Journal of Pharmacokinetics & Experimental Therapeutics

Stevens, J Pharmacokinet Exp Ther 2023, 6:6

Mini Review Open Access

A Brief Review on Medication in the Statin Family that Lowers Cholesterol -Atorvastatin (Lipitor)

John Stevens*

Department of Family and Community Medicine, University of North Texas Health Science Center, United States

Abstract

An HMG-CoA reductase inhibitor called atorvastatin is used to lower cholesterol levels and lessen the risk of cardiovascular disease, including as myocardial infarction and stroke. The objective of this paper is to provide a brief note on the pharmacokinetics of lipid-lowering medicine belonging to the statin class of drugs is Atorvastatin.

Keywords: Atorvastatin; Pharmacokinetics; Cardiovascular disease; Statin; Lipoprotein; Antilipemic

Introduction

A lipid-lowering medicine belonging to the statin class of drugs is atorvastatin. Statins lower aberrant levels of cholesterol and lipids, which eventually lowers the risk of cardiovascular disease. They achieve this by preventing the liver's endogenous manufacture of cholesterol. More precisely, statin drugs competitively block the HMG-CoA Reductase enzyme, which catalyses the conversion of HMG-CoA to mevalonic acid [1]. The creation of various substances involved in lipid metabolism and transport, including cholesterol, low-density lipoprotein (LDL), sometimes known as "bad cholesterol," and very-low-density lipoprotein, depends on this conversion, a crucial metabolic process (VLDL). For patients who have experienced a cardiovascular event and for those who are at moderate to high risk of developing cardiovascular disease, prescribing statins is regarded as standard treatment. The widespread use of statins in North America is a result of the evidence in favour of their usage, as well as their low risk of adverse effects and long-term advantages [2,3]. A number of dyslipidemias, including primary hyperlipidemia, mixed dyslipidemia, hypertriglyceridemia, primary dysbetalipoproteinemia, homozygous familial hypercholesterolemia, and heterozygous familial hypercholesterolemia in adolescents with failed dietary interventions are treatable with atorvastatin [4]. When high-density lipoprotein levels are present together with elevated plasma cholesterol, triglycerides, or both, the condition is referred to as dyslipidemia. Atherosclerosis is more likely to develop as a result of this disorder. When used in conjunction with dietary changes, atorvastatin is recommended for individuals who have cardiac risk factors and/or abnormal lipid profiles to help avoid cardiovascular events. In individuals without coronary heart disease but with several risk factors, as well as in those with type 2 diabetes and multiple risk factors but no coronary heart disease, atorvastatin can be administered as a preventative medication for myocardial infarction, stroke, revascularization, and angina. In individuals with coronary heart disease, atorvastatin may be used as a preventative measure for non-fatal myocardial infarction, fatal and non-fatal stroke, revascularization operations, hospitalisation for congestive heart failure, and angina.

Following any cardiovascular incident and for persons at moderate to high risk of developing cardiovascular disease (CVD), the prescription of statin drugs is generally accepted as standard therapy [5]. Diabetes mellitus, clinical atherosclerosis (including myocardial infarction, acute coronary syndromes, stable angina, documented coronary artery disease, stroke, trans ischemic attack (TIA), documented carotid disease, peripheral artery disease, and claudication), abdominal aortic aneurysm, chronic kidney disease, and significantly elevated LDL-C levels are among the conditions for which statins are recommended.

Pharmacodynamics

The oral antilipemic drug atorvastatin inhibits HMG-CoA reductase in a reversible manner. It raises plasma concentrations of HDL-C while decreasing levels of total cholesterol, low-density lipoprotein cholesterol (LDL-C), apolipoprotein B, non-high density lipoprotein cholesterol (non-HDL-C), and triglyceride (TG). Atherosclerosis and cardiovascular disease are related with high LDL-C, low HDL-C, and high TG concentrations in the plasma. A strong indicator of coronary artery disease is the ratio of total cholesterol to HDL-C, and higher ratios are linked to a higher risk of the condition. Lower cardiovascular risk is linked to higher HDL-C levels. A statin like atorvastatin lowers the risk of cardiovascular morbidity and death by lowering LDL-C and TG and raising HDL-C [6].

