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Research Article
Population Pharmacokinetics of Clarithromycin in Mexican Hospitalized Patients with Respiratory Disease: Evidence for a Reduced Clearance

[1]A.E. Lemus-Castellanos, [2,3]I.F. Trocóniz, [2]M.J. Garrido, [1]V. Granados-Soto and [4,5]F.J. Flores-Murrieta

[1]Neurobiology of Pain Laboratory, Departamento de Farmacobiología, Cinvestav, Sede Sur, Mexico City, Mexico
[2]Pharmacometrics and Systems Pharmacology, Departament of Pharmacy and Pharmaceutical Technology, School of Pharmacy, University of Navarra, Pamplona, Spain
[3]Instituto Navarra de Investigación Sanitaria (IdiSNA), Spain
[4]Unidad de Investigación en Farmacología, Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas, Mexico City, Mexico
[5]Sección de Estudios de Posgrado e Investigación, Escuela Superior de Medicina del Instituto Politécnico Nacional, Mexico City, Mexico

Abstract

Objective: To describe quantitatively the variability associated to the pharmacokinetic (PK) processes of clarithromycin (CLA) in Mexican hospitalized patients with respiratory infection and to determine whether the 6-beta-hydroxycortisol (6β-OHC)/cortisol ratio, among other factors would partially explain such variability. **Materials and Methods:** Fifty three patients aged >18 years with respiratory disease treated with CLA were included in the study. An average of 3 blood samples per patient were obtained at approximately the following Times After Dosing (TAD): 0.5, 1.25, 2, 3, 4, 6, 9 and 12 h. Clarithromycin was given orally or i.v., twice daily at the dose of 500 mg. Around the same times at which blood samples were collected, one urine sample was obtained for determining the 6β-OHC/cortisol ratio. The serum concentration vs time data of CLA were modeled using the population approach with NONMEM 7.2. **Results:** A one-compartment disposition model with first-order rate of absorption and concentration independent distribution and elimination provided a reasonable description of the data. Absolute bioavailability of CLA was not different from 1 ($p>0.05$). The population estimate of total clearance was 14.6 L h^{-1}, lower than that reported previously for healthy volunteers. Final population model included body weight as the unique covariate affecting the apparent volume of distribution. **Conclusion:** The study population showed a total clearance lower than that reported for healthy volunteers from other countries, probably due to the low activity of CYP3A determined in this population. However, the CYP3A activity level did not result as a significative covariable of the CLA total clearance.

Key words: Clarithromycin, population pharmacokinetics, CYP3A, 6β-OHC/cortisol ratio, TAD

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Corresponding Author: F.J. Flores-Murrieta, Unidad de Investigación en Farmacología,
Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas, Calz. de Tlalpan 4502, Col. Sección XVI, 14080 Mexico City, Mexico

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Clarithromycin (CLA) is a macrolide antibiotic with wide spectrum activity[1]. It is effective in the treatment of different hospital infections and in the eradication of *M. avium* complex (MAC), *M. chelonae* sp. and *Toxoplasma* sp. in patients with AIDS. Its main use is in the treatment of both acute (i.e., community-acquired pneumonia, bronchitis) and chronic (i.e., cystic fibrosis, panbronchiolitis, chronic obstructive pulmonary disease and non-cystic fibrosis bronchiectasis) respiratory tract infections (including also pharyngitis, sinusitis and otitis media)[2,3] under dosage schedule of 500 mg bid, administered intravenously or orally[4]. In addition, CLA has been suggested recently to treat treatment-refractory hypersomnolence and due to its immunomodulatory and antitumoral properties, in neoplastic diseases such as multiple myeloma and relapsed/refractory extranodal marginal zone lymphoma[5,6].

Clarithromycin is extensively metabolized into at least 8 metabolites but 14-hydroxyclarithromycin is the most important of them because contributes significantly to the antibiotic effect[7,8] and whose formation is mediated predominantly by CYP3A4[9-11]. It is known that CLA inhibits the activity (but not the expression) of this enzyme in a dose-dependent fashion[12,13] and at the same time, CLA pharmacokinetics could be affected by the presence of substrates or modulators of the CYP3A[14] which are co-medicated occasionally in hospitalized patients.

