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Doxorubicin pharmacokinetics: the effect of abnormal liver biochemistry tests

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Abstract We studied variability in doxorubicin pharmacokinetics in 24 patients with abnormal 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. The relationship between doxorubicin clearance (dose/AUC) and liver biochemistry tests (AST, bilirubin, albumin, alkaline phosphatase and indocyanine green clearance) was investigated. Patients with a raised bilirubin level had reduced doxorubicin clearance, but there was no clear relationship between the extent of this elevation and the reduction in doxorubicin clearance. Doxorubicin clearance was lower in patients with an isolated increase in AST than in those with normal liver biochemistry, but this difference was not statistically significant. Nevertheless, there was a significant correlation between reduced doxorubicin clearance and both raised serum AST levels and low indocyanine green clearance. These pharmacokinetic data suggest that current dose reductions based solely on the extent to which bilirubin is elevated may not be optimal.

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Introduction

The anthracyclines are amongst the most effective and widely used cytotoxic drugs. Anthracycline doses are conventionally adjusted according to the surface area of the patient and are often reduced in those with liver dysfunction. Despite these dose adjustments there is wide variation in doxorubicin pharmacokinetics. This raises the important question as to whether current practices for determination of doses in these patients are adequate. Inappropriate dosage may lead to suboptimal treatment in some patients whilst exposing others to the risk of unacceptable toxicity.

There remains considerable controversy as to the importance of liver dysfunction in patients treated with anthracyclines. As the main route of elimination for the anthracyclines is hepatic metabolism and biliary excretion, dose reductions seem reasonable in patients with abnormal liver biochemistry tests. Benjamin et al. [3] first described increased toxicity in eight patients with liver metastases treated with full doses of doxorubicin. Doxorubicin levels were increased in five of these patients. This excess toxicity was eliminated in a further seven patients with raised bilirubin levels or increased Bromsulphalein (BSP) retention in whom empirical dose reductions were made. A dose-reduction scheme based principally on a raised serum bilirubin level (Doxorubicin data sheet, Pharmacia and Upjohn) was widely adopted, but despite extensive use it has not been validated. Indeed, several studies have reported no consistent effect of liver dysfunction on doxorubicin pharmacokinetics [4, 7–9, 25]. Other groups have described altered pharmacokinetics of doxorubicin in patients with liver dysfunction, but this did not correlate with any single liver biochemistry test [15, 17, 19, 23].

With the introduction of epirubicin (4′-epidoxorubicin), Camaggi et al. [6, 7] described reduced elimination

in patients with liver metastases or biliary obstruction. Dose reductions, again based primarily on serum bilirubin levels, were recommended for epirubicin as for doxorubicin (Pharmorubicin data sheet, Pharmacia and Upjohn). However, in two recent studies we showed that epirubicin clearance was strongly correlated with serum aspartate aminotransferase (AST) rather than bilirubin levels [12, 28]. This led us to look again at the question as to how liver dysfunction affects doxorubicin pharmacokinetics. The current study does not address the question of altered pharmacokinetics of doxorubicin metabolites as they are not clinically important.

The main aim of the current study was to investigate the relationship between doxorubicin pharmacokinetics and conventional liver biochemistry tests. The relationship with indocyanine green (ICG) clearance, a measure of hepatic blood flow and liver function, was also studied. We have previously described sources of variability in doxorubicin pharmacokinetics in patients with normal liver biochemistry [13].

Patients and methods

Patients and treatment

Doxorubicin pharmacokinetics were studied in 24 patients, 17 women and 7 men, who had received no prior anthracycline treatment. Doxorubicin was given as a short i.v. infusion. Doses were determined by the clinician and pharmacokinetic studies were performed only during the first cycle of chemotherapy. Patients who were having doxorubicin as part of a combination chemotherapy regimen received the other cytotoxics after completion of the pharmacokinetic sampling. The study was approved by the local ethics committee and all patients gave informed consent to their participation in the study.

