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Lean body mass, body surface area and epirubicin kinetics

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For a number of cytotoxics, a relationship between efficacy and plasma concentrations has recently been demonstrated. Lean body mass has been demonstrated to be a useful parameter for predicting drug clearance for a number of non-cytotoxic drugs. However, the role of lean body mass in predicting drug clearance for any cytotoxic drug has not been previously reported. Our purpose was to investigate lean body mass as a predictor of epirubicin clearance. Pharmacokinetic studies were performed in 10 patients receiving single agent epirubicin. Although preliminary, this study suggests that lean body should be further evaluated and tested in dose optimization studies.

Key words: Body surface area, epirubicin, lean body mass.

Introduction

In contrast to the use of non-cytotoxic drugs (e.g. phenytoin, digoxin, etc.), pharmacological principles are not used routinely in the administration of anti-cancer drugs.[1] Apart from carboplatin[2] the prescribed dose of a particular cytotoxic agent is generally calculated using body surface area or occasionally total body weight as the independent variable. This approach results in large inter-patient variations in plasma drug concentrations.[1,2] Whilst this phenomenon has been widely recognized, until recently its significance in determining clinical outcome (host toxicity and/or tumor response) has been uncertain. In the past few years, a direct relationship between plasma concentrations and host toxicity (and tumor response) has been reported for a number of cytotoxics including adriamycin,[3] methotrexate[4] and etoposide.[5] These studies suggest that for the relevant anti-cancer drugs, the dose to be administered could be adjusted to result in predetermined plasma concentrations in order to achieve a predictable outcome.

The clearance of a drug administered intravenously can be calculated by dividing the dose administered by the area under the plasma concentration–time curve [from zero to infinity ($AUC_{(0\rightarrow\infty)}$)]. Thus for a given $AUC_{(0\rightarrow\infty)}$, the prescribed dose of a cytotoxic drug could be calculated if the clearance could be determined by non-pharmacological methods. Lean body mass has been shown to correlate with the clearance of a number of non-cytotoxic drugs. However, its relevance in the pharmacology of anti-cancer agents has not been previously reported.

In this study, the relationship between epirubicin toxicity and blood concentration was examined. In addition, we used dual energy X-ray absorptiometry to determine whether lean body mass correlated with epirubicin clearance.

Materials and methods

Eligibility criteria

Ten patients with advanced tumors who received single agent epirubicin were candidates for this study. Only patients receiving their first course of chemotherapy were eligible. All patients received 70 mg/m^2 of epirubicin. The eligibility criteria were required: normal renal and hepatic function as indicated by a serum creatinine ≤ 0.12 mmol/l, serum bilirubin ≤ 21 umol/l, AST less than twice normal and serum albumin > 25 g/l, ECOG performance ≤ 2, no third space collections and normal cardiac function as determined by clinical and radiological examination.

Estimation of lean body mass

In this present study, lean body mass was determined by dual energy X-ray absorptiometry. Dual

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energy X-ray absorptiometry is a precise and accurate means of measuring fat-free (~lean) body mass.[5] The correlation with gravimetric weight is 0.99. The method is based on the attenuation of two energies from an X-ray source by soft tissue and bone. The absorption characteristics of the two energies through each tissue are described by two simultaneous equations. The coefficient of variation is 1.5–2.5% for repeated measurements in the same individual at different times. This technique is a non-invasive procedure and does not result in patient discomfort. It involves the patient lying in an instrument similar to a CT scanner.[6] The method is routinely used clinically to determine bone density in elderly, frail patients with osteoporosis. The radiation exposure is < 5 mrem (less than one tenth of a chest X-ray).

Toxicity

All patients had a full blood examination performed after 14 days. The parameter of hematological toxicity for the purposes of this study was defined as the ratio of the day 14 to day 1 neutrophil count.[4,7,8]

Pharmacokinetic studies

Epirubicin was administered in 100 ml of normal saline solution at a constant rate over a 15 min period. Blood samples (5 ml) were collected prior to the infusion, at the end of the infusion, and 0, 2, 5, 10, 15, 30, 45, 60, 90, 120, 240, 360 and 480 min and 24, 48 and 72 h after the end of the infusion. The samples were centrifuged and the plasma stored at 4°C, until assayed.

