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Epirubicin in hepatocellular carcinoma: pharmacokinetics and clinical activity

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Abstract. The pharmacokinetics and clinical activity of epirubicin were investigated in 16 patients with hepatocellular carcinoma (HCC) who received epirubicin at 75 mg/m^2; the drug was given intravenously to 7 patients and via the hepatic artery to 9 patients (7 of whom also underwent embolisation). Lignocaine (1 mg/kg) was also given intravenously to 15 patients, and the metabolite monoethylglycinexylidide (MEGX) was measured as an indicator of liver function. Epirubicin clearance correlated with serum aspartate aminotransferase (AST), albumin and bilirubin values in patients treated intravenously or intraarterially. Although the route of administration did not affect the median total plasma clearance of epirubicin, early- and intermediate-phase clearance was higher following intraarterial administration. MEGX levels correlated with serum bilirubin levels but there was no correlation with albumin or AST values or epirubicin clearance. The rate of response to epirubicin was 3/13 (23%; 95% confidence interval, 8%–50%). Intravenous epirubicin was tolerated well, but intraarterial treatment was associated with significant morbidity. These data confirm that although current recommended dose adjustments are based primarily on serum bilirubin levels, altered epirubicin pharmacokinetics correlate more strongly with AST and albumin values than with serum bilirubin concentrations. However, at this dose and schedule, epirubicin has only modest activity against HCC.

Key words: Epirubicin – Pharmacokinetics – Hepatocellular carcinoma

Introduction

The anthracyclines are amongst the most widely used cytotoxic drugs. In the treatment of patients with hepatocellular carcinoma they are the most effective single agents, although response rates are modest. Doxorubicin achieves response rates of between 10% and 25% [1, 2]. In a review of 644 patients treated with doxorubicin the response rate was 19% and the median survival, only 4 months [3]. Similar results have been reported for epirubicin [4]. In an attempt to increase the treatment efficacy and reduce systemic toxicity, anthracyclines have been given by intrahepatic arterial infusion, often combined with embolisation [5]. However, the anthracyclines are eliminated primarily by the liver and their use in patients with abnormal liver biochemistry can be difficult [6, 7]. Currently the recommended dose reductions are based primarily on serum bilirubin levels. These dose adjustments have not been validated formally, although in patients with hepatocellular carcinoma, Johnson et al. [8] showed a relationship between the white cell nadir and the serum bilirubin concentration.

The effect of abnormal liver biochemistry on anthracycline metabolism has been controversial. Benjamin et al. [6] described increased toxicity and altered doxorubicin pharmacokinetics in patients with liver metastases. However, subsequent studies failed to confirm these findings in patients with liver metastases [9–11] or hepatocellular carcinoma [8]. Similarly, initial reports suggested that although epirubicin pharmacokinetics were altered in patients with liver metastases [7, 12], there was no clear relationship with individual liver biochemistry tests [13, 14]. Recently, however, a strong correlation between epirubicin clearance and serum aspartate aminotransferase (AST) values was shown in patients with breast cancer and liver metastases [15].

Since conventional liver biochemistry tests do not measure liver *function*, they may not be the optimal parameters to correlate with anthracycline pharmacokinetics. However, of the quantitative tests, indocyanine green (ICG) clearance is only weakly related to doxorubicin clearance

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in patients with liver metastases [16], and evaluation of bromosulphthalein (BSP) elimination has largely been abandoned due to toxicity. The metabolism of lignocaine to monoethylglycinexylidide (MEGX) in the liver by the cytochrome P450 PIII subfamily [17] has been proposed as a good index of graft function in orthotopic liver transplantation [18] and of hepatic function in patients with liver disease [19]. The relationship between lignocaine metabolism and anthracycline pharmacokinetics has not been previously described.

The first aim of the current study was to establish whether the correlation between conventional liver biochemistry tests and epirubicin pharmacokinetics could be confirmed in patients with hepatocellular carcinoma (HCC). Secondly, the relationship of lignocaine metabolism with both epirubicin pharmacokinetics and conventional liver biochemistry tests was investigated. Thirdly, the systemic pharmacokinetics of epirubicin given intraarterially and intravenously was compared. Finally, the clinical activity and toxicity of epirubicin given in this way to patients with HCC was assessed.

