Cancer Chemother Pharmacol (1995) 36: 473–476

ORIGINAL ARTICLE

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Gender affects doxorubicin pharmacokinetics in patients with normal liver biochemistry

Received 27 September 1994/Accepted 31 January 1995

Abstract We studied the variability in doxorubicin pharmacokinetics in 27 patients, all of whom had normal liver biochemistry tests. Blood samples were collected after the first cycle of single-agent doxorubicin given as an i.v. bolus and plasma levels were measured by high-performance liquid chromatography (HPLC). The relationship of doxorubicin clearance (dose/AUC) with biochemical tests (AST, bilirubin, alkaline phosphatase, albumin, creatinine) and physical characteristics (age, gender, height, weight, tumour type) was investigated. The 6 men had a significantly higher doxorubicin clearance than did the 21 women (median values, 59 and 27 $lh^{-1}m^{-2}$, respectively; $P = 0.002$). Doxorubicin clearance was significantly lower in patients with breast cancer than in those with other tumours (median values, 26 and 53 $lh^{-1}m^{-2}$, respectively; $P = 0.0008$). The other biochemical and physical parameters did not correlate with doxorubicin clearance. However, in multivariate analysis, gender was the only factor predicting doxorubicin clearance ($r^2 = 40\%$). The ratio of the AUCs for doxorubicinol and doxorubicin (R) was higher in the men than in the women (median values, 0.62 and 0.36, respectively; $P = 0.03$). We conclude that gender may be an important determinant of doxorubicin clearance in patients with normal liver biochemistry.

Key words Doxorubicin · Pharmacokinetics · Gender

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Introduction

The anthracyclines doxorubicin and epirubicin are amongst the most effective and widely employed cytotoxic agents in the treatment of solid tumours. Although anthracycline doses are conventionally adjusted according to the body surface area of the patient, there is wide variation in plasma pharmacokinetics. Liver dysfunction accounts for some of the variability seen in doxorubicin [2] and epirubicin pharmacokinetics [7, 16]. Nevertheless, especially in patients with normal liver biochemistry there remains a considerable range of values for anthracycline clearance for which a satisfactory explanation has not been found. This may be important since inappropriate dosage may lead to suboptimal treatment in some patients while exposing others to the risk of unacceptable toxicity.

The aim of the current analysis was to investigate the relationship of biochemical and physical characteristics with the variability in doxorubicin pharmacokinetics seen in patients with normal routine liver biochemistry tests.

Materials and methods

Patients and treatment

Doxorubicin pharmacokinetics were studied in 27 patients who had received no prior anthracycline treatment. Pharmacokinetic studies were performed only during their first cycle of doxorubicin given as a single agent. Patients received a range of doses since many were treated with doxorubicin as part of combination chemotherapy regimens. These patients received the remainder of their treatment after the completion of pharmacokinetic sampling. All patients gave informed consent to participate in the study.

Levels of serum AST, bilirubin, alkaline phosphatase, creatinine and albumin were determined within 24 h of treatment. Creatinine clearance was calculated using the Cockcroft formula [4]. The body size as indicated by the height, weight and surface area (BSA) of each patient was recorded on entry to the study. The extent to which

patients were above or below their ideal body weight (%IBW) was estimated using a standard formula [3].

Pharmacokinetics

For the measurement of doxorubicin and doxorubicinol levels, 7-ml blood samples were taken from an indwelling cannula. Samples were collected before treatment and then at 6, 9, 12, 15, 20 and 30 min and at 1, 2, 4, 6, 8, 10, 24, 30 and 48 h after the start of administration of doxorubicin. Each blood sample was taken into a tube containing lithium-heparin and then centrifuged and the plasma was stored at − 20 °C pending assay.

