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Epirubicin in patients with liver dysfunction: development and evaluation of a novel dose modification scheme

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Abstract

This study aimed to develop an epirubicin dose modification scheme in women with breast cancer and liver dysfunction. We first identified target areas under the concentration-time curve (AUCs) of 2400 and 1600 ng/ml.h from pharmacokinetic studies in 15 women with normal liver tests. In a second group of 16 women with abnormal liver biochemistry, the relationship between raised asparate aminotransferase (AST) and epirubicin clearance was: dose = AUC (97.5−34.2×log AST). Adaptive dosing was evaluated prospectively in a third group of 41 women with serum AST $\geqslant$2×normal±raised bilirubin. The median AUCs were 2444 and 1608 ng/ml.h, close to the high and low target AUCs, respectively. Variability in AUC was lower with adaptive dosing than in a fourth group given an unadjusted dose of epirubicin (coefficient of variation = 25.8, 30.0 and 46.5%, respectively; $P = 0.06$). Epirubicin dosing based on AST is safe and may reduce pharmacokinetic variability.

Keywords: Pharmacokinetics; Liver dysfunction; Breast Cancer; Chemotherapy; Epirubicin

1. Introduction

The anthracyclines are eliminated by the liver and dose modifications are often made in patients with abnormal liver biochemistry tests. However, inappropriate dose modifications may lead to sub-optimal treatment of some patients and unacceptable toxicity in others. The current study represents the first systematic attempt to validate anthracycline dose recommendations for patients with disturbed liver biochemistry.

More than 25 years ago Benjamin and colleagues [1] reported that the increased toxicity seen in eight patients with abnormal liver biochemistry who received full-dose doxorubicin was avoided by reducing the dose in six subsequent patients. Similarly, when epirubicin was introduced reduced clearance was described in six patients with liver metastases [2]. These observations led to the recommendation that doxorubicin and epirubicin dose modifications be based principally on serum bilirubin (Pharmacia and Upjohn, data sheets). Nevertheless, the issue of anthracycline dose modifications for liver dysfunction has remained unclear [3]. This was reflected in a study prescribing habits in UK oncologists that showed wide variability in anthracycline doses for patients with abnormal liver biochemistry [4].

Epirubicin clearance correlates with serum aspartate aminotransferase (AST) rather than bilirubin [5,6], and there is a strong relationship between area under the concentration–time curve (AUC) for epirubicin and myelosuppression [7]. This raised the question of whether the epirubicin dose could be modified according to serum AST, reducing the variability in drug exposure for patients with liver dysfunction.

The aims of the current study were (i) to use pharmacokinetic data from patients with liver dysfunction to devise an epirubicin dosage scheme based on serum AST, (ii) to test this scheme in a separate group of patients by comparing the AUC for epirubicin achieved using this scheme with that seen in patients for whom dose modifications were not made, and (iii) to make a

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preliminary evaluation of the efficacy and toxicity of epirubicin with the dose adjusted according to AST in women with breast cancer and liver metastases.

2. Patients and methods

2.1. Patients and treatment

These studies were approved by the hospital ethics committee. All women had histologically confirmed breast cancer and gave written, informed consent.

Separate groups of patient were used to identify 'target' AUCs, derive a dose modification scheme based on serum AST, test this scheme and finally to serve as controls.

2.1.1. Group 1: identification of target AUCs

Fifteen women with 'normal' liver biochemistry, defined as serum AST $\leqslant$twice the upper limit of the reference range and bilirubin $\leqslant$20 μmol/l, were treated with epirubicin at doses between 25 and 120 mg/m^2. These patients formed part of a study described elsewhere in Ref. [7]. Pharmacokinetic data from these women were used to define targets for a 'higher' and a 'lower' AUC, corresponding to that seen with epirubicin doses of 90 and 60 mg/m^2, respectively.

2.1.2. Group 2: relationship between AST and epirubicin pharmacokinetics

When the study was planned, data on the relationship between AST and epirubicin clearance were available for 16 women with breast cancer and abnormal liver tests who had been treated with 25 mg/m^2 epirubicin.

