

REVIEW ARTICLE



THE ROLE OF METOPROLOL SUCCINATE IN THE TREATMENT OF HYPERTENSION: A MINI REVIEW

Sanju Kumari*, Suneel Kumar Niranjana and Prabhakar

Institute of Pharmacy, Bundelkhand University, Jhansi-284128 (Uttar Pradesh), India

Received- 20/October/2020 Revised- 01/November/2020 Accepted- 08/November/2020 Published- 31/December/2020

ABSTRACT

The main risk factor for cardiovascular disease is hypertension. Approximately a third of people with hypertension are actually undiagnosed and about half of those diagnosed are not taking antihypertensive drugs. Every year, the World Health Organization (WHO) predicts that high blood pressure causes the death of at least nine million people worldwide, directly or indirectly. The β -adrenergic blocking agent Metoprolol has long been used to treat patients with hypertension.

KEYWORDS: Hypertension, Etiology, Hypertension diagnosis, Metoprolol succinate

Corresponding Author

Ms. Sanju Kumari,

Research Scholar, Institute of Pharmacy, Bundelkhand University, Jhansi-284128, (Uttar Pradesh), India

E-mail: san1857ju0581@gmail.com

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INTRODUCTION

In developed countries, the size of the elderly segment of the population is growing as the latter undergoes a demographic change with a concomitant rise in life expectancy. Indeed, it is estimated that most elderly people worldwide will live in developed countries by the year 2025^[1, 2]. In the near future, developed countries are therefore expected to face a massive burden of chronic non-communicable diseases.

Hypertension is one of the most significant treatable causes of mortality and morbidity in the elderly^[3] and accounts for a significant proportion of cardiovascular disorders in the elderly^[4-6]. Hypertension has been described by WHO^[7] as one of the world's most critical risk factors for morbidity and mortality and is responsible for the deaths of approximately nine million people per year. High blood pressure (BP), also referred to as hypertension, is characterised by the National Institute for Health and Care Excellence (NICE)^[8] in the UK, as a clinic blood pressure of 140/90 mmHg or higher confirmed by a subsequent ambulatory blood pressure monitoring daytime

average (or home blood pressure monitoring average) of 135/ 85 mmHg or higher. In older adults, high blood pressure does not only grow. In England, over 2.1 million individuals under 45 years of age had high blood pressure in 2015^[9]. This is important because hypertension treatment leads to a substantial reduction in the risk of subsequent cardiovascular disease^[10, 11].

Etiology

Blood pressure elevations in adolescents have also been correlated with etiological factors associated with hyper-tension in adults. Intrauterine malnutrition, a history of hypertension in the family, obesity, particularly excess abdominal fat, insulin resistance, high sodium dietary intake, low calcium, potassium and magnesium dietary intake, physical inactivity, high alcohol intake, tobacco use, drug use (e.g., cocaine, ecstasy, anabolic steroids), emotional stress, diet pill use, oral contraceptives are the factors associated with development of hypertension^[12, 13, 14]. Changes in foetal structure and metabolism can be programmed by insufficient nutritional supply, raising the risk of

hypertension and other diseases in later life [15]. The development of hypertension is also associated with hyper-insulinemia and insulin resistance, which contributes to several problems. Elevated levels of plasma insulin can trigger sensitivity to sodium [16, 17].

Adequate dietary intakes of potassium, calcium, and magnesium have been related to lower blood pressure in young people. Potassium and calcium intakes, especially in adolescent females, are below recommended levels, while median phosphorus and protein intakes, which encourage calcium loss, are high [18]. Lack of physical activity may increase the risk of developing hypertension by 20-50%.

Risk Factors

Having a personal family history of hypertension raises the risk that hypertension develops in an individual [19]. Essential hypertension in black people is four times more common than white people, speeds up faster and is often more severe with higher mortality in black patients. [19, 20, 21, 22]. Compared to average weight, obesity can increase the risk of hypertension by five times, and up to two-thirds of hypertension cases can be due to excess weight. In those with a body mass index greater than 25, more than 85% of cases occur [23].

Salt sensitivity, which is an environmental factor that has gained the most attention, is another risk factor. Around one-third of the critical hypertensive population is receptive to the intake of sodium [24]. The increased concentration of sodium ions activates the processes of ADH and thirst, leading to increased water reabsorption in the kidneys, concentrated urine, and thirst with higher water intake. In addition, contrary to this, the water movement between cells and the interstitium plays a minor role. There is debate about the relationship between sodium consumption and blood pressure. Blood pressure is lowered by lowering sodium intake, although the strength of the effect is insufficient to suggest a general reduction in salt intake [25].

