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Pharmacokinetic Study of IV Infusions of Adriamycin

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Summary. The plasma pharmacokinetics of adriamycin has been studied in 21 cancer patients (31–85 years old) without liver tumours after short (3.00 min) and prolonged (45 min–16 h) i.v. infusions.

The area under the plasma concentration-time curve and the maximum plasma concentration compensated for dose variation showed a more than 3-fold individual variation. The pharmacokinetics of adriamycin was linear. There was no pharmacokinetic rational for variation of the dose with the age of the patients.

There was good agreement between the measured plasma concentration-time curves for prolonged infusions and curves predicted from pharmacokinetic data from short term infusions.

Key words: adriamycin, cancer patients; infusion, pharmacokinetics

Adriamycin, an anthraquinone glycoside, has proved to be one of the most potent antineoplastic drugs [1, 2]. In addition to the toxic effects common to most antineoplastic drugs (bone marrow depression, alopecia, stomatitis, nausea and vomiting), the effective use of anthraquinone glycosides has been limited by the risk of congestive heart failure which is related to the cumulative dose [3, 4, 5]. Patients who would otherwise benefit from adriamycin therapy may not be able to receive it because of the risk or the actual development of lifethreatening disease.

Pharmacokinetic studies of adriamycin have mainly been focused on patients with liver cancer [6, 7, 8, 9, 10, 11, 12, 13]. Studies in cancer patients without liver tumours have indicated large inter-individual variation in its pharmacokinetics [8, 11, 12, 14, 15]. Some work has suggested that the pharmacokinetics of adriamycin is time- and dose-dependent [14, 16, 17, 18]. However, since the administration time has not been standardized (2–10 min infusion or "rapid

Table 1. Details of the patients

Patient No.	Sex	Age [years]	Diagnosis	Infusion time
1	Male	65	Bladder cancer	3 min
2	Female	65	Lymphoma	3 min, 16 h
3	Female	74	Bladder cancer	3 min, 4 h, 8 h
4	Male	43	Lymphoma	3 min, 2 h, 4 h
5	Male	67	Bladder cancer	3 min, 8 h, 16 h
6	Male	31	Gastro-intestinal cancer	3 min
7	Male	79	Bladder cancer	3 min, 45 min, 4 h, 8 h
8	Male	65	Oesophagus cancer	3 min
9	Male	74	Bladder cancer, lung metastases	3 min, 2 h
10	Male	64	Lymphoma	3 min, 45 min, 2 h
11	Male	60	Bladder cancer	3 min, 2 h
12	Male	50	Prostate cancer	3 min, 45 min
13	Male	50	Neoplasma pulm.	3 min
14	Male	50	Hodgkin's disease	3 min, 4 h
15	Male	62	Lymphoma	3 min, 4 h
16	Male	73	Lymphoma	3 min, 45 min
17	Female	64	Soft tissue sarcoma	3 min
18	Male	60	Carcinoma of parotic glands	3 min
19	Female	85	Soft tissue sarcoma	3 min
20	Male	55	Bladder cancer	3 min
21	Male	63	Chronic lymphatic leukemia	3 min

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Table 2. Plasma pharmacokinetics of adriamycin after a 3.00 min i.v. infusion