Plasma levels of doxorubicin and doxorubicinol were measured by a high-performance liquid chromatography (HPLC) technique with fluorescence detection. Usually doxorubicin and doxorubicinol were extracted using C_2 cassettes that were introduced into the solvent stream of the HPLC using an advanced automatic sample processor (AASP; Varian Associates) [6]. For the remaining samples, doxorubicin and doxorubicinol were extracted using a chloroform: 2-propanol (1 : 1, v/v) mixture [1]. Extracted residues were redissolved in 150 µl of solvent and 50 µl was injected into the HPLC system manually. Peak heights were measured by a computing integrator and peak height ratios were calculated with daunorubicin as the internal standard. The detection limit of the assay as determined using solid-phase extraction was < 1 ng/ml and that determined using solvent extraction was 4 ng/ml.

Doxorubicin pharmacokinetics were fitted to a three-compartment model using the Pharmkit programme [9] with sum of squares and Akaike's information criterion (AIC) assessing error and the 'goodness of fit'. The area under the concentration-time curve to 48 h (AUC_t) was calculated from the slopes and intercepts derived from Pharmkit. The AUC_t was extrapolated back to the end of the injection and corrected for the infusion time [8]. Since a range of doxorubicin doses was used, the basic pharmacokinetic parameter studied was drug clearance (cl_t) calculated as dose/AUC_t. The early (α), intermediate (β) and terminal (γ) half-lives ($t_{1/2}$) and the mean retention time (MRT), which is a measure of the period over which a molecule remains in the body, were also calculated using Pharmkit. Although doxorubicinol levels were measured, these data are not presented as the metabolite has much less biological activity than doxorubicin and is not clinically relevant.

Statistical analysis

The biochemical and pharmacokinetic parameters of pairs of patients groups were compared using the Mann-Whitney test. Relationships of pharmacokinetic parameters with liver biochemistry or other patients' characteristics were investigated using Pearson's correlation. Variables that were not normally distributed were expressed as $\log_{10}$ values. In a data set of this size a correlation coefficient, r, as low as 0.33 is statistically significant although it represents only a weak relationship. Therefore, only values of $r > 0.5$ were considered to have potentially important predictive use; a value of $r > 0.7$ was considered as showing a strong relationship. The relative contribution of each parameter test to the variability in doxorubicin pharmacokinetics was evaluated using stepwise linear regression analysis.

Results

Clinical and biochemical characteristics

The physical and biochemical characteristics of the patients are shown in Table 1. Since the aim of the study was to investigate variability in doxorubicin pharmacokinetics in patients with normal hepatic function, only patients with normal aspartate aminotransferase and serum bilirubin levels were included in this analysis. Patients with a raised serum alkaline phosphatase value were not excluded as many had breast cancer and bony metastases. In our unit, liver scans are carried out in patients with advanced breast cancer and normal liver biochemistry only if they have hepatomegaly or if it is a requirement of a specific research protocol. Patients with lymphoma had liver scans as part of routine staging. In all, 12 patients had liver scans, of which 3 confirmed the presence of liver metastases; these were seen in 1 man and 2 women. The remaining 15 patients showed no clinical evidence of liver involvement but a scan was not performed. There was no difference in the median ages of the men and women (58 and 54 years, respectively) or in their biochemical tests.

Table 1 Clinical and biochemical characteristics of patients (*alk. phos.* Alkaline phosphatase, *clin* clinically, *− ve* negative, *+ ve* positive)

Characteristics	
Number of patients	27
Median age, years (range)	54 (27–75)
Median AST, IU/1 (range)	28 (12–42)
Median bilirubin, IU/1 (range)	10 (2–20)
Median alk. phos., IU/l (range)	277 (110–737)
Median albumin, g/l (range)	40 (29–51)
Median creatinine, µmol/l (range)	86[a] (51–207)
Primary tumour:	
Breast	18
Lymphoma	7
Other	2
Liver metastases:	
Scan − ve	3
Scan + ve	9
Clin − ve[b]	15
Doxorubicin dose:	
< 25 mg/m²	3
26–50 mg/m²	8
51–75 mg/m²	14
76–100 mg/m²	2

