Chapter (11)

Selective Heart Rate-Lowering Agents

- The I$_f$ Current
- Ivabradine
Lowering of heart rate without any other direct cardiac effect offers several important advantages compared with most common treatment used in stable angina such as BABs or calcium channel blockers.

Preservation of left ventricular function-absence of negative inotropic effect makes this group of potential benefit for patients with left ventricular dysfunction and heart failure.

Unlike BABs, they preserve key parameters of cardiac adaptation to exercise, such as coronary vasodilation and increase in LV contractility.

**The \( I_f \) Current**

- Pacemaker cells in the heart have the unique ability to spontaneously generate slow diastolic depolarization that drives the membrane voltage away from the hyperpolarized level reached at the completion of one action potential towards the threshold level for initiating a subsequent action potential.
- Pacemaker activity involves the interplay between several ionic currents that influence the spontaneous diastolic depolarization of the sinoatrial node. They include \( I_f \) current and the calcium currents.
- \( I_f \) current is an ionic current that determines the slope of diastolic depolarization which in turn controls the heart beating rate.
- \( I_f \) current activation at the termination of an action potential controls the time intervals between successive action potentials.
- The channels responsible for the \( I_f \) current are known as HCN (hyperpolarization-activated, cyclic nucleotide-gated) channels.

**Ivabradine**

- The first specific heart rate-lowering agent to have completed clinical development for stable angina.
- A novel, effective and well tolerated antianginal drug.
- It is a specific and selective inhibitor of the inward \( f \) current (\( I_f \)) that contributes to the slow diastolic depolarization phase of the action potential in cardiac pacemaker cells and modulates heart rate.
- The high selectivity of ivabradine for \( I_f \) was associated with significant heart rate reduction while avoiding excessive bradycardia in healthy volunteers and patients with CAD.
- It restores the oxygen balance in the ischemic myocardium by reducing oxygen consumption.
- It has no peripheral effects.
- It has no depressant effect on cardiac conduction, LV function, or respiratory function and no deleterious influence on glucose and lipid metabolism.
- It does not show rebound phenomenon on treatment cessation.
Ivabradine was as efficient as atenolol in improving exercise capacity and reducing angina attack frequency in clinical trials.

Ivabradine is an effective anti-anginal and anti-ischemic agent, supporting the concept of specific and selective If current inhibition as a beneficial therapeutic strategy for patients with CAD and stable angina.

It can be a useful alternative in angina patients when BABs are contraindicated and for calcium antagonists in whom a decrease in blood pressure or in myocardial contractility would be undesirable.

**Dosage**

- There is dose-effect relationship, with efficacy at 5 mg twice daily and a further improvement at 7.5 and 10 mg twice daily, comparable to the effects obtained with atenolol 50 and 100 mg respectively.

**Other If current inhibitors (Investigational):**

- Zatebradine.
- Cilobradine.
REFERENCES AND SUGGESTED READINGS


15. Parker JO. Nitrates and angina pectoris. Am J Cardiol.1993;72:3C.


