Review Article

IT Medical Team
https://www.itmedicalteam.pl/

International Journal of Drug Development and Research
0975-9344

2022
Vol. 14 No. 10: 980

A Population Pharmacokinetic Model for Cyclosporine is being Developed Using Therapeutic Drug Monitoring Data

Jiyan K*

Department of Pharmaceutical Sciences, Faculty of Chemistry, Turkey

Corresponding author:
Jiyan K

tp.aobsilu.ff@arieromr

Department of Pharmaceutical Sciences, Faculty of Chemistry, Turkey

Citation: Jiyan K (2022) A Population Pharmacokinetic Model for Cyclosporine is being Developed Using Therapeutic Drug Monitoring Data. Int J Drug Dev Res J, Vol.14 No. 10: 980.

Abstract

To create a population pharmacokinetic model for TDM that can be used for Uruguayan patients receiving cyclosporine (CsA) medication. Methods and Patients, There were 53 patients in all who were receiving CsA treatment. The remaining 16 patients were taken into account for the evaluation of the predictive performances while the remaining 37 patients with at least one pharmacokinetic profile described with four samples were taken into consideration for model development. The Monolix software's nonlinear mixed effect modelling was used to estimate pharmacokinetic parameters, and the mlxR module in R 3.6.0 was used to run simulations. As a structural model, a two-compartment model with a first-order disposition model that takes lag time into account was adopted. Alpha-synucleinopathies and other neurodegenerative illnesses are currently being treated with therapeutic approaches that focus on increasing drug absorption into the brain. The suggested methods, such intranasal administration, should be able to get over the blood-brain barrier (BBB), and even when administered directly intracerebrally, they could need a carrier to speed up local drug release. We looked into how much alpha-synuclein aggregates there were in cultured cells using a model synthetic hydrogel that will be employed as a drug delivery system. The findings suggested that the synthetic polymer had an impact on alpha-synuclein aggregation and that it was important to examine any material's impact on the pathological process before using it as a medication carrier.

Keywords: Neurodegenerative; Synucleinopathies

Received: 26-Sept-2022, Manuscript No. ijddr-22-13130; **Editor assigned:** 30-Sept-2022, Preqc No. PQ-13130; **Reviewed:** 13-Oct-2022, QC No. ijddr-22-13130; **Revised:** 17-Oct-2022, Manuscript No. ijddr-22-13130 (R); **Published:** 28-Oct-2022, DOI: 10.36648/0975-9344.14.10.980

Introduction

Cyclosporine (CsA), a calcineurin inhibitor, was approved, ushering in a new era in immunopharmacology. The majority of immunosuppressive regimens used in organ transplantation have been built on the cyclic endecapeptide CsA. The Food and Drug Administration (FDA) recognised tacrolimus, another calcineurin inhibitor, as a superior substitute for CsA in 1994. Tacrolimus use, when compared to CsA, has been found in numerous trials to be related with a lower transplant rejection rate. Nevertheless, CsA is still widely used in clinical practise, primarily for the prevention of rejection in various types of organ transplantation, the prevention of graft-versus-host disease after bone-marrow transplantation, and in a variety of inflammatory and autoimmune diseases like nephrotic syndrome, Crohn's disease, psoriasis, and focal segmental glomerulosclerosis. CsA is substantially metabolised in the liver and gastrointestinal tract by CYP3A4 and to a lesser extent by CYP3A5, with the gut having a significantly higher concentration of this enzyme than the liver **[1-3].** This efflux pump is used to move CsA out of cells, which is a substrate of P-glycoprotein. Its poor bioavailability is caused by both CYP3A4 and the presence of Pgp in the gut. The patient's pathology, days post-transplantation, comedication, age, sex, body weight, and creatinine clearance are just a few of the variables that affect the pharmacokinetic characteristics of CsA. Additionally, because CsA has a limited therapeutic index, therapeutic drug monitoring (TDM) can be an effective technique for individualised therapy that reduces the likelihood of therapeutic failure.

