THE NORTHERN HOSPITAL

NEBIVOLOL

General T.J "Stonewall" Jackson, "Winchester photograph", taken by Nathaniel Routzahn, November 1862. US National Archives.

He had the strange combination of religious fanaticism and a glory in battle. He loved battle. His eyes would light up. They called him "old blue light" because of the way his eyes would light up in battle. He was totally fearless, had no thought whatsoever of danger at any time when the battle was on, and he could define what he wanted to do. He said, "Once you get them running, you stay right on top of them, and that way a small force can defeat a large one every time". He knew perfectly well that a reputation for victory would roll and build.

Shelby Foote, Civil War Historian

The battle of First Manassas had reached a critical point. Union General McDowell had finally got his flanking divisions over Bull Run Creek at Sudley Springs. With Colonel Ambrose Burnside's Rhode Islanders leading the charge a great wall of blue, 13,000 strong crashed into the Confederate left. Colonel Evans charged with guarding the stone bridge, sulking at having been stationed so far from where the supposed main action was to be, was forced to take matters into his own hands without awaiting orders. Thinking that Burnside's move was a mere feint, he led his 1000 South Carolinians and Louisianans upstream to block the Union force. The clash was sudden and unexpectedly furious.

Though the Confederates had gained a temporary advantage by firing the first surprise volley, it quickly became apparent that McDowell was present in great force. Soon enough Evan's force began to take a terrible pounding. General Barnard Bee hearing the heavy fighting to his left, also without waiting for orders, rushed to Evan's assistance with his Mississippians, Alabamans, and Georgians. These fire-eating cotton state units suddenly found themselves at the very heart of the battle, and they were being thoroughly whipped by the Federals. On nearby Lookout Hill the Confederate high command, under Generals Joe Johnston and P.T.G Beauregard looked across the field in horror to see the left flank of their army disintegrating before their very eyes. They had not anticipated that McDowell would attack in force to their left. Johnston and Beauregard had lost control of the battle. All seemed lost.

At this crucial juncture, an obscure artillery commander from Virginia, named Thomas J. Jackson rushed forward his gun batteries and lined them up on a commanding ridge. Panicked Confederates fleeing the Union advance streamed past Jackson's unit, one officer screaming at him as he ran past, "General, the day is going against us!" and urged him to flee as fast as he could. But Jackson did not flinch. By now 18,000 Union troops had gathered, but still Jackson did not budge. Calmly he rode up and down his line of his artillery, calling out over and over, "Steady men, all's well, all's well". What McDowell's by now frenzied men, thinking they were on the verge of a great victory, did not realize, was that the greatest artillery commander of the Civil War stood directly in their path!

On they came now, a vast blue horde, but still Jackson urged his men to stand firm. "Hold your fire until there're right on us", he called out. "Then fire, and charge immediately and give them the bayonet! And when you charge, I want you to yell like furies!"

Just as the first Union line got to point blank range Jackson gave the order to fire. Great swathes of Union soldiers fell to the ground, their comrades coming up behind them now suddenly hesitating. Again and again Jackson's artillery poured a deadly fire into the oncoming ranks. The Union tsunami faltered then stopped. Jackson then displayed one of his innumerable idiosyncrasies. He put his arm up into the air and held it there in a brutal resolve, despite a bullet passing through it. Some thought his gesture was one of a signal to advance but others believed him to be praying!

One of the most famous scenes in military history then played out.

General Bee screamed to his fleeing men, "Stop, look men. There is Jackson standing like a stone wall!" His men gave wild cheers and the sobriquet stuck - T.J Jackson had become "Stonewall Jackson". So inspired was Bee, that he turned his men around and charged back into the Union lines being killed instantly by an enemy volley of musket fire. But now, led by the inspiration of Jackson and Bee, Confederate lines had reformed and consolidated. The dashing Cavalry commander J.E.B Stuart then led a counter-charge and slowly the Federals began to fall back. At this point Jackson's men joined Stuart's charge.

"Yell like furies" Jackson had told his men, and for the first time in the Civil War, the chilling banshee squall of the rebel yell was heard, that would be echoed over a thousand battle fields in the years to come.

The hesitant Union retreat suddenly became a panicked full scale rout. Meanwhile Confederate units on lookout hill, seeing the battle turning in Southern favor started to cheer wildly. Johnston began to poor every unit he had into the area. McDowell's army was defeated. Federals scrambled frantically back across the Potomac, then fled from the battle field, not stopping till they got to Washington. It was a complete Confederate victory. The First Battle of Bull Run had also seen the birth of two Southern Legends, JEB Stuart and Stonewall Jackson.