Patient No.	Dose [mg]		C_1	C_2	C_3	α	β	γ	AUC	AUC/mg/m^{2}CL		C_{max}[b]/mg/m^2
		[mg/m^2]	[μg·ml^{-1}]	[μg·ml^{-1}] ×10	[μg·ml^{-1}] ×100	[min^{-1}] ×10	[min^{-1}] ×100	[min^{-1}] ×10000	[μg·min·ml^{-1}]		[1×min^{-1}]	×10
1	60	31.8	4.07	0.24	2.38	1.46	0.71	11.5	52.1	1.64	1.15	1.05
2	50	36.0	6.01	0.61	2.58	1.92	1.01	8.71	66.9	1.86	0.75	1.29
3	50	30.7	4.54	15.5	4.18	1.74	8.28	8.56	93.6	3.06	0.53	1.61
4	90	49.3	4.68	1.86	3.01	1.21	2.47	9.63	77.3	1.57	1.16	0.84
5	45	30.0	5.00	0.59	3.23	1.55	1.47	9.35	70.8	2.37	0.64	1.36
6	100	56.3	4.67	0.34	1.42	1.65	1.28	5.43	57.0	1.01	1.76	0.66
7	60	33.8	3.17	2.33	2.37	1.68	4.94	16.3	38.0	1.13	1.58	0.81
8	60	32.4	3.18	0.43	1.76	1.26	0.91	5.62	61.3	1.89	0.98	0.84
9	50	25.2	3.32	0.57	2.14	1.50	1.92	8.03	51.8	2.06	0.97	1.09
10	50	25.7	2.49	0.41	1.58	1.48	2.12	4.07	57.5	2.24	0.87	0.80
11	60	29.8	4.27	0.69	3.05	1.46	1.47	8.02	72.1	2.42	0.83	1.19
12	80	38.4	8.20	2.10	3.59	1.94	3.61	11.2	80.2	2.09	1.00	1.68
13	115	60.0	6.62	0.63	3.89	1.42	1.91	7.75	100	1.67	1.15	0.92
14	45	24.4	8.96	0.20	0.92	1.67	1.65	8.65	65.6	2.69	0.69	2.90
15	70	38.5	6.66	0.45	2.93	1.98	0.56	7.56	80.2	2.09	0.87	1.32
16	90	50.5	5.60	1.66	2.65	1.36	1.59	8.38	83.2	1.65	1.08	0.95
17	105	58.5	11.1	0.53	[a]	1.35	0.14	[a]	119	2.03	0.88	1.57
18	110	58.9	36.5	0.92	2.52	2.50	1.63	9.39	179	3.03	0.62	4.38
19	100	57.6	6.66	2.52	3.10	1.84	2.85	12.0	70.8	1.23	1.41	0.94
20	50	27.4	3.72	1.10	1.99	1.45	2.61	6.99	58.4	2.13	0.86	1.14
21	40	21.8	3.65	0.32	0.59	2.40	3.39	9.88	22.0	1.01	1.82	1.21

[a] 2-compartment model [b] μg/ml

bolus"), detailed evaluation of the pharmacokinetic variability is difficult.

Alteration of the adriamycin dose schedule has proved to be one of the most successful attempts to increase the therapeutic index of adriamycin. A weekly "low dose" regime (10–20 mg/m^2) of adriamycin is associated with a low frequency of side-effects, including less cardiac toxicity, but with retention of its anti-neoplastic activity [19, 20]. Prolonged (10–96 h) continous intravenous infusions of adriamycin seem to be even more advantageous than fractionated doses with the possibility of increasing the total dose and causing no more or even fewer side-effects [21, 22, 23, 24, 25].

In the present investigation the variation in the plasma pharmacokinetics of adriamycin within the dose level 20–60 mg/m^2 has been studied in cancer patients not having a liver neoplasm. The relationship between the maximum plasma concentration and the area under the plasma concentration-time curve for various infusion times has also been investigated.

Materials and Methods

Patients

Twenty one patients (4 females and 17 males), none with a malignant liver tumour, were included in the study. The mean age at first treatment was 62 years (range 31–85 years). Pertinent clinical data are included in Table 1.

Treatment Schedule

All patients were initially treated with a 3.00 min intravenous infusion of adriamycin (20–60 mg/m^2). Patients selected for further study were then randomized to receive a prolonged infusion of adriamycin (infusion times: 45 min, 2 h, 4 h, 8 h, and 16 h). The dose administered did not change with the infusion time. The treatment of some patients was repeatedly randomized amongst the prolonged infusions (Table 1) with intervals of 21 days.

The medium time between the short time infusion and the first prolonged infusion was 21 days (range 20–44 days).

Plasma Samples

Blood samples (5–7 ml) were collected in glass test tubes (Vacutainer) containing 250 IU heparin (freeze-dried). The blood samples were immediately centrifuged for 10 min to separate plasma. The plasma was removed and stored at −80 °C until analysis [26]. Blood samples were collected during the long term infusions and 5, 15, 30, 45 min and 1, 2, 3, 6, 12, 18, 24 h after the end of adriamycin administration.

