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Pharmacokinetics and metabolism of pirarubicin in humans: correlation with pharmacodynamics

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Abstract The pharmacokinetic monitoring of anthracycline-containing regimens is warranted because of the important toxicity of these drugs and because pharmacokinetic-pharmacodynamic relationships have been clearly established. We studied the pharmacokinetics of the new anthracycline pirarubicin in 80 courses of treatment performed in 27 patients, using a limited sampling protocol we had previously validated. We observed (for 47 of these courses) a significant correlation between the leucocyte cell kill and the pirarubicin area under the time × concentration curve, but the most significant correlation was obtained using the plasma concentration of doxorubicin, a metabolite of pirarubicin, at the end of the infusion. On the basis of this value, it is possible to predict for pirarubicin haematological toxicity in a way that can help the clinician in identifying patients at risk for toxicity.

Key words Pirarubicin · Pharmacokinetics · Pharmacodynamics · Anthracyclines · THP-Adriamycin

Introduction

Pirarubicin (4′-*O*-tetrahydropyranyl-doxorubicin) is a semi-synthetic derivative of doxorubicin. It had been selected in preclinical screens for its similar cytotoxic activity accompained by its reduced cardiac toxicity [17]. These features have been confirmed in clinical trials [2], and pirarubicin is now available in several countries with indications similar to those of doxorubicin. Several pharmacokinetics studies in humans have shown that its elimination can be fitted to a three-compartment model [6, 9, 12, 14, 16]. However, because of the very short initial half-life of the drug, its plasma decay can sometimes be fitted instead to a two-compartment model [10, 15]. In spite of having a shorter terminal half-life than doxorubicin, pirarubicin cannot be given at short intervals because of the constant risk of severe myelosuppression [2]. Doxorubicin and doxorubicinol are important metabolites of pirarubicin, and their protracted half-life [5] results in their accumulation in plasma upon repetitive administration of pirarubicin [14].

The main toxicity of pirarubicin is myelosuppression, predominantly leucopenia (especially neutropenia) and thromobocytopenia. This toxicity is dose-dependent and is correlated with pharmacokinetic parameters such as the area under the time × concentration curve (AUC) of pirarubicin or its metabolite doxorubicin [15]. Pharmacokinetic monitoring would therefore be useful for patients subjected to pirarubicin-containing chemotherapy. Such monitoring is not easy to perform routinely because it usually requires a large number of blood samples, which is uncomfortable for both patients and nurses [1]. However, the availability of limited sampling strategies often provides opportunities for such monitoring. We have developed and validated a limited sampling protocol using Bayesian estimation of the population pharmacokinetics of pirarubicin [8]. This model allows the estimation of pharmacokinetic parameters with only three blood samples. In these three samples, two metabolites (doxorubicin and doxorubicinol) were dosed simultaneously with pirarubicin. In the present study we established pharmacokinetic-pharmacodynamic relationships so as to determine the parameter most predictive for haematological toxicity.

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Patients and methods

Patients

A total of 80 courses were performed in 27 patients aged 27–75 years (mean, 60.4 years), who were treated for advanced cancers (breast carcinoma, 14; ovarian cancer, 4; myeloma, 2; bladder carcinoma, 2; non-Hodgkin's lymphoma, 2; lung cancer, 2; and neuroblastoma, 1). They received doses of pirarubicin ranging from 25 to 50 mg/m^2 (and never exceeding 75 mg), which were given as a slow intravenous infusion over a period of 5–15 min. Blood samples were obtained at the end of the infusion, within 5 min after disconnecting the syringe, and at 12 and 24 h after the infusion.

Drug extraction and analysis

Pirarubicin and its metabolites were extracted from plasma by a liquid-liquid extraction technique described elsewhere [7]. Concentrations were evaluated by high-performance liquid chromatography using a reverse-phase RP8 column and a mobile phase made of formate buffer (pH 4.0), methanol and acetonitrile. Detection was achieved by fluorometry using a very sensitive spectrofluorometer (Hitachi model F 1000) [7].

Analysis of the data

Estimation of the pharmacokinetic parameters of pirarubicin was achieved using the plasma concentrations measured in the three samples. Computation was performed using the population pharmacokinetics data established previously and presented in the accompanying paper [8]. All calculations were made using APIS software [3]. The pharmacokinetic parameters obtained for pirarubicin were the following: the plasma concentration at the end of the infusion ($pira_{ei}$), the total volume of distribution at steady state (V_{dss}), the elimination half-life of the first phase ($t_{1/2a}$), the elimination half-life of the second phase ($t_{1/2b}$), the AUC calculated from the beginning of the infusion and extrapolated to infinity ($AUCpira_{0-\infty}$), the AUC determined between 12 and 24 h post-infusion ($AUCpira_{12-24}$) and the total plasma clearance (Cl).

