

Anti-Hypertensive Potentiating Effects of Simvastatin on Amlodipine

Wajid Ali, Afsheen Siddiqi and Khadija Imran

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ABSTRACT

Objective: To determine the In vivo vasodilatory effect of simvastatin (Statin) in the presence of Amlodipine(Calcium Channel Blocker).

Study Design: Experimental animal study on rats

Place and Duration of Study: This study was conducted at the Department of Pharmacology, Ayub Medical College, Abbottabad from May 2015 to June 2016

Material and Methods: Hypertension was induced in rats by giving Depomedral TM injection subcutaneously (20mg/kg) of body weight for 1 week. For antihypertensive activity single dose follow up regimen of test drugs were used. Fluctuations in systolic blood pressure (SBP) was calculated using Non Invasive Blood Pressure (NIBP) System of power lab using rat tail cuff method.

Results: Our study showed significant results for lowering of systolic blood pressure in rats receiving Amlodipine alone and then Simvastatin in the presence of Amlodipine.

Conclusion: This study demonstrates that Simvastatin and Amlodipine when used in combination have potentiating or additive vasodilatory effects resulting in lowering of systolic blood pressure.

Key Words: Simvastatin, Amlodipine, systolic blood pressure (SBP), Cardiovascular diseases(CVDs)

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INTRODUCTION

Drug-drug interaction is the change in the response of a drug due to administration of another drug, and occurs, due to simultaneous administration of two or more than two drugs¹. Drug interactions are of two types that is interactions that take place inside & outside the body. Mixing of drugs in intravenous (IV) fluid may cause chemical reactions between drugs and the constituents of IV-fluid, this can be taken as an example of interactions occurring outside body². When drugs are taken by patient and then the drugs interact inside the body of patient then such interactions are interactions inside the body. Interactions can be Pharmacokinetic or Pharmacodynamic interactions. Interactions occurring during Absorption, Distribution, Metabolism & Excretion are Pharmacokinetic- interactions. Interactions between drugs having similar or antagonistic pharmacological effects and are due to either competition for the same receptor or drugs acting at a similar physiological system are Pharmacodynamic-interactions. Pharmacodynamic interactions can be the form of Addition, Synergism, Potentiation and Antagonism^{1,2}.

Department of Pharmacology, Ayub Medical College, Abbottabad.

Correspondence: Dr. Wajid Ali, Lecturer of of Pharmacology, Ayub Medical College, Abbottabad.

Contact No: 0333-5715816

Email: dr.wajidali161@gmail.com

Cardiovascular diseases are the most prevalent cause of mortality and morbidity^{3,4}. Epidemiological and outcomes research studies shows that the current treatment strategies are not sufficient in controlling the hypertension and dyslipidemia with single drug therapy alone. This is despite the availability of well tolerated anti-hypertensives and dyslipidemics. However, there is evidence that the addition of anti-hypertensives with lipid-lowering drugs confers cardiovascular benefits^{4,5}. WHO has approved many drugs for the treatment of cardiovascular diseases. The most important of which are statins, calcium channel blockers and anti-platelet drugs³. Most commonly the statins are used for the management of hypercholesterolemia and calcium channel blockers for hypertension, in patients who are hypertensive and obese. In patients of stroke these two drugs (Simvastatin and Amlodipine) from two different groups are sometimes used together to control hypertension and hypercholesterolemia simultaneously⁶.

But the effect of this combination is still not known. However it is postulated in some research papers through conduction of experiments in animal models that statins have positive effects on the voltage gated calcium-channels, means it up-regulates the voltage gated calcium channels⁷. Recently drug study findings have proved that statins have the calcium-channel blocking effects on rabbit's jejunum^{8,9}. In this study we want to know the combined vasodilatory effects of Simvastatin (Statin) and Amlodipine (Calcium channel blockers).

MATERIALS AND METHODS

We conducted this study in lab of Pharmacology department, Ayub Medical college, Abbottabad, from May 2016 to June 2017. Our experimental model for the study was Albino Rats. Standard laboratory diet was provided to rats in proper ventilated rooms. There were 4 groups consisting of 4 rats in each group.

1-Control group: No hypertension was induced and no drug given to this group.

2- Amlodipine group.

3- Amlodipine plus Simvastatin (EC₅₀ dose) group.

4- Amlodipine plus Simvastatin (double EC₅₀ dose) group.

In Rats of group 2, 3 & 4 hypertension was induced by injecting Depomedral TM subcutaneously (20mg/kg) of body weight for 1 week^{10,11}. Test drugs (Amlodipine & Simvastatin) were given for antihypertensive effects, via oral route using single dose phenomenon of

drugs^{12,13}. Systolic Blood pressure fluctuations (SBP) were recorded by using the Non Invasive Blood Pressure (NIBP) system of Power lab, using rat tail cuff method, on three different occasions i.e. Before hypertension induction, after hypertension induction (Pre-dose) and after test drug administration(Post-dose)^{14,15}. The observations were repeated 3-4 times for each rat and mean was calculated using Graph Pad Prism software version 6.¹⁶

RESULTS

Effects on systolic blood pressure (SBP) in hypertensive rats were observed and the data was statistically analyzed through ANOVA.

Control group: Mean baseline systolic blood pressure values were (142.16±6.33) and (14 ± 5.23) respectively at one week interval as shown in the table.