High levels of low-density lipoprotein (LDL) in particular are associated with elevated cholesterol levels, which are a significant risk factor for the emergence of CVD. 9 According to clinical research, atorvastatin lowers LDL-C and total cholesterol by 36-53%. 3 Atorvastatin decreased the levels of intermediate-density lipoprotein cholesterol in individuals with dysbetalipoproteinemia. Additionally, it has been proposed that atorvastatin may be able to restrict angiogenesis to some degree, which may be helpful in the management of chronic subdural hematoma [7].

Like other HMG-CoA reductase inhibitors, atorvastatin has a risk of drug-induced myopathy, which manifests as muscular aches, soreness, or weakening along with increased creatine kinase levels (CK). Rhabdomyolysis, a common manifestation of myopathy brought on by myoglobinuria, can occur with or without severe renal failure. The risk of statin-induced myopathy is dose-related, and after the medication is stopped, the symptoms usually go away. According

***Corresponding author:** John Stevens, Department of Family and Community Medicine, University of North Texas Health Science Center, United States, E-mail: john_29@hotmail.com

Received: 22-Nov-2022, Manuscript No. jpet-23-87593; **Editor assigned:** 24-Nov-2022, PreQC No. jpet-23-87593(PQ); **Reviewed:** 08-Dec-2022, QC No. jpet-23-87593; **Revised:** 13-Dec-2022, Manuscript No. jpet-23-87593(R); **Published:** 20-Dec-2022, DOI: 10.4172/jpet.1000159

Citation: Stevens J (2022) A Brief Review on Medication in the Statin Family that Lowers Cholesterol -Atorvastatin (Lipitor). J Pharmacokinet Exp Ther 6: 159.

to observational study findings, between 10 and 15 percent of statin users may develop muscular pain at some time during therapy [8]. Similar to other lipid-lowering treatments, statins have been linked to biochemical abnormalities in liver function. In clinical studies, 0.7% of patients who took atorvastatin experienced persistent increases in serum transaminases (> 3 times the upper limit of normal [ULN] occurring on two or more occasions). This result seems to be dose-dependent [9,10]. The risk of higher blood HbA1c and glucose levels is linked to statin use. An in vitro experiment showed that atorvastatin administration has a dose-dependent cytotoxic impact on human pancreatic islet cells. In addition, insulin secretion rates dropped in comparison to controls [11].

HMG-CoA reductase inhibitors prevent the synthesis of cholesterol and, in theory, might prevent the synthesis of gonadal and/or adrenal hormones. According to clinical research, atorvastatin and other HMG-CoA reductase inhibitors had no effect on plasma cortisol levels, baseline plasma testosterone levels, or adrenal reserve. Statins' impact on male fertility hasn't been well studied, though. It is uncertain how statins affect premenopausal women's pituitary-gonadal axis. Patients on atorvastatin and other statins have shown significant drops in blood levels of ubiquinone. A potential long-term statin-induced ubiquinone deficiency's clinical implications has not been determined. It has been suggested that individuals with borderline congestive heart failure may experience reduced cardiac performance as a result of a drop in myocardial ubiquinone levels.

The concurrent rise in Lp(a) lipoprotein concentrations in some patients may somewhat offset the positive effect of decreasing total cholesterol and LDL-C levels. High Lp(a) levels may be an important new risk factor for coronary heart disease, according to current information. According to another research, statins have distinct effects on Lp(a) levels in individuals with dyslipidemia depending on their apo(a) phenotype; they only raise Lp(a) levels in those with the low molecular weight apo(a) phenotype [12].

Mechanism of action

Atorvastatin is a statin drug that inhibits the enzyme HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase in a competitive manner. This enzyme catalyses the conversion of HMG-CoA to mevalonate, which is the first rate-limiting step in cholesterol production [13]. When liver cholesterol levels are lower, hepatic low-density lipoprotein (LDL) receptors are stimulated to become more active, increasing the amount of LDL that is absorbed by the liver. Additionally, atorvastatin decreases apolipoprotein B (apo B)-containing particles, serum triglycerides (TG), intermediate density lipoproteins (IDL), and very low density lipoprotein cholesterol (VLDL-C) while increasing high density lipoprotein cholesterol (HDL-C). Animal studies conducted in vitro and in vivo also show that atorvastatin, commonly known as a statin with pleiotropic effects, has vasculoprotective actions that are distinct from its lipid-lowering benefits. 25 Improved endothelial function, improved atherosclerotic plaque stability, decreased oxidative stress and inflammation, and suppression of the thrombogenic response are a few of these outcomes. Additionally, it was shown that statins bind allosteric ally to LFA-1, a key component of leukocyte trafficking and T cell activation [14].