A wide population variability in the CYP3A activity has been reported (upto 100 folds)[15]. It is known that CYP3A activity is lower in the Mexican population than in other populations. Drugs metabolized by CYP3A (such as nifedipine, cyclosporine, midazolam or sildenafil) show plasma concentration higher than those described in Caucasian populations[16-20]. Furthermore, a study performed in diabetic patients showed that the urinary ratio of 6β-hydroxycortisol/cortisol (6β-OHC/cortisol), a marker of CYP3A4 activity[21,22] was 4.4 in Mexicans, compared to a value of 6 in Caucasian population[23,24].

Up to date there is only one study about the population pharmacokinetics of CLA and 14-hydroxy-clarithromicyn, from which it is known the inhibition level that CLA produces on CYP3A4 after seven doses of 500 mg/12 h in healthy Caucasian volunteers (n = 12)[25]. However, a high degree of variability has been observed in the pharmacokinetics of CLA in patients with pulmonary infection[26] that could be related with therapeutic ineffectiveness[3] and a high frequency of adverse drug reactions in hospitalized patients[27,28]. Considering the multiple factors that could participate of such variability and the fact that the population approach allow to know which variables affect the pharmacokinetics of drugs, the main purpose of this study was to know if there is a difference in the CLA pharmacokinetics in hospitalized patients with respiratory disease in comparison with that known in healthy subjects that suggests an important clinical impact and should be considered to improve the treatment of this sort of patients.

If there would be such difference, the secondary objective would be to evaluate if that difference could be related to the activity level of CYP3A4 exhibited in Mexican population (as an indirect measure of the 6β-OHC/cortisol ratio, tested in urine) or to another covariable.

MATERIALS AND METHODS

Study design, data collection and considerations: A longitudinal, prospective, observational clinical study was performed in patients hospitalized in the floor area or ICU from National Institute of the Respiratory Diseases (México city) with documented or suspected respiratory infection (between July, 2012 and September, 2013). The study protocol was approved by IRB of the same hospital (N°C28-11) and was conducted in accordance with good clinical practices. Patients were enrolled in the study after informed consent was obtained. A total of 53 patients, aged ≥18 years and needing to be treated with CLA were included. Clinical analysis included blood count, blood chemistry, liver function, blood gases, microbiological analysis and physical examination. A severity of illness score (SOFA) was calculated. Creatinine clearance (CL_{CR}) was estimated through Cockcroft-Gault equation (C-G) considering three classes of patients depending on weight, in order to avoid under or overestimation as previously was described[29]. Weight categories and adjustments for C-G CL_{CR} calculations were based on the Body Mass Index (BMI) structure developed by the World Health Organization (WHO)[30] as follows:

- Underweight patients (BMI ≤ 18.5 kg m^{-2}):

$$CL_{CR}\,(mL\,min^{-1}) = \frac{(BW)(140-AGE)}{CRs \times 72}\,(0.85 \text{if female})$$

where, BW is the total body weight (kg), age is expressed in years (AGE) and CRs is serum creatinine (mg dL^{-1}).

- Normal weight patients (BMI 18.5-24.9 kg m^{-2}):

$$CL_{CR}\,(mL\,min^{-1}) = \frac{(IBW)(140-AGE)}{CRs \times 72}\,(0.85 \text{ if female})$$

where, IBW is the ideal body weight and is expressed in kg:

Males: IBW = 50 kg+(2.3 kg (height in inches-60))
Females: IBW = 45.5 kg+(2.3 kg (height in inches-60))

- Overweight, obese and morbidly obese patients (BMI≥25 kg m^{-2}):

$$CL_{CR}\,(mL\,min^{-1}) = \frac{(ABW0.4)(140-AGE)}{CRs \times 72}\,(0.85 \text{ if female})$$

where, ABW is the adjusted body weight (kg):

$$ABW_{0.4} = IBW+0.4\,(BW-IBW)$$

In order to evaluate the effect of co-medications on CYP3A activity, they were classified based on the literature data in inhibitors, inducers or substrates of CYP3A. Table 1 shows the list of potential covariates gathered from each patient and tested for significance during the population approach.