[a] $n = 23$

[b] patients had normal liver biochemistry and no hepatomegaly but a liver scan was not performed

Doxorubicin pharmacokinetics

The pharmacokinetic parameters for these patients are shown in Table 2. There was a linear relationship between dose and AUC_t ($r = 0.69$, $P = 0.001$). The

Table 2 Doxorubicin pharmacokinetic parameters (*Dox* Doxorubicin)

Median Pharmacokinetic value	Women ($n = 21$)	Men ($n = 6$)
Dox Cl_t, l/h*	44.8	113.2
(range)	(12.9–101.8)	(65.7–147.3)
Dox Cl_t, $l\,h^{-1}\,m^{-2}$	27.5	59.6
(range)	(7.8–71.9)	(39.8–92.1)
MRT, h*	31.9	49.2
(range)	(12.2–81.1)	(19.0–119.2)
Dox $t_{1/2\alpha}$, h	0.068	0.067
(range)	(0.038–0.096)	(0.053–0.08)
Dox $t_{1/2\beta}$, h	1.36	1.26
(range)	(0.426–7.21)	(0.362–2.03)
Dox $t_{1/2\gamma}$, h*	35.3	54.3
(range)	(20.6–67.4)	(13.3–91.2)
AUC R*	0.36	0.62
(range)	(0.16–0.53)	(0.35–0.79)

*$P \leq 0.05$ (shown in boldface type)

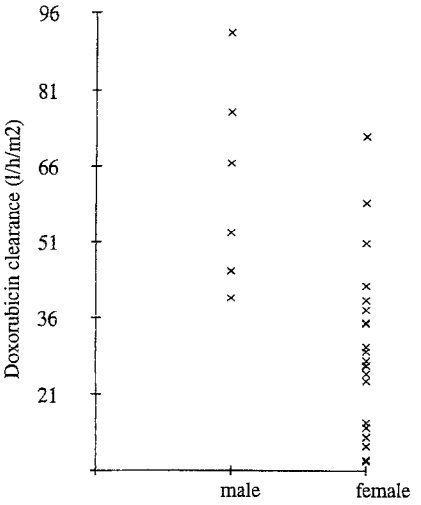

Fig. 1 Doxorubicin clearance in male and female patients with normal AST and bilirubin levels

Table 3 Relationship of liver biochemistry tests and physical characteristics with doxorubicin clearance (*Dox* Doxorubicin, *Alk. phos.* alkaline phosphatase)

Parameter	Correlation with Dox clearance	
	r	*P*
Age	0.15	0.22
Height	0.37	0.03
Weight	− 0.01	0.47
%IBW	− 0.30	0.06
BSA	0.24	0.12
AST	0.38	0.03
Alk. phos.	0.34	0.04
Bilirubin	0.18	0.19
Albumin	− 0.34	0.04
Creatinine (Cr)	0.25	0.10
Cr Clearance	− 0.09	0.33

relationship of doxorubicin clearance with patient characteristics (age, height, weight, %IBW, BSA and tumour type) and liver biochemistry (AST, bilirubin, albumin and alkaline phosphatase) was investigated (Table 3).

The influence of patient gender on doxorubicin clearance was also analyzed. Figure 1 shows that doxorubicin clearance was significantly higher in the 6 men than in the 21 women (median values, 113 and 44 l/h, respectively; $P = 0.0008$). This difference was also apparent when doxorubicin clearance was calculated taking BSA into account (median values, 59 and 27 $l\,h^{-1}\,m^{-2}$, respectively; $P = 0.002$). There was a significant difference between doxorubicin clearance in women with breast cancer and that in the remaining patients (median values, 26 and 53 $l\,h^{-1}\,m^{-2}$, respectively; $P = 0.0008$). However, in a multivariate analysis using all clinical and biochemical parameters (except creatinine clearance and albumin since these data were not available for all patients), gender was the only factor that predicted doxorubicin clearance. It accounted for half of the variability in doxorubicin clearance expressed in litres per hour ($r^2 = 49\%$) and for less than half of that expressed in litres per hour per square meter of BSA ($r^2 = 40\%$).

