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SHORT COMMUNICATION

Dexamethasone as a probe for CYP3A4 metabolism: evidence of gender effect

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Abstract
Background A study was conducted to evaluate prospectively the correlation between docetaxel clearance and pharmacokinetics of dexamethasone previously obtained in 21 patients.
Patients and methods Dexamethasone pharmacokinetics were performed in 17 patients 24 h before docetaxel treatment as monochemotherapy. Dexamethasone and docetaxel plasma concentrations were determined by HPLC methods. Determination of docetaxel unbound fraction in plasma was performed using microequilibrium dialysis.
Results Significant correlation was observed between observed plasma docetaxel clearances ($CL_{docetaxel}$) and values predicted from dexamethasone plasma clearance (CL_{dexa}), unbound plasma docetaxel fraction estimated from serum α1-acid glycoprotein level ($fu_{\alpha1-AAG}$), and hepatic metastasis status. However, after splitting of the prospective data set according to gender, no correlation was observed for males ($R^2 = 0.08$, NS, $n = 10$), then strong correlation was observed for females ($R^2 = 0.78$, $P < 0.01$, $n = 7$). Multivariate analysis was performed from data obtained in the women included in the first study and those of this prospective study ($n = 18$). Docetaxel CL was significantly correlated with CL_{dexa} ($P = 0.001$) and $fu_{\alpha1-AAG}$ ($P = 0.01$) according to the relationship (with ±95% confidence intervals): $CL_{docetaxel}$ (l/h) = 1.92 (±0.94) × CL_{dexa} (l/h) + 2.68 (±1.95) × $fu_{\alpha1-AAG}$ (%) ($R^2 = 0.68$).
Conclusion Dexamethasone may be used to predict docetaxel clearances in females, but not in males.

Keywords Cytochrome P450 3A4/5 · Dexamethasone · Docetaxel · Pharmacokinetics · Gender

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Introduction

We have previously shown that dexamethasone may be a probe of CYP3A metabolism. Indeed, we observed close relationships between dexamethasone plasma clearance (CL_{dexa}) and that of either vinorelbine [10] or docetaxel ($CL_{docetaxel}$) [9]. These three compounds are known to be eliminated mainly by CYP3A [6–8]. A pharmacokinetic study was performed in 17 additional patients in order to evaluate prospectively the equation we previously obtained [9] corresponding to CL_{dexa} and $CL_{docetaxel}$ [i.e., $CL_{docetaxel}$ (l/h) = 3.56 × $fu_{\alpha1-AAG}$ × (1–0.17 × HPMT) × (1 + 0.126 × CL_{dexa} (l/h)], with HPMT equal to 1 or 0 if presence or not respectively of hepatic metastasis, $fu_{\alpha1-AAG}$ (%) for estimated unbound fraction of docetaxel based on serum α1–acid glycoprotein level [11]. Moreover, since $fu_{\alpha1-AAG}$ was a significant covariate, the actual unbound fraction of docetaxel was measured. We report here the results of this prospective evaluation. Since quality of the prediction was strongly dependent of gender, analysis of the whole data (21 patients of the first study together with these 17 patients) was then performed by taking into account the gender covariate.

Patients and methods

Patients

The criteria for inclusion were identical to those of the first study (i.e., patients older than 18 years with proven solid malignancy who required a docetaxel based treatment) [9]. The study was approved by the regional ethical committee as a continuation of the first study. Written informed consent was obtained from all patients before they entered onto the study. Patients' characteristics are shown in Table 1.

Drug administration

Docetaxel (Taxotere©, Aventis Pharma, Paris, France) was administered intravenously (iv) over 1 h at doses ranging from 75 to 100 mg/m² depending on the standard regimen. All patients were treated with docetaxel monotherapy. Each patient received dexamethasone (20 mg, dexamethasone Qualimed©) diluted in 10 ml of 0.9% saline and administered iv for 5 min, 24 h before the docetaxel infusion. Each patient received a corticosteroid premedication as follows: prednisolone (20 mg, Solupred©) administered orally twice daily for 3 days (first tablet administered the evening before the docetaxel infusion). Antiemetic regimen was administered according to clinicians' practice.

Blood sampling and measurements

Samples for PK studies were obtained from all patients in the first cycle of therapy. The blood samples were collected into heparinized tubes through an indwelling cannula at the arm opposite to that used for drug administration: (a) before infusion, 30 min, 2 h, and 4 h after the beginning of the dexamethasone administration; (b) before infusion, 1.5 h, 3 h, and 7 h after the beginning of the docetaxel infusion. All blood samples were centrifuged immediately at 1,760 g for 10 min, the plasma was removed and kept at −20°C until analysis. Dexamethasone and docetaxel plasma concentrations were measured by reverse-phase high performance liquid chromatography (HPLC) using ultraviolet absorbance detection as previously published [9, 12]. The lower limits of quantification were 10 and 50 ng/ml, and the between-day CV was lower than 15.7 and 7.0% for docetaxel and dexamethasone, respectively. Determination of docetaxel unbound fraction in plasma was performed using microequilibrium dialysis, as described previously [1]. The within-run and between-run precisions of the dialysis method were less than 15% at all concentrations.

