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Comparative pharmacokinetics of doxorubicin given by three different schedules with equal dose intensity in patients with breast cancer

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Summary. The pharmacokinetics of doxorubicin given according to three different schedules with a similar dose-time intensity have been studied and compared in 16 women with metastatic breast cancer. Six patients were treated with doxorubicin 75 mg/m^2 by i.v. bolus repeated every 3 weeks; 5 patients received doxorubicin by 4-day continuous infusion every 3 weeks (4 at 75 mg/m^2 and 1 at 60 mg/m^2); 5 patients received 25 mg/m^2 by i.v. bolus given weekly. Timed blood samples were collected and plasma levels of doxorubicin and its metabolite doxorubicinol were measured by high-performance liquid chromatography with fluorescence detection. Peak plasma concentrations were measured, and areas under the concentration-time curves calculated. Peak plasma levels of doxorubicin were significantly lower with the 4-day infusion than with either of the bolus injections. The 4-day infusion, however, gave significantly greater total exposure to doxorubicin and doxorubicinol, as indicated by area under the concentration-time curve, than weekly or 3-weekly bolus treatment. A single bolus injection of doxorubicin 25 mg/m^2 yielded a total exposure to doxorubicin approximately half that achieved with a 75 mg/m^2 bolus injection. Over a 3-week period, therefore, total exposure to doxorubicin would be greater with the weekly low-dose schedule than with the 3-weekly administration. We conclude that drug scheduling has significant effects on doxorubicin pharmacokinetics.

Introduction

Anthracyclines are probably the single most active cytotoxic agents in the treatment of patients with advanced breast cancer [33]. Carmo-Pereira et al. [8] have demonstrated that doxorubicin given as an injection every 3 weeks gives a higher response rate at a high (70 mg/m^2) rather than a low (35 mg/m^2) dose. The optimum schedule of administration for doxorubicin has not, however, been established [3]. Doxorubicin is usually given as a bolus injection every 3 weeks, but weekly treatment is also effective and may reduce the incidence of cardiotoxicity [9]. When doxorubicin is given as a continuous infusion, toxicity may also be reduced whilst cytotoxic activity is retained [18, 20].

Doxorubicin pharmacokinetics have been widely studied following the administration of high-dose [10] and low-dose [15] bolus injections and with continuous infusions [1, 7, 34]. However, the pharmacokinetics of doxorubicin given according to these three different schedules with the same dose-time intensity have been compared in only one study [32]. The current report describes the pharmacokinetics of doxorubicin and its metabolite doxorubicinol, measured by a high-performance liquid chromatography (HPLC) technique. Patients with metastatic breast cancer were treated with doxorubicin given as a 3-weekly high-dose bolus injection, a 3-weekly continuous 4-day infusion, or a weekly low-dose bolus injection. Those patients treated with the weekly or 3-weekly bolus injections formed part of a larger randomized clinical study, the outcome of which has been reported separately [35].

Patients and methods

Sixteen women with metastatic breast cancer were studied. They had received no prior chemotherapy for advanced disease, and doxorubicin pharmacokinetics were studied only during their first cycle of treatment. None of the patients was taking drugs known to affect hepatic blood flow or drug metabolism. Patients with a raised serum bilirubin, or a serum aspartate transaminase more than twice the upper limit of normal, were excluded.

Doxorubicin was given according to one of three schedules, each with a planned dose-time intensity of 75 mg/m^2 every 3 weeks. A group of 6 patients received doxorubicin 75 mg/m^2 as a bolus injection every 3 weeks and 5 received 25 mg/m^2 as a bolus injection given weekly. The remaining 5 patients were treated with doxorubicin every 3 weeks given as a continuous 4-day infusion, 4 of them receiving doxorubicin 75 mg/m^2, whilst the remaining patient, who had undergone extensive

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Table 1. Clinical and biochemical characteristics of patients receiving each of the three treatment schedules

