Population pharmacokinetics of clindamycin orally and intravenously administered in patients with osteomyelitis

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Clindamycin pharmacokinetics have been studied in adult patients. Rifampicin co-administration could decrease clindamycin exposure.

WHAT THIS STUDY ADDS

- This clindamycin population analysis in patients with osteomyelitis provides useful insight into the fate of this drug and shows that clindamycin clearance increases with body weight. Moreover, this study shows a potential effect of combined rifampicin on clindamycin clearance and addresses sub-therapeutic clindamycin concentrations in heavier patients.

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AIMS

This study was performed to describe clindamycin, administered either orally or intravenously, concentration–time courses to patients with osteomyelitis, to study the effects of different covariates on clindamycin pharmacokinetics and to simulate an optimized administration scheme.

METHODS

Clindamycin concentrations were measured in 50 patients. A total of 122 plasma concentrations were available (58 from oral administration and 64 from i.v. infusion). A population pharmacokinetic model was developed with MONOLIX 4 software.

RESULTS

A one compartment model adequately described the data. Clindamycin clearance increased significantly with body weight (BW). The typical population estimates (interindividual variability) for clearance, volume of distribution and absorption rate constant were 16.2 l h⁻¹ (0.39), 70.2 l and 0.92 h⁻¹, respectively. The bioavailability of the oral form was estimated to be 87.6%. According to BW, theoretical doses needed to reach a C_{min} of 2 mg l⁻¹ were then calculated.

CONCLUSIONS

The current recommendation of 600 mg three times daily seems to be effective up to 75 kg but the dose should be raised to 900 mg three times daily thereafter. These assumptions should be prospectively confirmed.

Introduction

Osteomyelitis is an inflammation of bone caused by a pyogenic organism. It may remain localized or may spread

through the bone to involve the marrow, cortex, cancellous tissue and periosteum. The most common treatments for osteomyelitis are antibiotics and surgery to remove portions of bone that are infected or dead [1]. For optimal

results, antibiotic therapy must be started early, with antimicrobial agents administered for at least 4 to 6 weeks. However, despite continued research, most aspects of antibiotic treatment for osteomyelitis remain to be clearly understood. Indeed current data are sparse and no consensus guidelines are currently available [2]. Thus the treatment of osteomyelitis is still mostly based on expert opinions. Currently, clindamycin is an antimicrobial agent widely used for the treatment of bone and joint infections because of its activity against staphylococci, streptococci and anaerobic bacteria [3]. In addition, clindamycin has high levels of joint and bone penetration [4–6] and inhibits biofilm formation and bacterial adherence [7, 8]. Although its efficacy has been established in several experimental models [9, 10], only a few series on the clindamycin treatment of human bone and joint infections have been reported [11–13]. The current recommendation for the dosage of oral clindamycin is 150–300 mg every 6 h for moderately severe infection and 300–450 mg every 6 h for severe infection [14]. The dosage of clindamycin intravenously administered should be 600 mg–1.2 g day⁻¹ in two, three or four equal doses for serious infections and for more severe infections 1.2–2.7 g day⁻¹ in two, three or four equal doses. Clindamycin dosage modification is not necessary in patients with renal or hepatic insufficiency [14].

In the present study, we have developed a population pharmacokinetic model for clindamycin used in adults treated for bone and joint infections to study the influence of covariates (body weight, age, co-treatments) on pharmacokinetics. The main goal was then to optimize the dose of clindamycin given to patients with osteomyelitis.

Methods

Patients and treatment

This study was a retrospective study including all patients treated with clindamycin orally or intravenously from 2008 to 2010 in the department of orthopaedic surgery at Cochin Hospital, Paris. Ethics committee approval and patient consent are not compulsory in France in order to use retrospectively therapeutic drug monitoring data, so no informed consent had to be collected. The population comprised 50 patients, ranging in age from 18 to 93 years (mean 58.7 years) and in body weight from 23 to 133 kg (mean 70.9 kg). Patients received 600 mg clindamycin as a tablet or intravenous (i.v.) infusion three times a day over 20 min for the treatment of bone and joint infections, except for one patient who received 600 mg four times a day and an additional two patients who received 600 mg once a day. Clindamycin concentrations were monitored on a routine basis. All patients were sampled at steady-state. Renal failure was defined according to creatinine clearance rate estimated using the Cockcroft–Gault

formula. Hepatic function testing had been performed to detect hepatic failure.

Analytical method

Clindamycin was measured in a 500 µl plasma sample by high performance liquid chromatography. Propranolol was used as the internal standard. Clindamycin was extracted by solid phase extraction and separated on an Ultrasphère ODS column (150 by 4.6 mm). UV absorbance at 200 nm was used for the detection. The limit of quantification (LOQ) was 0.1 mg l⁻¹. Mean interassay precision at the low quantity controls was 18% and inaccuracy at the LOQ was 3.7% (percent deviation from the expected value). Overall recoveries were 75%.