Technology advancements and improvements in artificial intelligence approaches have been a major factor in the emergence of the precision medicine paradigm. As part of this strategy, many tactics are framed with the intention of tailoring medical care to the unique qualities of each patient. In order to distinguish patients within a population with similar general clinical conditions and subsequently modify the available therapeutic tools to optimise the clinical outcome at the individual level, tools that allow for patient differentiation are fed by genetic information, biomarkers, and phenotypic and psychosocial characteristics. Therefore, using computer models to help pharmacological decision-making falls under the purview of precision medicine. Recently, model-informed precision dosing, a method from the field of pharmacometrics, has been discussed (MIPD). The function of nerve cells is impacted by neurodegenerative illnesses such alpha-synucleinopathies, which can cause their death, destabilise the neural network, and result in the onset of sickness **[4]**. The presence of intracellular alpha-synuclein filamentous aggregates in degenerating cells in the form of Lewy bodies and Lewy neurites is a hallmark of alpha-synucleinopathies like Parkinson's disease and dementia with Lewy bodies, while they take the form of glial cytoplasmic inclusions in multiple system atrophy**[5]**. The transmission of alpha-synuclein aggregates from one cell to another is now understood to be a factor in the pathology's gradual progression.

There is presently no medication that can stop the neurodegenerative process from progressing, despite years of dedicated research. Only symptomatic alleviation and a halt to the progression of the disease are offered by the approved pharmaceutical treatments now in use. Inability to enter the brain at a therapeutic concentration is one of the key factors impacting medication efficacy and use. Intracranial injection of hydrogels for medication administration is one invasive treatment that has been developed to get around this restriction. To accomplish direct drug delivery to the brain, it is optimal to utilise a bioresorbable hydrogel that has been loaded with pharmaceuticals or modified cells **[6]**. This eliminates the need for surgical removal and instead ensures a constant supply of pharmaceuticals at a clinically relevant concentration. The nasal route of administration has recently attracted significant interest as an alternative to intracerebral delivery for the treatment of neurodegenerative illnesses, since it offers a noninvasive technique for fast drug adsorption despite the blood brain barrier's barrier-causing barrier (BBB). Using different biomolecules, the effectiveness of nasal drug uptake has been compared to intraperitoneal route, for example. The findings indicate that the number of molecules reaching the brain is more than 5 times higher with intranasal delivery than with intraperitoneal delivery. To improve drug absorption from the nasal cavity to the brain, various polymer compositions have been investigated. It has been demonstrated that one of them, mucoadhesive hydrogels, can extend the amount of time a medicine is in touch with the nasal mucosa **[7]**.

In intracerebral application, hydrogels come into touch with the brain tissue directly and may interact with the cells, leading to unintended side effects that alter cell activity. The nasal mucosa's susceptibility to hydrogel molecules hasn't been investigated for intranasal applications, but it's important to do so in order to rule out the possibility that lower-molecular-weight molecules might pass through the nasal barrier and enter the brain, where they might cause unwanted side effects.

Patients and Data Collection [8]

Retrospective analysis was performed using pharmacokinetic data from CsA TDM routine of patients receiving therapy for autoimmune disorders or organ transplantation. For the purpose of developing a model, data CsA blood concentrations were collected from individuals who had at least one pharmacokinetic profile characterised with four samples. The training data set was taken into account for this collection of patients (Group A). The TDM service's formulary was used to gather information on sex, age, body weight, medication history, dosing schedule, time since last dose, sampling time, details on concurrent drugs, and days post-transplant **[9]**. The database system at the hospital provided access to additional pertinent data from haematological and biochemical tests.

Monitoring CsA Concentration

In tubes containing EDTA, steady-state blood samples were taken at 0, 1, 2, 3, and 4 hours after the dose (C0-C1-C2-C3-C4). Chemiluminescent microparticle immunoassays (CMIA Architect®, Abbot Laboratories) were used to determine the CsA concentrations in whole blood samples. Up to 1500 ng/mL, linearity was demonstrated, and the lowest limit of quantification was 12.5 ng/mL. There were, correspondingly, 4.1, 2.6, and 0.56% coefficients of variation (precision) and 4.1, 8.3, and 6.2% relative errors (accuracy) for concentrations found at the lower, middle, and higher reaches of the calibration range.

