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The relative toxicity of intravenous and intraperitoneal doses of epirubicin

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Summary. The toxicity of single doses of the anthracycline epirubicin was compared in the rat after either the intravenous (i.v.; 2–6 mg/kg) or intraperitoneal (i.p.; 4–8 mg/kg) administration of the drug. These doses produced comparable acute toxicity that was characterised by a dose-dependent, transient reduction in body weight (< 15%) in the first 2 weeks after drug administration. Sequential measurements of cardiac output in animals that received i.v. doses of epirubicin showed that the time-related changes in cardiac function were biphasic. There was an initial decline in cardiac output in the first 12 weeks, which was followed by a phase of persistent depression in cardiac output between 12 weeks and 20 weeks. The time-related changes in cardiac function after i.p. doses of the drug were more variable, although the trend of changes, as after i.v. administration, appeared to be dose-dependent. Recovery of cardiac function occurred at 20 weeks after an i.p. dose of 4 mg/kg; however, after 6 mg/kg, cardiac function was significantly depressed after ≧16 weeks. For both routes of administration, the likelihood of late cardiac complications was dependent on the level of the reduction in cardiac output at 12 weeks. A study of the impairment of cardiac output and the incidence of cardiac-related mortality demonstrated that epirubicin was more cardiotoxic after i.v. administration. Equivalent cardiotoxic doses of epirubicin after i.v. and i.p. administration were highly linearly correlated ($r = 0.998$), although there appeared to be a threshold dose of 3.33 mg/kg after i.p. administration of the drug. Thus, the relative cardiotoxicity between the two routes of administration was found to be dependent on the drug dose and, hence, the level of effect. The difference in the effect was less for high drug doses. The LD_{50} for deaths due to cardiotoxicity at 20 weeks was 4.42 ± 0.42 mg/kg after i.v. administration, which was significantly lower than the value of 6.28 ± 0.41 mg/kg obtained after i.p. administration of the drug ($P < 0.01$). There was no qualitative difference in the histological lesions induced in the myocardium after the i.v. vs i.p. administration of epirubicin.

Introduction

In in vivo toxicity studies with anthracyclines, two principal routes of drug administration are commonly used: the intraperitoneal (i.p.) and intravenous (i.v.) routes. An i.p. injection has the advantage of being technically simpler, and it is a convenient method of drug administration in small animals, especially when the drug must be given as a number of small, repeated doses. In contrast, i.v. injections have mostly been used in single-dose studies. After the i.v. administration of anthracyclines, the extravasation of the drug at the site of injection can cause a severe local reaction; thus i.v. injections are less commonly given in experimental studies in which small, multiple doses are used. In the majority of clinical situations, anthracyclines are given i.v. to patients.

The differences in the toxicity of anthracyclines given by the i.v. vs i.p. routes have been recognised. Among the comments on the apparent discrepancies observed in the anti-tumour activities and toxicities of anthracyclines in published experimental data, Lenaz and Di Marco [8] have attributed these differences to the different routes of drug administration. These authors concluded that when anthracyclines were given i.p., they showed lower anti-tumour activity and greater toxicity than when given i.v. The results of a recent pharmacokinetic study in the nude mouse [6] have demonstrated significant differences after i.v. and i.p. administration of doxorubicin. This study showed that after i.p. administration, the AUCs in the heart, kidney and striated muscle were approximately half those following an i.v. injection. In spite of these reports, there have been very few systematic studies on the difference in toxicity, especially late cardiotoxicity, observed after the i.v. vs i.p. administration of anthracyclines.

Strocchi et al. [10] have recently suggested that epirubicin (a new doxorubicin analogue) could be used for local and regional therapies in which a first passage of the drug through the liver is required before the drug can reach the systemic circulation. Hepatic arterial and i.p. drug administration have been used in patients with liver and peritoneal metastases, respectively. The cardiotoxicity of i.p. administered anthracyclines and its relationship to that of i.v. administered anthracyclines therefore has important clinical implications. The present study was undertaken to investigate systematically the differences in the toxicity of epirubicin given by the i.p. vs i.v. routes of administration in a clinically relevant animal model [11, 12].

Materials and methods

Male rats of the Sprague-Dawley strain, aged 14 weeks, were used in this study. The drug epirubicin (Farmitalia; Milan, Italy) was dissolved in sterile water at a concentra-

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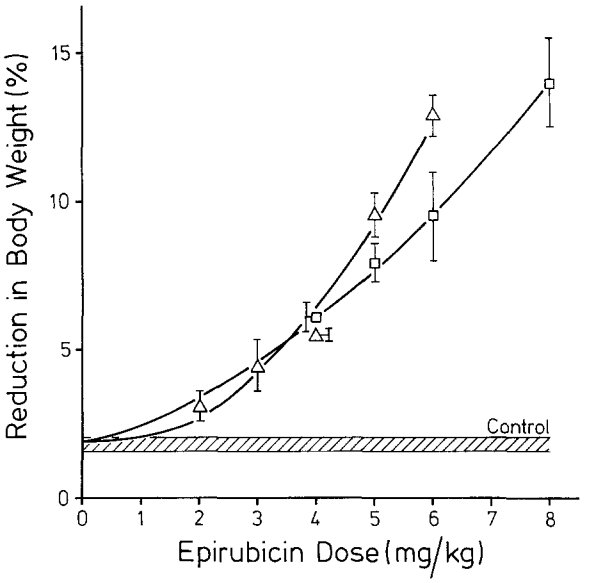

