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Effect of body weight on the pharmacokinetics of cyclophosphamide in breast cancer patients

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Summary. Cyclophosphamide pharmacokinetics have been studied in 16 female patients with advanced breast cancer. The group included 7 patients who were >20%, ≤30% over ideal body weight and 5 patients who were >30% over ideal body weight. Cyclophosphamide plasma elimination half-lives ranged between 152 and 984 min (mean 457 min), the apparent volume of distribution between 19.1 and 62.3 l (mean 36.1 l), and plasma clearance between 25.9 and 166.6 ml/min (mean 69.5 ml/min). There was a significant positive correlation ($r = 0.624$, $P = 0.010$) between body weight and plasma elimination half-life, and a significant negative correlation between body weight and cyclophosphamide clearance when normalized to body surface area ($r = 0.578$, $P = 0.019$) or normalized to ideal body weight ($r = 0.531$, $P = 0.0345$). The apparent volume of distribution did not correlate with body weight. The results show that cyclophosphamide disposition is altered in patients with increased body weight.

Introduction

Obesity can cause marked changes in the pharmacokinetics of some drugs [1, 4]. This can have a number of causes. The excess body mass of obese individuals contains a greater proportion of adipose tissue than normal body mass [23]. This can lead to altered drug distribution and changes in the apparent volume of distribution, with hydrophilic drugs being relatively excluded and lipophilic drugs more extensively distributed into the excess body mass [5]. There may be changes in the plasma protein binding of highly bound drugs in obese individuals [13]. Renal clearance of a number of drugs is increased in obese individuals [2, 6, 12, 17, 39] due to increased glomerular filtration [21] or increased tubular secretion [2, 12, 17]. Pathophysiological changes in the liver associated with obesity such as fatty infiltration and fibrosis [10] can lead to decreased drug oxidation [3, 5, 32]. Drug conjugation, on the other hand, is often increased in obese individuals [7, 8]. Finally, cardiac dysfunction in obese individuals can lead to altered hepatic blood flow [18], which might be expected to affect the elimination of drugs whose elimination is blood-flow-dependent.

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Obesity, defined as a total body weight (TBW) more than 20% above ideal body weight (IBW), occurs in 14% of males and 24% of females in the United States of America [15]. Some groups of cancer patients contain large numbers of obese individuals. A survey of 836 women on a variety of breast cancer protocols at Mayo Clinic showed that 68% were obese, 53% were more than 30% above IBW and 2% were more than 100% above IBW [34]. This is not surprising, since there is an association between obesity and breast cancer [30].

The effects of obesity upon the pharmacokinetics of anticancer drugs have received little attention. Changes in the blood concentration and rate of elimination of cytotoxic drugs that have a low therapeutic index and are administered at doses close to the maximum tolerated dose could have important consequences for drug toxicity, and possibly for the therapeutic effect [35]. In this study we report the effect of body weight upon the pharmacokinetics of cyclophosphamide in a group of women receiving cyclophosphamide as part of their treatment for advanced breast cancer. A preliminary report of this work has appeared elsewhere [36].

Methods

Sixteen female patients with advanced breast cancer were studied. They were part of the population of a randomized two-arm study receiving courses every 3 weeks of either cyclophosphamide, 150 mg/m^2, and 5-fluorouracil, 300 mg/m^2, daily for 5 days; or a single dose of cyclophosphamide, 400 mg/m^2, and doxorubicin, 40 mg/m^2. All the patients also received oral prednisone beginning on day 2 of treatment at 30 mg/day for 13 days, 20 mg/day for 7 days and 10 mg/day thereafter. The patients all had a serum creatinine less than 2.0 mg/dl and serum total bilirubin less than 2.0 mg/dl. No attempt was made to select obese patients for the study. IBW was calculated according to the formula IBW (females) = 100 lb ± 5 lb/in. above or below 5 f of height [5]. The obesity index was the total body weight divided by IBW. Pharmacology studies were conducted on day 1 of the first course of treatment and in 4 patients also on day 1 of the second course of treatment. Cyclophosphamide was administered as a short intravenous infusion over 10 to 15 min before giving the other drugs. Blood samples were collected into heparinized tubes at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6 and 7 h. Plasma was immediately separated and stored frozen at −70° C until