Another risk factor is Renin's elevation. In a negative feedback loop, Renin is an enzyme secreted by the juxtaglomerular apparatus of the kidney and connected to aldosterone. As a result, some patients with hypertension have been identified as having low-renin and others have

critical hypertension. In African Americans, low-renin hypertension is more prevalent than white Americans and may clarify why African Americans appear to respond to diuretic therapy better than drugs that interact with the Renin-angiotensin system. By inducing sodium retention through the following mechanism, high levels of renin predispose to hypertension:

Increased renin: Increased angiotensin II
Increased vasoconstriction, thirst/ADH and aldosterone → Increased sodium reabsorption in the kidneys (DCT and CD) Increased blood pressure.

Insulin resistance and/or hyperinsulinemia, which are components of syndrome X, or metabolic syndrome, can also be the cause of hypertension. Some authorities also say that potassium could both prevent hypertension and treat it [26].

The risk factor for developing hypertension could also be smoking tobacco, a recognised risk factor for other cardiovascular diseases [27]. Many studies have shown that patients with hypertension and their children manage salt differently.

It is proposed that leucocytes of hypertensive patients are found to have decreased sodium pump activity due to the existence of a sodium transport inhibitor [28]. This contributes to increased intracellular sodium, resulting in high intracellular calcium that is responsible for increased vascular sound. Renal sodium excretion is impaired due to abnormal sodium handling, which leads to an increase in extracellular fluid volume, increased venous return, and increased cardiac production. Autoregulation contributes to vasoconstriction and elevated peripheral vascular resistance to achieve tissue perfusion. Salt restriction interrupts the pathophysiological chain of events by reducing the volume of extracellular fluid and reducing blood pressure, similar to diuretic therapy [29].

Hypertension Diagnosis

Ambulatory blood pressure monitoring (ABPM) is known to be the most reliable way to detect hypertension after an individual has been checked and found to have high blood pressure and is advised by recommendations to regularly confirm elevated blood pressure readings [30, 31, 32]. Usually, ambulatory monitors have compact, continuously worn, electronic cuffs that track blood pressure every 15-30 minutes during the

day and 15-60 minutes overnight. Due to cost and time constraints^[33], ambulatory monitors may not be available to many clinicians and patients, despite their usefulness in diagnosis, and may be inconvenient and disruptive to daily life and sleep^[34, 35]. Advances in technology have, however, made it possible to create new 'cuff-less' BP monitoring devices that continuously track BP without interrupting everyday activities.

Smartphone or wearable sensor technologies are used for Cuff-less BP monitoring systems that can estimate BP from ECG signals, photo plethysmogram (PPG) signals (using infrared light on the finger to estimate skin blood flow), or a combination of both^[36]. For example, a wearable wrist band to collect PPG signals, a wearable heart rate belt to collect ECG signals, and a smartphone are one established system. The signals from the wearable system connect with the smartphone through Bluetooth to synchronise their measurements and stream the blood pressure of the wearer continuously. Other devices that have been developed utilise sensors in T-shirts^[37], placed behind the ear^[38] and in a computer mouse^[39] to calculate and record blood pressure measurements.

As with screening, to help in diagnosis, the use of 'smartphone applications' is increasingly common. One US app usage survey found that 31% of mobile phone owners used their phone to check for health information, with the largest proportion (52%) among smartphone users. While this is a highly expanding area, with > 180 apps now available to measure blood pressure, there was some involvement of medical experts listed in its creation in only 3.8 percent (7/184) of the blood pressure apps, and very few apps were robustly evaluated^[40].

Moreover, at present, no mobile applications have earned formal approval from the US Food and Drug Administration or the European Commission for use as measuring/diagnostic devices. The American Heart Association (AHA) has reported that there are too many errors with mobile app-based blood pressure measurements with smartphone blood pressure apps^[41] that are unreliable four out of five times when one popular mobile app was checked^[40, 41].

The lack of a widely accepted standard for the validation of this technology, and existing

protocols clearly do not provide them, is a critical problem for both apps and novel non-invasive devices. There are attempts to fix this^[42] with some clinical validation apps^[43, 44] to make the future look better. At present, however, there is limited incorporation of this technology into widespread clinical practice as a result of this key issue^[41].

Prevention

Therefore, it is advised that all cases of hypertension should limit their consumption of sodium to approximately 6 Gms per day of sodium chloride salt or 2,4 Gms per day of sodium. To achieve this degree of sodium restriction, the following steps should be taken^[40]. a) Reduce salt for cooking by 50%. b) Substitute natural foods for processed foods. c) Avoid salty snacks such as pickles, chutneys, pappad, salted nuts. d) Use salt substitutes containing potassium. f) Avoid medications such as antacids as these are rich in salt. It is now agreed that reducing salt intake is an essential. The universal recommendation is to consume less than 10 Gms of NaCl per day. WHO recommends 5 Gms or less especially in populations known to have a high salt intake or a high prevalence of blood pressure^[45].