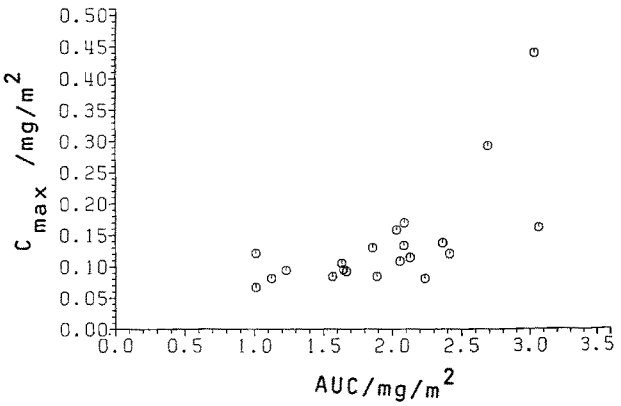


Fig. 1. Maximum adriamycin plasma concentration and area under plasma concentration-time curves. All values normalized for dose variation

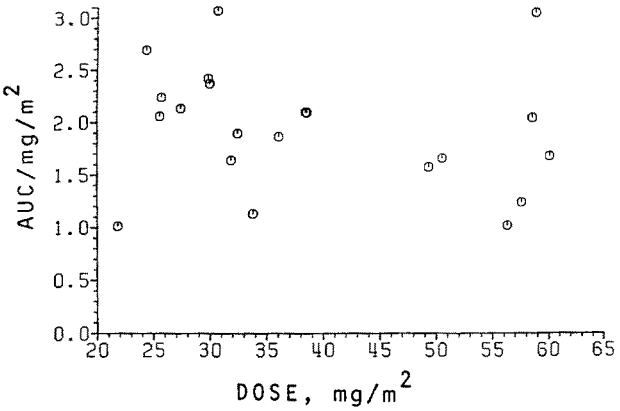


Fig. 2. Area under adriamycin plasma concentration-time curves and dose. AUC values normalized for dose variation

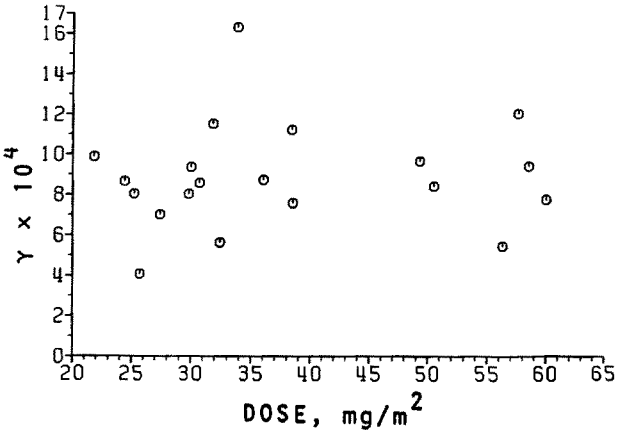


Fig. 3. Terminal elimination rate constant (γ) and adriamycin dose

Determination of Adriamycin and Adriamycinol

Plasma levels of adriamycin were assayed by an analytical method based on extraction and reversed-phase liquid chromatography [27]. One ml of plasma

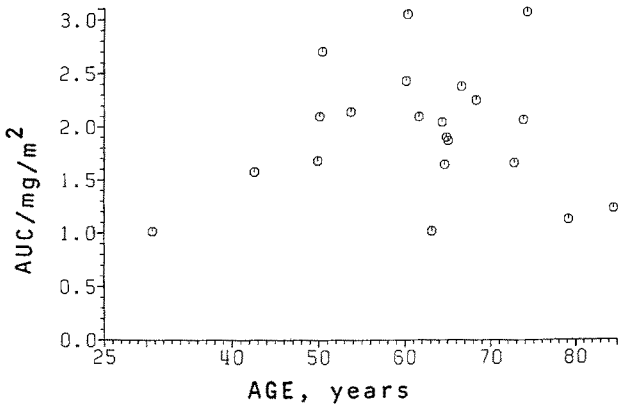


Fig. 4. Area under adriamycin plasma concentration-time curve and age. AUC values normalized for dose variation

was used for the analysis. All plasma concentration data used for the pharmacokinetic evaluation are the means of duplicate analyses.

Pharmacokinetic Evaluation

All pharmacokinetic constants were determined from post-infusion data by the "feathering" technique.