Analysis of epirubicin and its metabolites

Epirubicin and its metabolites were donated by Farmitalia Carlo Erba (Melbourne, Australia). Methotrexate which was used as the internal standard was supplied by Lederle Laboratories (Melbourne, Australia). High pressure liquid chromatography (HPLC) was performed on a BAS PM-60 pump (Bioanalytical Systems, IL), a FS-970 LC Fluorometer (Kratos Analytical Instruments, NJ) in sequence with a LC-6 UV/VIS absorbance detector (Bioanalytical Systems). A 3 μm ODS 100 mm × 3.2 mm column (Bioanalytical Systems) was used. Sep-pak C18 columns (Lida Manufacturing Corp., WI) were used for sample preparation.[9]

One millilitre of pH 8.85 phosphate buffer (0.05 M), containing EDTA (5 mM), and 0.1 ml methotrexate solution (2.5 mg/ml) were added to 1.0 ml plasma and vortex-mixed. The mixture was added to a Sep-pak column, pre-washed with 10 ml methanol followed by 10 ml of the phosphate buffer. The column was then washed with a further 1 ml of phosphate buffer and epirubicin was eluted with 1 ml acidified methanol (pH 3). The eluate was dried under a stream of nitrogen at 40°C, the residue was reconstituted in 0.2 ml HCl (0.02 M) and 20 μl was injected into the HPLC. The mobile phase consisted of acetonitrile and 0.05 M potassium dihydrogen phosphate solution (22:78) and 5 mM EDTA at pH 3.5. The pump flow rate was 0.8 ml/min and epirubicin and methotrexate were detected by fluorescence (260 nm excitation/550 nm emission) and uv (372 nm) detectors, respectively. The standard curve was linear for the range 1 ng/ml to 10 μg/ml, and this range was sufficient to measure all of the plasma concentrations of epirubicin and its metabolites encountered in the study. At a concentration of 20 ng/ml, the 'within day' coefficient of variation for replicate analyses was 3% ($n = 10$), while the day-to-day coefficient of variation was also 3% ($n = 10$).

Pharmacokinetic and statistical analyses

Post-infusion plasma epirubicin concentrations were fitted by a biexponential equation.[10] The area under the time–plasma concentration curve ($AUC_{(0\rightarrow\infty)}$) for epirubicin and its metabolites was calculated using the trapezoidal rule and extrapolated to infinite time ($AUC_{(0\rightarrow\infty)}$) using the terminal elimination rate constant. Clearance initial volume of distribution and equilibrium volume of distribution during the elimination phase were calculated for epirubicin from $AUC_{(0\rightarrow\infty)}$ by standand methods.[10]

Correlations between variables were analyzed by both linear regression and stepwise linear analysis. A probability less than or equal to 0.05 was considered statistically significant.

Results

Following the 15 min infusion of epirubicin, plasma epirubicin concentrations declined in a biexponential manner in all patients. The mean ± SEM for $AUC_{(0\rightarrow\infty)}$, clearance, elimination half-life, equilibrium volume of distribution and initial volume of

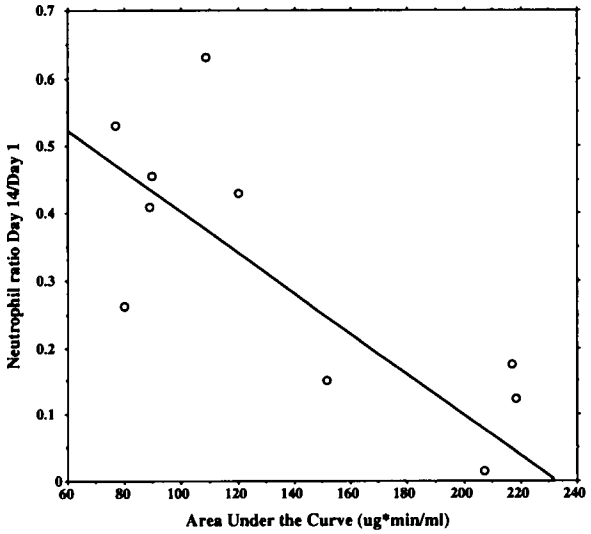

Figure 1. Relationship between toxicity (neutrophil count day 14 to day 1) versus $AUC_{(0\rightarrow\infty)}$.