2.1.3. Group 3: prospective testing of AST adjusted dosing

Forty-one women with abnormal liver biochemistry were treated with epirubicin at doses adjusted according to AST based on analyses of Groups 1 and 2. All had radiologically proven liver metastases, but the extent to which the liver was replaced by tumour was not assessed. Eligible patients had significantly abnormal liver biochemistry, defined as serum AST more than twice the upper limit of the reference range with or without bilirubin above the normal range of 20 μmol/l. Patients with isolated increases in serum alkaline phosphatase were not eligible as this may reflect the presence of bone rather than liver metastases.

Patients were treated with an epirubicin dose aimed at achieving a higher or lower target AUC according to their performance status, the extent of bone metastases or prior radiotherapy, and prior chemotherapy to reflect dosing in routine clinical practice. Chemotherapy was given every 3 weeks provided acute toxicities had been resolved. A White Blood Cell count (WBC) $\geqslant 3.0\times10^9$/l and platelets $\geqslant 100\times10^9$/l were required before the next cycle of epirubicin was given in patients treated at the high target AUC; for patients to be re-treated at the low target AUC a WBC $\geqslant 2.0\times10^9$/l with platelets $\geqslant 70\times10^9$/l was required. The dose of epirubicin was based on the serum AST determined within 24 h of treatment.

On subsequent cycles, epirubicin dose was altered primarily according to the AST on the day of treatment. Transfer between the two target AUCs was permitted if the performance status changed. If a patient's AST fell to less than twice the upper limit of normal, the dose of epirubicin was increased to 90 mg/m^2 in the high and 60 mg/m^2 in the low target AUC groups. In the event of World Health Organization (WHO) grade III or IV toxicity, a dose 75% of that based on the AST was recommended.

Treatment toxicity was assessed according to WHO criteria [8] and response by International Union Against Cancer (UICC) criteria [9]. Response duration, progression-free interval and survival were measured from the date of the first injection of epirubicin. Dose intensity was calculated as mg/m^2/week of epirubicin administered.

Blood was taken for pharmacokinetic analysis following the first cycle of treatment only as described below.

2.1.4. Group 4: comparator group

These 25 women with liver metastases and abnormal liver biochemistry served as a 'control' or comparator group. All received epirubicin 25 mg/m^2 given weekly; doses were not adjusted for abnormal liver biochemistry. Chemotherapy was, however, delayed if their blood count and other acute toxicities had not resolved.

2.2. Pharmacokinetics

The pharmacokinetic variability of the patients in Group 3 (for whom the dose was adjusted according to AST) was compared with data from the comparator Group 4. Blood samples were taken from an indwelling venous cannula before treatment, at 6, 12,15, 20, 30 and 45 min, then at 1, 2, 4, 8, 24, 30 and 48 h after the start of administration of epirubicin.

Each 7 ml sample was taken into a lithium heparin tube, centrifuged and the plasma stored at −20 °C pending analysis. Plasma levels of epirubicin and its metabolites were measured by high-performance liquid chromatography (HPLC) as previously described in Ref. [10]. Epirubicin pharmacokinetics were fitted to a three-compartment model using the 'Pharmkit' program [11] and AUC measured taking into account the differing infusion periods. As only the parent compound has significant cytotoxic activity [12], data on the pharmacokinetics of epirubicin alone are presented.

2.3. Statistics

The relationship between clinical or other variables and pharmacokinetic parameters was examined using the Pearson correlation. Those variables that were not normally distributed, such as AST, were expressed as $\log_{10}$ values. The Mann–Whitney test was used to compare clinical and biochemical characteristics of the patient groups.

To compare the distribution of AUC values for patients receiving AST adjusted epirubicin dosing (Group 3) with those treated with an unadjusted dose (Group 4), the values in each group were expressed as a percentage of the mean for that group. The variances were then compared using the variance ratio or F-test. This gives an F-statistic and *P* value that represents the probability of the two groups having the same, normalised variance.