In cardiac failure the heart is assailed on all sides by hordes of catecholamines. The stress to which it is thus subjected will begin to take its toll. Final defeat will appear imminent. However by the use of a defensive artillery in the form of beta blockers, defeat may yet be turned to victory! These agents specifically block myocardial beta receptors. By taking up defensive positions upon these receptors they stand like a stone wall thus ensuring a heroic turning of the tide!

NEBIVOLOL

Introduction

Nebivolol is a selective B1 blocking agent

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.

Because of individual variation in rates of metabolism, the dose of nebivolol should always be adjusted to the individual requirements of the patient: poor metbolizers therefore may require lower doses.

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.

Chemistry

Nebivolol is a racemic mixture of two enantiomers, d-nebivolol and l-nebivolol.

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

Preparations

Nebivolol hydrochloride as:

Tablets:

- 1.25 mg
- 5 mg
- 10 mg

Mechanism of Action

Nebivolol is a selective B1 blocking agent

Beta$_1$-selective (cardioselective) beta-blockers have a higher affinity for **beta$_1$** receptors in the heart, with less effect on beta$_2$ receptors in bronchi and peripheral vasculature;

Beta$_1$-selectivity however diminishes with higher doses.

It has no intrinsic sympathomimetic activity, (some older beta-blockers were partial agonists).

Pharmacodynamics

Nebivolol reduces the stimulant effect of catecholamines.

Cardiac effects include:

1. Decreased heart rate

2. Decreased cardiac contractility and cardiac output.

3. Reduction of blood pressure

Nebivolol also has some mild vasodilatory properties mediated through **nitric oxide** release.

At doses up to **10 mg**, it is selective for the beta-1 adrenergic receptor, but at higher doses (and in poor metabolisers) it inhibits both beta-1 and beta-2 adrenergic receptors.

Pharmacokinetics

Absorption:

- Nebivolol is rapidly absorbed after oral administration

Distribution

- Protein binding is high, at around 98 %.
- It is unknown if nebivolol crosses the human placenta.
- It is likely that nebivolol is excreted into human breast milk in small amounts only

Metabolism and excretion:

- Nebivolol is extensively metabolised, partly to *active* hydroxy metabolites.

  The metabolism of nebivolol (by aromatic hydroxylation) is subject to CYP2D6 dependent **genetic oxidative polymorphism**.

  The approximate oral bioavailability of nebivolol averages 13% in **fast metabolizers** and is virtually complete in **slow metabolizers**.

At steady state and at the same dose level, the peak plasma concentration of unchanged nebivolol is about 23 times higher in poor metabolizers than in extensive metabolizers.

Because of individual variation in rates of metabolism, the dose of nebivolol should always be adjusted to the individual requirements of the patient: poor metabolizers therefore may require lower doses.

- In fast metabolizers, (**most people**) the elimination half-life of nebivolol is around 10 hours. [5]

  In slow metabolizers, elimination half-life of nebivolol up to 50 hours.

Indications

The principle indications for nebivolol include:

1. Hypertension
2. Chronic stable systolic heart failure, with reduced ejection fraction as part of standard treatment (e.g. with ACE inhibitors and diuretics)
3. Angina

Contra-indications/precautions

Contraindications and precautions to the beta blockers as a group 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. AF 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 the agent.

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

Nebivolol is 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.

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

Maternal use of beta blockers have not been associated with an increased risk of congenital malformations .

While a single case report of nebivolol use during pregnancy did not describe the presence of malformations in the infant, adverse neonatal outcomes such as hypoglycaemia, polycythemia and hyponatraemia were reported.

Therefore, due to the potential risk of intrauterine growth restriction and other adverse outcomes, nebivolol should be discontinued in early pregnancy and changing to an alternative medicine such as methyldopa or labetalol is recommended.

If nebivolol is the treatment of choice, monitor for possible adverse effects such as neonatal bradycardia, hypotension and hypoglycaemia, and intrauterine growth restriction

Breast feeding

Reports describing the use nebivolol during breastfeeding have not been located.

Small amounts of nebivolol have been found to be excreted in the milk of lactating animals.

The high lipid solubility and plasma protein binding of the medicine, suggests that small amounts of nebivolol are likely to be excreted into human breast milk.

Therefore, consider an alternative medicine where possible.

If nebivolol is the medicine of choice, observe the breastfed infant for signs of hypotension and bradycardia.

Adverse Effects

Adverse effects to the beta blockers as a group include:

1. Bradycardia
2. Depressed cardiac contractility/ Hypotension
3. Conduction delays
4. VF in cases of A.F 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

Usual adult dosing is:

Hypertension: [2]

Oral, 5 mg once daily.