The pharmacokinetic parameters obtained for the metabolite doxorubicin included the following: the plasma concentration at the end of the infusion (dox_{ei}), and the AUC determined between 12 and 24 h post-infusion ($AUCdox_{12-24}$); for doxorubicinol we obtained the AUC determined between 12 and 24 h post-infusion ($AUCdoxol_{12-24}$).

In parallel, haematological data were obtained before pirarubicin administration (initial counts) and 10–15 days later (nadir). For each parameter (leucocytes — subdivided into neutrophils and lymphocytes — and platelets) we calculated the percentage of surviving cells as $SF = (nadir/initial) \times 100$ according to Ratain et al. [13]. Correlations between pharmacokinetic parameters and the natural logarithms of percentages of cell survival (pharmacodynamic parameters) were estimated using linear least-squares regression and the Pearson coefficient(r).

Results

Figure 1 shows a representative example of the plasma concentrations measured for pirarubicin and its metabolites in one patient. The differences in the elimination kinetics of the parent compound versus the metabolites can clearly be seen. It should be noted that doxorubicin was always present in the first sample collected but that doxorubicinol was never present in this sample (or at least was below the limit of detection of 50 pg/ml).

The pharmacokinetics parameters characterising pirarubicin and obtained from the 80 courses of treatment are presented in Table 1 together with the AUC12–24 ratios of metabolite/unchanged drug and the concentrations of pirarubicin and doxorubicin at the end of the infusion.

We present in Table 2 the correlation matrix between the pharmacokinetic and metabolic parameters of pirarubicin and the haematological data. Only 47 courses of treatment, involving 23 patients, could be included in the computation of the correlations because haematological data were not available in 33 cases. In one situation only was the Pearson coefficient r higher than 0.465, which represents significance at the $P < 0.001$ level; this was the correlation between the doxorubicin concentration at the end of the infusion (dox_{ei}) and the percentage of survival of leucocytes (Fig. 2). Since some patients also received cyclophosphamide, which can be responsible for myelosuppression, the 47 courses were separated into 2 groups: those associated with cyclophosphamide (26 courses) and

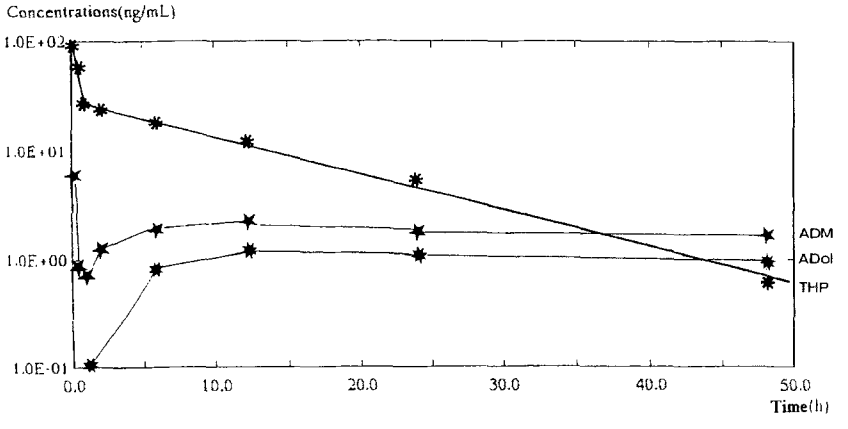

Fig. 1 Time course of the plasma decay of pirarubicin and its metabolites doxorubicin and doxorubicinol as determined in a representative patient who received a 10-min infusion of pirarubicin

Table 1 Pharmacokinetic and metabolic parameters of pirarubicin in 80 course performed in 27 patients (AUC Area under the time × concentration curve either from the beginning of the infusion to infinity (0– ∝) or from 12 to 24 h post-infusion, $pira_{ei}$ pirarubicin plasma concentration at the end of the pirarubicin infusion, dox_{ei} doxorubicin concentration at the end of the pirarubicin infusion)