The area under the plasma concentration-time curve (AUC) for a 3.00 min infusion was calculated according to Eq. (1); [28].

$$\mathrm{AUC} = \frac{C_1}{\alpha} + \frac{C_2}{\beta} + \frac{C_3}{\gamma} \quad (1)$$

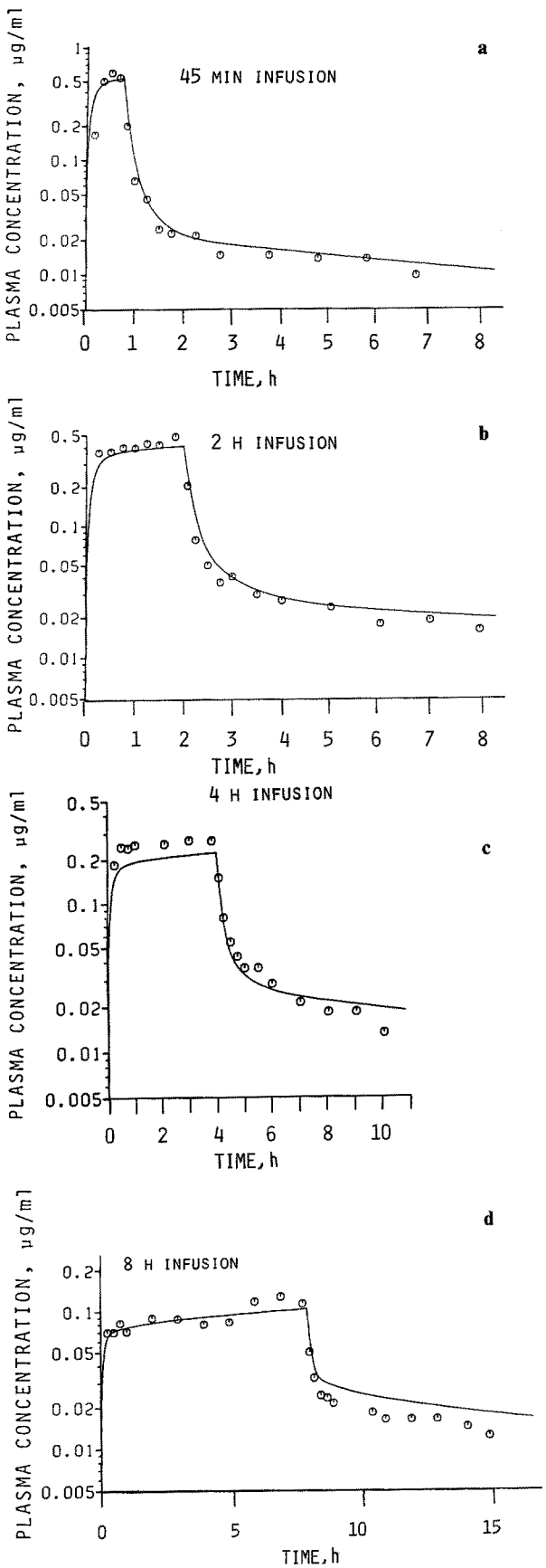
For prolonged infusions, the AUCs were calculated by the trapezoidal rule and the residual area to infinite time. The total plasma clearance CL was calculated as

$$\mathrm{CL} = \mathrm{D}/\mathrm{AUC} \quad (2)$$

where D is the administered dose of adriamycin.

Results and Discussion

It is generally accepted that the plasma pharmacokinetics of adriamycin following intravenous administration can be described by an open three compartment model [6, 8, 13, 15, 29], although early studies of the pharmacokinetics of adriamycin had suggested a biphasic distribution pattern [30]. Boston and Philips [16] recently found a change in pharmacokinetic model with the magnitude of the dose administered. However, their first data point was obtained 30 min after the end of administration, resulting in low precision of the initial half-life. Moreover, the analytical technique used (RIA) did not discriminate between