Fig. 1. Maximal percentage of reduction in body weight (±SE) in the first 21 days after the i.v. (△) or i.p. (□) administration of single doses of epirubicin. The reduction in body weight in "sham"-injected animals is also shown (*hatched area*)

tion of 2 mg/ml shortly before being used. During drug administration and for subsequent cardiac output measurements, animals were anaesthetised with choral hydrate (300 mg/kg).

For i.v. administration, single doses of 2, 3, 4, 5 and 6 mg/kg epirubicin were injected into the femoral vein. For i.p. administration, single doses of 4, 5, 6 and 8 mg/kg were injected into the lower right quadrant of the abdomen to avoid damage to vital organs. These i.v. and i.p. drug doses were selected based on the results of a pilot study and were expected to fulfill the following criteria:

1. These dose levels would produce very mild acute toxicity in the animals, and there would be no deaths in the first 5–6 weeks after drug administration. Therefore, late cardiotoxicity would not be complicated by the acute toxicity of the drug.
2. These doses would produce comparable general acute toxicity and late cardiotoxicity, which would allow the derivation of iso-effective doses following i.v. or i.p. administration of epirubicin in the rat.
3. These doses were in the range that would permit the construction of a good dose-response curve.

The injection rate of the drug was 2 ml/min for both routes of administration. There was an average of nine animals per dose group. "Sham" injections of saline were given to a group of ten control animals. To minimise the effect of circadian rhythms on the toxicity of epirubicin, drug administration was carried out between 13.30 and 15.30 hours.

The methods used to assess the general acute toxicity and the cardiotoxicity of epirubicin in the rat after drug administration have previously been described in detail [12]. Briefly, animals were examined daily for up to 3 weeks and then weekly for up to 20 weeks. The maximal reduction in body weight in the first 3 weeks after drug administration was used as an index for the assessment of general acute toxicity. The cardiotoxicity was assessed by measuring the cardiac output in drug-treated and control animals using an external counting technique. A radioactive tracer, technetium ($^{99m}TcO_4$), was injected as a bolus into the femoral vein of each anaesthetised animal. The activity-time curve over the pre-cardial region was recorded for 40 s using a NaI detector. Heart rate and ECG (lead I) were also determined concomitantly with the cardiac output measurement, using a human ECG monitor (Hewlett Packard 7830A) coupled to a scope memory (model VK-12-2, Seltek Instruments Ltd.) and a chart recorder.

Complete post-mortem examinations were carried out on rats that died during the course of experimental study as well as those killed at the end of the experiment (20 weeks); the heart, liver, kidney and lung were fixed for histological examination. Only animals that showed signs of heart failure were included in the final data analysis. Animals were considered to have died of heart failure when they showed signs of congestive heart failure at death (e.g. pleural effusion, ascites and/or general oedema) or had shown a >40% reduction in cardiac output prior to death and/or histological evidence of anthracycline-associated myocardial lesions with signs of pulmonary congestion [12]. In the present study, statistical differences between group means were analysed using Student's *t*-test (two-sided).

Results

At the doses used in this study, the general acute toxicity in the first 3 weeks after epirubicin administration was well tolerated; all animals appeared both healthy and normal. However, daily weighing of the animals during this period showed a transient reduction in body weight. In those receiving epirubicin either i.p. or i.v., the body weight reached a minimum approximately 6 days after drug administration, recovering to pre-treatment levels at around day 15. In control animals, a slight reduction in body weight, ~2%, was also recorded after the "sham" injection; the body weight measured in these animals reached a minimum 2–3 days after their injection, recovering to pre-treatment levels between days 4 and 5.

The maximal reduction in body weight recorded during the first 3 weeks in treated and control animals has been plotted as a function of epirubicin doses for both routes of administration in Fig. 1. The data for each route of administration was found to be best fitted by a linear-quadratic equation. For both routes of administration, the maximal reduction in body weight was dose-dependent. At epirubicin doses in the range of 2–6 mg/kg, the maximal reduction in body weight in the rats following either route of drug administration was not significantly different ($P < 0.05$). The extrapolation of the fitted curves to higher doses seemed to indicate a greater difference in the maximal reduction in body weight for doses of >6 mg/kg; however, the present data are insufficient to enable us to reach a firm conclusion.