Pharmacokinetic analysis

Concentration versus time profiles of both docetaxel and dexamethasone were analyzed using NONMEM (version V, level 1.1) and the PREDPP package [5] running on a personal computer.

Dexamethasone

Plasma concentrations of dexamethasone were analyzed according to a one-compartment model and first-order elimination with the first-order conditional estimation method to determine individual dexamethasone CL (CL_{dexa}) using the POSTHOC option of NONMEM Program.

Table 1 Patients characteristics and pharmacokinetic results

	Prospective data set (n = 17)	Whole data set (n = 38)
Characteristics		
Age (years)	62 (48–77)	58 (19–77)
Body weight (kg)	74 (57–93)	70 (49–106)
Body surface area (m²)[a]	1.82 (1.54–2.06)	1.72 (1.46–2.25)
Serum α1–acid glycoprotein (μM)	31.8 (12.9–60.5)	34.7 (12.9–70.9)
Female/male	7/10	18/20
Docetaxel dosage: 75/100 mg/m²	12/5	21/17
Hepatic metastases: yes/no	5/12	13/25
Tumour type: prostate/breast/others	8/6/3	12/15/11
Pharmacokinetic results		
Docetaxel clearance (l/h)	42.1 (23.2–56.7)	43.7 (23.2–57.1)
Unbound plasma docetaxel fraction (%)		
fu^{b}_{mes}	4.4 (3.1–6.0)	4.8 (2.6–8.1)
$fu^{c}_{\alpha 1-AAG}$	6.4 (5.0–7.7)	6.3 (4.7–7.8)
Dexamethasone clearance (l/h)	13.7 (7.2–20.0)	13.8 (7.2–27.2)

Values are in mean and ranges within parenthesis

[a] Calculated according to the Dubois formula

[b] Measured by microequilibrium dialysis

[c] Estimated from serum α1-acid glycoprotein level

Docetaxel

Individual docetaxel plasma CL ($CL_{docetaxel}$) was determined by Bayesian estimation using the POSTHOC option of NONMEM program according to the method of Baille et al. [2]. A three-compartment model was used with mean (and inter-patient coefficient of variation) population parameters as prior information: CL = 36.8 (47.5%) l/h, V = 7.83 (55.4%) l, k_{12} = 1.19 (74.8%) h^{-1}, k_{21} = 1.75 (113.1%) h^{-1}, k_{13} = 1.22 (36.1%) h^{-1}, k_{31} = 0.0879 (35.1%) h^{-1}.

Statistical analysis

The covariates tested were gender, CL_{dexa} (l/h), HPMT, $fu_{\alpha1-AAG}$ (%) for estimated unbound fraction of docetaxel based on serum α1–acid glycoprotein level [11], and fu_{mes} for measured unbound fraction of docetaxel. Pearson correlation or nonparametric (Spearman test) was used to assess association between docetaxel CL and each covariate. Stepwise multiple linear regression was performed on variables associated with a P values <0.20. Results were considered statistically significant when P values were <0.05. Multivariate analysis was performed using STATA Statistical Software (release 7.0, Stat Corporation, College Station, TX, USA).

Results

Measured unbound fraction

Mean values and range of measured unbound fraction (fu_{mes}) and unbound fraction estimated from AAG plasma levels ($fu_{\alpha1-AAG}$) are stated in Table 1. A weak correlation (r = 0.41, P < 0.05, n = 38) was observed between fu_{mes} and $fu_{\alpha1-AAG}$.

Prospective evaluation

Mean values and range of both docetaxel and dexamethasone are stated in Table 1. Significant correlation (R^2 = 0.39, P < 0.01, n = 17) between actual docetaxel clearance and predicted values based on $fu_{\alpha1-AAG}$ (%) and CL_{dexa} (l/h): CL (l/h) = 3.56 × $fu_{\alpha1-AAG}$ × (1–0.17 × MTHP) × (1 + 0.126 × CL_{dexa}). However, after splitting of the prospective data set according to gender, no correlation was observed for males (R^2 = 0.08, NS, n = 10), and a strong correlation was observed for females (R^2 = 0.78, P < 0.01, n = 7). A significant bias was observed between predicted and observed values (n = 17): mean percent error (±95% confidence interval) = +44% (±17%)