Patients and methods

Clinical study. A total of 16 patients with inoperable HCC were treated with epirubicin at 75 mg/m^2 between August 1991 and July 1992. In all patients the diagnosis of HCC was confirmed histologically. Except for one patient who had received a liver transplant 6 years previously, they had received no prior treatment for HCC.

Generally, patients with a single lesion and no extrahepatic tumour spread received their first cycle of epirubicin intraarterially; otherwise, chemotherapy was given intravenously as a bolus injection over 2 min at 3- to 4-week intervals. In the patients treated intraarterially the following procedure was adopted. A mixture was prepared comprising 150 mg epirubicin with 45 ml Omnipaque, a triiodinated, non-ionic water-soluble contrast medium (iodine content, 46.4%; Nycomed U.K. Ltd), to which 30 ml Lipiodol Ultra Fluid, an ethyl ester of poppyseed oil fatty acids (containing 38% iodine; Andre-Gelbe Laboratories, France), was added and mixed thoroughly. The hepatic artery was selectively catheterised using the Seldinger technique, and conventional rapid-sequence films were obtained by injecting non-ionic contrast medium to define the arterial anatomy. Epirubicin (75 mg/m^2) as an epirubicin/Omnipaque/Lipiodol mixture was delivered directly into the common hepatic artery as a bolus injection over approximately 5 min under radiological screening to confirm distribution to all branches of the hepatic artery. In most patients who were treated intraarterially, embolisation was performed using 10 ml Ivalon (Biodyne Inc., La Mesa, Calif., USA) injected immediately following chemotherapy.

Liver biochemistry tests [AST, alkaline phosphatase, serum albumin, bilirubin and γ-glutamyl transferase (γ-GT)] were performed on the morning of treatment. A full blood count, international normalized ratio (INR-based on prothrombin time) and alphafetoprotein (AFP) determination were also obtained prior to treatment. To measure liver function using the MEGX test, lignocaine was given intravenously to 15 patients on the day of treatment. Lignocaine (1 mg/kg) was injected over 2 min and a 10-ml blood sample was taken at 15 min. Plasma was separated and stored at –20° C, and the MEGX level was measured using a fluorescence polarisation immunoassay [18].

For each patient the best response to epirubicin was recorded. A response was defined as at least a 30% reduction in liver enlargement as assessed clinically by the extent of hepatomegaly below the costal margin or at least a 50% reduction in tumour diameter on serial ultrasound examination in patients with a solitary lesion. In addition, a response was recorded if there was at least a 50% fall in the serum AFP value (when the pretreatment level was greater than 250 ng/ml), providing there was no contradictory evidence from the other two criteria. Stable disease was defined as a less than 50% decrease in the size of the lesion as measured by ultrasound examination or a less than 50% decrease in the serum AFP concentration over a period of 4 weeks. An increase in AFP levels or liver size or the development of new metastases indicated progressive disease. Treatment toxicity was evaluated according to WHO criteria [20]. Nadir blood counts were not obtained routinely.

Pharmacology. Pharmacokinetics studies were undertaken in all patients following the first course of treatment only. Whole-blood samples were taken over a 48-h period following chemotherapy. Samples were taken at 6, 12, 15, 20 and 30 min, then at 1, 2, 4, 8, 24 and 48 h after the start of administration. Each 10-ml sample was taken into a tube containing lithium-heparin crystals and centrifuged, after which the separated plasma was stored at –20° C pending analysis.

Plasma levels of epirubicin and its metabolites were measured by high-performance liquid chromatography [21] using pure analytic standards provided by Farmitalia Carlo Erba (Milan, Italy). Briefly, 1-ml plasma samples are extracted using C2 cassettes, and the reverse-phase chromatography is performed with an Apex II 5-μm ODS column (10 cm × 5 mm). The isocratic mobile phase comprising acetonitrile – 0.019 *M* NaH_2PO_4 (pH 4.0) at 1 : 2.2 (v/v) had a flow rate of 1 ml/min, and the fluorescence-detector excitation and emission wavelengths were 480 and 580 nm, respectively. With this assay the mean recovery of epirubicin from plasma is 88%, and recovery of its metabolites is 51%–88%. The routine detection limit is 1 ng/ml for epirubicin and ranges from 0.5 to 1.0 ng/ml for the metabolites. The within-day and day-to-day precision of the assay was confirmed by coefficients of variation of less than 8% for epirubicin and for its metabolites. Daunorubicin acted as the internal standard.