Modelling strategy and population pharmacokinetic model

Data were analyzed using the nonlinear mixed effect modelling software program Monolix version 4 (<http://wfn.software.monolix.org>) [15]. Parameters were estimated by computing the maximum likelihood estimator of the parameters without any approximation of the model (no linearization) using the stochastic approximation expectation maximization (SAEM) algorithm combined to a Markov Chain Monte Carlo (MCMC) procedure. The number of MCMC chains was fixed to 10 for all estimations. Several structural pharmacokinetic models were investigated. Data were analyzed according to a one or two compartment model. A proportional model was used to describe the residual variability (ϵ) and the between subject variabilities (BSV or η) were ascribed to an exponential model. The exponential model is defined as follows: $\theta_i = \theta_{pop} \exp(\eta_i)$, where θ_i represents the pharmacokinetic parameter for the i^{th} individual, θ_{pop} is the typical value of pharmacokinetic parameter θ in the population (e.g. population mean), η_i quantifies the deviation of θ_i from θ_{pop} with a distribution of $(0, \omega^2)$.

Parameter shrinkage was calculated as $1 - SD(\eta_i)/\omega$, where $SD(\eta_i)$ and ω are the standard deviation of individual η parameters and the population model estimate of the BSV respectively [16]. The likelihood ratio test (LRT) including the log-likelihood, the Akaike information criterion (AIC) and the Bayesian information criterion (BIC) were used to test different hypotheses regarding the final model, covariate effect(s) on pharmacokinetic parameter(s), residual variability model (proportional vs. proportional plus additive error model) and structure of the variance-covariance matrix for the BSV parameters.

For evaluation of the goodness-of-fit, the following graphs were performed for the final model: observed and predicted concentrations vs. time, observed concentrations vs. population predictions, weighted residuals vs. time and weighted residuals vs. predictions. Similar graphs using individual predictive estimation were examined. Diagnostic graphics were obtained using the R program [17].

Model validation: Prediction-corrected visual predictive check (pcVPC) and normalized prediction distribution errors (NPDE)

Clindamycin concentration profiles were simulated and compared with the observed data to evaluate the predictive performance of the model. Prediction-corrected visual checks were used as informative diagnostic tools to allow inspection of model appropriateness across time as well as across covariate values [18]. The model was also assessed by the NPDE metrics [19].

Dose simulations

The most common causative organism of osteomyelitis in adults is *Staphylococcus aureus* which has a minimum inhibitory concentration (MIC) of 0.125 mg l⁻¹ [20]. In addition clindamycin shows a bone penetration of 30% [21] and a concentration : MIC ratio of 5 is required for time-dependent killing antibiotics [22] which is why a target of 2 mg l⁻¹ for minimum plasma concentration was chosen. The dose needed to achieve this target was then simulated.

Results

Demographic data

A total of 50 patients and 122 plasma concentrations were available for pharmacokinetic evaluation and statistical analysis, 22 patients received clindamycin orally and 22 intravenously. Six patients received clindamycin by both administration routes. Fifty-eight plasma concentrations were available from oral administration and 64 from i.v. infusion. The median dose was 26.0 mg kg⁻¹ day⁻¹ (min–max: 13.5–41.8) and was not significantly different for oral and i.v. administration (27.2 vs. 26.4 mg kg⁻¹ day⁻¹, $P = 0.38$, Mann–Whitney). The mean body weight was 70 kg with a 95% confidence interval of 45 kg to 113 kg. According to body mass index 24% of patients were in the normal weight range (BMI < 25 kg m⁻²), 68% were overweight (BMI from 25 to 30 kg m⁻²) and 8% were obese (BMI > 30 kg m⁻²). Table 1 summarizes patients' characteristics.

Population pharmacokinetics

A total of two concentrations were below the limit of quantification (BLQ) and were treated as left-censored data by the program. A one compartment model adequately described the data (Figure 1). The parameters of the model were the clearance (CL), the volume of distribution (V), the absorption rate constant (K_a) and the bioavailability of the oral form (F) deduced from i.v. infusion. Residual variability was best described by a proportional error model. BSVs were described by an exponential error model and retained only for apparent clearance. The bioavailability of the oral form was estimated using a logit-normal distribution (87.6%, standard error 0.09). The addition of the BW

Table 1

Characteristics of the 50 patients enrolled in the study

	Mean (SD)	Min–max
Age (years)	56.7 ± 3.0	18–93
Weight (kg)	69.9 ± 2.7	23–133
	<i>n</i>	%
Men	30	60.0%
Women	20	40.0%
Renal failure	5	10.0%
Hepatic failure	2	4.2%
Co-treated with rifampicin	4	8.0%

Figure 1

Observed plasma clindamycin concentrations (closed circles) and population pharmacokinetic based model-predicted clindamycin concentrations (curve) as a function of time for i.v. infusion (black) and oral dosing (blue)

covariate on the model (i) decreased the AIC/BIC criteria, (ii) resulted in a 5.86 units decrease in the objective function value and (iii) improved the goodness of fit. A relationship was found between clindamycin clearance and rifampicin association, the co-administration with rifampicin increased clindamycin clearance by 43% (standard error 0.17, $P = 0.04$, Wald test). However the LRT test (more conservative) was not significant due to the small number of patients treated with rifampicin. This covariate was therefore removed from the model. The final covariate model on clearance was: $CL = \theta_{CL} \times \left(\frac{BW}{70} \right)^{covBW}$ where θ_{CL} is the typical value of CL for an adult of 70 kg and covBW is the power estimated from the model.