The time-related changes in cardiac function in rats after i.v. injection are compared with those after i.p. injection in Fig. 2 for periods up to 20 weeks after drug administration. The cardiac output measured in animals receiving epirubicin relative to those in age-matched controls, i.e. the relative cardiac output, was used as the index for assessing the change in cardiac function. After the i.v. injection of epirubicin, the time-related changes in cardiac

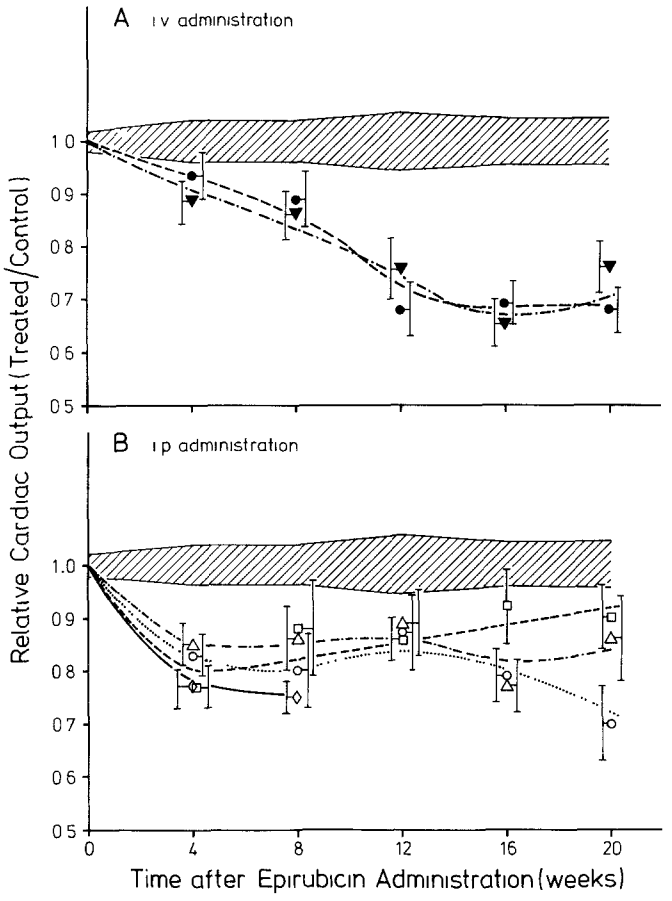

Fig. 2. Time-related changes in the relative cardiac output (±SE) of rats after single doses of epirubicin: *A*, i.v. administration (▼–·–·–▼, 2 mg/kg; ●–––––●, 3 mg/kg); *B* i.p. administration (□–––––□, 4 mg/kg; △–·–·–△, 5 mg/kg; ○· · · · ·○, 6 mg/kg; ◇———◇, 8 mg/kg)

output were biphasic. This has previously been discussed in detail [11, 12] and is illustrated in Fig. 2A for animals that received 2 and 3 mg/kg epirubicin. There was an initial, gradual decline in cardiac output in the first 12 weeks (phase I), followed by a phase of persistent depression in cardiac function (phase II). During phase II, the mean cardiac output measured in animals that had received i.v. epirubicin was ~70% of that measured in age-matched controls. Similar trends in the time-related changes in cardiac output have been followed by animals that survived treatment after higher drug doses [11].

After an i.p. injection of epirubicin, the trend of variation in cardiac output seemed to be dependent on the dose (Fig. 2B). At 4 weeks after i.p. epirubicin administration, all animals showed a significant reduction in cardiac output ($P < 0.001$). However, the mean cardiac function in animals that had received 4 mg/kg appeared to recover with time. From 16 weeks after i.p. administration, the cardiac output measured in this group of animals was not significantly different from that measured in age-matched controls ($P > 0.1$). For up to 8 weeks, the mean cardiac output measured in animals receiving 5 and 6 mg/kg epirubicin was significantly depressed to ~85% of that seen in age-matched controls ($P < 0.05$). The cardiac output in these animals then recovered approximately to control values at 12 weeks. However, after a further reduction in cardiac output at 16 weeks, animals that had received 5 mg/kg showed signs of recovery at 20 weeks, whereas those that had received a dose of 6 mg/kg showed a further reduction in cardiac output to ~70% of that measured in age-matched control animals. Animals receiving the highest i.p. dose, i.e. 8 mg/kg, showed a reduction of ~75% in cardiac output at 4 and 8 weeks; no accurate determination of their cardiac output could be made after 12 weeks due to the rapid deterioration of their cardiac condition as well as animal mortality.

The limitations of using the mean cardiac output as an index for assessing cardiac function in situations where animals die during the course of study have previously been discussed [11]. The number of animals included in the calculation of the mean cardiac output in Fig. 2 are shown in Table 1. The exclusion of animals in certain groups from the calculation of the mean cardiac output indicates that these data underestimate the true effect of epirubicin. Nevertheless, the data in Fig. 2 are sufficient to illustrate the difference in the patterns of changes in cardiac function with time after the i.p. vs i.v. injection of epirubicin.