The plasma epirubicin concentration-time data were fitted optimally to a three-compartment model or, if this was not possible, to a two-compartment model. The "Pharmkit" programme [22] was used to obtain the early (α), intermediate (β) and late (γ) half-lives ($t_{1/2}$). The area under the concentration-time curve to 48 h (AUC_t) was calculated from the slopes and intercepts derived from "Pharmkit", extrapolated back to the end of the infusion and corrected for the duration of the infusion [23]. The overall elimination of epirubicin from the plasma for up to 48 h was expressed as drug clearance (Cl_t = dose/AUC_t), which is the best pharmacokinetic measure of hepatic drug metabolism [24]. The early-phase clearance (Cl_α) was calculated as $\frac{1}{A/a}$, where A and a represent the intercept and the elimination rate constant, respectively. The intermediate- (Cl_β) and late-phase clearances (Cl_γ) were calculated in the same way from the appropriate intercepts and constants.

Statistical analysis. Since important parameters (serum AST and Cl_t) were not normally distributed, linear correlations could not be applied to these data. Therefore, to maintain uniformity in the analysis, rank correlations were used throughout to evaluate the extent of relationships of pharmacokinetic parameters with both pretreatment liver function and biochemical characteristics. Relationships were considered significant when the correlation coefficient (r) was greater than 0.5 and the P value was less than 0.05. Only values of $r > 0.5$ were considered to have potentially important predictive use, and $r > 0.7$ was considered as showing a strongly correlative relationship since at least 25% and 50%, respectively, of the variability is accounted for in such cases. Stepwise multiple-regression analysis was carried out to determine those biochemical parameters that independently predicted for epirubicin clearance.

The biochemical and pharmacokinetic parameters of the patients treated intravenously and those treated intraarterially were compared using the Mann-Whitney test. This test was also applied in comparing each individual time point to determine differences in the concentration-time curves for the two modes of treatment.

Table 1. Clinical and laboratory characteristics of the 16 patients investigated (*ref* reference value, *ALP* alkaline phosphatase)

	Treatment	
	Intravenous	Intraarterial
Number of patients	7	9
Sex (M/F)	5:2	7:2
Median age (range)	62 (39–74) years	58 (28–71) years
Median Karnofsky score (range)	80 (70–90)	90 (60–90)
Cirrhosis (Childs grade):		
A	0	4
B	3	1
C	1	2
No cirrhosis	1	1
Unknown	2	1
Tumour (Okuda stage):		
I	2	3
II	4	4
III	1	2
AFP (ng/ml):		
>250	4	5
<250	3	4
Portal vein invasion	2	1
Ascites	2	1
Extrahepatic metastases	2	0
Median AST (range) – ref: 10–50 IU/l	107 (41–188)	78 (21–560)
Median bilirubin (range) – ref: 3–20 μmol/l	29 (5–65)	23 (8–62)
Median ALP (range) – ref: 30–120 IU/l	292 (116–1110)	228 (87–891)
Median albumin (range) – ref: 35–50 g/l	31 (20–41)	36 (26–45)
Median INR (range)	1.0 (0.9–1.2)	1.1 (0.9–1.2)