3. Results

3.1. Development of the dose modification scheme (Groups 1 and 2)

The relationship between the epirubicin dose and AUC for the 15 patients in Group 1 with normal liver tests is shown in Fig. 1. From these data, a target AUC of 2400 ng/ml.h was identified as approximating to a 'standard' epirubicin dose of 90 mg/m^2 given every 3 weeks. The target AUC of 1600 ng/ml.h corresponded to a dose of 60 mg/m^2, which may be appropriate for patients with a lower performance status or reduced marrow reserve.

In the 16 women in Group 2 with abnormal liver biochemistry receiving 25 mg/m^2 epirubicin, there was a strong linear correlation ($r = 0.91$) between epirubicin clearance and $\log_{10}$ AST (Fig. 2): Clearance = (−34.2×log AST) + 97.5. Since dose = AUC× clearance, rearranging and substituting: dose = AUC (97.5−34.2×log AST).

For ease of use, epirubicin doses for high and low AUCs were calculated across a range of AST values (Table 1).

3.2. Pharmacokinetic evaluation (Groups 3 and 4)

Forty-one women in Group 3 were treated, 16 at the lower target AUC and 25 at the higher target AUC. Pharmacokinetic studies were successfully completed in 37 women, 14 treated at the lower and 23 at the higher AUC. The clinical characteristics of these women, in particular their liver biochemistry tests, did not differ significantly from those of the comparator group (Table 2).

The median AUCs of 2444 and 1608 ng/ml.h achieved with an epirubicin dose adjusted according to serum AST were very close to the high and low target AUCs (2400 and 1600 ng/ml.h, respectively). The variability in AUC, expressed as a coefficient of variation (CV) was substantially lower in women treated at doses determined by their AST at either high or low target AUC (CV = 25.8 and 30.0%, respectively), compared with those given a standard dose of epirubicin (CV = 46.5%), although this did not reach statistical significance ($P = 0.06$).

3.3. Clinical evaluation (Groups 3 and 4)

Of the 41 patients whose doses were adjusted according to their AST, 2 who continued chemotherapy

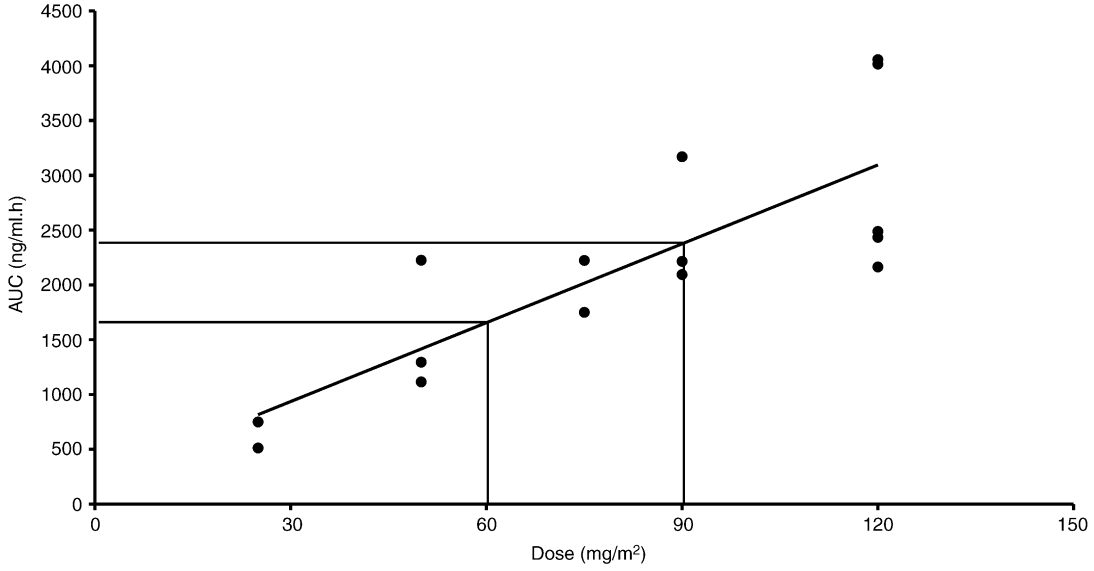

Fig. 1. Relationship between epirubicin dose and area under the concentration–time curve (AUC) in patients with normal liver biochemistry showing the AUCs corresponding to epirubicin doses of 60 and 90 mg/m^2.