The characteristics of the patients are shown in Table 1. All had abnormal liver biochemistry, defined as either serum AST or bilirubin values above the reference range for the hospital laboratory. Serum alkaline phosphatase was not included in this definition as many patients had advanced breast cancer and bone metastases. None of the patients had a history of alcoholic or other chronic liver disease. The diagnosis of liver metastases was confirmed radiologically in 18 of the 24 patients. The remaining 6 patients were not scanned and the diagnosis was made clinically on the basis of raised liver biochemistry tests and hepatomegaly. The extent to which the liver was replaced radiologically by tumour was not assessed, and histological confirmation of liver metastases was not sought. For this analysis, patients were divided into two groups as follows:

1. Group 1 – serum AST levels were above the upper limit of the reference range *but* serum bilirubin values lay within the reference range (18 patients).
2. Group 2 – both serum AST *and* bilirubin levels lay above the upper limit of the reference range (6 patients).

We subdivided the patients in this way for three reasons. Firstly, serum AST is frequently elevated in patients with liver metastases and a normal bilirubin level [18], but current dose recommendations do not encompass isolated increases in concentrations of aminotransferases. Secondly, serum AST may be of particular clinical relevance since it correlates best with survival in patients with breast cancer and liver metastases [21]. Finally, epirubicin clearance correlates with serum AST rather than bilirubin levels [12, 28].

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 [10].

Table 1 Clinical and biochemical characteristics of patients in groups 1 and 2 (*alk phos* Alkaline phosphatase)

Characteristics	Group 1	Group 2
Number of patients	18	6
Median age, years (range)	52 (24–79)	64 (52–83)
Median AST, IU/l (range)	100 (47–233)	159 (78–499)
Median bilirubin, μmol/l (range)	10 (3–17)	95 (30–296)
Median alk phos, IU/l (range)	404 (182–1947)	943 (400–2784)
Median albumin, g/l (range)	37[a] (29–48)	32 (31–39)
Median ICG Clearance (range)	8.7 (3.5–21.8)	2.1 (0.4–7.1)
Median creatinine, μmol/l (range)	80[b] (4–166)	54[c] (41–66)
Primary tumour:		
Breast	12	2
Lymphoma	3	1
Other	3	3
Doxorubicin dose:		
≤ 25 mg/m^2	3	4
26–50 mg/m^2	9	2
51–75 mg/m^2	6	0

[a] $n = 16$
[b] $n = 15$
[c] $n = 2$

Pharmacokinetics

For the measurement of doxorubicin and doxorubicinol levels a total of 15 blood samples were taken through an indwelling cannula from the end of the drug injection to 48 h after treatment. Each sample was collected 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 high-performance liquid chromatography (HPLC) with fluorescence detection. One of two methods was used to extract doxorubicin and doxorubicinol from plasma. In the first, C_2 cassettes were introduced into the solvent stream of the HPLC system via an advanced automatic sample processor (AASP; Varian Associates) [11]. The other extraction method used a chloroform:2-propanol (1:1) mixture [2]. Extracted residues were redissolved in 150 μl of solvent and 50 μl was injected into the HPLC system manually. In both cases, peak heights were measured by a computing integrator and peak height ratios were calculated with daunorubicin as the internal standard in all assay runs. The detection limit of the assay was <1 ng/ml using solid-phase extraction and 4 ng/ml using solvent extraction. For both methods the inter- and intra- assay variation was $<10\%$.

Doxorubicin pharmacokinetics were fitted to a three-compartment model by the "Pharmkit" programme [16] using sum of squares and Akaike's information criterion (AIC) to assess error and goodness of fit. The area under the concentration-time curve to 48 h (AUC_t) was calculated from the end of the injection and corrected to include the period of administration [14]. Since a range of doxorubicin doses was used, the pharmacokinetic parameter studied in detail was total plasma drug clearance (Cl), calculated as dose/AUC_t adjusted for surface area. The early (α), intermediate (β) and terminal (γ) half-lives and the mean retention time (MRT) were also calculated using "Pharmkit". The ratio of the AUCs

recorded for doxorubicin and doxorubicinol (AUC R) was calculated.