Results

Clinical study

The clinical and biochemical characteristics of the 16 patients are shown in Table 1. In all, 7 patients received epirubicin intravenously and 9 were treated via the hepatic artery; of the latter patients, 7 were embolised. The 7 patients treated intravenously received a mean of 3 cycles of epirubicin (range, 1–6); 1 patient responded and remains in remission at 8 months, 5 had progressive disease and 1 who was lost to follow-up is not evaluable for response. The 9 patients treated intraarterially received a mean of 3.2 cycles of epirubicin in total (range, 1–9); most underwent a single cycle of intraarterial therapy, with subsequent chemotherapy being given intravenously. Of the patients treated intraarterially, 2 responded with a survival of 14 and more than 15 months, respectively. Another 2 patients died of liver failure within 1 month, 1 refused further treatment and 1 who was lost to follow-up is not evaluable for response. In 1 patient, who received a second cycle of intraarterial epirubicin with chemoembolisation followed by further intravenous treatment, the disease stabilised at 7 months. A further patient received a liver transplant following chemoembolisation, after which he received adjuvant intravenous chemotherapy with epirubicin (75 mg/m^2), and he is free of recurrence at 7 months. The remaining patient treated intraarterially received a single cycle of treatment and has stable disease at 12 months.

In all, 13 of the 16 patients treated were evaluable for response to epirubicin. The response rate was 3/13 (23%; 95% confidence interval, 8%–50%). The median survival was 7.9 months. Treatment was generally well tolerated by the patients treated intravenously, with only 1 patient developing fever and rigors after injection. However, all patients treated intraarterially experienced fever, rigors, nausea, vomiting and abdominal pain that were more severe in the embolised patients. All patients developed reversible alopecia. There was no episode of neutropenic sepsis or severe (WHO grade 3 or 4) stomatitis.

Table 2. Correlation between liver tests and epirubicin clearance (*ALP* Alkaline phosphatase)

Liver test	Correlation with epirubicin clearance	
	r	*P*
AST	−0.78	<0.001
Albumin	−0.76	<0.001
Bilirubin	−0.53	0.02
INR	−0.55	0.02
ALP	−0.49	0.03
Creatinine	0.41	0.06
Gamma-GT	−0.40	0.06

Pharmacokinetic relationships with liver biochemistry tests

Epirubicin pharmacokinetics were fitted to a 3-compartment (14 patients) or a 2-compartment model (2 patients). Table 2 shows that there were strong correlations between total epirubicin clearance and levels of serum AST (Fig. 1) and albumin; serum bilirubin and INR values were less strongly correlated with total clearance. The relationships of total epirubicin clearance with alkaline phosphatase, creatinine and γ-GT levels did not reach significance according to the criteria described above. In a multiple-regression analysis of the ranked values, serum AST and albumin levels were of equal significance in predicting for overall epirubicin clearance ($r^2 = 66.4$). Liver biochemistry tests did not correlate with $\gamma t_{1/2}$ ($r < 0.5$; $P > 0.05$).

The relationship of lignocaine metabolism, as expressed by the 15-min MEGX concentration, with liver biochemistry tests and epirubicin pharmacokinetics was investigated in 15 patients. The MEGX concentration at 15 min correlated with serum bilirubin levels ($r = -0.76$; $P < 0.001$) and, to a lesser extent, with serum albumin ($r = 0.49$; $P = 0.03$) and AST values ($r = 0.43$; $P = 0.05$). There was no relationship with serum alkaline phosphatase, γ-GT or INR values ($r < 0.5$; $P > 0.05$). There was no significant relationship between MEGX levels and epirubicin clearance ($r = 0.40$; $P = 0.07$).