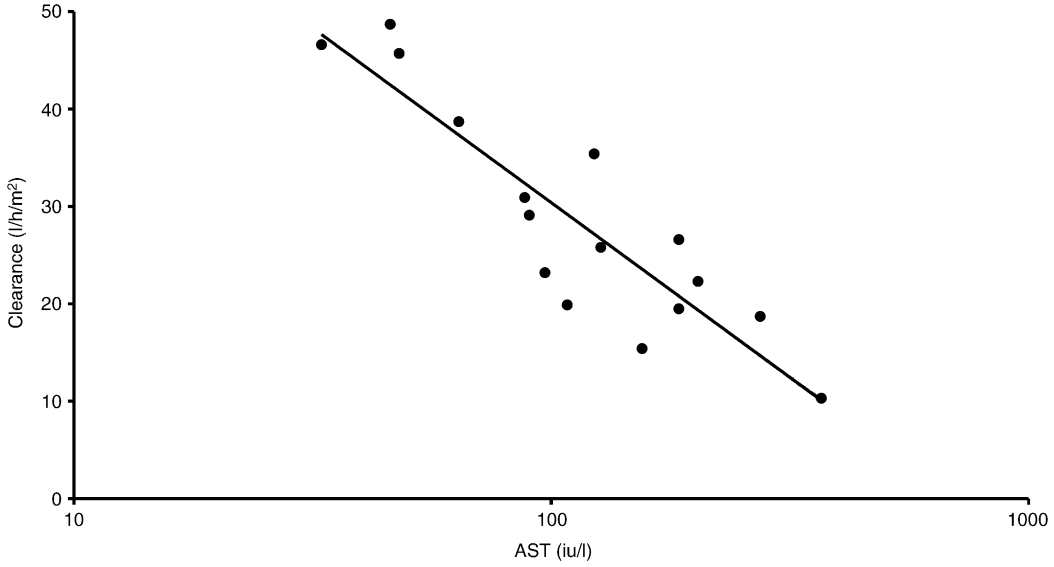

Fig. 2. Pretreatment aspartate aminotransferase (AST) versus epirubicin clearance in 16 women with abnormal liver biochemistry tests.

Table 1
Epirubicin dose according to serum AST for high and low target AUCs

High AUC (target 2400 ng/ml.h)		Low AUC (target 1600 ng/ml.h)	
AST (iu/l)	Dose (mg/m^2)	AST (iu/l)	Dose (mg/m^2)
86–99	75	86–106	50
100–114	70	107–131	45
115–131	65	132–162	40
132–151	60	163–200	35
152–174	55	201–248	30
175–200	50	249–306	25
201–231	45	307–467	20
232–266	40		
267–306	35		
307–352	30		
352–405	25		
406–538	20		

elsewhere are not clinically evaluable. The 39 evaluable patients received 128 cycles of epirubicin (median 3, range 1–6). The principal reasons for discontinuing treatment were completion of the planned six treatment cycles (13 women), progressive disease (19) or death (6), and patient choice (1).

Response to treatment could be assessed in 38 patients, 1 woman having died of a myocardial infarction 21 days after her first treatment. The radiological response rate was 10/38 (26%, with 95% confidence intervals (CI) of 15–42%); 6 patients (16%) had stable disease and 22 (58%) progressed on treatment. 9 of the objective 10 responders had improvement in their symptoms with reductions in anorexia, nausea, liver pain and improvement in performance status; 5 of the 6 women with stable disease also had symptomatic benefit. All 10 women with a partial response had an improvement in their liver biochemistry tests, although in 2 there was an initial deterioration; 9 had a major ($>50\%$) fall and 1 had a minor (25–50%) fall in AST. A high pre-treatment alkaline phosphatase level fell in 6 of the responders, but none of the responders had a raised baseline serum bilirubin. Of the 6 women with radiologically stable disease, 4 had significant improvement in their liver biochemistry tests. Median survival was 14 weeks (range 1–178 weeks) and median time to progression in all 39 women was 7.5 weeks.

