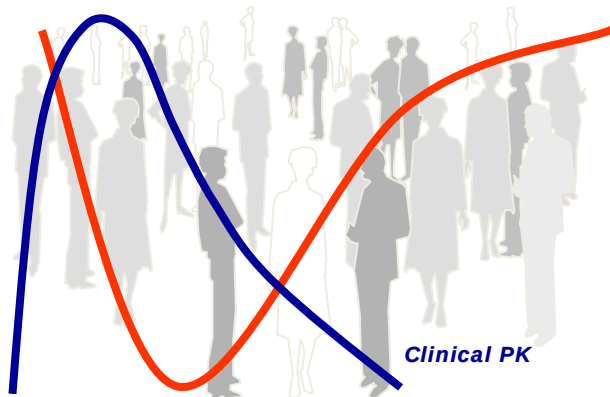


Population pharmacokinetic modelling to detect potential drug interaction using sparse sampling data



Anne Dubois, Maud Bénétou and Marylore Chenel

Department of Clinical Pharmacokinetics, Institut de Recherches Internationales Servier, Suresnes, France



Context

The cytochrome P450 isozymes or transporters (PgP, BcRP...) are implicated in the ADME of many drugs and may be influenced by the administration of others. Indeed, simultaneous administration of several treatments can lead to pharmacokinetic interactions (PKI) of one administered drug on another.

In this context, the co-administration of a drug S (in development at Servier) with different corticosteroids was investigated during a phase 2 clinical trial, as it was not possible to design a specific drug-drug interaction study (due to the properties of drug S). The objective of the present analysis was to evaluate the potential PKI of the drug S on the pharmacokinetics (PK) of the prednisolone using population PK modelling.

Material and Methods

1. Study design and data

The data were obtained from a ongoing clinical trial which evaluated the efficacy of drug S. To be selected in the study, the patient must be receiving stable oral dose of corticosteroids for at least 4 weeks. Currently, fifteen of the included patients received stable oral dose of prednisolone with different dosing regimens. Our analysis concerns the preliminary prednisolone data from these 15 patients.

Table 1: Individual dosing regimen

Dose of prednisolone (mg)		2.5	5	7.5	10	12.5
Number of patients*	Once a day	1	2	2	6	2
	Twice a day			1		

* One patient received decreasing dose of prednisolone (7.5 then 5 then 2.5 mg once a day) during the study

To measure the total plasma concentration of prednisolone, one PK sample was performed before any administration of drug S (visit V_0), and at each visit during the treatment period (visit V_1 to V_7). However, the sampling was not performed at all visits for all patients. A maximum of 4 observations per patient was available. For 2 patients, prednisolone concentrations were available only before drug S administration (V_0). For 7 patients, prednisolone concentrations were available only after drug S administration.

Table 2: Number of observations per patient

Number of observations	Number of patients
1	2 (one PK sample at V_0)
2	4
3	7
4	2

Table 3: Number of observations per visit

V_0	V_1	V_2	V_3	V_4	V_5	V_6	V_7	all
8	1	8	10	2	6	3	1	39

The lower limit of quantitation (LOQ) was 1 ng/mL. The time of the visits were not planned for these PK samples. So, the sampling was performed at different times after the last prednisolone administration. Furthermore, the time of the last prednisolone administration was given by the patient (uncertainty on these data). The observed times since last prednisolone administration (TAD) were between 1h and more than 24h. There were four TAD above 30h that we arbitrary considered equal to 30h.

2. Population PK modelling

Due to the very sparse sampling and the heterogeneous sampling times, classic statistical methods (e.g. ANOVA) could not be used to compare the prednisolone concentration level before and after drug S administration. So, we used published population PK modelling.

First we simulated unbound plasma prednisolone concentrations using the model of Mager et al [1].

$$C_{unbound}(t) = \frac{Dose \times k_a}{V \times (k_a - CL/V)} \times (\exp(-CL/V \times t) - \exp(-k_a \times t))$$

Then, we derived the corresponding total plasma concentrations using the model of Petersen et al [2] describing the nonlinear binding of prednisolone to the plasma proteins.

$$C_{total}(t) = \frac{B_{max} \times C_{unbound}(t)}{1 + K_1 \times C_{unbound}(t)} + (1 + K_2) \times C_{unbound}(t)$$