ICG at 0.25 mg/kg was given as a bolus injection to all patients prior to administration of doxorubicin, and serial blood samples were taken at between 4 and 25 min after the injection of ICG. Concentrations of ICG were measured spectrophotometrically [20] and ICG clearance was calculated [5].

Statistical analysis

The pharmacokinetic parameters of patients in groups 1 and 2 were compared with those we had previously reported in patients with normal liver biochemistry [13]. The biochemical and pharmacokinetic parameters of the patient groups were compared using the Kruskal-Wallis or Mann-Whitney tests, depending on the number of groups to be compared. Variables such as serum AST and bilirubin were not normally distributed ($P < 0.05$; Shapiro Francia test). Therefore, relationships of pharmacokinetic parameters with liver biochemistry were investigated using rank correlation. In a data set of 24 patients a correlation coefficient, r, as low as 0.33 is statistically significant ($P < 0.05$), although representing only a weak relationship. Therefore, only values of $r > 0.5$ were considered to have potentially important predictive use. The relative contribution of each biochemical test to the variability in the pharmacokinetic values was evaluated using stepwise linear regression analysis.

Results

Clinical and biochemical characteristics

The characteristics of the two groups of patients in the current study are shown in Table 1. Doxorubicin was given as a bolus i.v. injection (median duration 4 min, range 1–12 min). As expected, since doses were chosen on clinical grounds and were influenced by liver biochemistry tests, the median dose of doxorubicin delivered to patients in groups 1 and 2 differed significantly (45 and 25 mg/m^2, respectively; $P < 0.01$). By definition, the patients in group 2 had significantly higher bilirubin levels than those in group 1. The patients in group 2 also had higher serum AST values than those in group 1, although this difference did not reach statistical significance (159 and 100 Iu/l, respectively; $P = 0.08$).

Doxorubicin pharmacokinetics

The principal pharmacokinetic parameters recorded for patients in the two groups in the current study are shown in Table 2. Doxorubicin clearance determined in patients from groups 1 and 2 is compared in Fig. 1.

There were significant differences in doxorubicin clearance between patients who had an isolated increase in serum AST levels (group 1), patients with a raised bilirubin value (group 2), and those previously described as having normal liver tests [13] ($P < 0.0001$). Further investigation confirmed that doxorubicin clearance was lower in patients with a raised bilirubin level than in patients who had an isolated increase in serum AST levels (16.6 and 29.4 l h^{-1} m^{-2} respectively; $P = 0.009$) or those previously described as having normal liver tests (16.6 and 34.7 l h^{-1} m^{-2} respectively; $P = 0.034$). The six patients in group 2 had raised serum bilirubin values varying between 30 and 296 μmol/l. In these patients there was a trend for the level of serum bilirubin to be associated with reduced doxorubicin clearance, but this was not statistically significant ($r = -0.37$, $P = 0.2$).

Doxorubicin clearance was also lower for patients in group 1 with an isolated increase in serum AST than in those with normal liver biochemistry. However, this difference was not statistically significant (29.4 and 34.7 l h^{-1} m^{-2}, respectively; $P = 0.37$). Nevertheless, in these 18 patients with raised AST but normal bilirubin levels there was a correlation between the level of AST and doxorubicin clearance ($r = -0.5$, $P = 0.03$).

The relationship of doxorubicin clearance with liver biochemistry and renal function as determined for all 24 patients in a univariate analysis is shown in Table 3. When groups 1 and 2 are taken together, total doxorubicin clearance was negatively correlated with serum AST (Fig. 2) and positively correlated with ICG clearance (Fig. 3). A significant correlation was seen between

Table 2 Doxorubicin (*Dox*) pharmacokinetic parameters of patients in groups 1 and 2