Table 2 summarizes the final population pharmacokinetic estimates. All the parameters were well estimated

with low relative standard error (RSE%). The η shrinkage for clearance was 0.03, indicating that the empirical Bayesian estimates for individual clearance parameters are reliable.

Evaluation and validation

Figure 2 (pcVPC) shows that the average prediction matches the observed concentration–time courses and that the variability is reasonably estimated. The number

Table 2

Population pharmacokinetic parameters of clindamycin according to the model

Parameters	Mean	RSE (%)
Structural model		
K_a (h^{-1})	0.967	26
CL ($l\ h^{-1}$)	15.2	8
V (l)	66.2	9
F	0.876	11
cov_{WT}	0.497	36
Statistical model		
$\omega_{CL/F}$	0.39	12
σ	0.38	8

RSE%, relative standard error (standard error of estimate/estimate $\times$ 100); K_a , absorption rate constant; CL, elimination clearance; V , volume of distribution; F , bioavailability; σ , proportional residual variability estimate; ω , standard deviation of interindividual variability estimates. cov_{WT} is the influential factor of body weight on clindamycin clearance.

(%) of observed points within the 90% prediction interval was 88.7% and 92.8% for the i.v. infusion and oral form, respectively.

The mean and variance of the NPDE metrics were not significantly different from 0 ($P = 0.84$, Wilcoxon signed rank test) and 1 ($P = 0.83$, Fisher variance test), respectively, and their distribution was not different from a normal one ($P = 0.61$, Shapiro-Wilk test of normality) (Figure 3).

Dose simulations

Doses were simulated using Monte Carlo simulations in order to achieve a minimum target plasma concentration of $2\ mg\ l^{-1}$ (Figure 4).

The usual dose of 600 mg three times daily seems to be effective up to 75 kg body weight. The dose should be re-evaluated to 900 mg three times daily for heavier patients.

Discussion

This paper describes clindamycin pharmacokinetics in 50 patients with osteomyelitis treated with clindamycin orally or intravenously. Clindamycin concentrations were satisfactorily described by a one compartment model. In our model, an effect of body weight on clindamycin clearance has been observed. Pharmacokinetic drug interaction data in adults have shown that co-administration of rifampicin

Figure 2

PC-VPC (prediction-corrected visual predictive check) for clindamycin concentrations A) after i.v. administration and B) after oral dosing. The green lines show the 10th, 50th and 90th percentiles of observed data; the areas represent the 90% confidence interval around the simulated percentiles

Figure 3

Diagnostic plots: population weighted residuals (WRES) (A, C) and normalized prediction distribution error (NPDE) (B, D) as a function of time (A, B) and population prediction (C, D)

was associated with a decreased serum clindamycin concentration [13], presumably because rifampicin is known to be a potent inducer of hepatic cytochrome P450 and clindamycin is mainly eliminated via metabolism. An effect of rifampicin on clindamycin clearance was seen in our study. However the small number of patients co-treated with rifampicin did not provide enough power to keep this effect in the modelling. However the question of low clindamycin exposure in patients treated with concomitant rifampicin should be addressed.

The usual clindamycin dosage used in adults for the treatment of bone and joint infections is 600 mg every 8 h taken orally or administered intravenously. To check the consistency of the current clindamycin dosage we considered a target of 2 mg l⁻¹ for the minimum plasma concentration. The target minimum concentration of 2 mg l⁻¹ was determined by considering that (i) the *in vitro* MIC for methicillin-resistant *Staphylococcus aureus* strains is 0.125 mg l⁻¹ [20], (ii) reported clindamycin bone penetration rates of 30% [21] and (iii) a bone concentration : MIC

Figure 4

Dose ($\text{mg } 8 \text{ h}^{-1}$) needed to achieve a target minimum concentration of 2 mg l^{-1} for clindamycin as a function of body weight. Dashed lines correspond to 90% confidence interval. Horizontal green line correspond to the usual dose of 600 mg every 8 h

ratio of 5 is required for time-dependent killing antibiotics [22].

Body weight had the most important effect on clindamycin pharmacokinetics and thus our dosing recommendations are based on this factor. The usual dose of 600 mg three times daily seems to be effective until 75 kg body weight but may expose patients to sub-therapeutic concentrations thereafter. Thus the dose might be increased to 900 mg every 8 h for heavier patients.

In conclusion, this study reports clindamycin pharmacokinetics in adult patients with osteomyelitis. The clindamycin elimination clearance is related to body weight and seems to be influenced by rifampicin co-administration. According to this model, clindamycin dosing schemes were established as a function of body weight. These assumptions should be prospectively confirmed.

Competing Interests

There are no competing interests to declare.

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