Journal of Pharmacokinetics & Experimental Therapeutics

Lins, J Pharmacokinet Exp Ther 2022, 6:3

Short Communication Open Access

# Pharmacokinetics and Bio distribution of Atorvastatin in Healthy Female and Male Rats

**Robert L Lins***

*MD, PhD, Department of Nephrology-Hypertension, ACZA Stuivenberg & SGS Biopharma, Lange Beeldekensstraat 267, B-2060 Antwerpen, Belgium*

## Introduction

Atorvastatin (ATS) is the gold-standard treatment for hypercholesterolemia and the prevention of cardiovascular illnesses caused by dyslipidemia around the world. Physiologically based pharmacokinetic (PBPK) models have been positioned as a significant tool for the study of complex pharmacokinetic (PK) processes and their extrapolation in specific sub-populations, leading to regulatory acceptance [1]. In recent years, several PBPK models of ATS have been produced, each addressing a distinct element of ATS's PK features. The goals of this study are to I outline the physicochemical and pharmacokinetic properties involved in the time-course of ATS, and (ii) assess the primary highlights and limits of the PBPK models of ATS that have been published thus far. Common features relating to the physicochemical characteristics of ATS are included in the PBPK models. However, the analyte tested, the kind and influence of transporters and metabolic enzymes, and the permeability value employed all varies significantly. This review also outlines significant processes (lactonization, P-gp contribution, ATS-Ca solubility, simultaneous management of numerous analytes, and experimental data in the target population) that would improve PBPK model prediction and make it a useful tool for ATS dose optimization [2-4].

Patients with chronic renal failure frequently have a secondary form of complicated dyslipidaemia, and lipid-lowering therapy may be beneficial. Although atorvastatin has been proven to effectively lower levels of atherogenic lipoproteins in patients with renal failure, there is a paucity of pharmacokinetic data in haemodialysis patients. Hypercholesterolaemic haemodialysis patients were given 40 mg (n=12) or 80 mg (n=11) atorvastatin once daily for two weeks, initially as a single dose and subsequently continuously. LC/MS/MS was used to determine plasma levels of atorvastatin and its active and inactive metabolites, and pharmacokinetic characteristics (Cmax, tmax, AUC, t1/2) were compared between single and multiple dosing, as well as between different dosages [5].

After single and 2-week multiple dosing, the pharmacokinetic characteristics of the parent drug atorvastatin acid were not significantly altered; they demonstrated dosage proportionality between the 40 and 80 mg doses and were comparable to observations in healthy volunteers. The major active metabolite orthohydroxyatorvastatin and the inactive metabolites atorvastatin lactone and orthohydroxyatorvastatin lactone showed dose proportionality and absence of accumulation, but the active metabolite levels were lower and the inactive metabolites were higher than in healthy volunteers [6-8]. In the metabolic clearance of atorvastatin, the parahydroxymetabolites were just a minor route. Haemodialysis had no effect on atorvastatin or its metabolites clearance, and the medicine was well tolerated with no significant side effects. While there may be modest changes in atorvastatin metabolic processing in haemodialysis patients, active drug did not accumulate or demonstrate increased clearance, and levels were equivalent to those detected in healthy volunteers. As a result, there is no need to change the atorvastatin dosage in this patient population.

Statins are inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, which are commonly used to prevent cardiovascular disease. However, statins, notably atorvastatin, have been linked to a number of pleiotropic processes. As a result, using positron emission tomography (PET) to analyse [$^{18}$F]atorvastatin kinetics may help to clarify the mechanism of action of statins as well as the impact of sexual dimorphism, which is one of the most hotly discussed inter individual variables influencing therapeutic efficacy. [$^{18}$F] Atorvastatin was manufactured using a previously developed $^{18}$F-deoxyfluorination technique and tested in preclinical PET investigations in female and male Wistar rats (n = 7 for both groups) as well as ex vivo biodistribution. PET data was fitted to a variety of pharmacokinetic models, allowing for the estimation of key kinetic parameters. In comparison to the major target organ (liver), excretory routes (kidneys and small intestine), and stomach, PET imaging and bio distribution investigations revealed low absorption of [$^{18}$F]atorvastatin in all tissues [9].

The female liver's uptake of [$^{18}$F] atorvastatin was 38% higher than the male liver's. The irreversible 2-tissue compartment model fit the [$^{18}$F] atorvastatin kinetics in the liver the best. A strong correlation (R2 > 0.93) between quantitative Ki (the radiotracer's unidirectional net rate of influx between compartments) and semi-quantitative liver SUV (standard uptake value), measured between 40 and 90 minutes, revealed the possibility of using the latter parameter to monitor [$^{18}$F] atorvastatin uptake without the need for blood sampling. Female rats showed faster absorption and clearance in preclinical testing than male rats, possibly due to a higher efficiency for exchanges between artery input and hepatic tissue. Because of the sluggish [$^{18}$F]atorvastatin kinetics, equilibrium between liver and plasma concentrations was not established during the time period examined, making it difficult to gather adequate and reliable kinetic data to characterise the radiotracer pharmacokinetics over time. Nonetheless, the published findings suggest that, if all scans are performed at the same time, the SUV could be utilised as a simpler metric. Female rats showed faster absorption and clearance of [$^{18}$F] atorvastatin in preclinical PET experiments than male rats, possibly due to a better efficiency of exchange between arterial blood and hepatic tissue.