Drug administration: Clarithromycin (CLA) was given intravenously or orally twice daily at the dose of 500 mg. The CLA (Klaricid, Abbott Laboratories de México, S.A. de C.V.) was reconstituted according to the manufacturer guidelines, diluted in 100 mL of NaCl 0.9% and infused intravenously during 30-50 min or orally administered. The route of administration was chosen by the attending physician based on clinical or/and microbiological data for infection treatment or as prophylactic treatment. When CLA was administered orally, it was accompanied by food. The number of doses previously received and missing doses were known for each patient in the study at the time of the beginning of the current study.

Sample collection: Blood samples (7-8 mL) were obtained for determining the concentration of CLA in plasma approximately at the following Times After Dose (TAD): 0.5, 1.25, 2, 3, 4, 6, 9 and 12 h. An average of 3 blood samples for each patient was collected in heparinezed tubes, via a venous catheter. Around the same times at which blood samples were collected, one urine sample was obtained for determining the 6β-OHC/cortisol ratio and immediately stored at -80°C until analysis. Blood samples were immediately centrifuged at 3500 rpm at 4°C. The plasma was then separated and stored frozen at -80°C until analyzed by ultra-performance liquid chromatography.

Table 1: Summary of patient characteristics

Patient characteristic	No.	Mean	Range	Reference value
Demographics				
Male	37			
Female	16			
Body mass index (BMI kg m^{-2})	55	25.78	16.80-51.56	18.5-24.9
Body weight (BW kg)	53	69.68	38.5-132	NA
Age (AGE years)	53	46.38	18-88	NA
Others parameters				
Serum CR (mg dL^{-1})	53	0.77	0.34 - 1.85	0.7-1.2
Creatinine clearance (CL_{CR}) -Cockcroft-Gault- (mL min^{-1})	53	115.12	35.52-317.40	97-137
Albumin (ALB g dL^{-1})	53	2.81	1.22-4.67	3.5-4.8
Globulin (GB (g dL^{-1})	52	3.36	1.63-5.53	2.3-3.5
Total bilirubin (BILI mg dL^{-1})	53	0.72	0.25-2.09	0.3-1.2
Mean arterial pressure (MAP mmHg)	53	84.00	60-119	>60
CYP3A activity				
6β-OHC/cortisol ratio	37	1.41	0.11-7.33	4.4
SOFA score	53	2.68	0-12	0
***Co-medicated drugs**				
CYP3A4 inhibitors	53	2.42	1-5	NA
CYP3A4 substrates	53	0.83	0-5	NA
CYP3A4 inducers	53	0.64	0-2	NA

SOFA: Sequential organ failure assessment score, *Concomitant drugs were administered at different times during the study, this table only considers those administered in a period of one day prior to blood sampling, Reference value: Rectangle shows the variables which mean is outside the reported range for a healthy subject. The reference values of clinical parameters are those reported by the hospital laboratory, NA: Not apply

Analytical determination of CLA in plasma: Concentration values of total CLA in plasma were determined by a specific and validated analytical method[31]. Briefly, 0.5 mL plasma samples were alkalinized with sodium hydroxide and extracted with a mixture of n-hexane-isopropanol under agitation. Organic layer was evaporated and the dry residue was redissolved in mobile phase and injected into the chromatographic system. Separation of compounds was performed in an ultra-performance liquid chromatographic system using an Acquity BEH-HILI C column of 2.1×150 mm, 1.7 µm particle size eluted with a mixture of aqueous 0.01 M sodium monobasic phosphate solution with acetonitrile (20:80, v/v). The CLA was quantified by use of an ultraviolet detector ($\lambda = 205$ nm). Under these conditions, the lower limit of quantification of the technique was 0.5 µg mL^{-1}. Calibration curves were linear between this limit of quantification and 10 µg mL^{-1}. The accuracy and precision of inter-day and intra-day (studied over 3 days) assays were determined at three concentrations in the range of expected concentration. Calculated concentration never deviated more than 12% from nominal concentration. The inter-day and intra-day precision expressed as coefficient of variation, was always below 11%. These characteristics make this method suitable for performing pharmacokinetic studies of CLA.