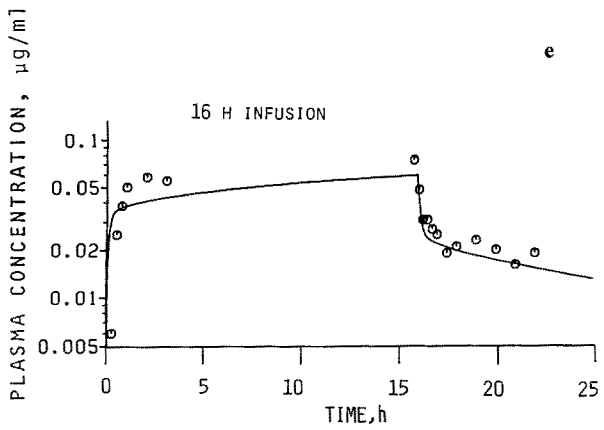


Fig. 5. Adriamycin plasma concentration-time curves for prolonged infusions ∘ = measured plasma concentrations. Solid lines are plasma concentrations predicted from bolus injection data by means of Eqs. (3) and (4). Data from Patient 7 (**a**), Patient 4 (**b** and **c**) and Patient 5 (**d** and **e**)

adriamycin and adriamycinol, a metabolite which has a plasma concentration of the same magnitude as the parent drug at least 12–48 h after administration [12, 15].

For an open three compartment model the plasma concentration C after the end of an intravenous infusion can be expressed by [28]:

$$C = C_1\left(\frac{e^{\alpha T}-1}{\alpha T}\right)e^{-\alpha t} + C_2\left(\frac{e^{\beta T}-1}{\beta T}\right)e^{-\beta t} + C_3\left(\frac{e^{\gamma T}-1}{\gamma T}\right)e^{-\gamma t} \quad (3)$$

where T is the infusion time and t is the time from the start of the infusion. During the infusion the plasma concentration is given by [28]:

$$C = \frac{C_1}{\alpha T}(1-e^{-\alpha t}) + \frac{C_2}{\beta T}(1-e^{-\beta t}) + \frac{C_3}{\gamma T}(1-e^{-\gamma t}) \quad (4)$$

Thus, it is possible to calculate C versus time curves for any infusion time from the pharmacokinetic constants C_1, C_2, C_3, α, β, and γ, under the assumption of linear pharmacokinetics.

In general, plasma concentration data obtained from a "bolus" injection (T→0) are used for the evaluation of the pharmacokinetic constants. In the present work we preferred to evaluate the pharmacokinetics from post-infusion data using a very short but well-defined infusion time (3.00 min) to minimize the errors originating from the very short half-life adriamycin in the alpha phase (typically 4 min). The pharmacokinetic parameters are presented in Table 2. Plasma concentration-time curves calculated by Eq. (3) and with the estimated constants closely fitted the experimental data; in general the calculat-

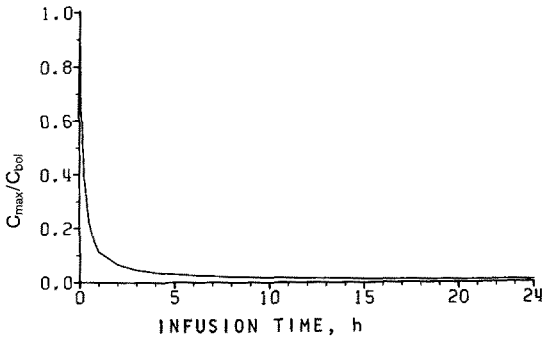


Fig. 6. C_{max}/C_{bol} and infusion time. The calculated curve is based on data in Table 2 and expresses the mean values of C_{max}/C_{bol} for the various infusion times

ed plasma concentrations deviated by less than 10% from the measured concentrations. Calculations using the constants given in Table 2 gave plasma half-lives of (mean ± SD) 4.3 ± 0.8 min, 44.5 ± 28.6 min, and 14.3 ± 4.7 h, respectively.

The plasma concentration data from Patient 17 were best fitted by a two-compartment model. The reason for this is unclear, but it might have been due to error in the sampling timing or aberrant drug disposition.

Large inter-individual variation in AUC and C_{max}, normalized for dose variation, was noticed (Fig. 1). The results presented in Fig. 1 underline the need for individualization of the adriamycin dose, not only in patients with liver tumours as previously stated [13].

Dose-dependent pharmacokinetics of adriamycin, resulting in a change in AUC/mg/m^2 and/or the terminal half-life time with dose has been reported [16, 18]. The results presented in Figs. 2 and 3 show that neither the AUC/mg/m^2 nor the values of γ varied with the dose ($p > 0.6$ and $p > 0.3$, respectively).