The distribution of animals according to the reduction in cardiac output at 12 and 20 weeks after the i.p. or i.v. administration of epirubicin are compared in Fig. 3. Animals receiving epirubicin were divided into three subgroups according to their reduction in cardiac output, namely: <10%, 10%–40% and >40% of that measured in age-matched control rats. Animals that were not included in the calculations of the mean cardiac output because of poorly defined isotopic activity-time curves or those that

Table 1. Number of rats alive in each dose group at the time of each cardiac output determination[a]

Route of administration	Dose (mg/kg)	Time of cardiac output evaluation after drug administration (weeks)					
		0	4	8	12	16	20
Intravenous	2	9 (9)	9 (9)	9 (9)	9 (9)	9 (9)	8 (8)
	3	10 (10)	10 (10)	10 (10)	9 (9)	9 (9)	8 (8)
Intraperitoneal	4	8 (8)	8 (8)	7 (7)	7 (7)	7 (7)	7 (7)
	5	9 (9)	9 (8)[b]	8 (7)[b]	7 (7)	7 (7)	7 (7)
	6	9 (9)	9 (9)	9 (9)	7 (7)	7 (7)	7 (7)
	8	8 (8)	8 (8)	8 (8)	2 (0)[b]	0 (0)	0 (0)

[a] Numbers in parentheses indicate the number of animals in which cardiac output could be obtained

[b] Groups in which animals were excluded from the calculation of the mean relative cardiac output. The activity-time curves measured from these animals were broad-peaked due to poor heart function. Uncertainties associated with re-circulation prevented the accurate calculation of cardiac output in one or two of these animals in each group

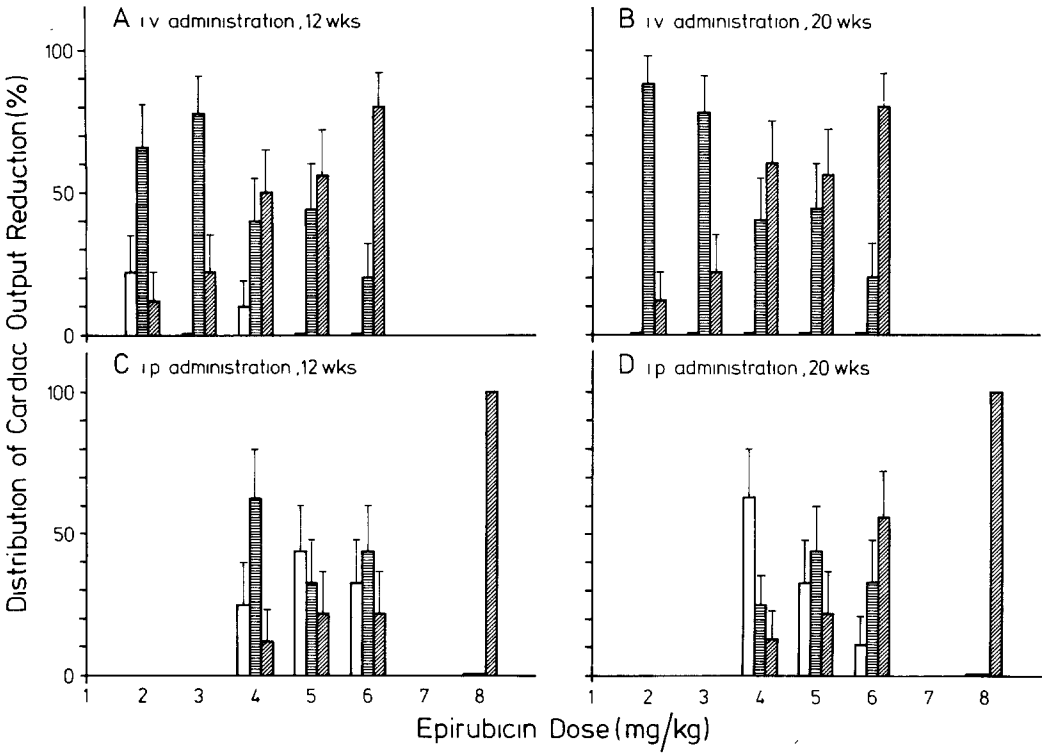

Fig. 3. Comparison of the proportional distribution of rats, showing a specific reduction in cardiac output at 12 and 20 weeks after the i.v. or i.p. administration of single doses of epirubicin (□, < 10%; ▤, 10–40%; ▨, > 40% reduction in cardiac output). *Bars* indicate SE

had died of cardiac failure have previously been shown to have a reduction of > 50% in cardiac output [11, 12]; in the present study, these rats were included in the last group, i.e. a reduction of > 40% in cardiac output. The values measured in animals with a < 10% reduction in cardiac output fell within 2 SD of the mean cardiac output measured in age-matched control rats; this difference was not significant.