Analytical determination of 6β-OHC/cortisol ratio in urine: Concentration values of 6β-OHC in urine were determined by a specific and validated analytical high-performance liquid chromatographic method. Briefly, 1.5 mL urine samples were alkalinized with sodium hydroxide and extracted with ethyl acetate. Organic layer was evaporated and dry residue was redissolved in mobile phase and injected into the chromatographic system. Separation of compounds was performed in a high-performance liquid chromatograph using a Princeton SPHER-100 C-18 column of 150x3.9 mm, 5 µm particle size eluted with a mixture of 0.025 M aqueous sodium monobasic phosphate solution with acetonitrile (82:18, v/v). The 6β-OHC was quantified by use of an ultraviolet detector ($\lambda = 245$ nm). The limit of quantification of the technique was 50 ng mL^{-1}. Calibration curves were linear between this limit of quantification and 1000 ng mL^{-1}. The accuracy and precision of inter-day and intra-day (studied over 3 days) assays were determined at three concentrations in the range of expected concentration. Calculated concentration never deviated more than 11% from nominal concentration. The inter-day and intra-day precision expressed as coefficient of variation, was always below 11%.

Urine cortisol was determined by using a commercial ELISA kit (RE52241, IBL International, Hamburg, Germany) in exact accordance with the manufacturer's instructions. Urine samples were defrosted and diluted 1:2 with incubation buffer to ensure that their cortisol values could be read from the standard curve. At the endpoint (after addition of stop solution) the 96-well plate were read at 450 nm. A Synergy HT, BioTek detection platform and Gen5™ data analysis software version 2.01.14 was used for quantification.

Population pharmacokinetic analysis: Clarithromycin (CLA) plasma concentrations were modelled through a non-linear mixed effect model using the software NONMEM 7.2 (Icon, Dublin, Ireland) with the First Order Conditional Estimation (FOCE) method and the INTERACTION option. The CLA absorption was described using a first order rate input model. The presence of a lag time was explored for significance. One and two-compartments structural models were evaluated to describe drug disposition. Model selection was based on (i) The decrease in the minimum value of the Objective Function Value (OFV) provided by NONMEM, where a difference of 3.84, 6.63 and 10.83 points in the OFV between two nested models differing in one parameter was significant at the 0.05, 0.01 and 0.001 levels of significance, respectively, (ii) The relative standard errors of the parameters, calculated as the ratio between the standard error provided by NONMEM and the parameter estimate and (iii) The goodness-of-fit (GOF) plots. Inter-Individual Variability (IIV) was modeled exponentially. The additive, proportional and combined models were tested to account for the residual variability.

Covariate selection: Patient characteristics as sex, BMI, BW, AGE, CL_{CR}, total bilirubin, mean arterial pressure, 6β-OHC/cortisol ratio, CYP3A4 inhibitors, substrates and inducers and SOFA score (Table 1) were explored as possible sources of IIV in CLA pharmacokinetics. Continuous variables were centered to the median value of the population. Covariate selection was carried out by the stepwise covariate model building (SCM tool in PsN 3.5.3). The following levels of significance were used during the forward inclusion and backward deletion 0.05 and 0.005, respectively. Simulations and GOF plots were also used to support the inclusion and deletion steps.

Model evaluation: Model evaluation was conducted by visually exploring GOF plots as a first indicator of model performance.

The precision of the final parameter estimates was evaluated by performing a non-parametric bootstrap analysis. Patients were randomly sampled with replacement from the data set used for building the model to create bootstrap data sets with the same sample size as the original. The final model was used to generate and analyze 1000 bootstrap data sets

(Bootstrap tool in PDxPop 5). The mean, 2.5th and 97.5th percentiles of the parameter estimates were reported in order to build the 95% bootstrap confidence intervals. A prediction and variability-corrected visual predictive check (pvcVPC)[32] was used to explore the performance of the final model (VPC tool in PsN 3.5.3). The pvcVPCs were constructed (i) with the 5th, 50th and 95th percentiles for the observed data (90% inter-percentile range) and (ii) Then, 1000 datasets were simulated from the final model parameter estimates and the 95% prediction intervals of the 5th, 50th and 95th percentiles based on the simulated datasets were calculated and represented for visual inspection.