The pharmacokinetic profile of atorvastatin is non-linear and dose-dependent. 4 After oral administration, it is absorbed relatively quickly. AUC of about 200 ng/h/ml is attained 1-2 hours after the initial administration of a dosage of 40 mg, leading to a peak plasma concentration of 28 ng/ml [15]. The significant first-pass metabolism of atorvastatin in the liver and gastrointestinal tract results in an absolute oral bioavailability of 14%. 2 When compared to morning medication delivery, plasma atorvastatin concentrations are lower (by about 30% for Cmax and AUC) after the evening dose. However, regardless of when a medicine is administered during the day, LDL-C is reduced in the same way. When atorvastatin is taken with meals, the Tmax is extended and the Cmax and AUC are decreased. An essential part of atorvastatin absorption is played by the membrane-bound protein known as breast cancer resistance protein (BCRP) [16]. Individuals with the 421AA genotype have lower functional activity and a 1.72-fold higher AUC for atorvastatin compared to study individuals with the control 421CC genotype, according to evidence from pharmacogenetic studies of the c.421C>A single nucleotide polymorphisms (SNPs) in the gene for BCRP. This has significant effects on how the drug's effectiveness and toxicity vary according on the individual, especially given that the BCRP c.421C> Asian people experience polymorphisms more frequently than Caucasian populations. Fluvastatin, Simvastatin, and Rosuvastatin are further statin medications affected by this mutation [17,18]. It has been demonstrated that atorvastatin pharmacokinetics are influenced by genetic variations in the OATP1B1 (organic-anion-transporting polypeptide 1B1) hepatic transporter encoded by the SCLCO1B1 gene. Evidence from pharmacogenetic investigations of the c.521T>C single nucleotide polymorphism (SNP) in the gene encoding OATP1B1 (SLCO1B1) showed that atorvastatin AUC was raised 2.45-fold for those who were homozygous for 521CC compared to people who were homozygous for 521TT [19]. Simvastatin, pitavastatin, rosuvastatin, and pravastatin are further statin medications affected by this polymorphism.

Metabolism

Atorvastatin is extensively metabolized, predominantly by Cytochrome P450 3A4 in the liver and gut, producing ortho- and parahydroxylated derivatives and other beta-oxidation products. The metabolites of atorvastatin are further lactonized by the enzymes UGT1A1 and UGT1A3, which create acyl glucuronide intermediates. These lactones exist in equilibrium and can hydrolyzed back to their corresponding acid forms. Ortho- and parahydroxylated metabolites had the same inhibitory effect on HMG-CoA reductase in vitro as atorvastatin. Active metabolites are responsible for around 70% of the circulating HMG-CoA reductase inhibitory activity.

Without enterohepatic recirculation, atorvastatin and its metabolites are mostly removed in the bile. There is very little atorvastatin renal elimination, which accounts for less than 1% of the dosage that is excreted. Atrastatin has a half-life of 14 hours, but that of its metabolites can be up to 30 hours.

Toxicity

The LD50 of oral atorvastatin in mice has been found to be greater than 5000 mg/kg. MSDS There have been reports of difficult breathing, jaundice, liver damage, dark urine, muscular discomfort, and convulsions in atorvastatin overdose instances [20].

Discussion

In the event of an overdose, symptomatic therapy is advised since hemodialysis is not anticipated to produce meaningful improvement due to the high plasma protein binding.

Conclusion

There was evidence of rhabdomyosarcoma, fibrosarcoma, liver

adenoma, and liver carcinoma in investigations on the carcinogenic effects of high dosages of atorvastatin. Aplasia, aspermia, low testis and epididymal weight, reduced sperm motility, decreased spermatid head concentration, and a rise in defective sperm were all observed in reproductive tests with high atorvastatin dosages.