	High-dose bolus ($n = 6$)	Low-dose bolus ($n = 5$)	4-Day infusion ($n = 5$)
Mean age (range) in years	48 (40–51)	56 (48–61)	52 (38–58)
Mean serum AST, units/l (range)	21 (15–26)	35 (24–51)	28 (18–42)
Mean serum bilirubin, μmol/l (range)	9 (8–20)	8 (3–14)	9 (8–29)
Mean serum creatinine, μmol/l (range)	82 (66–103)	83 (79–86)	83 (74–92)
Mean doxorubicin dose, mg/m^2 (range)	75	25	72 (60–75)
Mean administration time (range)	6.6 min (4–12)	2.2 min (1–3)	96 h

prior radiotherapy to the axial skeleton, received 60 mg/m^2. Each 4-day infusion was administered via an indwelling Hickman catheter using four elastomeric infusors (Travenol, Deerfield, USA). The infusors [12] each delivered a quarter of the total dose over 4 successive days, and each was removed after 24 h. A batch of four infusors was prepared on day 1 of treatment and kept at 4° C until used.

Blood samples were taken from an indwelling venous cannula, with the start of administration as time 0. Samples were collected before treatment and at 6, 9, 12, 15, 20, 30 and 45 min and 1, 2, 4, 6, 8, 10, 24, 30 and 48 h after the low-dose bolus injections. Sampling was extended to 72 h after the high-dose bolus injection. In patients treated by 4-day infusion, samples were taken before and during the infusion at 30 min, 1, 2, 6, 10, 24, 30, 48, 53, 72 and 96 h; samples were also obtained for up to 72 h after the end of the infusion. Each 7-ml sample was taken into a lithium heparin tube, and centrifuged, after which the separated plasma was stored at –20° C.

Plasma levels of doxorubicin and doxorubicinol were measured using a sensitive HPLC technique [11]. Mean recovery of doxorubicin is 76% and of doxorubicinol 77%. The detection limit of the assay is 0.4 ng/ml for both doxorubicin and doxorubicinol. The intra-assay coefficient of variation for doxorubicin is 4.3% and that for doxorubicinol is 4.7%. The inter-assay coefficient of variation is 4.9% for doxorubicin and 4.4% for doxorubicinol.

The peak plasma concentrations (PPC) of doxorubicin and doxorubicinol were measured. Initial estimates of the pharmacokinetic parameters were obtained using a three-compartment model. These estimates were used with the MULTI pharmacokinetics program [36] to obtain the α, β, and γ doxorubicin half-lives, the derived peak plasma concentration (C_o) and the terminal elimination constant (K_{el}).

The area under the plasma drug concentration-time curve (AUC) to 72 h was determined for doxorubicin and doxorubicinol. The linear trapezoidal approximation was used to estimate AUC. The AUC was not derived by extrapolation back to Co. However, the AUC was extrapolated to 72 h after the end of treatment in all three groups where necessary. The clearance (Cl) and volume of distribution (V_D) for doxorubicin were calculated in all patients receiving the high- or low-dose bolus injections. The ratio (R) of the AUC for doxorubicinol to the AUC for doxorubicin was calculated. Comparison between the pharmacokinetic parameters of all three administration schedules were made using the Kruskal-Wallis one-way analysis of variance; where only the two doxorubicin 75 mg/m^2 schedules were compared the Mann-Whitney test was used.

The stability of doxorubicin in the infusate was evaluated using two infusors kept at 4° C for 3 days and at body temperature for 24 h to mimic the maximum storage and administration times in this group of patients. Timed samples were taken from the infusors and assayed as above.

Results

The clinical characteristics and treatment details of the patients receiving each of the three schedules are shown in Table 1. Two patients, each of whom was treated with doxorubicin 25 mg/m^2, had mildly elevated serum aspartate transaminase (AST) levels (51 units/l in both patients; normal value <43 units/l) and evidence of liver metastases on radionuclide liver scan. Serum bilirubin was normal (<20 μmol/l) in all 16 patients. There were no other significant differences in the clinical and biochemical characteristics of the three groups of patients.