RESULTS

Patient characteristics: A total of 53 patients were enrolled for the pharmacokinetic study of CLA. The percentage of female patients was 30%. The CLA was administered intravenously to 24 patients (45%), orally to 28 patients (53%) and only one patient received CLA through both routes of administration during the sampling period. The main prescription reason was community-acquired pneumonia (CAP) (68%), followed by other types of pneumonia (11%). Figure 1 shows the different diagnoses of patients included in this study and their corresponding percentage to which CLA was prescribed.

Table 1 displays a summary of main demographic data from patients together with other biochemical data and health score that were considered as covariates for the analysis. The 6β-OHC concentration was the only variable that could not be determined in all samples due to interferences present in the biological matrix. The sample size of the 6β-OHC/cortisol ratio diminished from 53-37. In addition to CLA, all patients received at least another CYP3A inhibitor (omeprazole or ranitidine, principally), 45% received a CYP3A substrate and 60% received some CYP3A inductor. In general the study population suffered overweight or obesity, hypoalbuminemia and showed a CYP3A activity level lower than the value previously reported for Mexican population (measured through the urinary ratio of 6-βOHC/cortisol). Approximately 21% of the population was over 60 years of age.

CLA doses and serum concentrations: In general, the prescribed dose of CLA was 500 mg every 12 h for all patients. When deviations of this scheme were observed, they were taken into account in the database. The number of average doses previously administered to the start of the study was 11.8 (range, 1-26). A total of 165 values of CLA concentration from 53 patients were measured. Concentration data outside the range of the calibration curve were ignored. In total, 144 concentration data were used to develop the population PK model. Figure 2 shows the CLA serum concentrations as a function of time after dose for both type of administration: intravenous or oral.

Population pharmacokinetics analysis: A one-compartment disposition model with first-order rate of absorption and concentration independent distribution and elimination provided a reasonable description of the data. Absolute

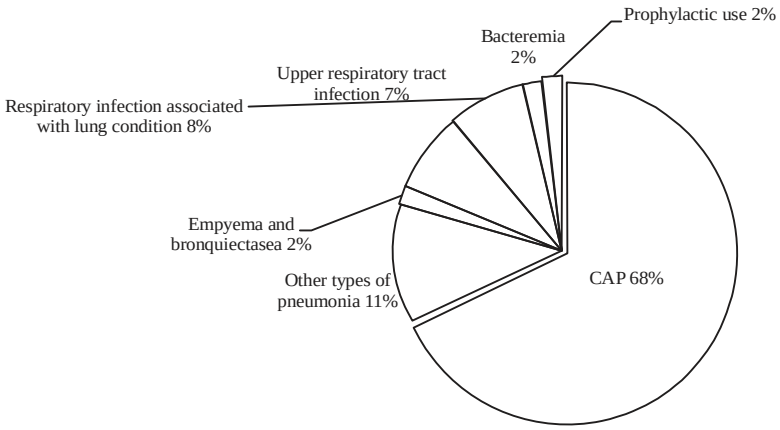

Fig. 1: Prescription reasons of CLA to the study population (in percentage). The community-acquired pneumonia (CAP) was the main cause of administration of CLA. Other types of pneumonia included nosocomial pneumonia, interstitial pneumonia and pneumonia of the right upper lobe. The lung conditions associated with respiratory infections were pulmonary fibrosis, cor pulmonale and chronic obstructive pulmonary disease

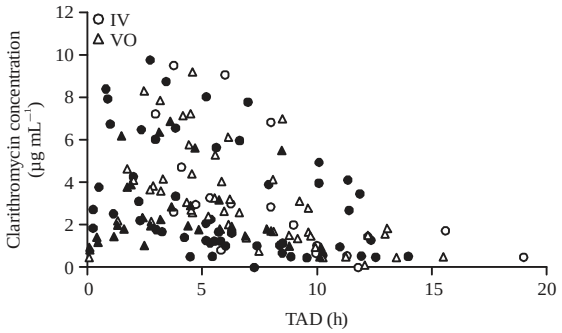

Fig. 2: Serum concentration profile of CLA in function of the route of administration. The triangles represent the serum concentrations of CLA from the oral administration (VO) and the circles those from the intravenous administration (IV), TAD: Time after dose