> 65 years, CrCl < 30 mL/minute, moderate hepatic impairment (Child-Pugh class B), 2.5 mg once daily

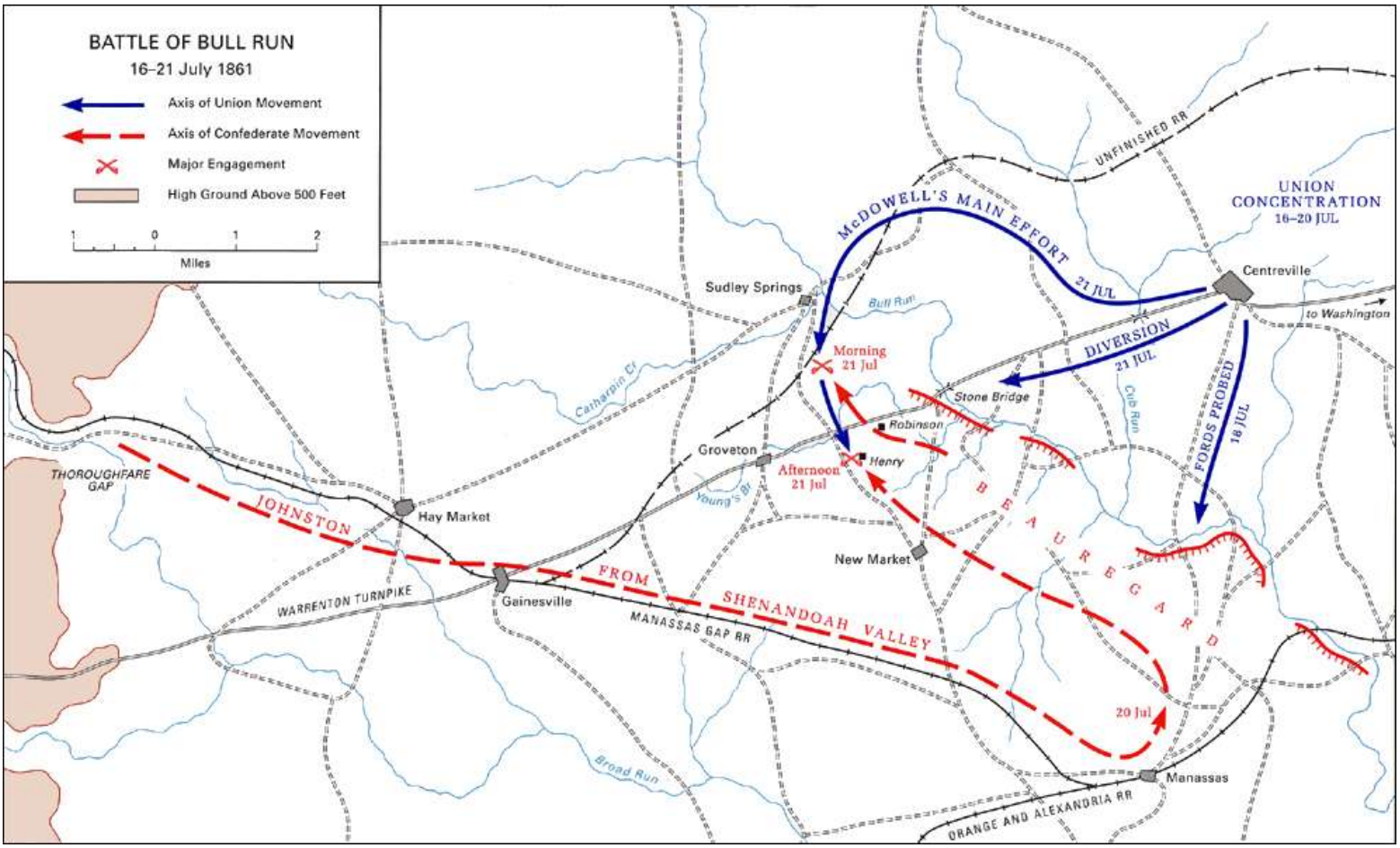
Increase if tolerated to 5 mg once daily.

Heart failure:

Oral, initially 1.25 mg once daily.

If tolerated, double the dose every 1 - 2 weeks to a maximum of **10 mg** once daily.

Stonewall Jackson monument, Manassas, Virginia.



References

1. eTG - November 2017
2. Nebivolol in Australian Medicines Handbook Website Accessed January 2018.
3. Nebivolol in MIMs Website, 1 June 2017.
4. Nebivolol in RWH Pregnancy & Breastfeeding Guidelines; 15 December 2017.
5. Nebivolol in Aust Prescr 2010; 33:52-91 Apr 2010
    - DOI: 10.18773/austprescr.2010.023

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