Population pharmacokinetic analysis of ciprofloxacin in intensive care unit adult patients

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BACKGROUND

Previous studies in patients raised the question of the appropriateness of fluoroquinolones dosage regimens regarding drug efficacy and selection of bacterial resistance. This is a major issue for Intensive Care Unit (ICU) patients who represent a highly heterogeneous population. In order to provide optimal dosage regimens for this population, it is necessary to properly characterise the pharmacokinetics (PK) of fluoroquinolones in these patients.

OBJECTIVES

To propose optimal dosage regimens for ICU patients in order to achieve relevant PK/PD targets. It is the largest ciprofloxacin population PK analysis performed to date in this population of patients.

METHODS

The study was carried out on 119 patients entering the ICU of the University Hospital of Toulouse-Rangueil, France, over a total period of 6 years (from 2003 to 2008). Overall, patients were relatively old (61±17 years), weighing 77±16 kg, with a total of 88 men (74%) and 31 women (26%). Serum ciprofloxacin concentrations of the 119 ICU patients were determined at various times after i.v. infusion at standard doses and on several occasions using a validated HPLC method. Among the 119 patients included in the study, most of the patients (83%; N=99) were treated with a 400 mg dose b.i.d. Eleven patients received 400 mg of ciprofloxacin t.i.d., 6 patients received 200 mg b.i.d. (as a 30-min infusion), 2 patients received 400 mg o.d., and 1 patient received 600 mg b.i.d. Two-thirds of the patients were used for model building (N=79, 453 concentrations) and one-third for model evaluation (N=40, 242 concentrations). Population PK analysis was carried out with NONMEM 6 (FOCE-I). In contrast to previous studies [1,2], interoccasion variability was assessed. Evaluation of the model was performed using visual predictive checks (VPC) and normalised prediction distribution errors (NPDE) [3]. AUC_{24h}/MIC and C_{max}/MIC ratios were calculated for each patient to assess whether the respective targets of 100 h and 8 were reached for the dosage regimens given in the study. PK/PD simulations were further carried out in the 119 patients of the study to assess other dosage regimens of ciprofloxacin with respect to the AUC_{24h}/MIC target.

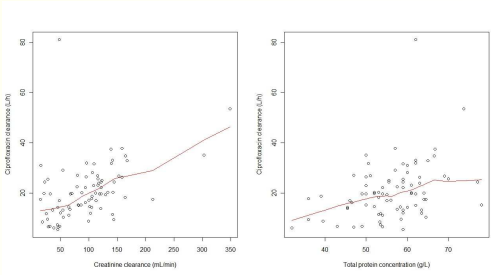

Figure 1: Relationships between individual predictions of ciprofloxacin clearance calculated from the basic model (using the EBEs of random effects for interindividual variability) and the two final covariates: creatinine clearance (Cockcroft and Gault formula) and total protein concentration in blood. The continuous lines represent a tendency curve.

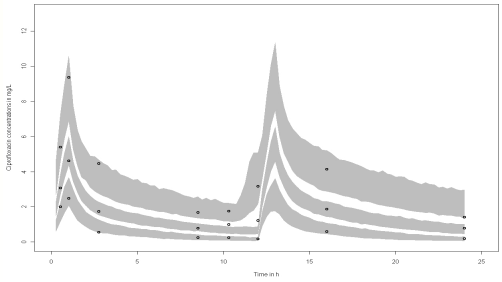

Figure 2: VPC performed on the validation data set for the evaluation of the final pharmacokinetic model developed on the building data set. Grey areas refer (from bottom to top) to the 95% confidence intervals of the 5th, 50th and 95th percentiles according to the model. Dots represent the percentiles 5th, 50th and 95th calculated from the observations of the validation data set in each bin (8 bins in total).

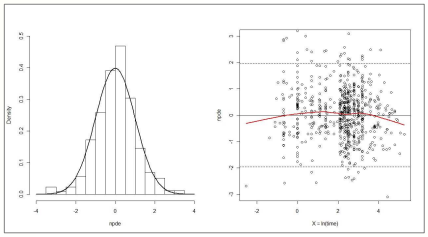

Figure 3: NPDE performed for the global data set.

Left-hand side: Histogram of NPDE with the probability density function of the standard normal distribution overlaid (continuous line). Right-hand side: Plot of NPDE (o) *versus* time (in a semi-logarithmic scale), with a tendency curve. The dashed lines (---) represent the 95% prediction interval for a standard normal distribution.