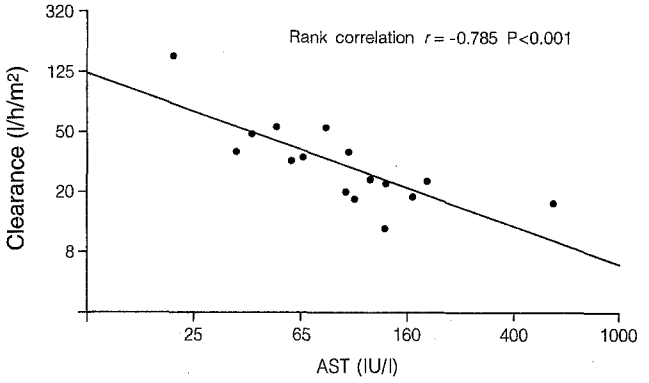

Fig. 1. Correlation between serum AST values and epirubicin clearance

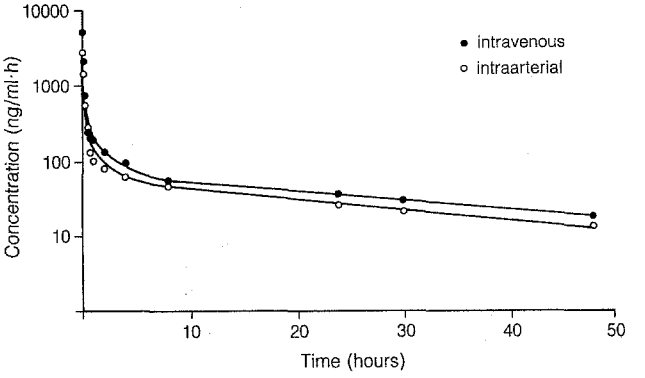

Fig. 2. Composite concentration-time curves generated for patients treated intraarterially (o) and intravenously (x)

Influence of the route of administration on pharmacokinetic relationships

There was no significant difference in the pretreatment biochemical parameters of the patients treated intraarterially and intravenously (all P values >0.05). The composite concentration-time curves generated for patients treated intraarterially and those treated intravenously are shown in Fig. 2. When the median epirubicin concentrations at each of the time points were compared, epirubicin concentrations were significantly lower in the patients treated intraarterially than in those treated intravenously at 6 min (5082 and 2719 ng/ml, respectively; $P = 0.019$), 12 min (2095 and 1449 ng/ml, respectively; $P = 0.044$) and 1 h (194 and 103 ng/ml, respectively; $P = 0.05$). The median total clearance of epirubicin in patients treated intravenously was not significantly different from that in patients treated intraarterially (24.2 and 37.3 l/h, respectively; $P = 0.46$). In the 14 patients whose data were fitted to a 3-compartment model there was a trend for early-phase clearance to be higher after intraarterial rather than intravenous administration, but this did not reach statistical significance (247.7 and 139.1 l/h, respectively; $P = 0.07$); Cl_β was significantly higher for intraarterial than for intravenous treatment (331.4 and 166.5 l/h, respectively; $P = 0.03$). There was no significant difference in Cl_γ following intraarterial versus intravenous administration of epirubicin (31.5 and 34.1 l/h, respectively; $P = 0.75$).

The statistically significant relationships described above between overall clearance and serum AST and albumin levels were present both in patients treated intraarterially ($r = 0.80$, $P = 0.005$ and $r = 0.83$, $P = 0.003$, respectively) and in those treated intravenously ($r = 0.76$, $P = 0.02$ and $r = 0.69$, $P = 0.04$, respectively).

Discussion

The question of whether disturbed liver function, as reflected by abnormal liver biochemistry, influences anthracycline pharmacokinetics remained unresolved until recently. A correlation between serum AST levels and epirubicin pharmacokinetics was first proved in patients with breast cancer and liver metastases [15]. The most important result of the current study was confirmation of this relationship in a separate group of patients with HCC.

Although Camaggi et al. [7] had shown that epirubicin clearance was reduced in patients with liver metastases, no correlation was found between any single liver biochemistry test in that investigation or other early studies [12–14]. By contrast, in the current study, correlations were noted between epirubicin clearance and AST, albumin, INR and bilirubin values. The failure of the early studies to detect these relationships can probably be explained principally by the small number of patients studied. In the only prior study of a large, homogeneous group of patients, altered epirubicin pharmacokinetics correlated with serum AST levels but not with other biochemical parameters [15]. However, in that study the disturbances in serum albumin and bilirubin levels were less marked than those described in the current report, which may explain the failure of the former to detect relationships with epirubicin pharmacokinetic parameters. Interestingly, in the patients with HCC the multivariate analysis confirmed that the serum AST concentration is the best predictor of altered epirubicin pharmacokinetics.

AST is a microsomal enzyme present in hepatocytes but also in other tissues. Increased activity of AST in the serum indicates damage to hepatocytes or other tissues. The synthesis of serum proteins, as indicated by albumin levels and coagulation tests, reflect liver function more directly. Similarly, bilirubin is metabolised by hepatocytes and actively secreted into the biliary system. Therefore, it is perhaps surprising that epirubicin pharmacokinetics correlate more strongly with serum AST levels than with bilirubin, albumin or INR values. The metabolism of lignocaine correlated with serum bilirubin concentrations, confirming that MEGX levels reflect liver function in patients with HCC, although the clinical utility of MEGX measurements cannot be assessed in this small study. However, there was no significant relationship between MEGX levels and epirubicin pharmacokinetics.

