fix the unbelievably complex theological mess that his predecessors had gotten themselves into. By the time of Pope Anastasius, the Western Roman Empire had fallen (476 A.D) and splintered into various barbarian kingdoms. Italy was ruled by a barbarian Ostrogoth, Theodoric, who was desperate to be recognized by the Eastern Emperor, also confusingly named Anastasius, (491-518). Both Pope Anastasius and Emperor Anastasius were keen for a rapprochement. As Pope Anastasius actually had a good relationship with Theodoric, the Emperor saw his chance. He would recognize Theodoric as King of the West, if in return the Pope would adopt a softer line on Monophysitism. The Pope was happy to accept this. But then another disaster reared its head - within Rome itself schism broke out - between the compromisers and the hard liners who would have no compromise all! When Pope Anastasius suddenly and unexpectedly died in 498, the hard liners gleefully saw his death as the rightful vengeance of God. The schism finally ended under the Emperor Justin I in 519. He was not a supporter of Monophysitism; the matter was settled, he agreed with Rome, Dyophysitism would be the accepted and universal orthodoxy.

History is written by the victors, and history has not been kind to the memory of Pope Anastasius II. Dyophysitism became the Christian orthodoxy, and by the Middle Ages Anastasius II had come to be seen as a heretic himself !- a harsh judgment for one who merely sought compromise to heal the impossible divisions within the church that existed at that time. Indeed millennia later Anastasius would have been a long forgotten footnote to one of the interminable and archaic theological quarrels of the early history of the church - if it wasn't for one most monumentally unfortunate fact- he was immortalized by Dante Alighieri in his great "Divine Comedy" as one of the Popes he encountered in Hell! And as if this wasn't enough, he was placed in one of the very worst places within it - in the Sixth circle, within the iron City of Dis, ruled by the rebel angels - a place reserved for heretics! As Dante and his guide Virgil approach this horrific realm, they are suddenly overcome by an unspeakable stench. It is the stench of rotting flesh. These heretics are forced to lie entombed "alive" in a stone coffin wallowing in their own corruption for all eternity. The stench is so overpowering that Dante and Virgil are forced to retreat and wait awhile in order to try and become at least a little acclimatized, before they attempt to continue their journey. One of these great stone coffins, Dante noted, contained Pope Anastasius II!

With regard to beta blocker use in patients with heart failure - there exists a medical schism between Emergency Physicians and Cardiologists! In the ED setting of unstable, acutely decompensated patients, beta blockade is a very great heresy! "Heart failure" to an Emergency Physician has quite a different meaning to the consulting room Cardiologist - acute pulmonary edema and cardiogenic shock are quite different entities compared to swollen ankles and an inability to complete one's shopping. In the latter situations, however there is a definite role for compromise, and certain beta blockers (but not all) will have some overall benefit, despite some increased risks.

CARVEDILOL

Introduction

Carvedilol is a non-selective beta blocker and an alpha 1 blocking agent, (similar to labetalol).

Beta-blockers are not usually recommended first line treatment of uncomplicated essential hypertension as they are associated with reduced protection against stroke in the elderly. [2]

Clinical trials have however demonstrated unequivocally beneficial effects of *some* **beta blockers** in **combination with ACEI** in patients with **heart failure and left ventricular systolic dysfunction.** [1]

This combination leads to improved left ventricular ejection fraction, reduced hospitalisations and reduced mortality, including reduction in sudden deaths.

The beta blockers which are recommended for adjunctive treatment in heart failure include:

- **Carvedilol**
- Bisoprolol
- Metoprolol succinate
- Nebivolol.

Patients already on a beta blocker for a comorbidity (e.g. angina or hypertension) should be switched to one of the beta blockers recommended for heart failure

Limited studies have not thus far shown benefit of beta-blocker therapy over placebo in patients with heart failure with **preserved** ejection fractions.

History

The Scottish pharmacologist, **Sir James W. Black** discovered the first clinically used beta blocker, propranolol in 1964.