It is obvious from Fig. 3 that at the same dose epirubicin was more cardiotoxic when injected i.v. than when given i.p. After i.v. administration, 6.4% of all animals receiving the drug showed a < 10% reduction in cardiac output at 12 weeks; however, by 20 weeks, the cardiac function in all animals receiving the drug i.v. was significantly impaired (i.e. with a reduction of > 10% in cardiac output). On the other hand, after i.p. administration, 26.5% of all animals receiving the drug showed a reduction of < 10% in cardiac output at 12 and 20 weeks after its administration.

There was an indication of a dose-dependent change in the distribution of animals according to their reduction in cardiac output after the i.p. administration of epirubicin. After 4 mg/kg i.p., the proportion of animals showing a reduction of < 10% in cardiac output increased from 25% at 12 weeks to 65% at 20 weeks, suggesting the recovery of cardiac function in some of these animals. After a dose of 6 mg/kg i.p., the proportion of animals showing a reduction of > 40% in cardiac output increased from 20% at 12 weeks to 55% at 20 weeks, indicating a deterioration in cardiac function over this period.

The dose-related changes in the percentage incidence of animals showing a reduction of ≧ 30% and ≧ 40% in cardiac output at 12 and 20 weeks after single i.v. or i.p. doses of epirubicin are shown in Fig. 4. The slopes of the dose-response curves after i.v. or i.p. doses of drug were similar; however, at both 12 and 20 weeks, the dose-response curves were shifted to higher doses for both levels of damage tested after i.p. administration of the drug. The ED_{50} values (± SE) for a reduction of ≧ 30% and ≧ 40% in cardiac output were 6.04 ± 0.44 and 6.41 ± 0.47 mg/kg, respectively, after i.p. injection and 3.34 ± 0.40 and 4.39 ± 0.41 mg/kg, respectively, after i.v. injection at 12 weeks, compared with 5.01 ± 0.36 and 5.83 ± 0.39 mg/kg, respectively, after i.p. injection and 2.87 ± 0.36 and 4.25 ± 0.38 mg/kg, respectively, after i.v. injection at 20 weeks. For both time points and both levels of damage tested, the ED_{50} values after i.p. injection were significantly higher than those after i.v. injection ($P < 0.05$). For both routes of administration, there was no significant difference in the ED_{50} values evaluated at 12 weeks and those evaluated at 20 weeks ($P > 0.05$).

Equivalent cardiotoxic doses of epirubicin, given either i.p. ($D_{i\,p}$) or i.v. ($D_{i.v.}$), were derived from the dose-effect curves obtained at 12 weeks after drug administration (Fig. 4A). For the two levels of effects, assessed in terms of a reduction of ≧ 30% and ≧ 40% in cardiac output, the equivalent doses associated with a 10%, 20%, 30%, ... 90% incidence of these specific effects were calculated and plotted against each other in Fig. 5. It is clear that values of $D_{i.p.}$ and $D_{i.v.}$ are highly linearly correlated ($r = 0.998$). $D_{i\,v.}$ and $D_{i.p.}$ can be related by the equation

$$D_{i\,p} = 0.75 D_{i\,v.} + 3.33, \quad (1)$$

suggesting a threshold dose of 3.33 mg/kg epirubicin after i.p. administration when the reduction in cardiac output is used to assess cardiotoxicity.

The durations of animal survival following the i.v. or i.p. administration of epirubicin are compared in Fig. 6. After i.v. administration, the majority of animals that died

