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An Overview of Metoprolol

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ABSTRACT
Metoprolol is a common medication used by the elderly because it is affordable and has proven to decrease mortality in cardiovascular disease. Multiple studies have reported central nervous system (CNS) side effects associated with use of beta-blockers. The risk of b
We present the case of an 84-year-old male presented to the clinic complaining of increased confusion, fatigue, lightheadedness, nightmares, sleep disturbance, and gait problems for four weeks. The patient was evaluated for neurogenic and cardiogenic causes of his symptoms and both were ruled out. We believe that further review of his medical chart and medication reconciliation will lead us to the underlying cause of his symptoms.
Despite being an effective treatment option, there are risks associated with beta-blocker therapy. The most common symptoms are psychiatric conditions, bizarre and vivid dreams, sleep disturbances, delirium, psychosis, and visual hallucinations. Elderly patients who are started on beta-blockers require close monitoring for any adverse neurological symptoms.
KEYWORDS: Metoprolol toxicity, metoprolol side effects, CNS side effects, metoprolol therapy, bizzare and vivid dreams, sleep disturbances, delirium, beta-blocker side effects.

I. INTRODUCTION

Metoprolol is FDA-approved to treat angina, heart failure, myocardial infarction, atrial fibrillation/flutter, and hypertension. Off-label uses include supraventricular tachycardia and thyroid storm. Both oral and intravenous preparations are available. There are immediate and extended-release preparations available orally. There is controversy regarding the selection of beta-blockers in the management of the above conditions. There is also conflicting evidence regarding the optimal choice of a particular beta-blocker in treating each specific disease. This activity will highlight the mechanism of action, adverse event profile, pharmacology, monitoring, and relevant interactions of metoprolol, pertinent for members of the interprofessional team in the treatment of patients with conditions where it is of clinical value. Chronic heart failure is emerging as a major global health problem associated with structural or functional alterations of the myocardium involving adrenergic receptor stimulation and adrenergic system activation, leading to myocardial fibrosis and remodeling.1,2 Despite advancements in the management of CHF, the risk of morbidity and mortality remains substantially high, with a prevalence of approximately 5.7 million in the US and is expected to increase to 8 million by 20303 and over 4.2 million in China. Moreover, it puts a huge economic burden on the healthcare system as this chronic condition of CHF leads to poor quality-of-life (QoL)5,6 and loss of work productivity.

Beta-blockers remain the mainstay of treatment for patients with CHF because of their inherent property to counteract the sympathetic over-activity associated with left ventricular dysfunction, in addition to lowering the heart rate (HR), contractility, and blood pressure, thus lowering the mortality of CHF.2,8,9 The beneficial effects of beta-blockers are further supported by a meta-analysis of randomized control trials (RCTs) showing total reduction of mortality and heart failure-related sudden death in patients with CHF.

Metoprolol, a cardio-selective beta-blocker, has shown reduction in CHF mortality2 and improved QoL and mobility.12,15,16 However, this well-established beneficial effect of beta-blocker is associated with CNS side-effects such as depressionand anxiety,20 which are ultimately responsible for decreased QoL and increased risk of mortality among patients with CHF.However, some

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studies show contrasting results, with no increase in depressive symptoms.

In addition, it is unknown whether the neuropsychiatric adverse effects and increase in depression and anxiety in CHF are associated with metoprolol or are pre-existing but remain unnoticed during the initiation of the therapy, which places beta-blockers in a controversial position despite their well-established benefits. Furthermore, reduction in spontaneous motor activity was observed.

II. RESULTS AND DISCUSSION:

In this study, we explored the effect of metoprolol on change in cardiac function, motor function, QoL, and mental status of CHF patients with respect to gender, age, and different metoprolol doses. Our findings highlight that metoprolol treatment with respect to gender showed improved cardiac and motor function, better QoL, and increased depression but decreased anxiety scores. With regard to age, metoprolol treatment had shown improved cardiac and motor function and improved QoL with higher depression and decreased anxiety scores. Furthermore, there were no significant differences with different doses of metoprolol in cardiac, motor, QoL, and mental status in patients with CHF.

Gender-related differences in the pharmacokinetics of metoprolol are well established.24 In our study, a reduction in HR from baseline to 12 months was observed in both the genders. SBP was higher in women at all time points, and reduction in SBP was observed at 12 months. A similar pattern of responses was also reported in previous studies.16,25 Moreover, in our study, both EF and CI were similar between men and women. Motor function was evaluated using 6MWT and VSAQ scores, which are reliable tools to evaluate functional capacity and prognosis.26,27 In our study, metoprolol also improved the motor function of male and female patients with CHF. In both men and women, improvement in the QoL was observed as a biphasic response with both SF-8 and MLHFQ scales after metoprolol treatment. Previous studies using various questionnaires have also demonstrated improvement in QoL with metoprolol usage among patients with CHF.16,28,29

Neurohormonal dysfunction due to pathophysiological modifications caused by prolonged anxiety and depression can lead to cardiac abnormalities.30,31 In addition, symptoms of depression and anxiety are often unrecognized,32 which results in disease progression.33 Our study results demonstrated that metoprolol treatment increased the HADS depression scores and decreased the anxiety scores among both men and women.