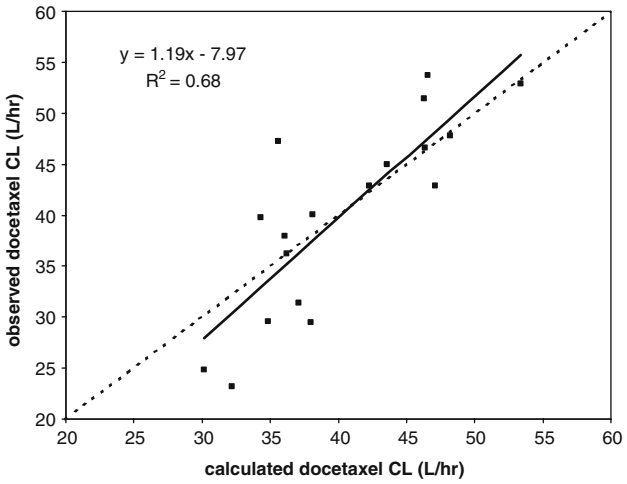

Fig. 1 Observed docetaxel clearance versus values estimated according to the regression line based on plasma dexamethasone clearance (CL_{dexa} in l/h) and estimated unbound fraction ($fu_{\alpha1-AAG}$ in %) in female: docetaxel CL (l/h) = 1.92 × CL_{dexa} + 2.68 × $fu_{\alpha1-AAG}$

Multivariate analysis

Multivariate analysis of the whole data set (n = 38 patients) allowed to identify CL_{dexa} as the only covariate significantly (P = 0.005) correlated with docetaxel CL. Separate multivariate analyses were then performed from data obtained either in male or in female patients. For females, docetaxel CL was significantly correlated with both CL_{dexa} (P = 0.001) and $fu_{\alpha1-AAG}$ (P = 0.01). The regression line [i.e., docetaxel CL (l/h) = 1.92 (±0.94) × CL_{dexa} + 2.68 (±1.95) × $fu_{\alpha1-AAG}$ (R^2 = 0.68)] is shown in Fig. 1. For males, no covariate was significantly correlated with docetaxel clearance. For each multivariate analysis, substitution of $fu_{\alpha1-AAG}$ by measured unbound fraction (fu_{mes}) was associated with a worse relationship between docetaxel CL and covariates, whatever the data (whole data set, male patients, or female patients).

Discussion

The results of the prospective evaluation can be considered as positive since a significant correlation was observed between observed and predicted docetaxel clearance. However, the heterogeneity of the results between males and females cannot be ignored. In males, observed and predicted values were not correlated. In contrast, analysis of the data from the seven females included in prospective study as that from all the females (n = 18) showed a good correlation between CL_{dexa} and docetaxel CL. The correlation was

improved by also considering $fu_{\alpha 1-AAG}$. Docetaxel CL tends to decrease with increasing AAG as a consequence of the binding of docetaxel to this plasma protein [3, 11]. We have then included measurement of unbound fraction of docetaxel in this study. Interestingly, $fu_{\alpha 1-AAG}$ was associated with a stronger predictive value of $CL_{docetaxel}$ than fu_{mes} was. The first one was directly estimated from AAG plasma levels that is itself dependent of inflammatory status of the patients. There may be some confounding factor between AAG levels and docetaxel CL. Concerning the disparity of the results in terms of predictive value of CL_{dexa} between females and males, there is no obvious explanation. Indeed, when mean values (inter-patient coefficient of variation) of clearance are considered, there are similar differences between males and females for docetaxel [46.8 (14%) and 40.2 (23%) l/h, $P < 0.05$, respectively] and dexamethasone [14.9 (30%) and 12.3 (23%) l/h, $P < 0.05$, respectively]. This gender effect may be due to another factor linked to the disease differing in the present subpopulation of males or females. Fifteen of the 18 females were treated with docetaxel for breast cancer, whereas 12 of the 20 males had prostate cancer. Baker et al. [4] observed larger docetaxel CL in castrate patients with metastatic prostate cancer than that in non-castrate patients. Some hormonal factors may change metabolism of docetaxel but not that of dexamethasone in males. Lastly, we should emphasize that the inter-individual variability of docetaxel CL was larger within females than within males making easier the identification of marker in the first subgroup.

In conclusion, these results support the use of dexamethasone to individualize docetaxel dosing in females. In particular, determination of CL_{dexa} may help to decrease more rationally the docetaxel dose than we do according to the actual guideline (i.e., dose decrease of 25% if alanine aminotransferase or aspartate aminotransferase over 1.5-fold, and alkaline phosphatase over 2.5-fold the normal superior limit, and contra-indication if over 3.5- and 6-fold, respectively). Although the calculated CL values were higher than the actual values for patients with the lowest docetaxel CL (Fig. 1), these patients have been recognized as "poor metabolizer" then their hepatic enzymes were normal. Moreover, the only one patient with increased hepatic enzymes had an observed docetaxel CL (i.e., 44.9 l/h) slightly larger than the mean value, and correctly predicted from the CL_{dexa} equation (i.e., 43.5 l/h).

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