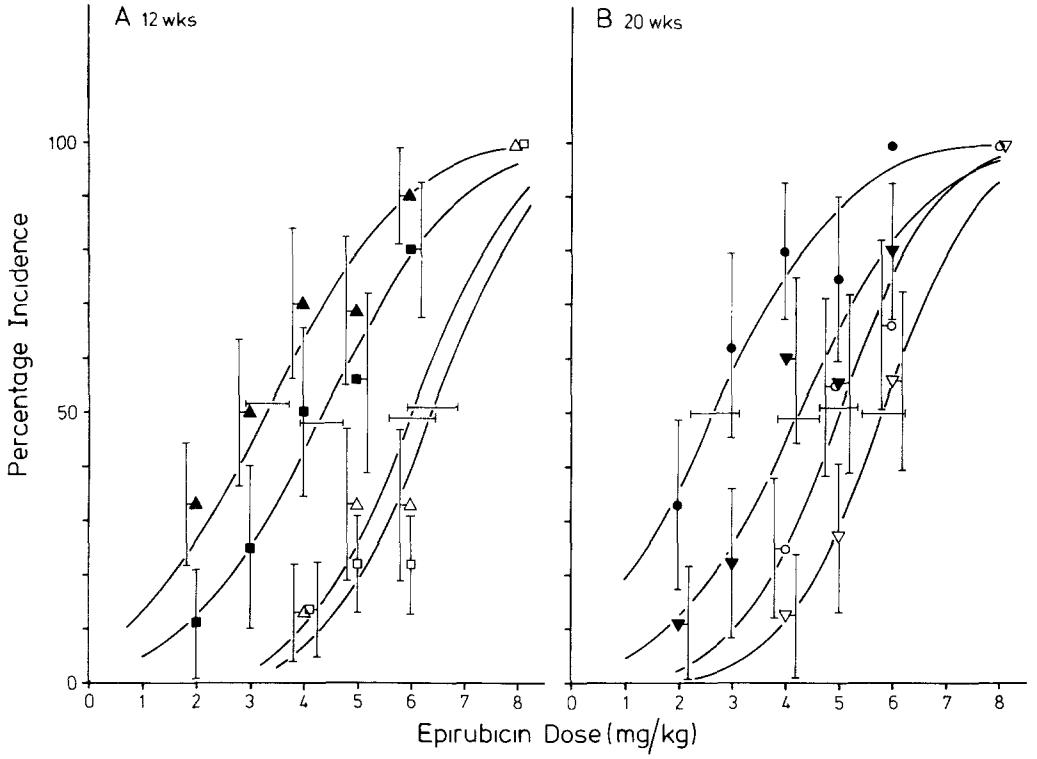

Fig. 4. Percentage of animals showing a given level of reduction in cardiac output at 12 and 20 weeks after single doses of epirubicin. *Closed symbols*, after i.v. administration; *open symbols*, after i.p. administration (▲, △, ●, ○, ≧30%; ■, □, ▼, ▽, ≧40% reduction in cardiac output. *Bars* indicate SE

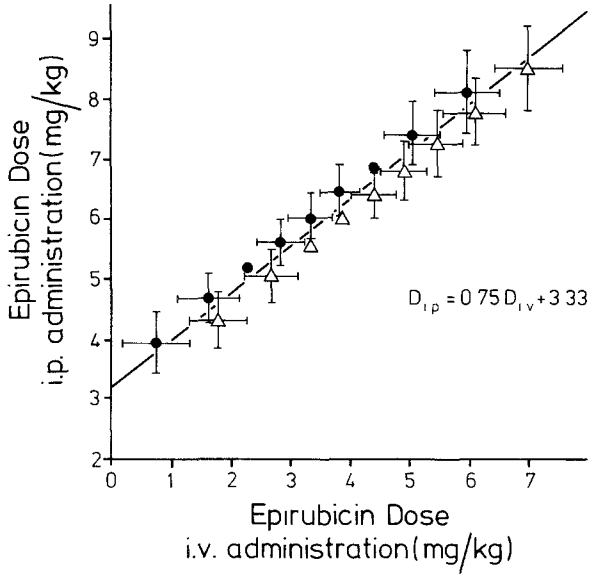

Fig. 5. Equivalent cardiotoxic doses of epirubicin given i.v. or i.p. for two levels of cardiac damage (●, ≧30%; △, ≧40% reduction in cardiac output). *Bars* indicate SE

of heart failure were found dead between weeks 8 and 13, i.e. towards the end of the phase of the initial decline in cardiac output (phase I) and around the beginning of phase II. The number of deaths due to cardiotoxicity was dose-dependent; this trend also seemed to hold true in animals receiving i.p. epirubicin, although the incidence of cardiotoxicity-related mortality was low for i.p. doses of ≦6 mg/kg. The LD_{50} for deaths due to cardiotoxicity at 20 weeks was 6.28 ± 0.41 mg/kg after i.p. administration, which was significantly higher than that of 4.42 ± 0.42 mg/kg after i.v. drug administration ($P < 0.01$).

The number of animals dying between 12 and 20 weeks after epirubicin administration in relation to the number showing a reduction of ≧40% or <40% in cardiac output at 12 weeks are shown in Table 2. After the i.v. administration of epirubicin, 7 of the 9 animals with a ≧40% reduction in cardiac output at 12 weeks subsequently developed severe, late cardiac complications and died between 12 and 20 weeks after drug administration. Only 1 of 28 with a <40% reduction in cardiac output at 12 weeks died of heart failure in the same period. The probability of the development of late cardiac complication seemed to be dependent only on the level of reduction in cardiac output at 12 weeks, not on the dose of epirubicin the animals had received. A similar correlation existed after the i.p. administration of epirubicin; the 2 animals that showed a ≧40% reduction in cardiac output at 12 weeks died of heart failure between 12 weeks and 20 weeks, and all 21 animals with a <40% reduction in cardiac output at 12 weeks lived until the end of this study.

Histological investigations carried out in animals that died or were killed at the end of the experimental period showed characteristic anthracycline-induced lesions in the myocardium, including vacuolation of myocytes, interstitial oedema, loss of striation and myofibre atrophy. There was no qualitative difference between the lesions observed after the different routes of drug administration.