The age-dependent pharmacokinetics of adriamycin was studied by Robert et al. [15, 31, 32], with conflicting results. A reduction in the dose of adriamycin in elderly patients has been recommended due to their low clearance as compared to younger patients [31, 32]. The AUCs in patients with breast cancer treated with adriamycin 50 mg/m^2 did not vary with the age of the patients [15]. The results in Fig. 4, which show no tendency for the AUC/mg/m^2 to vary with the age of the patients ($p > 0.8$), do not support a need for a reduction in the dose of adriamycin in elderly patients from the pharmacokinetic point of view.

The possibilities of predicting plasma concentration-time curves for various infusion times by means of Eqs. (3) and (4), and using pharmacokinetic data from a "bolus" injection, are illustrated in Fig. 5 a–e. Visual inspection shows very close agreement between the calculated and measured plasma concentrations. No systematic deviation between them was found, thus establishing that the pharmacokinetics of adriamycin is linear and time independent over the period studied (≤ 60 days), results which are in conflict with previous reports [14, 17, 22, 33, 34, 35].

Maximum Plasma Concentration and Infusion Time

From Eqs. (3) and (4) the follows that the maximum plasma concentration is obtained at the end of the infusion, i.e. when $t = T$. Eqs. (3) and (4) can then be transformed to:

$$C_{max} = C_1 \frac{1 - e^{-\alpha T}}{\alpha T} + C_2 \frac{1 - e^{-\beta T}}{\beta T} + C_3 \frac{1 - e^{-\gamma T}}{\gamma T} \quad (5)$$

The influence of the infusion time on the maximum plasma concentration is illustrated in Fig. 6. Calculation of the quotient C_{max}/C_{bol}, where C_{bol} is the calculated maximum plasma concentration after a bolus injection (i.e. $T = 0$) is based on pharmacokinetic constants from Table 2, and is valid under the assumption of linear pharmacokinetics. C_{max}/C_{bol} decreases drastically with increasing infusion time when $T < 2$ h. The infusion time had only a minor influence on the quotient when $T > 5$ h.

Comparison of observed and calculated quotients C_{max}/C_{bol} for the various infusion times is presented in Table 3, verifing the validity of the curve in Fig. 6.

No systematic study of the influence of infusion time on the pharmacokinetics of adriamycin has previously been reported. An increase in the infusion time from 5 min to 24 h, 48 h and 96 h, led to a decreased in C_{max} from 1.31 μg/ml to 0.237 μg/ml, 0.133 μg/ml and 0.097 μg/ml, respectively [26]. The calculated quotient C_{max}/C_{bol} was 0.48, 0.30 and 0.26 for infusion times of 24 h, 48 h and 96 h, respectively [36]. Baurain et al. [37] reported a 15-fold reduction in C_{max} after intravenous administration of adriamycin to rabbits as a 69 min infusion instead of a bolus injection. It should be noted that the plasma concentration data used in [24] and [36] for the 5 min infusion and bolus injections, respectively, are "extrapolated" values, which might partly account for difference between those results and the values reported here, where the comparison of C_{max} and C_{bol} relied on data obtained from the same patient. Moreover, the adriamycin concentration in [24] and [36] was determined from total fluorescence data, a technique in which adriamycinol is codetermined, thus significantly increasing the estimated adriamycin concentrations during prolonged infusions.

Table 3. Infusion time and relative maximum plasma concentration

Infusion time	$C_{max}/C_{bol} \cdot 10^2$			
	Found	*n*	Calculated[a]	*n*
45 min	17.4±4.6[b]	4	15.0±3.1	21
2 h	8.4±1.4	4	6.2±1.3	21
4 h	3.9±2.2	5	3.3±0.7	21
8 h	2.9±1.5	3	1.9±0.4	21
16 h	1.3	2	1.1±0.3	21

[a] Calculated from data in Table 2 using Eq. (5)
[b] Mean ±SD

Table 4. Infusion time and relative area under adriamycin plasma concentration time curves

Infusion time	AUC_{Inf}/AUC_{Bol}	*n*
45 min	1.04±0.18[a]	4
2 h	0.95±0.15	4
4 h	0.85±0.26	5
8 h	0.83	2[b]
16 h	1.15	2