The finding, now confirmed in a second group of patients, that the serum AST level predicts for altered epirubicin pharmacokinetics raises important questions about the use of anthracyclines in patients with abnormal liver

biochemistry. Firstly, a predictable relationship has not been shown between liver biochemistry tests and doxorubicin pharmacokinetics [8–11]. The reason for this difference between the two anthracyclines, which vary only in the orientation of the -OH group at the C-4′ position on the daunosamine sugar, is not clear. This structural variation permits extensive hepatic glucuronidation of epirubicin but not doxorubicin [25] and may underlie the difference between the two drugs regarding the effect of disturbed liver biochemistry tests on the pharmacokinetics. Glucuronidation of most, but not all, drugs is preserved in patients with hepatic impairment [26]. The description by Robert et al. [27] of an association between reduced plasma fibrinogen or alpha 2-globulin levels and decreased epirubicin glucuronidation supports the hypothesis that epirubicin glucuronidation may be impaired in patients with liver disease. Since disturbed liver biochemistry tests have a more predictable effect on the pharmacokinetics of epirubicin than on that of doxorubicin, it may be preferable to use epirubicin in these patients.

The second question raised by these findings is whether epirubicin dose modifications should be recommended according to the level of serum AST. Definitive dose recommendations depend on proving a relationship between pharmacokinetic parameters and either treatment efficacy or toxicity. Anthracycline pharmacodynamics have not been widely studied. However, in 55 patients treated with epirubicin, Jakobsen et al. [28] demonstrated a correlation between the epirubicin AUC and neutropenia. Hu et al. [29] related epirubicin pharmacokinetics to the response in patients with nasopharyngeal carcinoma. Similarly, in patients with acute non-lymphocytic leukaemia, high doxorubicin levels were associated with prolonged remission [30] With the new anthracycline, iododoxorubicin, the AUC correlates with myelosuppression [31]. Unfortunately, the low response rate and inavailability of nadir blood counts precluded pharmacodynamic analyses in the current study. Nethertheless, taken together, previous studies do suggest there is a relationship between the pharmacokinetics of anthracyclines and their biological effects.

The anthracyclines are the most effective agents in the treatment of HCC, but response rates are modest [1–3]. In a prospective randomized trial, patients treated with doxorubicin had a median survival of just 10.6 weeks as compared with 7.5 weeks for those receiving no antitumour therapy [32]. Intraarterial administration has been used in an attempt to enhance the treatment efficacy without increasing systemic toxicity. Leung et al. [33] described intraarterial epirubicin as having fewer side effects than intravenous treatment. The response rate obtained in the current study was in line with those reported previously [4, 33], but the acute toxicities of intraarterial epirubicin were significant, possibly because of concomitant embolisation in 7 of the 9 patients. Previous pharmacokinetics studies had suggested that the total epirubicin clearance was substantially higher following intraarterial administration [34, 35] and that this may reduce systemic toxicity. The current study shows that, as reported for doxorubicin [36], the pharmacokinetic parameters, including overall clearance, are not significantly influenced by the route of administration and that it is unlikely that intraarterial treatment reduces systemic exposure to epirubicin and its toxicities. Although overall epirubicin clearance is unaffected by the route of administration, there may be a reduction in early- and intermediate-phase clearance due to an enhanced first-pass effect. These differences may be the result of including Lipiodol in the intraarterial administration.

In summary, the current study confirms the relationship between abnormal liver biochemistry tests and altered epirubicin pharmacokinetics. The serum AST concentration is the best predictor of epirubicin pharmacokinetics, suggesting that a raised level of serum AST may be a better basis for dose reductions than an increased bilirubin level as currently recommended. Although lignocaine metabolism correlated with serum bilirubin values, the MEGX test did not predict epirubicin kinetics. Intraarterial administration of epirubicin was associated with significant acute toxicity without reducing systemic exposure to epirubicin. At the dose and schedule reported, epirubicin had only modest activity against HCC.

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