He was awarded the Nobel Prize for Physiology or Medicine in 1988 for his work that led to the development of propranolol and cimetidine.

Carvedilol was developed by Fritz Wiedemann at Boehringer Mannheim and was initially approved in the U.S in 1995 for the treatment of patients with essential hypertension.

In May 1997, Carvedilol became the first adrenoreceptor-blocking drug to receive approval for the treatment of symptomatic heart failure.

Preparation

Preparations include:

Tablets:

- 3.125 mg, 6.25mg, 12.5 mg, 25 mg.

Physiology

Three types of beta adrenergic receptors are known, designated:

1. **Beta 1:**
   - These are located mainly in the heart and in the kidneys.

     In the heart they increase chronotropy and inotropy.

     They enhance lipolysis in adipose tissue.
2. **Beta 2:**
   - These are located mainly in the lungs, GIT, liver, uterus, vascular smooth muscle, and skeletal muscle. They result in smooth muscle relaxation.

     In blood vessels, they result in vasodilation.

     In the lungs they result in bronchodilation.

     In the GIT they reduce motility.
3. **Beta 3:**
   - These are located in fat cells

     These enhance lipolysis in adipose tissue.

Classification

Beta blockers may be loosely classified as:

1. Beta blockers with some intrinsic sympathomimetic activity (ISA).

   These agents are capable of exerting low-level agonist activity at the β-adrenergic receptor while simultaneously acting as a receptor site antagonist

Examples include:

- Pindolol

2. Non-selective blocking agents, (i.e block beta1 and beta2 receptors):

   Examples include:

   - Propranolol
   - Sotalol (this agent also has class III antiarrhythmic activity).
   - Timolol

3. Selective (B1) blocking agents:

   Examples include:

   - Atenolol
   - Bisoprolol
   - Esmolol
   - Metoprolol
   - Nebivolol

4. Alpha and non-selective beta Blocking agents:

   Examples include:

   - **Carvedilol**
   - Labetalol

Mechanism of Action

Carvedilol acts via:

- Beta 1 blockade
- Beta 2 blockade
- Alpha 1 blockade.

Pharmacodynamics

Carvedilol reduces the stimulant effect of catecholamines.

Effects include:

1. Decreased heart rate
2. Decreased cardiac contractility and cardiac output.
3. Reduction of blood pressure
4. Vasodilation via its beta 2 effects and alpha blocking effects.
    - Beta 1 blockade prevents reflex tachycardia.
5. Carvedilol has no intrinsic sympathomimetic activity
6. Like propranolol, it does have some membrane stabilising properties.

Pharmacokinetics

Absorption:

- Carvedilol is rapidly and extensively absorbed following oral administration.

  The absolute bioavailability of carvedilol is approximately 25%.

Distribution:

- Carvedilol is very highly bound to plasma proteins, primarily albumin (> 98%).
- Carvedilol is highly lipophilic; the volume of distribution is approximately 2 L/kg and is increased in patients with liver disease.
- In usual therapeutic dosing carvedilol is unlikely to accumulate during long-term treatment.

Metabolism and excretion:

- Carvedilol is extensively metabolised in the liver via the P450 oxidation enzymes and glucuronidation into a variety of metabolites which are mainly excreted in the bile.

Indications

These include:

1. Chronic systolic heart failure as part of standard treatment with ACE inhibitors, and diuretics. This is the principle indication for carvedilol.

Other generic beta blocking indications in general include:

2. Hypertension (adjunctive, rather than first line).

3. Angina

4. Tachyarrhythmias

5. Post MI

Contraindications/ Precautions

These include:

1. Significant sinus bradycardia, (< 45-50)

2. Shock states/ Hypotension

3. Significant conduction disease:

    - Second/ third degree heart block

    - Sick sinus syndrome, (sinus nodal dysfunction).

    First degree block is generally considered a relative contraindication - use with caution.