Epirubicin was generally well tolerated and there were no treatment-related deaths. During the full course of treatment, 3 women had grade 3 and 4 had grade 4 neutropenia; one episode of neutropenia was associated with grade 4 thrombocytopenia, and 3 with infection. 2 women developed grade 3 stomatitis. Toxicity could be related to pharmacokinetic parameters in the 26 women for whom nadir blood counts were also available. Grade 3/4 haematological or clinical toxicity occurred with equal frequency in women treated with high and low target AUCs (6/18 and 2/8, respectively; $P=1.0$). The median AUCs achieved in women with and without significant toxicity were 2547 and 2291 ng/ml.h, respectively ($P=0.55$).

In all, 26 patients (66%) had dose modifications, 1 having a dose increment and a later reduction. The epirubicin dose was increased in 17 women; in 14 this was due to a fall in serum AST, the remaining 3 patients with extensive bone metastases tolerated the first cycle at a low AUC without toxicity and were changed to a high target AUC. Dosage was reduced in 10 women, 7 due to a rise in AST and 3 because of toxicity. The median dose intensity was 15 mg/m^2/week (range 6.7–32.2 mg/m^2). Amongst women who received more

Table 2
Clinical characteristics, dose and AUC for patients dosed according to serum AST ($n=37$) and comparator group treated with 25 mg/m^2 epirubicin ($n=25$)

	High target AUC ($n=23$)	Low target AUC ($n=14$)	25 mg/m^2 comparator ($n=25$)
Median dose (mg/m^2) (range)	50 (20–75)	38 (20–50)	25 (N/A)
Median AUC (ng/ml.h) (range)	2444 (1045–4020)	1608 (1034–2682)	1120 (546–2772)
Median Cl (l/h/m^2) (range)	36.4 (14.8–55.4)	31.7 (22.2–66.4)	36 (15.1–80.6)
Median age (yrs) (range)	62 (40–72)	55 (35–68)	58 (58 (37–72)
Median AST (iu/l) (range)	162 (102–437)	190 (87–530)	123 (48–489)
Median bilirubin (μmol/l) (range)	14 (6–205)	18 (4–282)	15 (5–224)
Median ALP (iu/l) (range)	907 (150–2851)	667 (84–2281)	810 (246–2972)
Median albumin (g/l) (range)	35 (25–43)	34 (28–42)	35 (19–44)
WHO PS[a]			
0	0	0	–
1	16	6	–
2	6	5	–
3	1	3	–
4	0	0	–

WHO, World Health Organization; N/A, not available.
[a] Performance Status (PS) not available in 25 mg/m^2 comparator group.

than one cycle of treatment, the median dose intensity was 20 mg/m^2 (range 10.8–32.2 mg/m^2).

4. Discussion

The current study has shown the feasibility of modifying the epirubicin dose by serum AST. The most important finding is that this achieved the target AUCs and reduced variability in exposure to epirubicin due to liver dysfunction. This may be an alternative to current dose modifications which are often empirical, or based on alternative dosing strategies such as weekly treatment [13,14].

The principal of adjusting chemotherapy dosing by organ function is well established for carboplatin which is eliminated by the kidney and routinely dosed according to renal function [15]. Two assumptions underpin the application of using serum AST to adjust the epirubicin dose. The first is that liver biochemistry tests have a predictable effect on epirubicin pharmacokinetics. Previously, there have been conflicting reports of how liver dysfunction affects epirubicin pharmacokinetics [2,16–18]. However, when the current study was planned, our preliminary results had identified a correlation between AST and epirubicin clearance. This raised the possibility of devising a dose modification scheme based on liver biochemistry tests, and final results from two studies confirmed this relationship [5,6]. The second assumption implicit in this study, is that biological activity is determined by exposure to epirubicin as reflected by AUC. This is supported by the correlation between epirubicin AUC and both neutropenia and stomatitis [7,19,20]. Similarly, with both doxorubicin [21,22] and iodoxorubicin [23] AUC correlates with myelosuppression. The evidence that pharmacokinetic parameters correlate with response is less clear. Nevertheless, such relationships have been reported for epirubicin in patients with nasopharyngeal carcinoma [24] and for doxorubicin in both acute non-lymphocytic leukaemia [25] and breast cancer [26] patients. These studies suggest that AUC is an important determinant of the antitumour activity, although one large study failed to confirm such a relationship [19]. Nevertheless, there are good grounds for basing the epirubicin dose on serum AST levels.