Discussion

In in vivo toxicity studies, the biological outcome of a dose of drug can be influenced by a number of factors. In preliminary experiments carried out by the present investi-

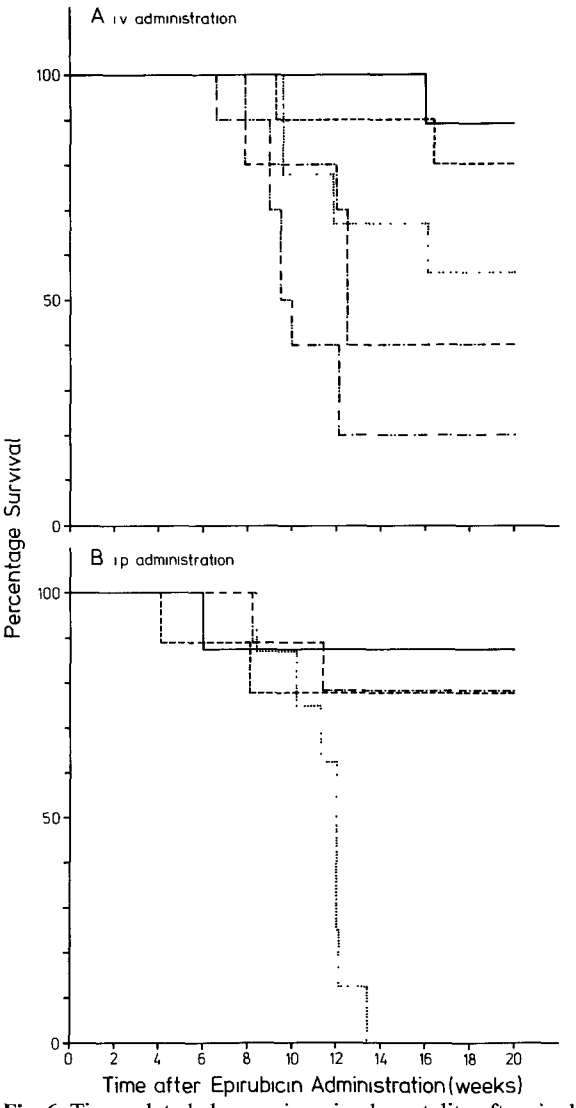

Fig. 6. Time-related changes in animal mortality after single doses of epirubicin: *A*, after i.v. administration (———, 2 mg/kg; – – – –, 3 mg/kg; – · – · –, 4 mg/kg, ... , 5 mg/kg; – · · – · · –, 6 mg/kg; *B*, after i.p. administration (———, 4 mg/kg, – – – –, 5 mg/kg; – · – · –, 6 mg/kg; . . . . . , 8 mg/kg)

gators, the possible effects of circadian rhythms on the toxicity of epirubicin were studied. Animal mortality within 2 weeks was compared in two groups of animals receiving an i.v. dose of 10 mg/kg between 09.30 and 10.00 hours and between 16.30 and 17.00 hours. Four of the five animals that received the drug in the morning died within the first 2 weeks, whereas only one of the five animals that received the drug in the late afternoon died during this period. Although the number of animals per group was small, the difference was significant ($P < 0.05$). This result is consistent with those previously reported in experimental studies on the mouse and rat [7]. The effect of circadian timing in cancer chemotherapy has also been reported in clinical studies [5]. To minimise the possible effect of circadian timing on the toxicity of epirubicin, the time of drug administration was kept at between 13.30 and 15.30 hours in the present study.

It has frequently been stated that anthracyclines are less toxic and more active against solid tumours when given i.v. than when injected i.p. [3, 8]. The increased toxicity after i.p. administration has been attributed to peritonitis, and the peritoneal adhesions occurred as a result of the physical presence of the drug in the peritoneal cavity [8]. This local toxicity has often limited the total dose of anthracycline that can be given i.p. The difference in toxicity after the i.v. vs i.p. injection of anthracyclines was very marked. For daunomycin, the LD_{50} was 26 mg/kg after i.v. administration vs 10 mg/kg after i.p. injection [8].

In the present study, where the reduction in body weight was used as an index of acute toxicity, for doses of $\leqq 6$ mg/kg no significant differences were found following i.v. vs i.p. injections of epirubicin. Since epirubicin can produce toxic effects on both the bone marrow and the gut, the interpretation of the present observations is complex. However, it can be concluded that for single doses of $\leqq 6$ mg/kg epirubicin at a concentration of 2 mg/ml, the acutely toxic effects produced by the i.v. or i.p. administration of the drug on the bone marrow and the gut were very mild and that epirubicin given i.p. at these dose levels did not produce life-threatening peritonitis or peritoneal adhesion in the rat. The latter finding could be due to the low i.p. dose used in the present study or to the fact that epirubicin was less effective in producing peritonitis or peritoneal adhesion in the rat. The i.p. administration of epirubicin has been reported not to produce peritonitis in patients, which is at variance with data in the literature concerning the effects of i.p. doses of doxorubicin [10]. For higher epirubicin doses, i.e. >6 mg/kg, extrapolation of the linear quadratic fit to the present data seems to suggest that when given i.v., epirubicin was more toxic than when given i.p.. However, the present data are insufficient to enable us to reach firm conclusions.

