ORIGINAL RESEARCH PAPER

Pharmacology

KEY WORDS: diabetes, amlodipine, atenolol, enalapril

OBSERVATIONAL STUDY SHOWING INDIERCT EVIDENCE OF VASODILATOR ANTIHYPERTERNSIVE CONCOMITANT THERAPY WITH ATORVASTATIN PRECIPITATING DIABETES MELLITUS IN OPD PATIENTS OF TERTIARY CARE HOSPITAL

Dr.N.D Balani Professor and HOD, Dept of Pharmacology, Government Medical College Akola

Dr. Renuka Harwani* 3rd year Junior Resident, Dept of pharmacology, Government Medical College Akola *Corresponding Author

Dr. Sudharam T. Bhagwate Associate Professor, Dept of Pharmacology, Government Medical College Akola

ABSTRACT

Records of 536 patients receiving amlodipine, atenolol, enalapril for hypertension with altered lipid profile were collected from HMIS, Government Medical College Akola. Data of these patients was collected and analyzed for diabetes mellitus development with concomitant atorvastatin therapy. It was observed that amlodipine, enalapril plus low dose aspirin receiving patients developed diabetes mellitus when concomitantly atorvastatin was being taken (22 out of 268 against 2 patients out of 268 who developed diabetes with atorvastatin with low dose aspirin-total 22 out 268 i.e 8.20 %. There were 17 patients on amlodipine enalapril plus aspirin. 3 were on atenolol and aspirin. The difference among these being i.e 7.4 % is statistically significant. The incident diabetes with vasodilator plus aspirin plus atorvastatin was found to be 6.3 %. This observation gives indirect clue that vasodilator (amlodipine, enalapril plus low dose aspirin plus atorvastatin may cause diabetes mellitus).

Introduction:

The statins are the most effective and best-tolerated agents for treating dyslipidemia.[1] various studies have suggested that statins may be associated with a higher incidence of new cases of diabetes.[2-5] Meta-analysis study of 3 randomized trial, TNT (Treating to New Targets) trial, IDEAL (Incremental Decrease in End Points Through Aggressive Lipid Lowering), SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) trial where TNT trial showed the incidence of NOD with atorvastatin 80 mg and 10 mg was 9.24% and 8.11% respectively. On the other hand, Post hoc analysis of the West of Scotland Coronary Prevention Study (WOSCOPS) showed the relationship between statins and diabetes and showed that pravastatin was associated with a 30% reduced risk of new onset diabetes compared with placebo (OR = 0.70).[6]

At our tertiary care hospital, it was observed that atorvastatin was prescribed in patients of hypertension and heart disease as a concomitantly administered drug along with amlodipine, atenolol, enalapril each of these combined with low dose aspirin. We planned a study to see which antihypertensive causes higher percentage of incident diabetes mellitus when combined with atorvastatin.

Material and methods:

Records of 268 patients in each of the test and control group (total 536 patients) were collected from HMIS online database. The incident diabetes was observed from these data in previous three years of treatment with different antihypertensive plus low dose aspirin plus atorvastatin (10 and 20 mg). the doses of amlodipine and enalapril prescribed to the patients (5 mg each), and dose of aspirin prescribed was 75 mg daily. Dose of atenolol was 25 and 50 mg along with similar doses of aspirin and atorvastatin. The patient were in age group of 40-86 years of either sex (155 male Vs 113 female). All were ambulant OPD patients. There was no advice on dietary modifications in prescriptions. This constituted the test group whereas another 268 prescriptions of patients receiving antihypertensive with low dose aspirin of similar age sex composition without dietary advice constituted the control group. Number of patients developing incident diabetes mellitus were recorded from this collected data in both test and control groups and difference was analyzed statistically applying chi square test. Observations and result were tabulated.