Parameter	Mean	SD
Distribution half-life $t_{1/2}\alpha$ (h)	0.22	0.11
Elimination half-life $t_{1/2}\beta$ (h)	11.1	3.9
Volume of distribution V_{dss} (l/m^2)	1749	805
Total plasma clearance Cl ($l\,h^{-1}/m^{-2}$)	140	77
Pirarubicin AUC 0– ∝ ($ng\,ml^{-1}\,h\,mg^{-1}\,m^{-2}$)	8.68	3.48
$Pira_{ei}$ (ng ml)	158	122
Dox_{ei} (ng/ml)	12.5	9.2
Pirarubicin AUC_{12-24}($ng\,ml^{-1}\,h\,mg^{-1}\,m^{-2}$)	1.78	0.86
Doxorubicin AUC_{12-24}($ng\,ml^{-1}\,h\,mg^{-1}\,m^{-2}$)	0.90	0.48
Doxorubicinol AUC_{12-24}($ng\,ml^{-1}\,h\,mg^{-1}\,m^{-2}$)	0.32	0.26
AUC ratio dox/pira	0.61	0.39
AUC ratio doxol/pira	0.23	0.19

Table 2 Correlation matrix between pharmacokinetic parameters and haematological data[a]

	ln leucocytes	ln neutrophils	ln lymphocytes	ln platelets
$t_{1/2}\alpha$	0.067	− 0.078	0.079	− 0.113
$T_{1/2}\alpha$	− 0.146	− 0.028	0.063	− 0.025
V_{dss}	− 0.028	0.008	0.132	0.206
Cl	0.032	0.011	0.162	0.268
$AUCpira_{0-\infty}$	**− 0.364**	− 0.259	− 0.025	− 0.175
$Pira_{ei}$	**− 0.339**	− 0.173	− 0.109	0.208
Dox_{ei}	**− 0.520**	− 0.271	− 0.127	0.104
$AUCpira_{12-24}$	**− 0.313**	− 0.227	− 0.052	− 0.209
$AUCdox_{12-24}$	− 0.134	− 0.038	− 0.074	0.016
$AUCdoxol_{12-24}$	− 0.286	− 0.131	0.005	− 0.039
AUC ratio dox/pira	0.073	0.071	0.044	0.162
AUC ratio doxol/pira	0.016	0.044	0.138	0.239

[a]Data represent natural logarithms of percentages of survival for leucocytes, neutrophils, lymphocytes and platelets, respectively. Values in boldface represent significant correlations at the $P < 0.01$ level

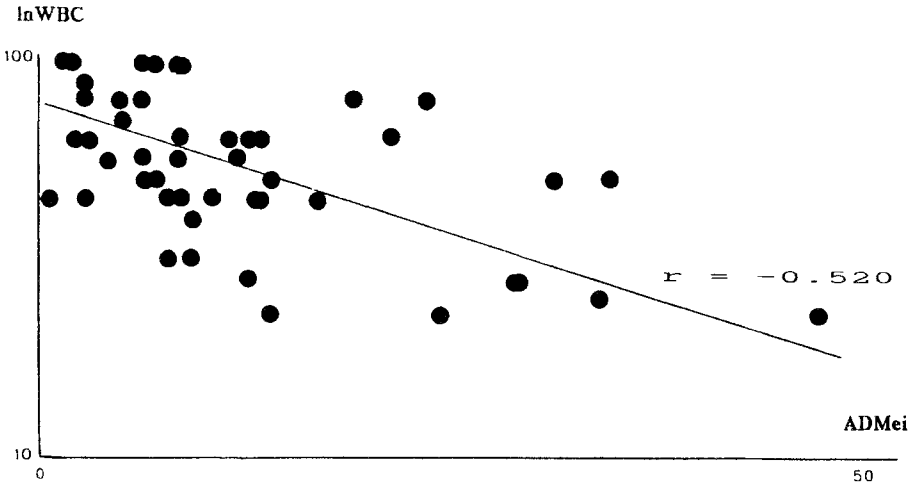

Fig. 2 Relationship between the doxorubicin plasma concentration at the end of the pirarubicin infusion and the percentage of survival of leucocytes, plotted on a logarithmic scale ($r = -0.520$, $P < 0.001$)

those not associated with this drug (21 courses). The same significant correlation was obtained in both groups [respectively, $r = -0.552$ ($P < 0.01$) and $r = -0.582$ ($P < 0.01$)], and therapy associated with pirarubicin was not considered further. Other significant correlations were observed at the $P < 0.01$ level; these were correlations between the leucocyte percentage of survival and the pirarubicin concentration at the end of the infusion ($pira_{ei}$) as well as the pirarubicin AUC (either total or between 12 and 24 h post-infusion).