distribution were 136 ± 19 μg/ml/min, 1082 ± 163 ml/min, 48.6 ± 9.5 h, 6814 ± 293 l and 127 ± 48 l, respectively. Linear regression analysis demonstrated a correlation between toxicity and $AUC_{(0\rightarrow\infty)}$ ($r = 0.65$, $p < 0.05$, Figure 1). There was a significant correlation between epirubicin clearance and lean body mass ($r = 0.65$, $p < 0.05$, Figure 2). By contrast, there was no significant correlation between drug clearance and body surface area (Figure 2) or total body mass ($p > 0.05$), respectively, or between volume of distribution and lean body mass ($p > 0.05$). No correlation was found between toxicity and initial volume of distribution ($p > 0.05$). No episodes of neutropenic septicaemia or grade 4 mucositis were noted in this group of 10 patients.

The AUC for the 13-OH metabolite and the two glucoronides were 330, 125 and 330 μg/ml/min. There was no significant correlation between the AUC and any of the metabolites with neutrophil toxicity. Neither was there any correlation between the total AUC and neutrophil toxicity.

A stepwise linear regression, without forced variables, was performed comparing AUC of epirubicin and its metabolites with neutrophil toxicity. Using this analysis, 69% of the variance in neutrophil toxicity could be accounted for by AUC of epirubicin and the first glucoronide metabolite. If age was forced into the equation, 80% of the variability in neutrophil toxicity could be accounted for by age, AUC of epirubicin and AUC of the first glucoronide metabolite.

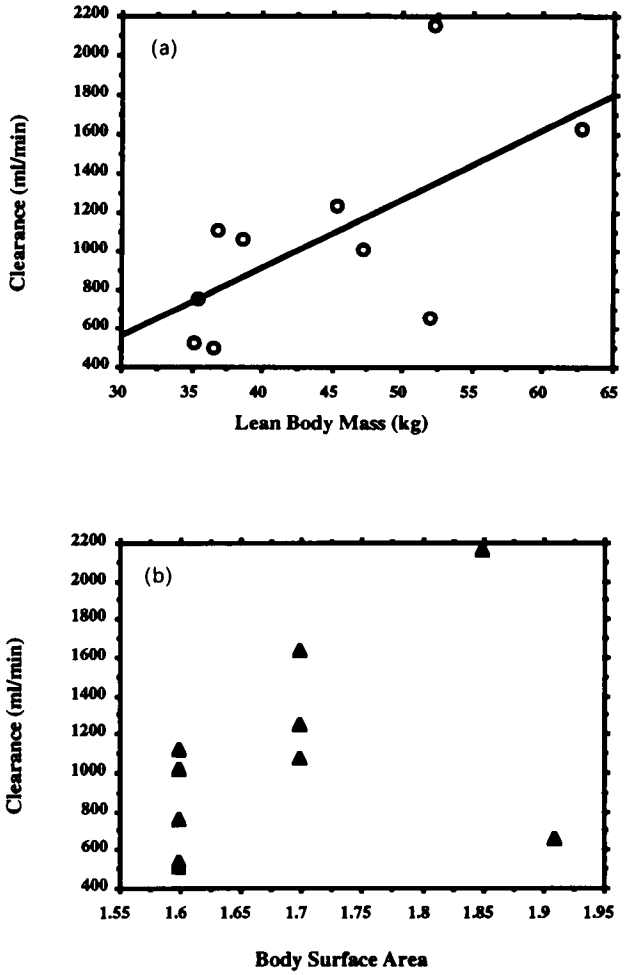

Figure 2. Relationship between plasma epirubicin clearance with lean body mass (a) and body surface area (b) in 10 patients receiving i.v. epirubicin at a dose of 70 mg/m^2.