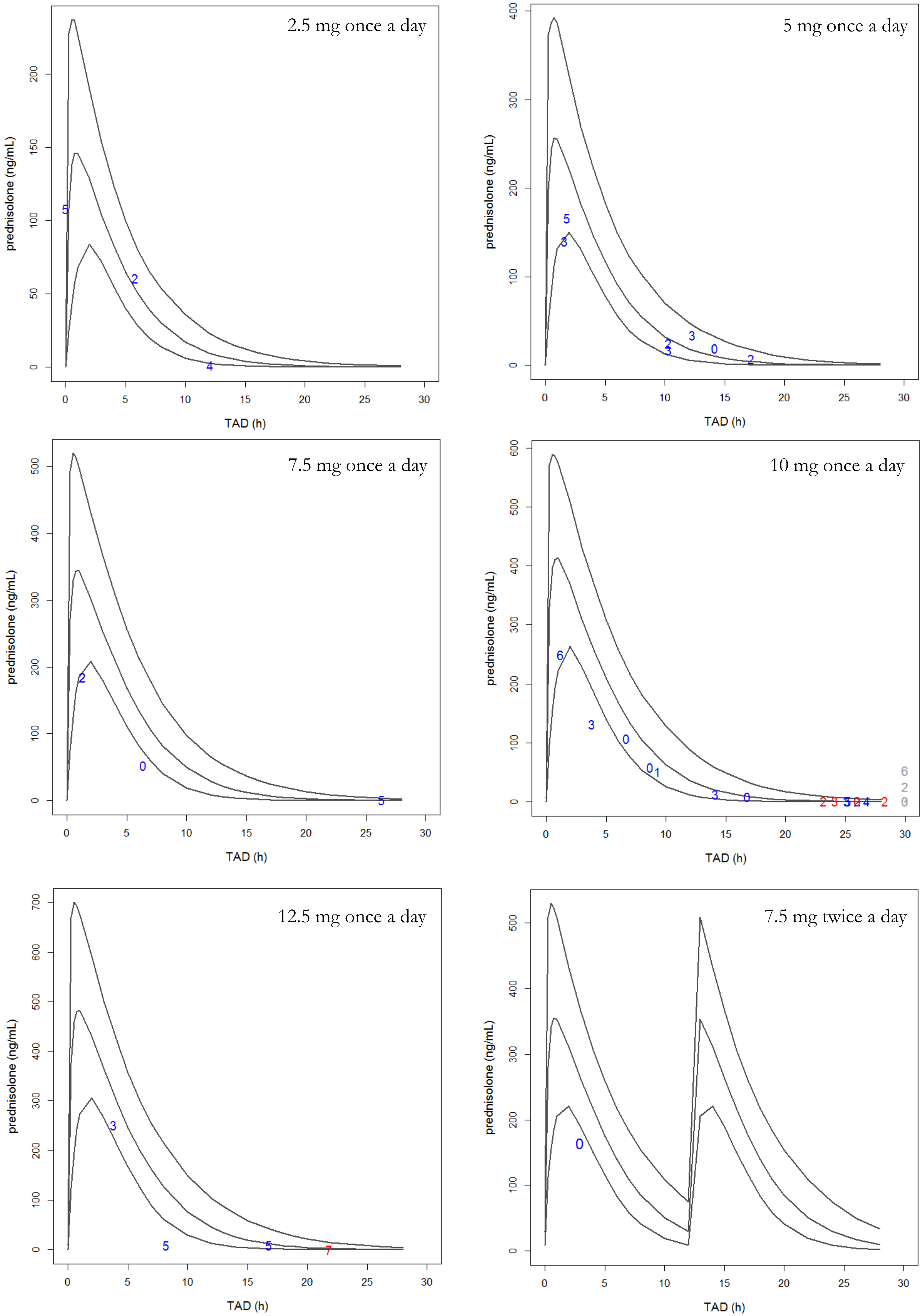
Table 4: Population PK parameters used to simulate total plasma concentrations of prednisolone

	Typical value	Inter-individual variability (CV, %)
k_a (h ⁻¹)	2.84	110
V (L)	156	20
CL (L/h)	45.3	8.1
B_{max} (-)	6.77	27
K_1 (M ⁻¹)	0.95×10^7	1.3
K_2 (-)	0.80	0.6

We computed the 5th, 50th and 95th percentiles of the distribution of the simulated plasma concentration (i.e. C_{total}) for each dosing regimen. Then, we graphically compared the predicted and observed plasma concentrations.

Results

Figure 1: External visual predictive check of the total plasma concentration of prednisolone at steady state, and after different dosing regimens



The curves represent the 5th, 50th and 95th percentiles of the simulated PK profiles
0, 1, 2, 3, 4, 5, 6, 7: observations at visit V_0 , V_1 , V_2 , V_3 , V_4 , V_5 , V_6 , or V_7 , respectively
TAD: time after last dose of prednisolone, concentration above the LOQ or below the LOQ, TAD>30h

Total plasma prednisolone concentrations were slightly under predicted by the model. However, this tendency was observed for concentrations measured before and after the administration of drug S. There was no major difference observed between the prednisolone concentration level before and after drug S administration.

Conclusion

Using population PK modelling, we demonstrated that there is no major PK interaction of drug S on prednisolone. This methodology could be applied for the other drugs co-administered with drug S.

However, could such approach be accepted by the regulatory agencies to conclude on PKI ?

[1] Mager D, et al. *Journal of Clinical Pharmacology*. 2003.
[2] Petersen K, et al. *Cancer Chemotherapy and Pharmacology*. 2003.