Acknowledgement

Not applicable.

Conflict of Interest

Author declares no conflict of interest.

References

1. Moghadasian MH (1999) Clinical pharmacology of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. Life Sci 65: 29-37.
2. Anderson TJ, Gregoire J, Pearson GJ, Barry AR, Couture P, et al. (2016) 2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. Can J Cardiol 32: 1263-1282.
3. Grundy SM, Stone NJ (2019) 2018 American Heart Association/American College of Cardiology Multisociety Guideline on the Management of Blood Cholesterol: Primary Prevention. JAMA Cardiol 4: 589-591.
4. Ye YC, Zhao XL, Zhang SY (2015) Use of atorvastatin in lipid disorders and cardiovascular disease in Chinese patients. Chin Med J 128: 259-266.
5. Henwood JM, Heel RC (1988) Lovastatin. A preliminary review of its pharmacodynamic properties and therapeutic use in hyperlipidaemia. Drugs 36: 429-454.
6. Bradford RH, Shear CL, Chremos AN, Dujovne CA, Franklin FA, et al (1994) Expanded Clinical Evaluation of Lovastatin (EXCEL) study results: two-year efficacy and safety follow-up. Am J Cardiol 74: 667-673.
7. Qiu S, Zhuo W, Sun C, Su Z, Yan A, et al. (2017) Effects of atorvastatin on chronic subdural hematoma: A systematic review. Medicine 96: 7290.
8. Harper CR, Jacobson TA (2007) The broad spectrum of statin myopathy: from myalgia to rhabdomyolysis. Curr Opin Lipidol 18: 401-408.
9. Sattar N, Taskinen MR (2012) Statins are diabetogenic–myth or reality?. Atheroscler Suppl 13: 1-10.
10. Betteridge DJ, Carmena R (2016) The diabetogenic action of statins-mechanisms and clinical implications. Nat Rev Endocrinol 12: 99-110.
11. Zhao W, Zhao SP (2015) Different effects of statins on induction of diabetes mellitus: an experimental study. Drug Des Devel Ther 24: 211-223.
12. Yahya R, Berk K, Verhoeven A, Bos S, van der Zee L, et al. (2019) Statin treatment increases lipoprotein(a) levels in subjects with low molecular weight apolipoprotein(a) phenotype. Atherosclerosis 289: 201-205
13. Moghadasian MH (1999) Clinical pharmacology of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. Life Sci 65: 329-337.
14. Okano M, Xie S, Li E (1998) Cloning and characterization of a family of novel mammalian DNA (cytosine-5) methyltransferases. Nat Gen 19: 219-220.
15. Lins RL, Matthys KE, Verpooten GA, Peeters PC, Dratwa M, et al (2003) Pharmacokinetics of atorvastatin and its metabolites after single and multiple dosing in hypercholesterolaemic haemodialysis patients. Nephrol Dial Transplant 18: 967-976.
16. Elsby R, Hilgendorf C, Fenner K (2012) Understanding the critical disposition pathways of statins to assess drug-drug interaction risk during drug development: it's not just about OATP1B1. Clin Pharmacol Ther 92: 584-598.
17. Keskitalo JE, Zolk O, Fromm MF, Kurkinen KJ, Neuvonen PJ, et al. (2009) ABCG2 polymorphism markedly affects the pharmacokinetics of atorvastatin and rosuvastatin. Clin Pharmacol Ther 86: 197-203.
18. Lee E, Ryan S, Birmingham B, Zalikowski J, March R, et al. (2005) Rosuvastatin pharmacokinetics and pharmacogenetics in white and Asian subjects residing in the same environment. Clin Pharmacol Ther 78: 330-341.
19. Pasanen MK, Fredrikson H, Neuvonen PJ, Niemi M (2007) Different effects of SLCO1B1 polymorphism on the pharmacokinetics of atorvastatin and rosuvastatin. Clin Pharmacol Ther 82: 726-733.
20. Neuvonen PJ, Niemi M, Backman JT (2006) Drug interactions with lipid□ lowering drugs: mechanisms and clinical relevance. Clin Pharmacol Ther 80: 565-581.