In our study, in patients aged <60 and ≥60 years, significant and expected reductions in HR and SBP were observed; however, the reductions were observed only at 12 months of metoprolol treatment, and no changes were observed at baseline and 1, 3, and 6 months in both the age groups.

Cardiac function post-metoprolol treatment evaluated by EF and CI showed a biphasic response, with an initial decrease at 1 month and significant improvement of both EF and CI by 12 months in both the age groups (<60 and ≥60 years). This further confirms that the beta-blocker action of metoprolol on both EF and CI is independent of age.34 A study conducted by Neto et al35 also reported similar findings. Motor function evaluated by 6MWT and VSAQ also showed an initial decrease at 1 month and improvement by 12 months post-metoprolol treatment. This finding correlates with the decrease in cardiac function at 1 month as patients with CHF encounter myopathy of both cardiac and skeletal muscles,36 which further validated the deterioration of motor function in these patients.37,38

QoL after metoprolol treatment has also shown a similar trend as cardiac and motor function in patients with CHF, with an initial decline in QoL at the end of 1 month and subsequent improvement by 12 months. Patients with CHF are prone to anxiety and depression due to neurohormonal dysregulation,32 and evidence suggests that elders are more susceptible to depression and anxiety, which impact their QoL.39,40 Our study showed higher HADS depression scores, indicating improvement in depression, but lower HADS anxiety scores, denoting that patients with CHF express more anxiety, and higher CBI scores with better burn out status in both the age groups (<60 and ≥60 years).

In our study, we also examined the dose-mediated effect of metoprolol on cardiac, motor, QoL, and mental status of patients with CHF. A slight decrease in EF and no change in CI were observed with an increase in the dose of metoprolol. A study conducted by Zhang et al41 also showed no significant changes in the cardiac function with different doses of metoprolol. No dose-dependent changes with metoprolol were

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observed in motor function and QoL. However, a good correlation between QoL and clinical outcomes was reported by other studies.42,43 Metoprolol use in the treatment of CHF could worsen pre-existing depression or lead to depression.31 In our study, mental status measured with HADS depression, HADS anxiety, and CBI scores did not show much difference with dose increment of metoprolol.

The strength of our study was that we have provided comprehensive evidence involving the effect of gender, age, and metoprolol dose on cardiac, motor, QoL, and mental status of patients with CHF at baseline and 1, 3, 6, and 12 months. Our study also had certain limitations. First, we did not include a control group or use placebo to compare the outcomes with the treatment groups. Second, most of the questionnaires were self-administered instead of an interview-based method, which might have resulted in variances in responses. Third, we followed patients with CHF for 1 year, and thus, long-term mortality and metoprolol influence on different outcomes could not be captured. Finally, other confounding factors including age, sample size, and comorbidity medications taken could have influenced the study findings.

DRUG ADMINISTRATION

Drug formulations

A modified-release formulation of metoprolol has been associated with more skin reactions, probably due to the succinate component, instead of the tartrate component used in the old fast-acting formulation [5].

Drug overdose

In 2004, among 2.4 million cases of toxic exposure, 5.6% of all cases of adult poisoning were by cardiovascular medications. Poisoning with a beta-blocker usually results in cardiovascular and central nervous system effects. Acute myocardial infarction after poisoning with metoprolol has been reported in the presence of pre-existing coronary artery disease [6].

A 56-year-old woman with history of coronary artery disease took 15 tablets of metoprolol 100 mg. After 2 hours her blood pressure was 66/44 mmHg, heart rate 46/minute; she was disoriented and confused and reported chest pain. There was ST segment elevation and increased markers of cardiac damage. She had a 45% global ejection fraction and coronary angiography showed a 90% occlusion in the right coronary artery, an 80% occlusion in the left coronary artery, and a 40% occlusion in the circumferential artery.

MECHANISM OF ACTION

Metoprolol is a cardio selective beta-1-adrenergic receptor inhibitor that competitively blocks beta1 receptors with minimal or no effects on beta-2 receptors at oral doses of less than 100 mg in adults. It decreases cardiac output by negative inotropic and chronotropic effects. Metoprolol does not exhibit membrane stabilizing or intrinsic sympathomimetic activity. Administration of metoprolol to normal subjects results in a reduction in heart rate and cardiac output; this appears to be related to the dose and concentration of the drug. Metoprolol is mainly lipophilic, and its distribution is typical of a basic lipophilic drug. Based on animal studies, it appears to be almost completely absorbed from the gastrointestinal (GI) tract when taken orally.