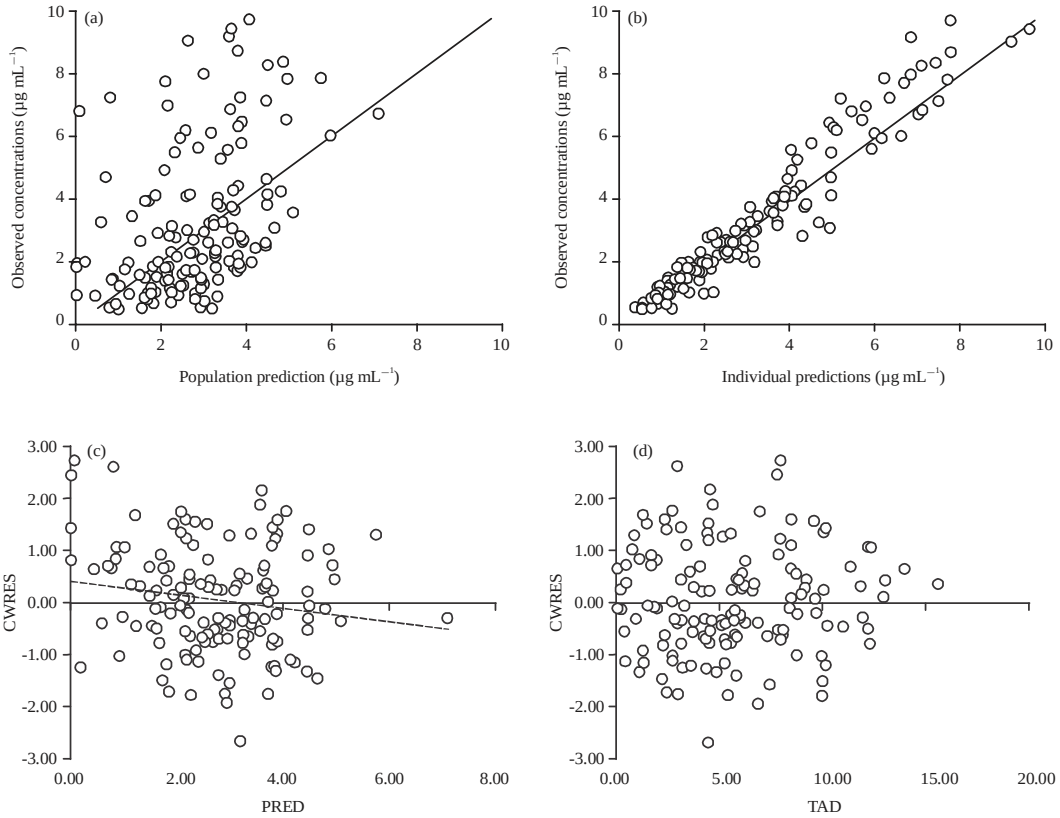

Fig. 3(a-d): Goodness-of-fit plots for the final model of clarithromycin, CWRES: Conditional weighted residuals, TAD: Time after dose and PRED: Prediction

bioavailability of CLA was not significantly different from 1 ($p>0.05$). Data supported the inclusion of IIV on the total plasma clearance (CL), apparent volume of distribution (V) but not on Ka, the first order rate constant of absorption and lag time. Residual variability was best described by a combined (proportional plus additive) error model.

After analyzing different covariates, the selected population PK model included body weight as the sole covariate affecting V. Table 2 summarizes the population parameter estimates of the selected model. Pharmacokinetic parameters were reliably estimated as indicated by the low percentage of relative standard errors. The following diagnostic plots were valuated: Observed concentrations vs population and individual predicted concentrations and conditional weighted residuals vs population predictions and vs Time After Dose (TAD). Figure 3 displays these diagnostic plots where no trends are observed indicating proper model performance.