liposomal formulation of irinotecan (ONIVYDE) has been approved by FDA and widely applied in the treatment of pancreatic cancer. ONIVYDE is a novel liposome formulation, entrapping CPT-11 in the aqueous core of vesicles using a modified gradient

***Corresponding author:** Robert L. Lins, MD, PhD, Department of Nephrology–Hypertension, ACZA Stuivenberg & SGS Biopharma, Lange Beeldekensstraat 267, B-2060 Antwerpen, Belgium, E-mail: robert.lins@pro.tiscali.be

**Received:** 02-Jun-2022, Manuscript No. jpet-22-65663; **Editor assigned:** 04-Jun-2022, PreQC No. jpet-22-65663 (PQ); **Reviewed:** 18-Jun-2022, QC No. jpet-22-65663; **Revised:** 21-Jun-2022, Manuscript No. jpet-22-65663 (R); **Published:** 28-Jun-2022, DOI: 10.4172/jpet.1000142

**Citation:** Lins RL (2022) Pharmacokinetics and Bio distribution of Atorvastatin in Healthy Female and Male Rats. J Pharmacokinet Exp Ther 6: 142.

loading method. Due to toxicity concerns, it is essential to explore a rapid and reliable method to effectively isolate and quantify the non-liposomal, namely, free CPT-11and total CPT-11 in plasma. This study focuses on separation of non-liposomal CPT-11, evaluation of the pharmacokinetics of free CPT-11 and total CPT-11 and bio-distribution after intravenous administration of CPT-11 liposome. Free CPT-11 in plasma was separated by solid-phase extraction (SPE). The amount of total CPT-11 and main metabolite 7-ethyl-10-hydroxycamptothecin (SN-38) in plasma was quantified by ultra-performance liquid chromatography–MS/MS. The calibration curves fitted well and lower limit of quantitation for SN-38, free CPT-11, total CPT-11 and CPT-11 in tissue and were 5 ng/ml, 10 ng/ml, 4.44 ng/ml and 25 ng/ml respectively. The recoveries, precision and accuracy of the method appear satisfactory. Using this method, the pharmacokinetics and bio-distribution of CPT-11 liposome formulation after an intravenous dose of 2.5 mg/kg were then investigated [10].

## Conclusion

In this study, a selective and sensitive UPLC–MS/MS method coupled with SPE technique was developed to quantify the F-CPT-11 and T-CPT-11 in rat plasma. And SPE method was feasible for separating F-CPT from liposome. The UPLC–MS/MS method was then successfully applied for pharmacokinetic and bio-distribution studies of CPT-11 liposome. The result showed that the validated method would be helpful for toxicity assessment of CPT-11 loaded-liposome.

### References

1. Alessandra B and Simona S (2019) Industrial applications of immobilized enzymes - A review. Mol Catal 479: 1 -20.
2. Ahmad R and Sardar M (2015) Enzyme immobilization: an overview on nanoparticles as immobilization matrix. Anal Biochem 4(2): 1-8.
3. Bernal C, Rodríguez K and Martinez R (2018) Integrating enzyme immobilization and protein engineering: an alternative path for the development of novel and improved industrial biocatalysts. Biotechnol Adv 36: 1470–1480.
4. Arasaratnam V, Galaev IY and Mattiasson B (2000) Reversibility soluble biocatalyst: Optimization of trypsin coupling to Eudargit S-100 and biocatalyst activity in soluble and precipitated forms. *Enzyme and* Microb Technol 27(3):254-263.
5. Ahmed SA, El-Shayeb NM, Hashem AM and Abdel-Fattah AF (2013) Biochemical studies on immobilized fungal β-glucosidase. Braz J Chem Eng 30: 747 – 758.
6. Akakuru OU and Isiuku BO (2017) Chitosan hydrogels and their glutaraldehyde-crosslinked counterparts as potential drug release and tissue engineering systems - synthesis, characterization, swelling kinetics and mechanism. J Phys Chem Biophys 7(3):1-7.
7. Rajendran K, Anwar A, Khan NA (2019) Oleic Acid Coated Silver Nanoparticles Showed Better in Vitro Amoebicidal Effects against Naegleria fowleri than Amphotericin B. ACS chemical neuroscience 16: 2431-2437.
8. Tonomura Y, Yamamoto E, Kondo C (2009) Amphotericin B-induced nephrotoxicity: characterization of blood and urinary biochemistry and renal morphology in mice. Human Exp Toxicol 28:293-300.
9. Visvesvara GS, Moura H, Schuster FL (2007) Pathogenic and opportunistic free-living amoebae: *Acanthamoeba* spp., *Balamuthia mandrillaris*, *Naegleria fowleri*, and *Sappiniadiploidea*. FEMS Immunol Med Microbiol 50:1-26.
10. Bhamra R, Sa'ad A, Bolcsak LE, Jan off S (1997) Behavior of amphotericin B lipid complex in plasma in vitro and in the circulation of rats. Antimicrobial agents and chemotherapy 41(5): 886-892.