There is significant hepatic first-pass elimination, which results in around 50% of the oral dose reaching the systemic circulation. It is 11% bound to serum albumin. The half-life of metoprolol is about 3 to 4 hours in most patients for non-extended release tabs. Metoprolol excretion principally occurs via the kidneys.[10] Metoprolol succinate produces more level drug concentrations as compared to metoprolol tartrate, which has more peak-to-trough variation. However, despite these differences in pharmacokinetics, studies have concluded that both agents produce similar clinical effects, both acute and chronic.

PHARMACOKINETICS AND PHARMACODYNAMICS

Administration of metoprolol in normal subjects is widely reported to produce a dose-dependent reduction on heart rate and cardiac output.1 This effect is generated due to a decreased cardiac excitability, cardiac output, and myocardial oxygen demand.6 In the case of arrhythmias, metoprolol produces its effect by reducing the slope of the pacemaker potential as well as suppressing the rate of atrioventricular conduction.7

The Metoprolol Atherosclerosis Prevention in Hypertensives (MAPHY) trial showed a significant improvement in sudden cardiac death and myocardial infarction when patients were given with metoprolol as compared with diuretics. As well, in clinical trials performed in 1990, metoprolol reduces mortality and re-infarction in 17% of the individuals when administered

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chronically after an episode of myocardial infarction.

Absorption

When metoprolol is administered orally, it is almost completely absorbed in the gastrointestinal tract.1 The maximum serum concentration is achieved 20 min after intravenous administration and 1-2 hours after oral administration. The bioavailability of metoprolol is of 100% when administered intravenously and when administered orally it presents about 50% for the tartrate derivative and 40% for the succinate derivative.5

The absorption of metoprolol in the form of the tartrate derivative is increased by the concomitant administration of food.5

Volume of distribution

The reported volume of distribution of metoprolol is 4.2 L/kg.5 Due to the characteristics of metoprolol, this molecule is able to cross the blood-brain barrier and even 78% of the administered drug can be found in cerebrospinal fluid.11

Protein binding

Metoprolol is not highly bound to plasma proteins and only about 11% of the administered dose is found bound. It is mainly bound to serum albumin.1

Metabolism

Metoprolol goes through significant first-pass hepatic metabolism which covers around 50% of the administered dose.1 The metabolism of metoprolol is mainly driven by the activity of CYP2D63 and to a lesser extent due to the activity of CYP3A4. The metabolism of metoprolol is mainly represented by reactions of hydroxylation and O-demethylation.9

Metoprolol

Alpha-Hydroxymetoprolol
O-Demethylmetoprolol
Deisopropylmetoprolol

Route of elimination

Metoprolol is mainly excreted via the kidneys. From the eliminated dose, less than 5% is recovered unchanged.1

Half-life

The immediate release formulations of metoprolol present a half-life of about 3-7 hours.1

Clearance

The reported clearance rate on patients with normal kidney function is 0.8 L/min. In cirrhotic patients, the clearance rate changes to 0.61 L/min.4

ADVERSE EFFECTS

Most adverse effects of metoprolol are manifestations of beta-adrenoceptor blockade. These include bradycardia, hypotension, AV block, and cold extremities. Particularly in patients with preexisting asthma or obstructive pulmonary disease, metoprolol may precipitate bronchospasm and should be avoided. Symptoms of congestive heart failure may be worsened if metoproolol therapy is initiated too aggressively in patients who remain compensated due to increased sympathetic tone. Rebound or withdrawal angina, hypertension, arrhythmias, myocardial infarction, and sudden death may occur upon abrupt discontinuation of metoprolol therapy. Metoprolol may be detrimental in vasospastic angina. By blocking catecholamine-induced glycogenolysis, beta-adrenoceptor antagonists may prolong, worsen, and mask several signs of hypoglycemia induced by antidiabetic drugs. However, as a beta-1 subtype selective beta-adrenoceptor antagonist, metoprolol would have less of an inpact on glucose metabolism than nonselective antagonists. Beta-adrenoceptor antagonists increase triglyceride, LDL, and VLDL cholesterol and decrease HDL cholesterol. Other adverse effects of metoprolol include sexual dysfunction, dizziness, fatigue, depression, sedation, vivid dreams, and sleep disturbances. Diarrhea is the most common gastrointestinal side effect reported with metoprolol Hutchison and Shahan .