The ratio of the AUC_t, for doxorubicinol and the AUC_t for doxorubicin (R) was higher in the men that in the women, although this difference did not reach statistical significance (0.62 and 0.36, respectively; $P = 0.03$). The terminal half-life ($t_{1/2\gamma}$) of doxorubicin was longer for men and for women (median values, 54.3 and 35.3 h, respectively; $P = 0.05$).

Discussion

The most important finding of this study is that much of the variability in doxorubicin pharmacokinetics in patients with normal liver biochemistry can be explained by patients' gender. Doxorubicin clearance was significantly higher in the men than in the women. No other physical or biochemical characteristic significantly influenced doxorubicin clearance in these patients with normal serum AST and bilirubin values.

Over half of the patients did not have a liver scan. We cannot exclude the possibility that a preponderance of occult liver metastases in the women contributed to their lower doxorubicin clearance. There is, however, no evidence that the presence of liver metastases affects doxorubicin pharmacokinetics in patients with normal liver biochemistry. Moreover, the finding in the current study that gender influences doxorubicin clearance is supported by an earlier population analysis of epirubicin pharmacokinetics [18] suggesting that epirubicin clearance may be lower in women than in men.

Rodvold et al. [15] reported reduced doxorubicin clearance in obese patients, all of whom were women. However, in the current study, body weight did not influence doxorubicin pharmacokinetics. The large surface area of men as compared with women may account for some of the difference seen in doxorubicin clearance. However, when clearance was calculated taking BSA into account the difference in doxorubicin clearance remained highly significant. Important gender-related differences in drug metabolism are generally not seen in humans, but clearance of benzodiazepines [5], paracetamol [10] and salicylcic acid [11] is substantially higher in men than in women. Unlike doxorubicin, these drugs primarily undergo glucuronidation. In the current study a higher proportion of doxoubicinol was detected in the men, indicating that they may have greater aldoketoreductase activity than do the women.

The important practical question raised by this study is whether the pharmacokinetic relationship between doxorubicin clearance and gender is significantly clinically. This cannot be answered by the current study, in which patients had a variety of types of cancer and often received other cytotoxics on the completion of pharmacokinetic sampling. However, several studies have related anthracycline pharmacokinetics to both treatment efficacy and toxicity. High doxorubicin levels were associated with prolonged remission duration in patients with acute nonlymphocytic leukaemia [13]. Similarly, Robert et al. [14] correlated early-phase doxorubicin pharmacokinetics with response in patients with breast cancer. Similarly, with regard to treatment toxicity, the doxorubicin AUC correlated with myelosuppression in patients with small-cell lung cancer [12]. Similarly, the AUC of iododoxorubicin correlates with myelosuppression [14, 17]. These data suggest that there is a relationship between anthracycline pharmacokinetics and treatment outcome and that pharmacokinetic variability may be clinically important.

It is perhaps surprising that the effect of gender on the pharmacokinetics of anthracyclines has not been evaluated more widely. However, the systematic effect of liver dysfunction on anthracycline pharmacokinetics has only recently been clarified [16]. The finding that the sex of a patient affects doxorubicin clearance needs to be confirmed. It will also be important to establish whether there is a relationship between gender and pharmacodynamic parameters such as toxicity or response to treatment. If it is confirmed that doxorubicin clearance is higher in men than in women and that this is clinically relevant, the dosage recommendations for anthracyclines may need to be reconsidered.

Acknowledgements We thank Ms. D. Herriott, who performed part of the HPLC analysis, and Ms. A. Curnow and Ms. M. Lawrence, who helped with data collection. This work was supported in part by grants from the Hans Oppenheimer Trust and Farmitalia Carlo Erba.

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