Median pharmacokinetic value	Group 1	Group 2
Dox Clt, l h^{-1} m^{-2}	29.4	16.6
(range)	(14.6–120)	9.2–28.3)
Dox MRT, h	18.9	53.3
(range)	(15.9–92.6)	(19.0–74.5)
Dox α-$t_{1/2}$, h	0.08	0.08
(range)	(0.04–0.15)	(0.06–0.13)
Dox β-$t_{1/2}$, h	1.8	0.87
(range)	(0.3–3.5)	(0.5–4.3)
Dox γ-$t_{1/2}$, h	46.3	44.7
(range)	(16.7–71.6)	(20.1–56.7)
AUC R	0.42[a]	0.53
(range)	(0.2–1.3)	(0.3–2.0)

[a] $n = 16$

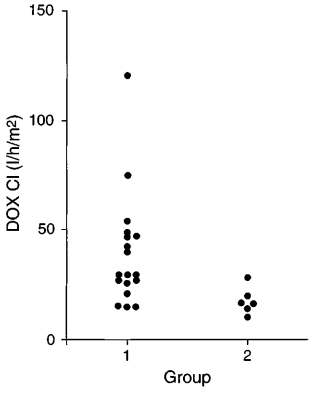

Fig. 1 Total doxorubicin clearance in patients with raised AST but normal bilirubin levels (group 1) and raised AST and bilirubin values (group 2)

Table 3 Relationships between liver biochemistry tests, physical characteristics and doxorubicin (*Dox*) clearance ($n = 24$)[a] (*alk phos* Alkaline phosphatase)

Parameter	Correlation with dox clearance (l/h/m^2)	
	r	*P*
ICG clearance (ml/min^{-1} kg^{-1})	*0.55*	*0.003*
log AST (IU/l)	*−0.56*	*0.002*
Alk phos (IU/l)	−0.31	0.09
Log bilirubin (μmol/l)	−0.35	0.04
Albumin (g/l)[b]	0.44	0.02
Creatinine (Cr)[c] (μmol/l)	*0.54*	*0.003*
Cr clearance[c] (ml/min)	0.32	0.09
Age	*−0.51*	*0.005*

[a] Values in *italics* represent $r > 0.5$ and $P < 0.05$
[b] $n = 22$
[c] $n = 17$

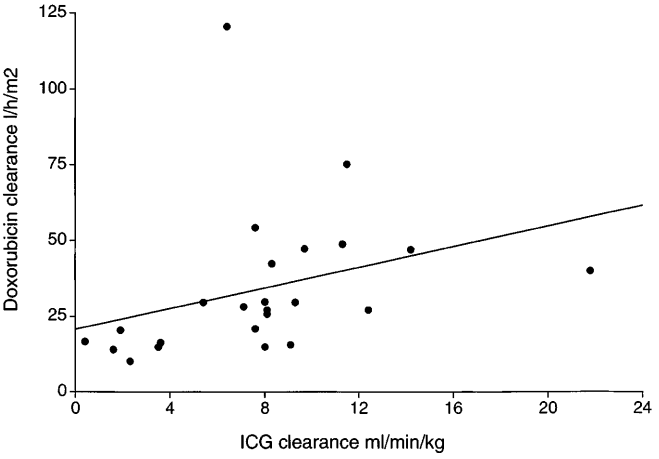

Fig. 3 Correlation between ICG clearance and total doxorubicin clearance in patients with raised AST ± raised bilirubin levels (group 1 and 2). $r = 0.54$; $P = 0.004$

doxorubicin clearance and serum creatinine concentration but not with calculated creatinine clearance. Alkaline phosphatase and albumin showed no correlation with doxorubicin clearance. The correlation between bilirubin and doxorubicin clearance was statistically significant but weak ($P = 0.04$, $r = -0.35$) and was considered not to have potentially important predictive use. In this univariate analysis, age was negatively correlated with doxorubicin clearance. However, there was no difference in doxorubicin clearance between men and women (27.0 and 27.1 l h^{-1} m^{-2}, respectively; $P = 0.95$).