Table 1: Parameter estimates of the final population pharmacokinetic model developed for ciprofloxacin in intensive care unit patients from the building or global data set

Model parameter	Model building data set	Global data set
Structural model		
CL[a] (L/h)		
θ 1	9.6 (27%)	10 (17%)
θ 2	8.9 (29%)	7.6 (29%)
θ 3	1.2 (22%)	1.4 (19%)
θ 4	1.2 (24%)	0.78 (41%)
V1 (L)	46 (14%)	46 (14%)
Q (L/h)	39 (29%)	43 (32%)
V2 (L)	66 (12%)	70 (15%)
Interindividual variability (IIV)		
IIV_{CL} (%)	36 (24%)	37 (20%)
IIV_{V1} (%)	45 (40%)	53 (37%)
IIV_{V2} (%)	53 (49%)	58 (43%)
Interoccasion variability (IOV)		
IOV_{CL} (%)	18 (50%)	26 (39%)
Residual variability (%)	23 (7.2%)	23 (6.4%)

[a] $CL = [\theta 1 + \theta 2 \times (CL_{Cr\ Cockcroft}/96.4)^{\theta 3}] \times [(PROT/56.1)^{\theta 4}]$

Relative standard errors (expressed as percentages) are given in brackets.

CL, ciprofloxacin clearance; V1, volume of the central compartment; V2, volume of the peripheral compartment; Q, intercompartmental clearance; CL_{Cr} Cockcroft, creatinine clearance calculated with Cockcroft and Gault formula (mL/min); PROT, total protein concentration in blood (g/L).

RESULTS

A two-compartment model was found to best fit concentration data. Creatinine clearance using Cockcroft and Gault formula and total protein concentration in blood were identified as relevant covariates on ciprofloxacin clearance and explained a large part of interindividual variability. Indeed, inclusion of $CL_{Cr\ Cockcroft}$ in the basic model decreased interindividual variability on CL from 57 to 42%. Further inclusion of PROT decreased interindividual variability on CL from 42 to 36%. Only moderate interoccasion variability on clearance could be estimated (26%). Finally, PK/PD simulations showed that the dosage regimen of 400 mg b.i.d. used in 83% of patients did not allow to reach the PK/PD target for *P. aeruginosa* nor *Enterobacteriaceae*. The percentage of patients reaching the target was much higher with other tested dosage regimens (400 mg t.i.d., 600 mg b.i.d or 1200 mg o.d.) with small differences between them as expected.

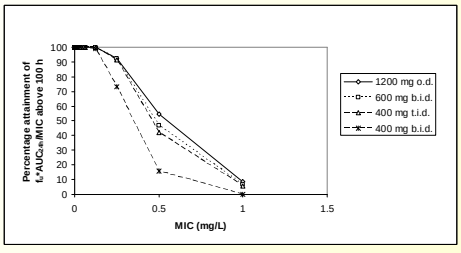

Figure 4: Attainment of f_u*AUC_{24h}/MIC ratio of ≥100 h at *in vitro* MIC values varying from 0.002 mg/L to 1.0 mg/L after PK/PD simulations of different dosage regimens (1200 mg o.d., 600 mg b.i.d., 400 mg t.i.d. and 400 mg b.i.d.) for the 119 ICU patients of the study.

CONCLUSION

The present analysis confirms previous findings i.e. a large interindividual variability on ciprofloxacin clearance which is partly explained by creatinine clearance [1,2]. More importantly, PK/PD assessment support the use of ciprofloxacin dosages higher than the one currently used in the majority of our ICU patients. More complex PK/PD simulations are on the way to account for the whole distribution of MIC, prevalence of bacteria subpopulations and other PK/PD targets.

References:

[1] Forrest A et al. Development of a population pharmacokinetic model and optimal sampling strategies for intravenous ciprofloxacin. Antimicrob Agents Chemother 1993; 37:1065-1072.

[2] Conil J-M et al. Ciprofloxacin use in critically ill patients: pharmacokinetic and pharmacodynamic approaches. Int J Antimicrob Agents 2008; 32:505-510.

[3] Brendel K et al. Metrics for external model evaluation with an application to the population pharmacokinetics of gliclazide. Pharm Res 2006; 23(9):2036-2049.

Acknowledgment: Dalia Khachman was supported by a doctoral scholarship from the Lebanese National Council for Scientific Research (Beirut, Lebanon).