Figures 1 and 2 show the composite concentration-time curves for doxorubicin and doxorubicinol, respectively, for

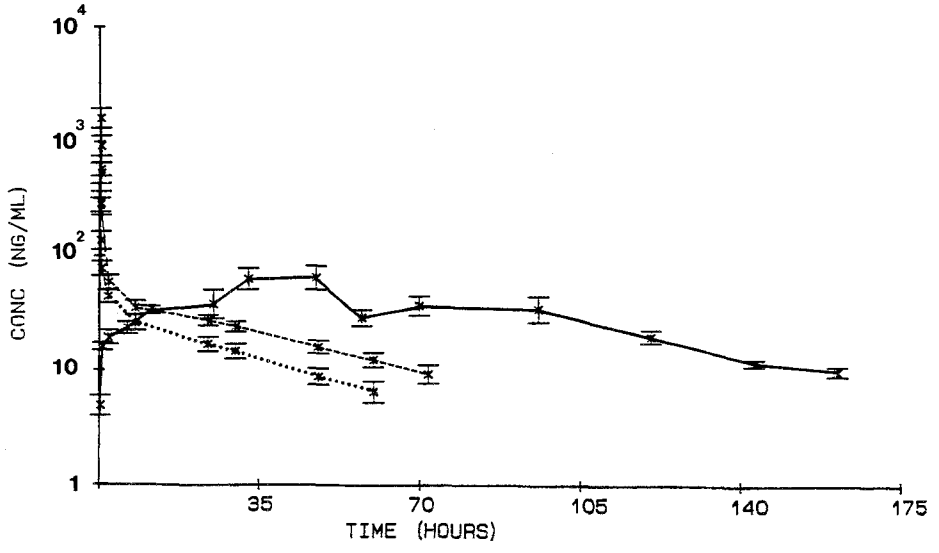

Fig. 1. Concentration-time curves (mean ± SEM) for doxorubicin following administration of doxorubicin:– – –, 75 mg/m^2 bolus; . . . ., 25 mg/m^2 bolus; ——, 75 mg/m^2 by continuous 4-day infusion

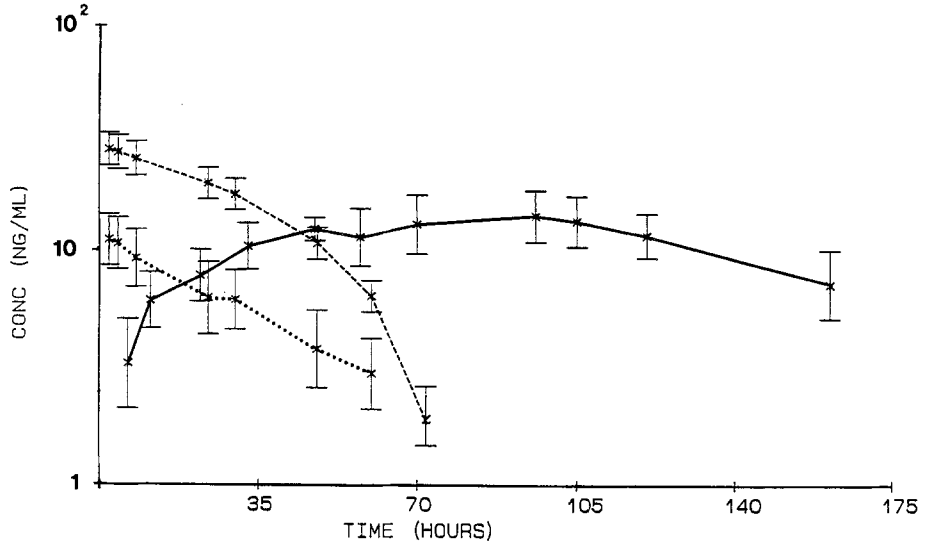

Fig. 2. Concentration-time curves (means ± SEM) for doxorubicinol following administration of doxorubicin: – – –, 75 mg/m^2 bolus; . . . ., 25 mg/m^2 bolus; ——, 75 mg/m^2 continuous 4-day infusion