Observations and results:

Table 1 and Fig 1: showing incident diabetes in control group (without atorvastatin) receiving antihypertensive and low dose aspirin

Concomitant Drug Therapy	Control Group	No of patients who developed DM
Amlodepine	171	2
Atenolol	32	2
Enalapril	33	1

DM- Diabetes Mellitus

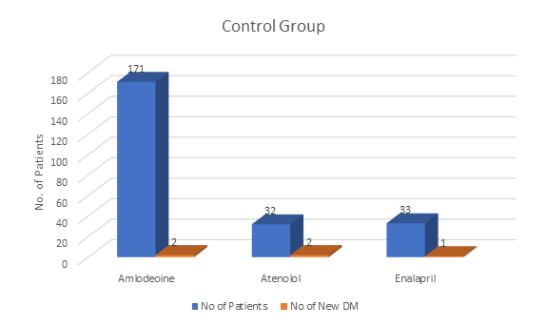

Fig 1

Table 2 and Fig 2: showing incident diabetes mellitus in test group patients receiving antihypertensive plus low dose aspirin plus atorvastatin (10 mg and 20 mg)

Concomitant Drug Therapy	Test Group	No of patients who delevoped DM
Amlodipine	177	17
Atenolol	62	3
Enalapril	31	2

DM-Diabetes Mellitus

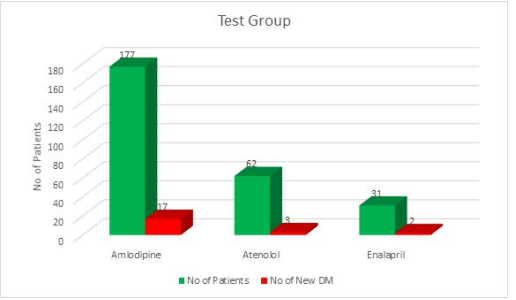

Fig 2

Fig 3: showing number of patients who developed incident diabetes with atorvastatin concomitant antihypertensive/ digoxin plus low dose aspirin

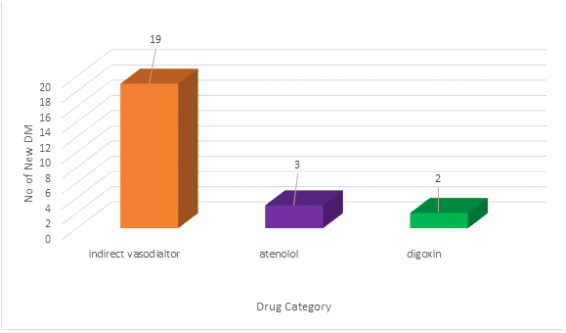

Fig 3

Another 2 patients who were receiving digoxin plus low dose aspirin who developed incident diabetes mellitus are not included in above table 2

From table of observations it is evident that the patient of control group 5 out of 268 developed incident diabetes mellitus. These patients were not receiving antihypertensive. In table 2 i.e test group 17 patients receiving amlodipine plus low dose aspirin plus atorvastatin, 2 patients receiving enalapril plus low dose aspirin plus atorvastatin, and 3 patients receiving atenolol plus low dose aspirin plus atorvastatin- overall total 22 patients receiving antihypertensive and 2 more patients (not shown in table receiving digoxin along with low dose aspirin have developed incident diabetes after mean duration of 18 months of treatment. Overall 19 patients out of 24 who developed incident diabetes have received indirect vasodilators antihypertensive.

Discussion:

Sampson et al.[7] proposed that the effects of statins on new onset diabetes may centre on altered insulin secretion rather than insulin sensitivity via multiple mechanisms that compromise the functions of pancreatic beta cells. The hypothetical paradigm proposed involves (i) inhibition of intracellular glucose arrival via glucose transporter (GLUT2) which initiates the cascades for insulin secretion, (ii) inhibition of glucokinase by plasma derived cholesterol which is in abundance when de novo synthesis of cholesterol is inhibited, (iii) reduction in ATP production due to suppression of ubiquinine (CoQ10) leading to inhibition of insulin secretions, (iv) suppression of isoprenoid synthesis causing down-regulation of the glucose transport system (GLUT4) which is important in glucose uptake, (v) the pro-inflammatory and oxidative effects of plasma derived cholesterol and (vi) induction of beta cell apoptosis due to cytokine-induced over production of nitric oxide.