Model of Pharmacokinetics for Cyclosporine [10]

Metrics and graphical diagnostics were used to guide the development of the model. Using the Akaike information criterion (AIC) and a visual evaluation of goodness of fit plots, the model data fit was evaluated. These comprised population observations versus model predictions, population residuals, normalised prediction distribution errors (NPDE) versus time and versus the dependent variable. Last but not least, TDM data has a significant variation in dose regimes because these prediction-corrected visual predictive checks (pcVPC) were used as the primary simulation-based diagnostic in model evaluation. According to the typical population forecast for the median time in the bin, the observed and simulated drug concentrations in this graph have both been standardised.

One ml of Roswell Park Memorial Institute (RPMI) medium containing 10% foetal bovine serum, 1% penicillin/streptomycin (Gibco), and 1% L-glutamine (Gibco) was mixed with 100 l of Pluronic 68 10% solution to create a PEG-PPO-PEG solution (Sigma Aldrich). The hydrogel was created by pouring 750 l of the finished solution into a silicon mould and allowing it to fully gel at 37°C for 30 minutes. After that, 1.5 ml of RPMI medium was added. The PEG-PPO-PEG hydrogel dissolution products were collected after 24 hours and used for in vitro cell testing.

Screening for Cytotoxicity

Human neuroblastoma cell line SH-SY5Y was used in the MTT

experiment to assess the cytotoxicity of hydrogel. To achieve confluence, SH-SY5Y cells were grown on a 96-multiwell plate for 24 hours at a cell density of 8 104 cells/well. The culture medium was then withdrawn and replaced with the PEG-PPO-PEG hydrogel supernatant at dilutions of 1:1 and 1:5 v:v. 20% dimethyl sulfoxide was added to the media to produce a positive control, which caused full cell death. Normal medium was used for the negative control. The supernatant was carefully collected after a 24-hour incubation period, and the MTT assay was carried out in accordance with the supplier's instructions.

Discussion

The final significant covariate in the model, creatinine clearance, showed a negative connection with CsA apparent clearance, i.e., a lower creatinine clearance is connected with a higher CsA apparent clearance. To calculate CsA clearance under renal impairment and make the appropriate dose changes, it is particularly important to quantify this covariate effect. Background information on this effect, which we believe influences CsA disposition, is provided by earlier studies conducted by our research team on the role of cardiovascular physiology in pharmacokinetic processes. Despite the fact that CsA exhibits intestinal and hepatic metabolism, renally impaired patients may experience problems with their clearance of the drug due to a change in the relative blood flow fractions provided to the various organs. The fraction of blood flow directed to the splanchnic area will increase when the renal blood flow is compromised, which can happen as a result of CsA-induced toxicity or CsA subtherapeutic levels in renal transplant patients, increasing CsA systemic clearance. As both measurements are thought to share predictive and mechanistic information on CsA clearance, this covariable was chosen over postoperative days. When a kidney transplant is successful, the organism accepts the graft over time and the creatinine level returns to normal, which reduces blood flow to the splanchnic region and, consequently, CsA clearance. Immediately following the transplant, renal blood flow is minimal and creatinine levels are high. However, grafts only operate adequately for a short while, and both functionality and creatinine clearance decline over time. Interesting outcomes were seen after the model was implemented in a clinical environment. The MPPEs for C1 and C2 were below 50%, which is not excessive when taking into account the pharmacokinetic variability of CsA. These predictions were performed for new patients using only the population pharmacokinetic model and the individual creatinine clearance value (both inter- and intraindividual). For this initial instance, the estimation of C0 produced subpar results. However, after the patient data was included, this significantly improved, with the MPPE dropping from 98% to 27% on the third occurrence. While the prediction of C2 was greatly improved for the second and third times, accuracy indicators for C1 also showed a significant improvement. It is important to recognise some of the study's limitations. The reason for treatment (renal transplantation or autoimmune disease) was examined in our data as a covariate, and the results showed that none of the pharmacokinetic parameters were significantly different. However, because there were relatively few subjects in each group, these findings may not be definitive. As a result, the described CYA population pharmacokinetic model should be externally tested with the target population before being implemented in other centres because the lack of numerous validation cohorts restricts the extrapolation of model predictions in other populations.