Table 3 Distribution of toxic courses according to the doxorubicin plasma concentration at the end of the infusion

Leucopenia	Doxorubicin plasma concentration at end of infusion	
	$Dox_{ei} < 13$ ng/ml ($n = 35$)	$Dox_{ei} \geq 13$ ng/ml ($n = 12$)
Percentage of survival < 50% at nadir	32%	75%
Percentage of survival < 25% at nadir	0%	50%

From the study of the correlation between the doxorubicin concentration at the end of the infusion (dox_{ei}) and the percentage of survival of leucocytes, we could separate the 47 courses of treatment into 2 classes (Table 3): when dox_{ei} was lower than 13 ng/ml, no patient presented a leucocyte survival of lower than 25%, and only 32% of the patients had a leucocyte percentage of survival ranging between 25% and 50%; when dox_{ei} was equal to or higher than 13 ng/ml, 75% of the patients had a leucocyte survival of lower than 50%, whereas 50% had a leucocyte survival of lower than 25%.

Discussion

We succeeded in analysing 80 courses of treatment with pirarubicin in 27 patients; estimation of pirarubicin pharmacokinetic parameters was done using a limited sampling model (3 samples) we had validated previously [8]. These kinetic parameters were in the range of the values reported in the literature using 10–12 samples per patient [6, 9, 10, 12, 14–16] and therefore justified the use of the limited sampling strategy. The metabolites of pirarubicin, doxorubicin and doxorubicinol, had not been included in the model, and only the following model-independent parameters were thus computed for them: the concentration at the end of the infusion (dox_{ei} and $doxol_{ei}$) and the AUCs determined between 12 and 24 h post-infusion as obtained by the trapezoidal rule. To compare the metabolite AUC with the unchanged-drug AUC, the same model-independent estimation of pirarubicin AUC_{12-24} was computed; the AUC ratios of metabolite/unchanged drug are in agreement with those reported in the literature [6, 12, 14], with the exception of the observations of Miller and Schmidt [9], who found much higher levels of doxorubicin.

It is remarkable that doxorubicin was present in the first blood sample, representing about 9% of the pirarubicin concentration in the same sample; this has previously been mentioned [4]. It has been shown that the pharmaceutical preparations of pirarubicin did not contain more than 1% doxorubicin (by vol.) and that pirarubicin could not be transformed (in blood) in vitro into doxorubicin [11]. To avoid any non-metabolic transformation, all blood samples were immediately cooled at 4 °C, centrifuged at that temperature and processed within a few hours; under our extraction and analysis conditions, authentic standards of pirarubicin do not contain a quantifiable trace of doxorubicin. We therefore concluded that the doxorubicin resulted only from a rapid metabolic conversion of pirarubicin.

Among the 80 courses studied, only 47 could be evaluated from a pharmacodynamic point of view, because the nadir blood cell count were not available in 33 cases; generally, this was due to a late control of haematological toxicity (> 15 days between treatment and blood cell counts). The use of natural logarithms of the percentages of survival of blood cells has been recommended by Ratain et al. [13] for the evaluation of correlations with pharmacodynamic parameters. The best correlation was obtained between leucocyte survival and the doxorubicin concentration at the end of the infusion ($r = -0.520$, $P < 0.001$). This correlation was maintained regardless of whether cyclophosphamide was associated with pirarubicin in the treatment of the patients. This results was therefore independent of the concomitant administration of cyclophosphamide. Our observation does not signify that the doxorubicin concentration at the end of the infusion is strictly responsible for leucocyte killing but indicates that it can be used as the most significant marker of leucopenia. It is unusual to observe that a parameter simply obtained at the end of an infusion is correlated with the effect of a drug, especially because the precise timing of sampling in relation to infusion is not possible for the nurse in charge of the sampling and because the exact duration of the infusion varied between 5 and 15 min. The very significant relationship between the pharmacokinetic and the pharmacodynamic parameters reveals in fact that the sampling made at the end of the infusion can provide useful information and should not be neglected as it usually is. Other correlations were less significant, especially those between AUCpira and leucocyte percentages of survival; they appear to be in agreement with other observations made on pharmacokinetic-pharmacodynamic relationships [15]. In contrast, we could not show any correlation with platelet survival as observed by Robert et al. [15]; this discrepancy might be due to our clinically heterogeneous population in contrast to that entered in the previous study.

In conclusion, we propose a simple predictive evaluation of pirarubicin haematological toxicity according

to the level of doxorubicin at the end of the infusion: a concentration exceeding 13 ng/ml will cause a > 75% fall in leucocyte counts in half of the patients; this can help the clinican in deciding which patients should benefit from the use of growth factors to limit the toxicity of the course of treatment.

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