Lipophilic statins (atorvastatin, simvastatin) particularly high dose, inhibit glucose-stimulated elevations of free Ca in the cytoplasm of beta cells and interferes isoprenoid biosynthesis, thus may cause impaired insulin secretion and exacerbation of insulin resistance.[8,9] In a study done on the effects of various statins on the glucose-transporter-4, atorvastatin but not other statins seemed to have a detrimental effect on glucose metabolism via this mechanism.[10]

Meta-analysis was performed to assess the effects of statin treatment on insulin sensitivity. No significant effect was observed overall, but subset analyses suggested that pravastatin use was associated with a modest increase in insulin sensitivity (0.342 standard deviations, 95% CI 0.032- 0.651), simvastatin with a modest decline in insulin sensitivity (20.321 standard deviations, 95% CI 20.526 to 0.177), atorvastatin [SMD 0.019 (0.243 to 0.205); p = 0.87] and rosuvastatin [SMD 0.037 (95% CI 0.223 to 0.148); p = 0.69)] non-significantly reduced insulin sensitivity, When the studies comparing atorvastatin, rosuvastatin and simvastatin to placebo/control were combined, insulin sensitivity was significantly reduced [SMD 0.149 (95% CI 0.284 to 0.013); p = 0.03].[11]

In our observational study, the concomitant administration of indirect vasodilators antihypertensive has caused incident diabetes in 19 out of 22 antihypertensive receiving patients i.e 86 % risk of incident diabetes.

Vascular pleosynergism benefit of combination of atorvastatin and amlodipine has been reported in comparison to placebo but atorvastatin reducing insulin sensitivity probably placed a dominant role causing rise in the blood sugar and incident diabetes.[12]

It is beyond the scope of this study to establish a correlation between indirect vasodilator antihypertensive with atorvastatin to produce diabetes in baseline non-diabetics subjects. This requires to be confirmed by other studies. We therefore suggest to avoid combination of indirect vasodilator with atorvastatin in maintanence dose therapy which is required to given for longer time (more than 12 months). However for the purpose of controlling the altered lipid profile in needy patients, pravastatin can be preferred over atorvastatin.

Conclusion:

Atorvastatin should better be avoided in combination with indirect vasodilator in needy patients for the risk of developing incident diabetes which have been observed in this study as 8.2 %.

Acknowledgement:

we are thankful to Dean and HMIS team working in GMCH akola for their valuable cooperation.

Conflict of interet: Nil

References:

1. Bersot TP. Drug Therapy for Hypercholestrolemia and Dyslipidemia. In Brunton LL, Chabner BA, Knollmann BC; Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th edition, New York Mc Graw Hill, 2011,p 807-908
2. Rajpathak SN, Kumbhani DJ, Crandall J, Barzilai N, Alderman M, Ridker PM. Statin therapy and risk of developing type 2 diabetes: a meta-analysis. Diabetes Care. 2009 Oct;32(10):1924–9.
3. 12. Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, de Craen AJ, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. The Lancet. 2010 Feb;375(9716):735–42.
4. Preiss D, Seshasai SRK, Welsh P, Murphy SA, Ho JE, Waters DD, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. JAMA. 2011 Jun 22;305(24):2556–64.
5. Ridker PM, Pradhan A, MacFadyen JG, Libby P, Glynn RJ. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. The Lancet. 2012 Aug;380(9841):565–71
6. Waters DD, Ho JE, DeMicco DA, Breazna A, Arsenault BJ, Wun CC, et al. Predictors of new-onset diabetes in patients treated with atorvastatin: Results from 3 large randomized clinical trials. J Am Coll Cardiol. 2011;57(14):1535–45.
7. Sampson UK, Linton MF, Fazio S. Are statins diabetogenic? Curr Opin Cardiol 2011;26:342-7.
8. Zaharan NL, Williams D, Bennett K. Statins and risk of treated incident diabetes in a primary care population. Br J Clin Pharmacol. 2013;75(4):1118–24.
9. Koh KK, Sakuma I, Quon MJ. Differential metabolic effects of distinct statins. Atherosclerosis. 2011;215(1):1–8.
10. Nakata M, Nagasaka S, Kusaka I, Matsuoka H, Ishibashi S, Yada T. Effects of statins on the adipocyte maturation and expression of glucose transporter 4 (SLC2A4): implications in glycaemic control. Diabetologia 2006;49:1881-92.
11. Baker WL, Talati R, White CM, Coleman CI. Differing effect of statins on insulin sensitivity in non-diabetics: A systematic review and meta-analysis. Diabetes Res Clin Pract. 2010 Jan;87(1):98–107.
12. Csaszar A. [Vascular pleiosynergism--a new concept?]. Orv Hetil. 2006 Oct;147(41):1973–6.