Conclusions

In order to forecast CsA whole blood concentrations in the clinical context for patients under various dosing regimens and diseases, a population pharmacokinetic model of CsA was created and put into use. The only significant covariate capable of partially explaining the interindividual variation in CsA apparent clearance was found to be creatinine clearance. When individual patient data and Bayesian forecasting were added, the model's good predictive ability dramatically increased, making it a powerful tool for dose adjustment. Drug carriers are a useful instrument for facilitating the delivery of medications to the intended tissues. The use of hydrogels for medication delivery to the brain via intracerebral injection and intranasal administration has cleared the way for the creation of novel medicines for the treatment of neurodegenerative illnesses in recent years. While only a small amount of low molecular weight hydrogel dissolution products may pass through the nasal mucosa and reach the brain cells when hydrogels are administered intravenously, cells are in direct contact with the carrier material and its dissolution products when administered intracerebrally. Investigation is needed into how hydrogel dissolution products affect the evolution of pathology, especially in conditions where protein clumps are known to move from one cell to another, such as alpha-synucleinopathies. This study used an in vitro approach to investigate the effects of PEG-PPO-PEG hydrogel dissolving products on FF infection of SH-SY5Y cells. The results demonstrated that when cells were infected and cultivated in the presence of hydrogel dissolution products, there was a significant increase in the number of SH-SY5Y cells that had FF fibrils (FF cells) per picture and an increase in FF fibrils inside FF cells. The potential of this hydrogel to increase FF aggregates may have a significant impact on the course of the pathology, limiting its efficacy and causing unintended contributions.

Acknowledgement

The author would like to acknowledge his Department of Pharmaceutical Sciences, Faculty of Chemistry, Turkey for their support during this work.

Conflict of Interest

The author has no known conflicts of interested associated with this paper.

References

1 Grimm M, Rinaldi M, Yonan N A (2006) Superior prevention of acute rejection by tacrolimus vs. cyclosporine in heart transplant recipients - a large European trial. American Journal of Transplantation. 6(6): 1387-1397.

2 Webster AC, Woodroffe R C, Taylor R S, Chapman J R, Craig J C (2005) Tacrolimus versus ciclosporin as primary immunosuppression for kidney transplant recipients: meta-analysis and meta-regression of randomised trial data. BMJ 331(7520): 780-810.

3 Azarfar A, Ravanshad Y, Mehrad Majd H (2018) Comparison of tacrolimus and cyclosporine for immunosuppression after renal transplantation: an updated systematic review and meta-analysis. Saudi Journal of Kidney Diseases and Transplantation 29(6): 1376-1385.

4 Gao X, Ma Y, Sun L, Chen D, Mei C (2014) Cyclosporine A for the treatment of refractory nephrotic syndrome with renal dysfunction. Experimental and Therapeutic Medicine 7(2): 447-450.

5 https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD000297.pub2/abstract

6 https://www.sciencedirect.com/science/article/abs/pii/S0270929503700266

7 Dai Y, Iwanaga K, Lin Y S (2004) In vitro metabolism of cyclosporine a by human kidney CYP3A5. Biochemical Pharmacology 68(9): 1889-1902.

8 Von Richter O, Burk O, Fromm M F, Thon K P (2004) Cytochrome P450 3A4 and P-glycoprotein expression in human small intestinal enterocytes and hepatocytes: a comparative analysis in paired tissue specimens. Clinical Pharmacology and Therapeutics 75(3): 172-183.

9 Staatz C E, Goodman LK, Tett S E (2010) Effect of CYP3A and ABCB1 single nucleotide polymorphisms on the pharmacokinetics and pharmacodynamics of calcineurin inhibitors: part I. Clinical Pharmacokinetics 49(3): 141-175.

10 https://accp1.onlinelibrary.wiley.com/doi/abs/10.1002/jcph.123.