The current study has shown that adjusting epirubicin dose according to the serum AST level is safe and retains clinical activity. It also appears to be effective in reducing pharmacokinetic variability. The median AUCs achieved when modifying AST according to AST deviated little from the target AUCs (2444 compared with 2400 ng/ml.h, and 1608 compared with 1600 ng/ml.h, respectively). This is encouraging, but does not address the question of whether variability in drug exposure is reduced by adjusting the dose for serum AST. We are fortunate, however, in having two earlier studies with which to make comparisons. Both the earlier studies had the same eligibility criteria as the current study [13,14], but patients received 25 mg/m^2 epirubicin given weekly. There was no significant difference between the current study and the earlier ones with respect to serum AST (4.0- and 3.8-fold greater than the upper limit of normal, respectively), bilirubin (18 and 17

μmol/l, respectively) or albumin (34 and 35 g/l, respectively). The median performance status of the patients treated with an epirubicin dose adjusted by serum AST was, however, better than that of those treated with weekly epirubicin 25 mg/m^2 (Eastern Cooperative Oncology Group (ECOG) 1 and 2, respectively).

Women treated in the current study with an epirubicin dose adjusted according to AST levels had a response rate of 26% (95% CI 15–42%), very similar to that of 30% that was achieved with weekly epirubicin 25 mg/m^2 [13,14]. Likewise, there was no difference between the current study and the earlier ones with respect to the median response duration (34 and 31 weeks, respectively) or survival (14 weeks in both studies). This reflects the poor prognosis of these patients, although in the current study the median survival for the 10 responders was 95 weeks. Epirubicin has been well tolerated in all of these studies, with no obvious difference when adjusting the dose according to AST levels. The most clinically significant toxicity, grade 2 or 3 stomatitis, was experienced by 15% of patients in the current study with the dose adjusted according to AST levels and 18% of those receiving weekly epirubicin.

There was, however, a considerable difference in the dose intensity administered between the patients treated with epirubicin dose adjusted according to AST levels and those receiving weekly epirubicin 25 mg/m^2 (medians of 15 and 25 mg/m^2/week, respectively). Although dosing according to AST had no obvious adverse effect on the therapeutic efficacy, a relationship between the epirubicin dose and response has previously been described in Ref. [19]. The current dose modification scheme based on AST may not, therefore, be optimal because of the lower delivered dose intensity. Interestingly, when we subsequently derived another dosing scheme based on the relationship between AST and epirubicin clearance in a larger group of patients [6], this generated epirubicin doses between 4 and 35% greater than those used in the current study. We are, therefore, re-evaluating epirubicin pharmacokinetics in a larger group of patients using a population-based approach including factors such as age [27], gender [27,28] and obesity [29] that may also influence anthracycline kinetics.

Epirubicin dosing according to the serum AST level is feasible, safe and retains activity in women with liver metastases who have abnormal liver biochemistry tests. Weekly anthracycline treatment may be associated with greater psychological distress [30] and these patients have a poor prognosis so time spent making additional visits to the hospital should be avoided if possible. These considerations favour 3-weekly treatment over weekly chemotherapy, but the benefits of dosing modified by AST could only be demonstrated in a large, randomised trial. We believe this would be premature until a more robust dose modification scheme has been defined. Nevertheless, our experience modifying dose according to AST suggests that there is scope for more rational anthracycline dosing in this important group of patients.

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