In a forward stepwise linear regression analysis of all 24 patients using the same variables, serum AST correlated most strongly with doxorubicin clearance ($r^2 = 40\%$). ICG clearance was no longer significant in this analysis. The relationship between doxorubicin clearance and serum creatinine concentration was not confirmed in the multivariate analysis, again probably because serum creatinine also correlated with AST ($r = 0.36$, $P = 0.08$). Similarly, age was found to correlate both with AST and with ICG clearance ($r = 0.31$ and $r = -0.08$, respectively).

Discussion

The most important finding of this study is that although abnormalities in liver biochemistry tests account for a significant proportion of the variability in doxorubicin pharmacokinetics, current dose modifications

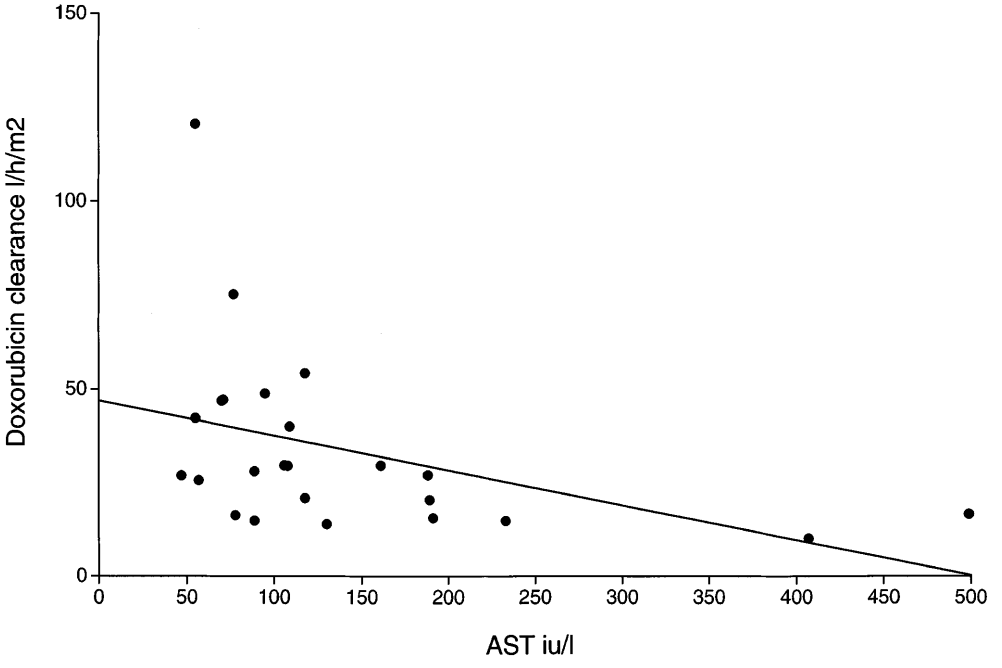

Fig. 2 Correlation between serum AST levels and doxorubicin clearance in patients with raised AST ± raised bilirubin values (groups 1 and 2). $r = 0.56$; $P < 0.002$

may not be optimal. At present, dose reductions are recommended only for patients with raised serum bilirubin levels, and the extent of the dose reduction is based on the degree to which the bilirubin is elevated. The observation that the serum AST level correlates with reduced clearance suggests that dose recommendations should also take into account serum transaminases.

The current study confirms that in patients with a raised serum bilirubin value doxorubicin clearance is approximately halved as compared with those with either normal liver biochemistry or an isolated increase in AST concentration. Interestingly, the elimination half-lives were the same in the two groups; hence, it appears that this effect may be due to changes in drug distribution. This 50% reduction in doxorubicin clearance appears to be in line with the current recommendations for patients with up to a 3-fold elevation of bilirubin. However, four of these six patients had a >3-fold increase in serum bilirubin (values of 91, 99, 276 and 296 μmol/l). We did not see any pharmacokinetic evidence to support the currently recommended reduction to 25% of the doxorubicin dose for these patients.