DRUG-DRUG INTERACTIONS

INTEGRATE DRUG-DRUG INTERACTIONS IN YOUR SOFTWARE

Abacavir - Metoprolol may decrease the excretion rate of Abacavir which could result in a higher serum level.

Abaloparatide - The risk or severity of adverse effects can be increased when Metoprolol is combined with Abaloparatide.

Abatacept - The metabolism of Metoprolol can be increased when combined with Abatacept.

Abiraterone - The metabolism of Metoprolol can be decreased when combined with Abiraterone.

Acarbose -The therapeutic efficacy of Acarbose can be increased when used in combination with Metoprolol.

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METAPROLOL SIDE EFFECTS

Metoprolol side effects

Metoprolol oral tablet can cause certain side effects.

More common side effects

The more common side effects that can occur with metoprolol include:

- tiredness
- dizziness
- diarrhea
- constipation
- breathing problems such as shortness of breath, cough, and wheezing
- bradycardia (heart rate that's slower than normal)
- reduced interest in sex
- rash

If these effects are mild, they may go away within a few days or a couple of weeks. If they're more severe or don't go away, talk to your doctor or pharmacist.

Serious side effects

Call your doctor right away if you have serious side effects. Call 911 if your symptoms feel life-threatening or if you think you're having a medical emergency. Serious side effects and their symptoms can include the following:

- Low blood pressure (hypotension). Symptoms can include:
- severe dizziness
- light headedness
- fainting
- Cold hands and feet.

Symptoms can include:

- hands and feet that are cold and may be painful
- Very slow heart rate (severe bradycardia)
- Extreme fatigue.

Symptoms can include:

- feeling more tired than usual
- tiredness that gets progressively worse each day
- Serious depression.

Symptoms can include:

- continuous feelings of sadness or anxiety
- feelings of hopelessness or worthlessness
- lack of interest in hobbies you once enjoyed
- eating too much or too little
- trouble concentrating

TOXICITY

Treatment will vary based on the amount of metoprolol amount taken, comorbidities, age, and other co-investments. On arrival, assess ABCs and monitor appropriate blood work, including coingestants, ECG, large-bore IVs, and pregnancy status if female. Consult poison control/toxicology early in the course. Treatment choices include volume resuscitation, activated charcoal, whole bowel irrigation, nasogastric lavage, atropine, glucagon, calcium gluconate/calcium chloride, high-dose insulin, vasopressors, Intralipid, transcutaneous, or transvenous pacemaker. Cardiac status and a current fluid balance will guide volume resuscitation. Activated charcoal is typically given 1 g/kg and usually only has efficacy if dosed within 1 to 2 hours of ingestion. If the patient has any altered mentation, caution is necessary to the possibility of aspiration. Whole bowel irrigation should be a consideration for extended-release preparations or large-quantity ingestion.

Nasogastric lavage is usually ineffective, except for large-quantity ingestions. The clinician may consider atropine use, although it is typically ineffective in moderate-to-severe overdoses. Calcium administration to increase intracellular calcium at a dose of 60 mg/kg over 5 to 10 minutes of calcium gluconate. Calcium chloride at a dose of 10 to 20 mL of a 10% solution is an option if central access is obtained. Glucagon dosing is 50 mcg/kg as a bolus with titration of drip. High-dose insulin at a dose of 1 unit per kilogram bolus followed by 1 unit per kilogram per hour drip.

Administration with dextrose with a drip titrating to euglycemia as well as potassium repletion as needed. Vasopressors with epinephrine or norepinephrine titrated rate and blood pressure. Intralipid IV lipid emulsion therapy can serve as a lipid sink that extracts the drug from the myocyte. It may also provide free fatty acids as a substrate. It should be noted that the use of this medication will affect some laboratory monitoring. Consider a transcutaneous or transvenous pacemaker. Extracorporeal membrane oxygenation (ECMO) should be considered for refractory cases. If the clinician is concerned about intentional overdose, they should order a mandatory psychiatric evaluation. There may also be a need for the possibility of co-ingestants and treatment of those as well. For non-extended or non-sustained-release preparations, 4 to 6 hours of observation without any derangement of mental status or vital signs is sufficient. Any extended-release or sustained-release preparation requires 12 to 24 hours of

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telemetry observation, depending on the preparation. Extra caution should be considered in the pediatric population as very low amounts, including one pill or even one-half pill, can cause cardiovascular collapse and death.

III. CONCLUSION:

Gender-related differences were mostly observed in mental status after metoprolol treatment, suggesting that psychological response to metoprolol differs between men and women. Metoprolol has demonstrated age-independent improvement in cardiac function, motor function, and QoL, whereas an increase in depression and burnout as well as improvement in anxiety scores were observed. Up titration of metoprolol to target dose showed no significant difference in clinical outcomes.

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