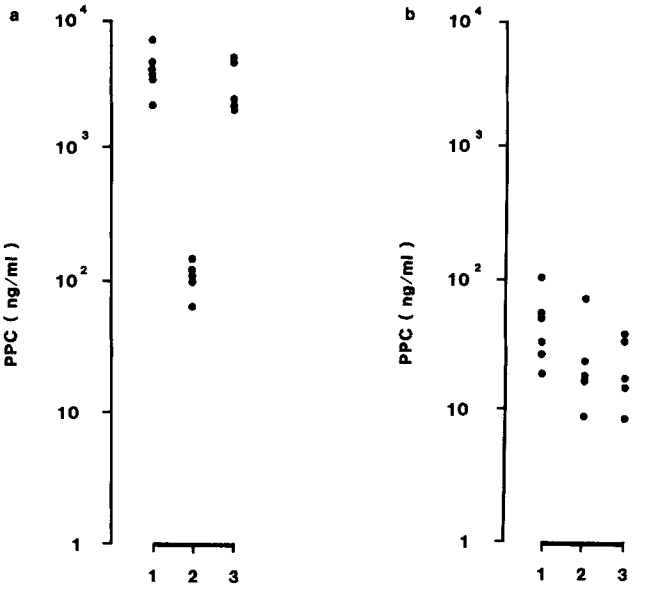

Fig. 3 a, b. Peak plasma concentration of **a** doxorubicin, **b** doxorubicinol. *Column 1*, 75 mg/m^2 bolus; *column 2*, 75 mg/m^2 4-day infusion; *column 3*, 25 mg/m^2 bolus

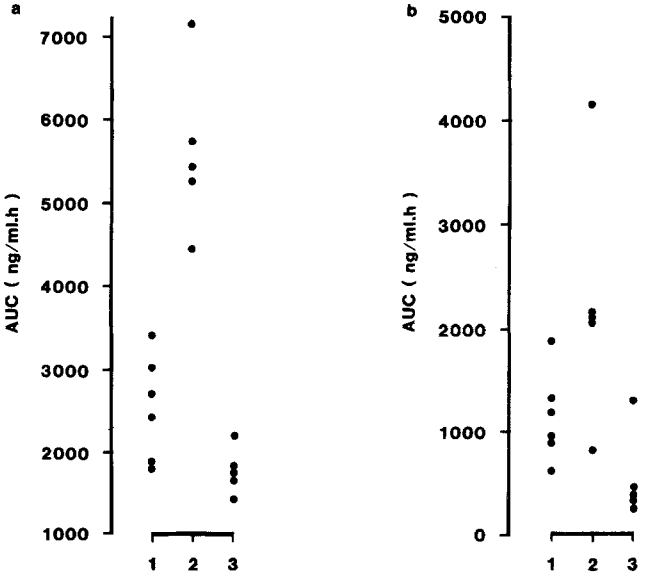

Fig. 4 a, b. Area under the concentration-time curve for **a** doxorubicin **b** doxorubicinol. *Column 1*, 75 mg/m^2 bolus; *column 2*, 75 mg/m^2 4-day infusion; *column 3*, 25 mg/m^2 bolus

each of the three schedules. Doxorubicin levels were initially high following bolus injections of 25 mg/m^2 or 75 mg/m^2 and fell rapidly in a triexponential manner. By contrast, doxorubicin levels rose during the continuous infusions, but peak levels were much lower than with either the high- or the low-dose bolus injections. For doxorubicinol the concentration-time curves of the high- and low-dose boluses were similar, but again the pattern was markedly different with the 4-day infusion.