We have previously shown that for epirubicin, serum AST values reflect the effect of liver dysfunction on drug clearance more sensitively and reliably than do bilirubin levels [12,28]. The current study suggests that there is also a correlation between AST and doxorubicin clearance in patients with abnormal liver biochemistry. However, there may be important differences between doxorubicin and epirubicin with regard to the effect of liver dysfunction on their pharmacokinetics. Firstly, although patients in this study with increased AST but normal bilirubin levels had lower doxorubicin clearance than those with normal liver tests, this difference was modest and not statistically significant. By contrast, epirubicin clearance is significantly lower in patients with an isolated increase in AST than in those with normal liver biochemistry [28]. Secondly, in patients with abnormal liver biochemistry, differences in serum AST values may account for more of the variability in clearance of epirubicin [12, 28] as opposed to doxorubicin (r^2 = 50% and 40%, respectively). These differences may be accounted for by the extensive glucuronidation of epirubicin that is not seen with doxorubicin. The current study suggests that there is a relationship between an isolated elevation of AST and reduced doxorubicin clearance, but its importance is difficult to quantify.

The effect of liver dysfunction on doxorubicin pharmacokinetics has been disputed. There are several possible explanations for the disparity between our data and the findings of earlier pharmacokinetics studies. Firstly, many previous investigations involved small groups of patients [15, 23, 27] and had with little power to detect differences in pharmacokinetics, whereas the current study included a larger number of patients with well-defined abnormalities of liver biochemistry. Secondly, estimation of pharmacokinetic parameters is difficult in studies that collect samples for only a very limited period [19]. In the current study, patients were sampled for up to 48 h and AUC_t was adjusted to consider different infusion times, which may be important as treatment times vary, affecting estimates of pharmacokinetic parameters [14]. Thirdly, in contrast to some early studies, we calculated doxorubicin clearance [4, 8, 9], which is the best pharmacokinetic measure of hepatic metabolism [22]. Finally, conventional liver biochemistry tests may not be the appropriate measures for detection of liver impairment. They reflect liver damage rather than hepatic function, which can be estimated by measurements such as ICG clearance. In the current study, ICG clearance correlated strongly with reduced doxorubicin clearance, but in the multivariate analysis it did not add to the liver biochemistry tests. Moreover, as the measurement of ICG levels is time-consuming and not widely available, it appears not to be useful in this setting.

As a relationship has been demonstrated between liver biochemistry tests and doxorubicin pharmacokinetics, the important practical question is whether this relationship is clinically significant. The design of the current study, with some patients receiving other cytotoxics on completion of the pharmacokinetic sampling, precluded evaluation of doxorubicin pharmacodynamics. Indeed, few studies have related anthracycline kinetics to treatment efficacy and toxicity. High doxorubicin levels, however, were associated with prolonged remission duration in patients with acute non-lymphocytic leukaemia [24]. Similarly, Robert et al. [26] correlated early-phase doxorubicin pharmacokinetics with response in patients with breast cancer. With regard to treatment toxicity, the doxorubicin AUC correlated with myelosuppression in.patients receiving bolus [23] or continuous-infusion [1] treatment. These relationships between doxorubicin pharmacokinetics and treatment outcome suggest that pharmacokinetic variability is clinically important. The association between abnormal liver biochemistry and altered doxorubicin kinetics is therefore a reasonable starting point for considerations of new dose modifications in patients with hepatic dysfunction.

This study confirms that there is a systematic relationship between raised biochemistry liver tests and reduced doxorubicin clearance. Patients with a raised bilirubin level do have reduced doxorubicin clearance. However, amongst patients with a raised bilirubin value there was no clear relationship between the extent of this elevation and the reduction in doxorubicin clearance. These pharmacokinetic data suggest that a dose reduction to 50% may be appropriate in patients with a raised level of bilirubin. The question as to whether the currently recommended further reduction to 25% is appropriate for patients with a >3-fold increase in serum bilirubin remains unresolved. By contrast, the relationship between serum AST levels and reduced doxorubicin clearance suggests the possibility that a dose reduction to 75% may be appropriate in patients with an elevated

AST value, although this is less clear for doxorubicin than for epirubicin. These findings emphasise the continuing need for dose recommendations to be validated prospectively in a large group of patients with abnormal liver biochemistry.

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