Table 1. Pharmacokinetics of cyclophosphamide in breast cancer patients
Cyclophosphamide plasma pharmacokinetics were studied in female breast cancer patients receiving cyclophosphamide and 5-fluorouracil (CF) or cyclophosphamide and doxorubicin (CD)
IBW was calculated as 100 lb ± 5 lb/in. above or below 5 ft. height. TBW, total body weight; obesity index, TBW/IBW; $t_{1/2}$, plasma half-life; V_d, apparent volume of distribution; Cl, total body clearance. Where two values are given the patient was studied during both the first and the second course of treatment

Patient	Regimen	Dose (mg/m^2)	TBW (kg)	Obesity index	$t_{1/2}$ (min)	V_d (l)	V_d (l/m^2)	Cl (ml/min)	Cl $l/min/m^{-2}$
1	CF	150	68.1	1.41	381	50.8	29.2	91.0	52.3
					375	73.8	42.4	136.1	78.2
2	CD	440	84.5	1.40	327	22.6	11.3	47.8	23.9
					374	20.6	10.3	38.0	19.0
3	CD	400	71.0	1.25	448	30.4	16.9	47.0	26.1
4	CD	400	69.2	1.25	152	36.6	20.5	166.6	93.1
5	CF	150	84.4	1.40	714	47.8	23.9	50.6	25.3
					870	55.0	27.5	43.8	21.9
6	CD	400	64.7	1.25	254	19.1	11.3	51.1	30.0
7	CD	400	90.5	1.49	740	38.7	18.4	40.0	19.0
8	CF	150	59.6	1.17	362	45.4	28.4	100.6	62.9
9	CF	150	64.8	1.29	224	25.2	14.8	80.8	47.5
10	CD	400	68.4	1.29	719	26.8	15.2	25.9	14.7
11	CD	400	51.7	1.13	149	23.8	17.0	111.6	79.3
12	CF	150	75.9	1.28	984	53.6	29.8	37.8	21.0
13	CD	400	62.9	0.90	361	26.4	15.0	50.6	28.8
14	CD	400	68.5	1.27	624	33.4	19.0	37.1	21.1
					434	28.2	16.0	45.0	25.6
15	CF	150	63.7	1.18	287	42.4	24.9	102.6	60.4
16	CD	400	70.5	1.31	578	43.2	25.4	51.7	30.4
Mean ± SD			69.9 ± 9.9	1.27 ± 0.14	457 ± 246	36.1 ± 12.7	20.5 ± 7.1	69.5 ± 38.8	40.3 ± 24.3

assay. Cyclophosphamide was assayed by a previously reported capillary gas chromatography procedure [26] which was a modification of the method of Juma et al. [28].

Cyclophosphamide plasma concentration data were fitted to a single-compartment open model using the NONLIN least-squares regression analysis program [31] with a weighting factor of $1/y$. Pharmacokinetic parameters were calculated according to the method of Wagner [42].

Results

The group of 16 patients included 7 patients who were obese (>20%, ≤30% over IBW) and 5 patients who were severely obese (>30% over IBW). The individual pharmacokinetic parameters for cyclophosphamide elimination in the 16 patients are shown in Table 1. In 4 patients there was an initial cyclophosphamide plasma half-life of 4 to 8 min (not shown), but this was not seen in the majority of patients because of insufficient early time points. In patients where cyclophosphamide pharmacokinetics were studied on the first and second courses of treatment similar values were obtained. Although the patients were receiving oral prednisone at the time of the second pharmacokinetic study, this treatment has been reported not to alter cyclophosphamide pharmacokinetics [11]. The mean of the pharmacokinetic values from the two courses were used in the subsequent analysis. Cyclophosphamide has been reported not to exhibit dose-dependent pharmacokinetics over the dose range employed in this study [25]. We found also that the dose of cyclophosphamide had no significant effect upon the pharmacokinetic parameters, and the results from the two groups of patients were combined. A significant positive correlation was found between body weight and cyclophosphamide plasma elimination half-life ($r = 0.624$, $P = 0.010$), and a significant negative correlation between body weight and cyclophosphamide clearance normalized to body surface area ($r = 0.578$, $P = 0.019$) (Fig. 1). A significant negative correlation also existed between body weight and cyclophospha-