The PPC of doxorubicin and doxorubicinol measured in the three groups of patients studied are shown in Fig. 3. Marked fluctuations in doxorubicin levels were observed in 4 patients during the 4-day infusion period at times corresponding to the infusor being changed. The median PPC of doxorubicin with the 4-day infusion (113 ng/ml), however, was significantly lower than that for either the high-dose (3719 ng/ml) or the low-dose (2322 ng/ml) bolus injections (P = 0.008). The PPC of doxorubicin, which was measured in the first sample taken after bolus injection, did not differ significantly for doxorubicin 25 mg/m^2 and 75 mg/m^2 (P = 0.5). The PPC of doxorubicinol achieved with the three schedules did not differ significantly (P = 0.09).

Figure 4 shows the AUC for doxorubicin and doxorubicinol in the 3 groups of patients. The highest median AUC for doxorubicin was achieved with the continuous 4-day infusion (5449 ng/ml.h) and was significantly greater than the AUC for doxorubicin following the 75 mg/m^2 (2591 ng/ml.h) bolus injection (P = 0.008). For doxorubicinol, the median AUC with the 4-day infusion (2119 ng/ml.h) was greater than that achieved with the high-dose (1081 ng/ml.h) bolus injection, although this did not reach statistical significance (P = 0.05). After doxorubicin 25 mg/m^2 by bolus injection, the median AUC for

Table 2. Median values for pharmacokinetic parameters of doxorubicin following bolus injections of 25 mg/m² and 75 mg/m²

	C_o (ng/ml)	$\alpha t_{1/2}$(h)	$\beta t_{1/2}$(h)	$\gamma t_{1/2}$(h)	Cl(l/h)	V_D(l)	R
25 mg/m²							
i. v. bolus (mean)	6982	0.08	3.7	31.5	21.4	1081	0.26
range	4504–16356	0.06–0.11	1.3–15.4	21.0–67.3	16.1–27.8	673–1563	0.14–0.72
75 mg/m²							
i. v. bolus (mean)	14947	0.08	2.4	33.0	44.1	2198	0.44
range	8544–17848	0.06–0.09	0.5–4.5	21.0–55.9	36.2–79.9	1922–3620	0.14–0.72

doxorubicin and doxorubicinol were 1619 ng/ml.h and 378 ng/ml.h respectively.

The mean values and ranges for the remaining pharmacokinetic parameters of doxorubicin following high-dose and low-dose bolus injection are shown in Table 2. The derived peak plasma concentration for doxorubicin, Co, was higher with the 75 mg/m² than with the 25 mg/m² injection, but this difference did not reach statistical significance ($P = 0.08$). Total doxorubicin clearance and volume of distribution were significantly higher with the high-dose bolus injection ($P = 0.006$). There was, however, no significant difference between the α, β or γ half-lives of doxorubicin for the two bolus regimens. The conversion of doxorubicin to doxorubicinol, as assessed by the ratio of their respective AUC (R), was also similar for the high- and low-dose bolus injections.

Doxorubicin was stable in the infusate at 4° C, with a fall of less than 1% in concentration over 72 h. Over 24 h in the infusate at body temperature the doxorubicin concentration again fell by less than 1%.

Discussion

Dose intensification and changes in treatment scheduling have been investigated as possible ways of increasing the efficacy of chemotherapy [5a, 17, 19, 22, 35]. The latter approach has been encouraged by the suggestion that toxicity is related to peak drug levels, whereas efficacy may be determined by total drug exposure. This hypothesis has not been validated in clinical practice. Indeed, the optimal dose schedule for doxorubicin, which is one of the most widely used cytotoxic agents, is not known [3].