[a] Mean ±SD
[b] Postinfusion data for pat. 7 are missing

Table 5. Infusion time and normalized maximum adriamycin plasma concentration

Infusion time	C_{max}[a]/mg/m^2	*n*
3.00 min	0.135 ±0.086[b]	21
45 min	0.0216±0.0033	4
2 h	0.010 ±0.002	4
4 h	0.0063±0.004	5
8 h	0.0041±0.0006	3
16 h	0.0022	2

[a] μg/ml
[b] Mean ±SD

The following relation between total plasma clearance, CL, and the steady state plasma concentration, C^{SS} is valid [28]:

$$CL = \frac{D/T}{C^{SS}} \quad (6)$$

A comparision of C^{SS}, calculated from data in Table 2 using Eq. (6), and C_{max}, calculated by means of Eq. (5), showed that for most patients infusion times of the order of 72–84 h would be required to achieve a steady state plasma concentration.

Area under Plasma Concentration-Time Curve and Infusion Time

A comparison of the areas under plasma concentration-time curves after bolus injection and long time infusions is presented in Table 4. The quotient AUC_{Inf}/AUC_{Bol} was close to unity and was independent upon the infusion time, which further supports the assumption of linear pharmacokinetics for adriamycin.

Plasma Pharmacokinetics – Influence on Therapeutic Activity and Side-Effects

The cytostatic effect of adriamycin in vitro and in vivo has been correlated with the area under the plasma concentration-time curve, AUC [38, 39]. The side-effects can either be correlated with AUC and/or the maximum plasma concentration, C_{max}. Five-fold variation in the AUC and in the maximum plasma concentration after normalization for dose variation, AUC/mg/m^2 and C_{max}/mg/m^2, respectively, was observed after administration of adriamycin as a 3.00 min intravenous infusion to patients with liver cancer but with a normal or only slightly elevated serum bilirubin level [13]. The results in Table 2 and Fig. 1 further support the need for better base for standardization of doses of adriamycin.

Adriamycin side effects reported to be decreased by a fall in C_{max} include cardiac toxicity, nausea and vomiting [21, 23, 24, 25, 40, 41]. The haematological toxicity of adriamycin has been correlated with the AUC (25 and Schulmeister L, personal communication), but some authors claim that reduction in C_{max} results in a decrease in this side-effect (22 and Sonnenfeld P., personal communication). It is unclear at present whether alopecia is associated with a high value of the AUC or C_{max} [25, 40, 41]. Under the assumption of linear pharmacokinetics the values of AUC and C_{max} are proportional to the amount of drug administered as a bolus injection in the individual patient. It is possible to reduce C_{max} by dose fractionation and prolonging infusions without a concomitant decrease in AUC. Hence, a change in the normal intravenous bolus injection schedule offers a way to increase the therapeutic index of adriamycin. The present results show that C_{max} was reduced 25-fold compared to a bolus injection by use of an infusion time of 4 h without affecting AUC. Normalized maximum plasma concentrations (C_{max}/mg/m^2) for the various infusion times are presented in Table 5. It has been reported [42] that side effects correlated with the peak plasma concentration were clinically tolerable when the plasma concentration was less than 60 ng/ml, i.e. at a dose of 30 mg/m^2 the infusion time should be at least 16 h, as calculated from Table 5.

A pharmacokinetic study of a weekly low dose regimen (10–20 mg/m^2) of adriamycin revealed a 3–5 fold reduction in C_{max} compared to the generally

recommended schedule (50–75 mg/m^2 every 3 weeks); Mattson W et al., personal communication. Prolonged infusions of adriamycin seem from this point of view, therefore, to be even more benefical than a weekly low dose regime. Clinically, unchanged or even somewhat increased therapeutic efficacy has been reported following prolonged (10–96 h) intravenous infusion of adriamycin as compared to bolus injections [21, 22, 23, 24, 25]. The antitumour efficacy of adriamycin infusions lasting < 10 h has not yet been evaluated.

Infusion therapy with chemotherapeutic agents offers, at least theoretically, the possibility of increasing the tumouricidal effect, based on the fact that in most tumours, particularly solid neoplasms, only a small proportion of cells is in the growth cycle phase and so are likely to be responsive to the drug. In tumours with a long doubling time and a large proportion of cells in the G_0 phase, the timing of the drug-tumour interaction may not be optimal with an intermittent schedule [41].

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