Discussion

Cytotoxic drugs have a narrow therapeutic window. These drugs are currently administered in standardized doses according to body surface area or, less commonly, total body weight. As this practice results in highly variable outcomes, better methods for individualizing cytotoxic doses need to be developed.[1,2] For other classes of drugs where there is a known relationship between plasma concentration and effect (e.g. phenytoin, theophylline), pharmacokinetic techniques have proved very useful in individualizing therapy.[11,12]

In this study, there was a good correlation between epirubicin toxicity (ratio of neutrophil counts day 14/day 1) and the area under the plasma concentration–time curve ($AUC_{(0\rightarrow\infty)}$) of epirubicin (Figure 1). However, there was no correlation be-

tween toxicity and either initial or equilibrium volume of distribution. The relationship between epirubicin toxicity and the $AUC_{(0\rightarrow\infty)}$ is consistent with findings for several other cytotoxic drugs.[2] Plasma drug concentrations have been shown to correlate with the toxicity of carboplatin,[2] cytosine arabinoside,[13] adriamycin,[14] cyclophosphamide and etoposide.[17] Furthermore, using stepwise linear regression, age of the patient, AUC of epirubicin and the first glucoroconide accounted for 80% of the variability in the neutrophil toxicity. This suggests that the use of pharmacokinetic parameters combined with other patient variables analyzed by stepwise linear regression may be a useful in accounting for the variability in toxicity noted in patients. These approaches may be useful in defining the parameters that may predict toxicity in prospective studies.

In children with leukemia and normal renal and hepatic function, Evans *et al.*[13] demonstrated that the dose of methotrexate required to achieve a target $AUC_{(0\rightarrow\infty)}$ varied from 0.91 to 3.7 g/m^2. This represented a 4-fold difference in the dose administered. Despite this wide range in the dose of methotrexate, no major differences in drug toxicity were noted, confirming the suggestion that plasma concentrations and not dose (calculated on the basis of body surface area) is the important parameter for predicting toxicity.

Previous studies have also found a good correlation between drug efficacy and plasma concentrations. Remission rates in patients with acute lymphocytic leukaemia[4] and nasopharyngeal carcinoma[3] were shown to correlate with the plasma concentrations of methotrexate and adriamycin, respectively. Disease free and overall survivals were significantly longer in those patients with leukemia who achieved a steady state plasma concentration of greater than 16 kM methotrexate. Similarly, for adriamycin, response correlated with plasma concentrations.[14]

In the present study, plasma clearance of epirubicin was determined and was found to vary widely among the 10 patients (500–2000 ml/min). These values are consistent with those published previously,[15] as were the values for apparent volume of distribution and elimination half-life. There was a good correlation between the plasma clearance of epirubicin and patient's lean body mass, whereas there was no correlation with body surface area (Figure 2) or total body weight. Moreover, it suggests that lean body mass may be a useful predictor of epirubicin clearance. This suggests that epirubicin clearance may be predicted by lean body mass and that it may be superior to body surface area; however, further studies will be required to confirm this finding.

Lean body mass has been found to be a good predictor of plasma clearance for several other drugs. Crankshaw[16] demonstrated that total plasma thiopentone clearance correlated with lean body mass and the correlation was superior to that with total body weight. Zarowitz[17] calculated lean body mass and total body water in patients receiving theophylline and found that theophylline clearance correlated well with lean body mass. Like epirubicin, both thiopentone and theophylline are eliminated mainly by metabolism in the liver. Lean body mass has also been found to be a better predictor than body surface area for drugs eliminated by renal excretion.[18,20]

In conclusion, in this group of patients these data suggest that there is a relationship between epirubicin toxicity and plasma epirubicin concentrations. Furthermore, this study identifies that lean body mass may be a useful parameter for prediction of epirubicin clearance. Lean body mass was identified in this study as a useful predictor for epirubicin clearance but other factors may need to be incorporated to improve the predictive accuracy. These findings are preliminary and require further investigation but if confirmed may be a useful approach in dose optimization studies for epirubicin.

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