Table 2: Population pharmacokinetic model estimates, shrinkage values and bootstrap results for clarithromycin

Parameters	Estimate RSE (%)	Shrinkage (%)	Bootstrap median	(2.5th-97.5th percentile)
Ka (h^{-1})	1.16 (30)		1.54	0.66-4.36
V (L) = $\theta_V \times (e^{0.017 \times (BW-70)})$	129 (15)		127	90.5-180
CL (L h^{-1})	14.60 (8)		14.51	12.2-16.8
F	1 (fix)		1	1-1
ALAG (h)	1.03 (7)		1.03	0.70-1.28
Inter-individual variability (IIV)				
IIV_V (%)	36 (54)	28.5	0.36	0.03-0.80
IIV_{CL} (%)	33 (20)	8.2	0.32	0.20-0.47
Residual variability		25.9		
$Error_{additive}$ (%)	23 (26)		0.23	0.08-0.41
$Error_{proporcional}$ (%)	23 (13)		0.22	0.12-0.30

Ka: First order rate constant of absorption, ALAG: Lag time, F: Bioavailability, V: Distribution volume, CL: Clearance, BW: Body weight and RSE: Relative standard error

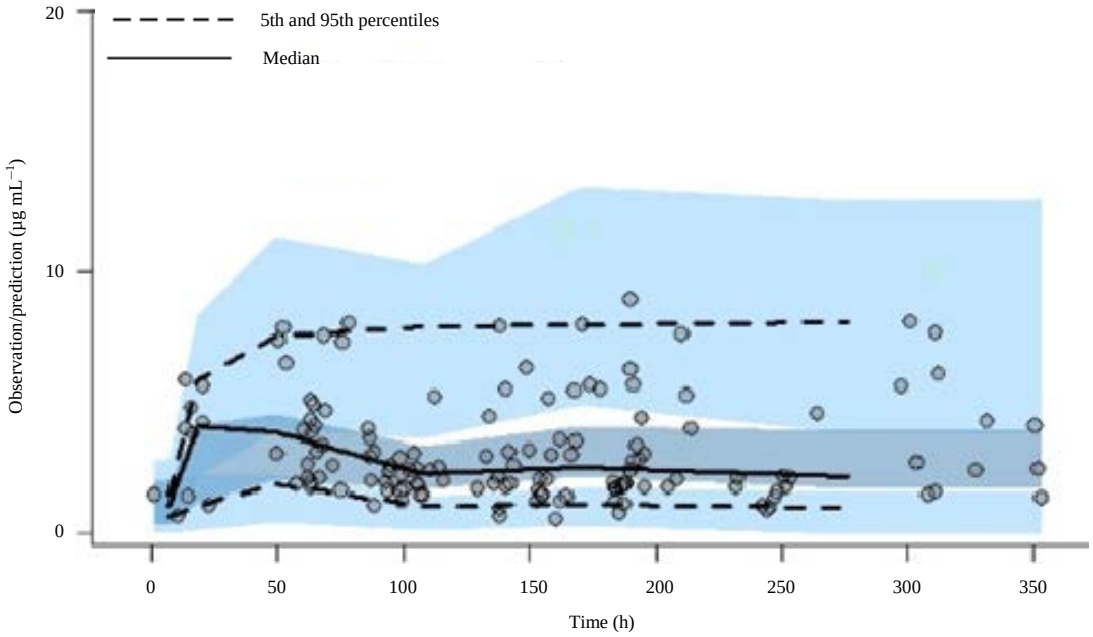

Fig. 4: Result from the pvcVPC of CLA. The mid-blue shading represents the simulation-based 95% prediction intervals for the median, the sky blue shading shows the simulation-based 95% prediction intervals for the percentiles 5th and 95th, respectively

Model evaluation: As shown also in Table 2, the mean parameter estimates obtained from the bootstrap process were very similar to those previously obtained with the original dataset. Furthermore, visual inspection of pvcVPC showed a good correlation between the percentile intervals obtained by simulations from the selected model and raw data (Fig. 4) indicating that the typical tendency and the dispersion of the data were well captured.

DISCUSSION

In this study, the population pharmacokinetics of CLA, a substrate and inhibitor of CYP3A4 was characterized in Mexican patients with respiratory infection. The originality of this work resides on the fact of being the first population approach of CLA performed on a clinical condition, whose findings would let to health care professionals to have a more complete understanding about the considerations that should be taken account in order to improve the current treatment for this population kind and that some of them had been previously ignored in the hospital environment.