4. Supraventricular tachyarrhythmias due to **by-pass tracts:**

    - Blockade of the A-V node in situations such as WPW AF, by these agents will allow an unrestricted pathway via the bundle of Kent into the ventricles and risk the precipitation of VF.

5. Situations of compromised cardiac output:

    - Cardiogenic shock

    - Overt cardiac failure

    - **Right ventricular compromise:**

        ♥ Right ventricular failure secondary to pulmonary hypertension

        ♥ Significant right ventricular hypertrophy

6. Asthma/ COPD:

- Note that the use of "cardio-selective" beta-blockers can still result in significant bronchospasm in the predisposed, (i.e. asthma and COPD patients).

7. Known hypersensitivity to carvedilol.

8. Untreated alpha receptor stimulation:

Phaeochromocytoma:

- Patients with phaeochromocytoma should receive an alpha-blocking agent prior to beta-blocker administration to avoid severe hypertension.

Sympathomimetic drug overdose:

- **Note that beta blockers are contraindicated in amphetamine toxicity.**

  Beta-blockers are **not** recommended, as they will leave alpha effects unopposed. Treating with beta-blocker to control the heart rate will leave an unopposed alpha activity that aggravates vasoconstriction, (beta $_2$ effects are blocked).

9. Calcium channel 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. Patients with vasospastic disorders:

- Raynaud's syndrome (and similar)

11. **Prinzmetal angina** may be worsened by beta-blockers in general.

12. Patients with a history of anaphylactic reactions:

- Beta-blockers in general may prevent the therapeutic response to usual doses of adrenaline for anaphylaxis.

Pregnancy

Carvedilol is classed 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.

Breast feeding

Caution, insufficient data

Adverse Effects

The important ones include:

1. Bradycardia

2. Depressed cardiac contractility/ Hypotension

3. Conduction delays

4. VF in cases of supraventricular tachyarrhythmias due to **bypass tracts.**

5. Bronchospasm in predisposed (asthma/ COPD)

6. Allergic including **anaphylaxis** reactions may be exacerbated by beta-blockade, and are more difficult to treat with adrenaline

7. Beta-blockers may impair peripheral circulation in patients with pre-existing peripheral vascular disease.

8. Impairment of normal sympathetic responses:

   Beta blockers may reduce the normal sympathetic response to many illnesses and by so doing may mask underlying and potentially serious pathologies.

   Important examples include the masking of **early tachycardic** responses to:

   - Hypoglycaemia
   - Hypovolemia in general, including blood loss.
   - Infection and sepsis
   - Hypoxia in general, e.g. pulmonary embolism.

Occasionally less significant effects of oral therapy may include:

9. Lethargy/ fatigue

10. Disturbed sleep (nightmares)

Dosing

In general for beta blockers in heart failure, “start low and go slow”.

Use: [1]

- Commence carvedilol 3.125 mg orally, twice daily.

  Dose may then be doubled every 2 to 4 weeks providing the patient is stable, aiming to increase the dose to **25 mg twice daily.**

Patients with heart failure are often very sensitive to beta blockers.

Major complications of beta-blocker therapy in patients with heart failure include initial worsening of the failure, severe hypotension and bradyarrhythmias.

These complications are due to the drug blocking sympathetic nervous system support for the failing heart and can be minimised by: [1]

- **Not initiating beta-blocker therapy during a period of acute decompensation**
- Starting therapy with very low doses
- Increasing the dose very gradually
- Monitoring the patient frequently with symptom and daily weight monitoring
- Adjusting the dose of other drugs, such as diuretics and ACEI, to compensate for any tendency to increased heart failure.
- Avoiding simultaneous addition of vasodilator drugs.
- Avoiding concomitant use of diltiazem or verapamil.

References

1. eTG - November 2015

2. Carvedilol in Australian Medicines Handbook Website, Accessed January 2016.

3. Carvedilol in MIMs 1 October 2015.

Dr J. Hayes
2 September 2016.