Although the pharmacokinetics of doxorubicin given by different schedules have been compared previously, the patients studied had a variety of malignancies, had received prior chemotherapy, or were given doxorubicin in combination with other cytotoxic agents [5, 31, 32]. In this study patients with metastatic breast cancer were treated with doxorubicin given as a single agent by weekly bolus injection, 3-weekly bolus injections, or continuous 4-day infusions. Each regimen had the same planned dose-time intensity. Patients were studied only during the first cycle of chemotherapy, as doxorubicin pharmacokinetics may be affected by repeated administration [15, 21]. The groups of patients did not differ significantly in factors that may influence doxorubicin pharmacokinetics such as age [28] and liver biochemistry [2].

Our results show that drug scheduling has an important effect on doxorubicin pharmacokinetics. The continuous 4-day infusion gave measured peak doxorubicin levels approximately 40-fold less than conventional 3-weekly bolus treatment, as previously reported [31, 32]. Nevertheless, the 4-day infusion resulted in greater total exposure to doxorubicin than the same dose of doxorubicin given as a bolus injection. Riggs et al. [26] reported that giving doxorubicin as a 4-day infusion led to reduced peak plasma levels without compromising total drug exposure. Other studies have also shown a trend towards a higher AUC when doxorubicin is given as a prolonged infusion rather than a bolus injection [5, 20, 32]. The current study, however, is the first to demonstrate a significant increase in doxorubicin AUC when it is given by 4-day infusion rather than conventional bolus administration.

After a single bolus injection of doxorubicin 25 mg/m², the measured peak doxorubicin levels observed were similar to those for a 75 mg/m² bolus injection. The same pattern was seen for Co, the derived PPC. The explanation for this observation may be that the duration of administration was greater for the high-dose than for the low-dose bolus injection.

The AUC for doxorubicin 75 mg/m² was only twice that for 25 mg/m². Two patients treated with the low-dose bolus injections had liver metastases and mildly elevated AST. Gillies et al. [16] showed that AST level did not correlate with doxorubicin clearance, and these two patients did not have the highest AUC in this group. It is unlikely, therefore, that this imbalance between the groups influenced our results. Although biliary excretion is the major route of elimination for doxorubicin, urinary excretion accounts for about 13% of total clearance [25]. The pattern of urinary excretion suggests a renal threshold for doxorubicin. This may account at least in part for the pattern of AUC and PPC seen in the current study following bolus injection of doxorubicin at high and low doses.

Previous studies have described both dose-dependent [4, 30] and dose-independent [13, 14, 24] pharmacokinetics for doxorubicin. In the current study doxorubicin clearance was significantly higher with the high-dose bolus than with the low-dose bolus injection. Thus, over a 3-week period, during which time the dose intensity of all three schedules was the same, total doxorubicin exposure with three bolus injections of 25 mg/m² was likely to have been greater than with a single 75 mg/m² bolus injection, and closer to that observed with the 4-day 75 mg/m² continuous infusion.

The importance of pharmacokinetic factors in the treatment of patients with doxorubicin remains uncertain. Studies of tumor cells in culture have shown that for some cell lines peak drug concentration determines the cytotoxity of

doxorubicin, whereas for other cell lines the duration of treatment is a more important factor [27]. Attempts to correlate pharmacokinetic parameters of doxorubicin with clinical efficacy have had only limited success. However, Robert et al. [29] demonstrated a significant correlation between early phase doxorubicin pharmacokinetics and response in patients with locally advanced breast cancer. High plasma doxorubicin levels were also associated with the duration of remission in patients with acute nonlymphocytic leukaemia [23].

There have been no controlled, randomised clinical trials comparing doxorubicin given by bolus injection with doxorubicin by continuous 4-day infusion. However, the patients treated in this study with weekly or 3-weekly bolus injections formed part of a larger randomised clinical study [35]. The response rate according to UICC criteria, survival and treatment toxicity were the same for doxorubicin 75 mg/m^2 given as a bolus 3 weekly and 25 mg/m^2 given weekly.

In conclusion, we have shown significant differences in measured PPC and AUC when doxorubicin is given by different schedules with a similar the same dose-time intensity. The optimal dose schedule for doxorubicin needs to be determined, and clinical trials should include pharmacokinetic studies.

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