Additionally to the disease influence on the pharmacokinetics of CLA, there is evidence about interethnic differences in the pharmacokinetics of the drugs metabolized by CYP3A4[16-20,33-35]. It has been described that CLA metabolism is determined by the activity of CYP3A4[26]. However, it seems

that this is not the only pathway in which interethnic differences have been reported. It is known, that CLA is a substrate of MDR1[36,37] and interethnic differences in this pathway have also been reported[38]. Another important aspect is that several drugs metabolized by CYP3A4 that are substrates of MDR1 reached higher concentrations in Mexicans[16,19,22,33] and when administered intravenously, a decreased clearance has been reported[18,19]. Although, these differences have been reported, the genetic basis of such differences have not been fully established, since changes in the distribution of CYP3A4 alleles observed in different populations have not correlated with the pharmacokinetic profile of drugs metabolized by this pathway[39].

Results obtained in this study, when the population approach have been carried out, serum concentration vs time data of CLA were better described by a one-compartment model as previously reported[25,40]. A greater magnitude of IIV was observed in patients (IIV_V = 36%, IIV_{CL} = 33%) compared to that reported in healthy volunteers (IIV_V = 25%, IIV_{CL} = 17%)[25], as expected due to heterogeneity of the evaluated populations. The population estimates observed in this study for lag time = 1.03 h, Ka = 1.16 h^{-1} and V = 129 L (Table 2) are in agreement with those reported in the literature for healthy subjects obtained after oral administration of multiple dosing of 500 mg of CLA[1,14,41], whereas, CL was lower in the current population.

It is important to note two important aspects. On one hand, it was observed that volume of distribution was significantly influenced by BW. According to the established model and through simulations when a patient has a BW higher than 74 kg the reached concentrations were lower than the MIC reported for CLA (1 μg mL^{-1}) for the main etiologic agents of respiratory diseases as *Streptococcus pneumoniae*, *Staphylococcus* sp., *Haemophilus influenzae* and *Moraxella catarrhalis*[42], which may lead to inefficacy of CLA. On the other hand, clearance obtained was lower than the reported values in healthy volunteers, which could be explained by the low activity of CYP3A4 of Mexican population. It is also known that CLA is an inhibitor of CYP3A and it can inhibit its own metabolism (approximately 50-70% after seven doses of 500 mg bid in healthy subjects)[25]. Although our patients had received a mean of 12 doses, the inhibitory effect on CYP3A4 was in the same magnitude (approximately 70% respect to 4.4 reported in healthy subjects). However, an interethnic variability may not be ruled out. When urine excreted 6β-OHC/cortisol ratio (a marker of CYP3A) was measured, it was observed that average value was of 1.47, (Table 1), contrasting with the values reported in Japanese women (around 8), Caucasian women (around 5.5)[23,43], Mexican healthy volunteers (around 4.4) and Mexicans diabetic patients (around 4.2)[24], indicating a reduced activity of CYP3A. As consequences of the decrease in the CLA_{CL}, the half-life ($t_{1/2}$) incremented from 4.8 h, reported in healthy volunteers for the dose of 500 mg bid at the steady-state[12] to 5.89 h. An increased bioavailability was observed; estimated valued in this study was 100%, which contrast with the values reported in healthy volunteers after administration of a single oral dose (55%)[33,44]. Although, a reduced CLA_{CL} was observed, 6β-OHC/cortisol ratio was not a covariable that explained the variability in the clearance of the drug. This may be due to different possibilities, one of them is that all subjects that participate in the study showed reduced activity of CYP3A4 (a low value of the 6β-OHC/cortisol ratio, 1.47) so that variations around this short value could be so slight as to observe an impact on CLA clearance; another possibility is that 6β-OHC/cortisol ratio may not be a predictive marker of CLA clearance (due to CYP3A4 activity)[45]. In this sense, it has been reported that 6β-OHC/cortisol ratio is a good marker for clearance of drugs such as midazolam[46], but failed to predict clearance of other CYP3A4 substrates. Additionally, CLA is a MDR1 substrate and clearance of the drug may be influenced by this transporter[36,37].

CONCLUSION

In conclusion, a model to describe and predict CLA concentrations after its administration in patients with respiratory disease was developed. The patient body weight can partially explain IIV in the apparent volume distribution of CLA. On the other hand, it is important to highlight that a reduced activity of CYP3A (measured as 6β-OHC/cortisol ratio) was observed, by this covariable did not contribute to explain the pharmacokinetic variability of CLA, but its clinical impact should not be ruled out.

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