A review on Nifedipine co-administered with Metoprolol succinate for the treatment of hypertension

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Abstract
Hypertension and Angina pectoris area major public health problem in the developed Countries recently. Hypertension and Angina Pectoris are frequently treated with antihypertensive drugs like calcium-channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin II (AT1) receptor blockers, and statins. Nifedipine is calcium-channel blockers and widely used in treatment of Angina pectoris condition. Metoprolol Succinate is Beta-adrenoceptor blocker and widely used in treatment of hypertension condition. Combination of Nifedipine and Metoprolol Succinate is used in the treatment of cardiovascular diseases like hypertension and Angina Pectoris. So this combination therapy gives antihypertensive and Angina Pectoris effects in the treatment of cardiac diseases.

Keywords: Nifedipine, Metoprolol Succinate, Antihypertensive, Angina Pectoris, Pharmacology, Combination Therapy.

1. Introduction
In recently, two major problems are being observed in among people like hypertension and Angina Pectoris. So, Nifedipine is used in combination with Metoprolol Succinate to treat hypertension and Angina Pectoris, respectively, in cardiovascular patients.

Nifedipine 4-(2'-Nitrophenyl)-2,6-dimethyl-1,4-dihydropyridin-3,5-dicarbonsauredimethyl ester is a peripheral and coronary vasodilator drug of the calcium channel blockers.[1] Nifedipine has been formulated as both a long- and short-acting 1,4-dihydropyridine calcium channel blocker. It acts primarily on vascular smooth muscle cells by stabilizing voltage-gated L-type calcium channels in their inactive conformation.

Nifedipine inhibits the influx of calcium (Ca2+) ions during membrane depolarization of cardiac and vascular smooth muscle. The therapeutic benefits of nifedipine in supraventricular tachycardias are related to its ability to slow AV nodal conduction time and prolong AV nodal refractoriness. Nifedipine converts paroxysmal supraventricular tachycardia (PSVT) to normal sinus rhythm by interrupting the re-entry circuit in AV nodal re-entrant tachycardias and reciprocating tachycardias, e.g., Wolff-Parkinson-White syndrome (WPW). Like other calcium channel antagonists, because of its effect on vascular smooth muscle, nifedipine decreases total peripheral resistance resulting in a decrease in both systolic and diastolic blood pressure.[2]

Metoprolol succinate, (1)-isopropylamino)-3-[p-(2-methoxyethyl)phenoxy]-2-propanol succinate type of anti-hypertensive drug. Metoprolol is a cardioselective β1-adrenergic blocking agent used for acute myocardial infarction (MI), heart failure, angina pectoris and mild to moderate hypertension. It may also be used for
supraventricular and tachyarrhythmias and prophylaxis for migraine headaches. Metoprolol is structurally similar to bisoprolol, acebutolol and atenolol in that it has two substituents in the para position of the benzene ring.[3] The β1-selectivity of these agents is thought to be due in part to the large substituents in the para position. At low doses, metoprolol selectively blocks cardiac β1-adrenergic receptors with little activity against β2-adrenergic receptors of the lungs and vascular smooth muscle. Receptor selectivity decreases with higher doses. Unlike propranolol and pindolol, metoprolol does not exhibit membrane-stabilizing or intrinsic sympathomimetic activity.[4]

2. Mechanism of action

2.1 Nifedipine

Nifedipine decreases arterial smooth muscle contractility and subsequent vasoconstriction by inhibiting the influx of calcium ions through L-type calcium channels. Calcium ions entering the cell through these channels bind to calmodulin. Calcium-bound calmodulin then binds to and activates myosin light chain kinase (MLCK). Activated MLCK catalyzes the phosphorylation of the regulatory light chain subunit of myosin, a key step in muscle contraction. Signal amplification is achieved by calcium-induced calcium release from the sarcoplasmic reticulum through ryanodine receptors. Inhibition of the initial influx of calcium inhibits the contractile processes of smooth muscle cells, causing dilation of the coronary and systemic arteries, increased oxygen delivery to the myocardial tissue, decreased total peripheral resistance, decreased systemic blood pressure and decreased after load. The vasodilatory effects of nifedipine result in an overall decrease in blood pressure.[5]