Although the present studies demonstrated that the i.v. and i.p. doses of epirubicin used produced comparable, acutely toxic effects in the rat, significantly different cardiotoxicity was observed. This was shown by a study of the distribution of the reduction in cardiac output in animals, using ED_{50} values (for a given reduction in cardiac function) and the cardiotoxicity-related mortality. All parameters indicated that when given i.v., epirubicin was more cardiotoxic than when given i.p..

The doses of epirubicin showing equivalent cardiotoxicity after i.p. and i.v. administration were highly linearly correlated but were shown to be dependent on the dose levels at which damage was assessed. For example, epirubicin doses of 6 and 8 mg/kg given i.p. were equivalent in cardiotoxicity to i.v. doses of 3.6 and 6.2 mg/kg, respectively. This corresponds to a reduction of 41% and 22% in doses if the i.v. route was used instead of i.p. administration to achieve the same degree of cardiotoxicity.

Very little information is available on the relative cardiotoxicity of anthracyclines administered i.v. and i.p. However, the dependence of drug toxicity on the route of injection has been demonstrated in a number of other systems. In measurements of lung ventilation in mice treated with bleomycin, the drug was found to produce more damage to the lung when given i.v. than when injected i.p. [4]. In the in vivo and in situ assay of the clonogenic response of cells to cytotoxic agents, the mode of administration of the agent has also been found to be one of the key factors that significantly affects the final biological outcome [9]. Thus, in view of these results and the present findings, the appropriate route of drug administration should be care-

Table 2. Number of animals dying between 12 and 20 weeks after epirubicin administration in relation to the number showing a reduction of ≧40% or <40% in cardiac output (COP) at 12 weeks

Route of administration	Dose (mg/kg)	≧40% reduction in COP		<40% reduction in COP	
		At risk (*n*)	Deaths (*n*)	At risk (*n*)	Deaths (*n*)
Intravenous	2	1	1	8	0
	3	2	1	7	0
	4	2	2	6	1[a]
	5	2	1	5	0
	6	2	2	2	0
Totals	–	9	7	28	1
Intraperitoneal	4	0	0	7	0
	5	0	0	7	0
	6	0	0	7	0
	8	2	2	0	0
Totals	–	2	2	21	0

[a] This animal was killed 48 h after the COP determination at 12 weeks due to a rapid deterioration in its general health. Previous COP values were 61.4%. 57.5% and 92.0% of age-matched control values at 4, 8 and 12 weeks, respectively. Post-mortem examination revealed necrosis of one-third of the heart tissue and general cardiac atrophy

fully chosen to suit the aim of each experimental investigation, and in any intercomparison of experimental data, the route of drug administration should be taken into account.

The difference seen in the present investigations in the cardiotoxicity of epirubicin given i.v. vs i.p. could be explained by the results of recent pharmacokinetic studies [6]. A study of Adriamycin pharmacokinetics after i.v. and i.p. administration in the nude mouse has shown that both the peak Adriamycin concentration in heart tissue and the AUC in the heart were smaller after i.p. than after i.v. injections. These pharmacokinetic differences could have a considerable influence on the toxicity observed. Recent studies have suggested that the cardiotoxicity of anthracyclines is proportional to the peak drug level in the heart tissue [13]. Furthermore, the AUC in the heart reflects the time spent by the drug in the vicinity of heart tissue. Thus, a reduction in the peak drug concentration and the reduction of the AUC in the heart after i.p. administration could result in a reduction in cardiotoxicity. Although no comparable studies have been carried out using epirubicin, other comparative pharmacokinetic investigations in mice and rats have shown that the differences in the pharmacokinetic behaviour of Adriamycin and epirubicin in these two animal species is very small [1, 2].

The low concentration of anthracycline in the heart (and in other tissues) after i.p. administration vs i.v. administration could be attributed to first-passage metabolism and a partial hepatobiliary excretion of the metabolites. When injected i.v., epirubicin goes directly to the heart and is then distributed amongst the tissues through the systemic vascular system. However, when given i.p., this drug is first absorbed by the portal system and arrives at the liver via the portal vessels. The liver is the major site of anthracycline metabolism [1, 2, 10]. A considerable fraction of the injected epirubicin dose could well be metabolised by the liver before it reaches the heart. This first-passage effect through the liver has been demonstrated in human studies [10].

Thus, in summary, at the i.p. and i.v. doses used in this study, the acute toxicity of epirubicin was well tolerated and there were no significant differences in acute toxicity produced in the rats. However, at these doses, epirubicin was more cardiotoxic when given i.v. than when given i.p.; the reduction in cardiotoxicity could be attributed to the first passage effect via the liver and the partial hepatobiliary excretion of metabolities of epirubicin.

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