Table: Effect of drugs (test and standard) on fall in systolic blood pressure (Mean blood pressure n=4)

	Group 1		Group 2		Group 3		Group 4	
	Control group		Amlodipine group (Standard)		Amlodipine+Simvastatin (EC ₅₀ dose)		Amlodipine+Simvastatin (Double EC ₅₀ dose)	
	Initial BP	Bp after 1 week	Pre dose SBP	Post dose SBP	Pre dose SBP	Post dose SBP	Pre dose SBP	Post dose SBP
	120.2	121	203	184	185	162	191	161
	138.1	139	205	183	185	162	184	149
	135.18	136	178	173	182	165	188	162
	175.16	170	212	192	173	155	172	147
Mean SBP± SD	142.16± 6.33	141.5±5.23	199.5±7.73	183±5.7	181.25±3.2	161±2.3	183±4.54	154±5.3
*Mean↓ in SBP	No change		16.5mmHg		20.25mmHg		28.25mmHg	
*% fall in SBP	No change		100% (standard)		122.72%		171.21%	

*Mean Fall in SBP= Pre dose – Post dose.

$$*\% \text{ fall in the mean SBP by Amlodipine (standard)} = \frac{\text{Mean fall in SBP by Amlodipine}}{\text{Mean fall in SBP by Amlodipine}} \times 100 = \frac{16.5}{16.5} \times 100 = 100\%$$

$$*\text{ fall in mean SBP by Amlodipine+Simvastatin (EC}_{50}) = \frac{\text{Mean fall in SBP by Amlodipine+Simvastatin (EC}_{50})}{\text{Mean fall in SBP by Amlodipine}} \times 100$$

$$= \frac{20.25}{16.5} \times 100 = 122.72\%$$

$$*\text{ fall in mean SBP by Amlodipine+Simvastatin (Double EC}_{50}) = \frac{\text{Mean fall in SBP by Amlodipine+Simvastatin (EC}_{50})}{\text{Mean fall in SBP by Amlodipine}} \times 100$$

$$= \frac{28.25}{16.5} \times 100 = 171.21\%$$

Amlodipine group: Pre-dose mean systolic blood pressure was (199.5±7.73) and post dose mean systolic blood pressure was (183±5.7) with (p=0.0011) as shown in table. The fall in systolic blood pressure is 16.5 mmHg. Mean fall of Systolic blood pressure by Amlodipine is taken as standard to compare all other mean falls caused by combination of simvastatin and Amlodipine. % fall by Amlodipine is taken as 100%.

Amlodipine plus Simvastatin (EC₅₀) group: Simvastatin (EC₅₀) in the presence of Amlodipine was given through oral route following single dose phenomenon. Pre-dose mean systolic blood pressure was (181.25±3.2) and post-dose mean systolic blood pressure was (161±2.3) with (p=0.0038), the mean fall in systolic blood pressure was 22.5mmHg. % fall in mean systolic blood pressure by Amlodipine plus Simvastatin (EC₅₀ dose) is 122.72%.

Amlodipine plus Simvastatin (Double EC₅₀): Simvastatin (Double EC₅₀) in the presence of Amlodipine was given through oral route following single dose phenomenon. Pre dose mean systolic blood pressure was (183±4.54) and post dose systolic blood pressure after the administration of Amlodipine and Simvastatin (Double EC₅₀) was (154±5.3) with (p=0.0010), the mean fall in systolic blood pressure was 28.25mmHg. % fall in mean systolic blood pressure by Amlodipine plus Simvastatin (Double EC₅₀) was 171.21%.^{17,18,19}

DISCUSSION

In modern era, the practice of poly pharmacy is widely prevalent throughout the world. Clinicians use the poly pharmacy to treat most of the diseases such as cardiovascular diseases like stroke, which needs to be treated with combination of drugs like statins for hypercholesterolemia and calcium channel blockers for hypertension, but the combined effects of these drugs, still to be answered.

This in vivo study was designed to know the possible combined effects of simvastatin and Amlodipine on key physiological variables like systolic blood pressure (SBP). The Simvastatin was tested in the presence of Amlodipine, the standard calcium channel blocker that affects the vascular tone and subsequently blood pressure of test animals.

Moreover, Amlodipine alone was also tested in the same experimental animals to quantify the blood pressure lowering effects. Effects of Amlodipine alone show a mean fall in blood pressure of 16.5 mmHg, assuming Amlodipine as standard drug. While mean fall in blood pressure by Amlodipine + Simvastatin (EC₅₀ and Double EC₅₀ dose) are 20.25 and 28.25 mmHg respectively.

Percent falls in mean systolic blood pressure (SBP) by Amlodipine is 100% (standard), Amlodipine plus Simvastatin (EC₅₀) is 122.72 % and Amlodipine+ Simvastatin (Double EC₅₀ dose) is 171.21%. So, by

comparison the greatest percent fall in mean SBP was done by Amlodipine plus Simvastatin (Double EC₅₀) then by Amlodipine+Simvastatin (EC₅₀) then by Amlodipine alone.

171.21% > 122.72% > 100% (Standard).

Results of our study were supported by a research work conducted by Ali N, in which it was proved that statins have calcium channel antagonistic activity⁸. Another, study conducted by Clunn GF, which shows that statins upregulates the calcium channels in vascular smooth muscles (VSM) also strongly supports our study.⁷

CONCLUSION

Based on the findings of our experimental works, it is concluded that when Simvastatin and Amlodipine are used in combination in patients suffering from hypertension and hypercholesterolemia simultaneously, then these two drugs have additive or potentiating effects on systolic blood pressure (SBP) which explicit the pharmacodynamic interactions between Amlodipine and Simvastatin.

This may sometime distort the therapeutic or pharmaceutical cure plan defined for patients who have hypercholesterolemia or are hypertensives.

Author's Contribution:

Concept & Design of Study: Wajid Ali
 Drafting: Afsheen Siddiqi
 Data Analysis: Afsheen Siddiqi
 Revisiting Critically: Afsheen Siddiqi, Khadija Imran
 Final Approval of version: Wajid Ali

Conflict of Interest: The study has no conflict of interest to declare by any author.

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