There is a sustained rise in blood pressure from chain smokers. So, smoking prevention is a must here. These are commonly practised for reducing tension. Meditation is not possible to date with any clear evidence in support of the benefits of yoga. Nevertheless, the availability of some regulated research, its overall cost efficiency and its lack of side effects make further yoga research a top priority. Clinically several clinical trials are in progress^[46]. A close link between obesity and hypertension has been shown by epidemiological studies. It is therefore very important to preserve the health of the body and to protect the body from obesity^[47]. Hypertension is avoided by maintaining good health and exercising regularly. It is really important to eat a healthy diet and control blood pressure.

Treatment

One of the medications used to alleviate hypertension is a beta-blocker. This works by making our heart beat with less intensity and more steadily, thus lowering blood pressure. But it is found that they are less effective than other therapies. Blockers of the calcium channel are

very beneficial because they prevent calcium from entering the heart and blood vessel muscle cells. This procedure enlarges the arteries and decreases blood pressure.

Metoprolol Succinate

Metoprolol was first made in 1969, patented in 1970, and approved for medical use in 1982 [48, 49]. It is on the World Health Organization's List of Essential Medicines, the safest and most effective medicines needed in a health system [50]. In 2017, it was the sixth most commonly prescribed medication in the United States, with more than 68 million prescriptions.

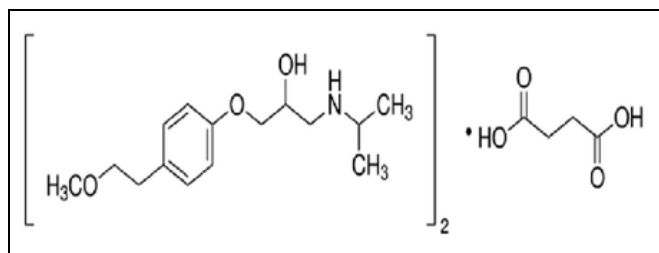


Figure 1: Metoprolol Succinate

Clinical Pharmacology

The beta-blocking role of metoprolol in humans has been confirmed by clinical pharmacology trials, as shown by:

1. Heart rate reduction & cardiac output at rest upon exercise.
2. Decrease of systolic blood pressure while exercising.
3. Isoproterenol-induced tachycardia inhibition.
4. Reflex orthostatic tachycardia reduction.

Pharmacokinetics

Metoprolol absorption in man is rapid and complete. However, plasma levels after oral administration of traditional metoprolol tablets are approximately 50% of the levels after IV administration, suggesting approximately 50% first-pass metabolism. Metoprolol crosses the BBB and, at a concentration of 78% of the concurrent plasma concentration, has been registered in the CSF. The levels of plasma achieved are highly variable following oral administration. Just a small fraction of the drug is bound to human serum albumin (approximately 12 percent). Metabolised mainly by CYP2D6. Elimination is mostly due to biotransformation in the liver and the half-life of plasma varies from around 3 to 7 hours.

Mechanism of Action

1. Competitive catecholamine antagonism at peripheral (particularly cardiac) adrenergic neuron sites, resulting in reduced cardiac production.
2. A main effect that contributes to decreased sympathetic outflow to the periphery.
3. Suppression of activity of renin.

Drug Interactions

When administered with beta-blocking agents, catecholamine depleting drugs (e.g., reserpine, monoamine oxidase (MAO) inhibitors) can have an additive effect. Watch patients treated with extended release tablets of Metoprolol succinate plus catecholamine depletion for signs of hypotension or marked bradycardia that can cause vertigo, syncope or postural hypotension^[51].

CONCLUSION

WHO has established hypertension as one of the most important risk factors for morbidity and mortality worldwide, and studies show that many people remain sub-optimally regulated despite good evidence for treatment. Therefore, innovative techniques, including new technology, are required to enhance the community's monitoring, identification, and management of increased blood pressure. The metoprolol succinate formulation has unique pharmacokinetic and pharmacodynamic properties that distinguish it from metoprolol and other β -blockers.

ACKNOWLEDGEMENT

Authors are thankful to Dr. Suneel Kumar Niranjana (Assistant Professor) Institute of Pharmacy, Bundelkhand University, Jhansi for his valuable suggestion in writing this paper.

CONFLICT OF INTEREST

None

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How to cite this article:

Kumari S, Niranjana SK and Prabhakar. "The role of Metoprolol succinate in the treatment of hypertension: a mini review". International Journal of Recent Research in Pharmacy (IJRRP), 2020; 1(1A), pp. 190-195.