2.2 Metoprolol Succinate

Metoprolol competes with adrenergic neurotransmitters such as catecholamines for binding at beta(1)-adrenergic receptors in the heart. Beta(1)-receptor blockade results in a decrease in heart rate, cardiac output, and blood pressure.[7]

Metoprolol succinate decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses. In man, Metoprolol succinate prevents spontaneous and ergonovine-provoked coronary artery spasm. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. Such data have no predictive value with respect to effects in patients with poor ventricular function, and increased heart failure has been reported in patients with pre-existing impairment of ventricular function. Resting heart rate is usually slightly reduced by Metoprolol succinate. So the Metoprolol succinate is used in hypertension and angina.[9]

3. Combination Therapy

Assessment of the efficacy and tolerance of delayed-action nifedipine as the monotherapy or in combination with metoprolol in patients with arterial hypertension. Treatment with nifedipin-retard alone resulted in lowering of systolic arterial pressure. The combined treatment produced a more pronounced fall both in systolic and diastolic pressure. Diastolic left-ventricular function improved in combined therapy. Side effects observed in nifedipin-retard monotherapy got much more weaker when this drug combined with metoprolol.[10] Combination therapy with a beta-adrenergic blocking agent and dihydropyridine calcium antagonist is a logical approach to the treatment of stable angina pectoris. However, it is not clear whether, in individual
patient, this combined therapy is more effective than monotherapy.[11] A pharmaceutical dosage form for treatment of cardiovascular disorders suitable for once daily administration comprising a fixed dose combination of metoprolol in extended release form and one or more calcium channel blockers along with one or more rate controlling excipients. The once-a-day dosage form may be prepared by compressing a first layer comprising an extended release metoprolol along with one or more rate controlling excipients and a second layer comprising one or more calcium channel blocker, angiotensin receptor blocker or ACE inhibitor, one or more pharmaceutically acceptable excipients and, optionally with rate controlling excipient into a bi-layer tablet. In a further embodiment, the bi-layer dosage form is prepared by blending metoprolol with rate controlling excipient and other pharmaceutically acceptable excipients. The prepared blend was compressed to form a first layer. Onto this first layer a blend comprising calcium channel blocker, angiotensin receptor blocker or ACE inhibitor with one or more pharmaceutically acceptable excipients is compressed to form a bi-layer tablet. The present invention further provides a method of treating one or more disorders selected from heart failure, angina, myocardial infarction, arteriosclerosis, diabetic nephropathy, diabetic cardiomyopathy, renal insufficiency, peripheral vascular disease, left ventricular hypertrophy, cognitive dysfunction, and chronic heart failure, wherein the method comprises administering a pharmaceutical dosage form of the present invention to a patient in need of such treatment.[12]

Table 1: Pharmacokinetics profile of Nifedipine and Metoprolol Succinate

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Nifedipine</th>
<th>Metoprolol Succinate*&lt;sup&gt;[3,7,15]&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>Absorbed from the gastrointestinal tract</td>
<td>Absorbed from the gastrointestinal tract</td>
</tr>
<tr>
<td>Distribution</td>
<td>92-98%</td>
<td>70-80%</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hepatic metabolism via cytochrome P450 system</td>
<td>Hepatic metabolism via cytochrome P450 system</td>
</tr>
<tr>
<td>Elimination</td>
<td>Excreted in urine</td>
<td>Excreted in urine</td>
</tr>
</tbody>
</table>

4. Conclusion

Presented systematic review gives new combination approach for antihypertensive and angina pectoris drug treatment. In this first drug Nifedipine is 1, 4-dihydropyridine derivative used as Ca<sup>2+</sup> channel blocker, anti anginal and coronary vasodilator. Metoprolol succinate is a cardio selective β1-adrenergic blocking agent used for acute myocardial infarction, heart failure, angina pectoris and mild to moderate hypertension. It may also be used for supraventricular and tachyarrhythmias and prophylaxis migraine headaches. Combination of nifedipine-retard with metoprolol provides better clinical response and tolerance than monotherapy with nifedipine-retard.

Reference