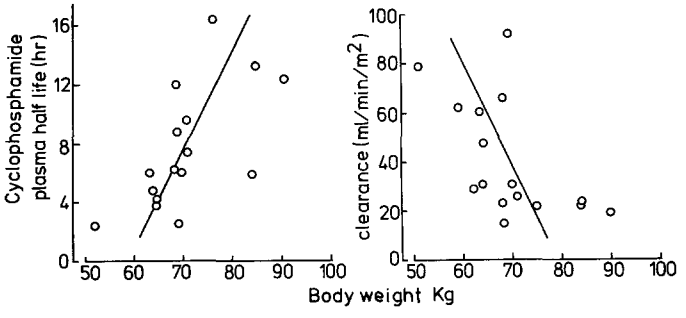

Fig. 1. Relationship between body weight and cyclophosphamide pharmacokinetics. *Left panel*, cyclophosphamide plasma half-life and body weight ($r = 0.624$, $P = 0.010$); *right panel*, cyclophosphamide body clearance normalized to surface area and body weight ($r = 0.578$, $P = 0.019$)

mide clearance normalized to ideal body weight (r = 0.531, P = 0.034). Body weight did not correlate significantly with total cyclophosphamide clearance (r = 0.468, P = 0.067) or cyclophosphamide clearance normalized to total body weight (r = 0.270, P = 0.312). Obesity index did not correlate significantly with cyclophosphamide plasma elimination half-life (r = 0.408, P = 0.117), or with cyclophosphamide clearance normalized to body surface area (r = 0.251, P = 0.347), normalized to TBW (r = 0.108, P = 0.696) or normalized to IBW (r = 0.157, P = 0.561). The apparent volume of distribution of cyclophosphamide, either total or normalized to body surface area or body weight did not correlate significantly with body weight or obesity index.

There was no significant correlation between the effect of treatment, measured as the white blood cell nadir on the first course of treatment or tumor response, and any cyclophosphamide pharmacokinetic parameter (these results are not presented).

Discussion

Women receiving treatment on breast cancer protocols are more obese than women in the general population [34]. In the present group of 16 patients 7 patients were obese (>20%, ≤30% over IBW) and 5 patients were severely obese (>30% over IBW). This is similar to the distribution of obesity we have seen in women treated in other breast cancer studies at our institution [34]. Previous studies of cyclophosphamide pharmacokinetics in a variety of groups of cancer patients have revealed considerable interpatient variability [14, 27, 29, 33, 37, 41]. Values for the plasma elimination half-life of cyclophosphamide have been reported as between 108 and 960 min, the apparent volume of distribution between 0.29 and 2.49 l/kg and total body clearance between 35 and 200 ml/min. A similar range of pharmacokinetic parameters was seen in the present study. It should be noted that the patients were studied for only 7 h, which is less than ideal for the longer plasma half-lives seen. However, reproducible results were obtained when cyclophosphamide pharmacokinetics were studied in some patients for a second time. A major factor for the variability in cyclophosphamide pharmacokinetics between patients was body weight. There was a significant decrease in the total body clearance of cyclophosphamide with increase in body weight. This was seen whether clearance was normalized to body surface area or to IBW. There was no significant change in the cyclophosphamide apparent volume of distribution with body weight. The elimination half-life of cyclophosphamide, which is a function of both the apparent volume of distribution and of clearance, showed a significant increase with increase with body weight. There was no significant correlation between cyclophosphamide pharmacokinetic parameters and obesity index. This may be because IBW, which was used to calculate the obesity index, was derived only from measurement of the patients' height and did not take account of any other factors.

To our knowledge there has been only one previous study of the effect of body weight upon the pharmacokinetics of an anticancer drug. D'Incalci et al. [19] reported no difference in the plasma area under the concentration time curve for hexamethylmelamine administered orally to patients of low body weight, ideal body weight and high body weight. The oral absorption of hexamethylmelamine is very variable, however, [20] and this might obscure a relationship between body weight and plasma concentrations of hexamethylmelamine.

Cyclophosphamide is eliminated from the body primarily by metabolism by hepatic microsomal cytochrome P-450, and very little drug is excreted in the urine [40]. The decrease in cyclophosphamide clearance with increase in body weight presumably reflects a decrease in the metabolism of cyclophosphamide by hepatic cytochrome P-450. Hepatic cytochrome P-450 has been reported to be lower in obese than in non-obese mice [22]. The clearance of phenobarbital, which is also metabolized by hepatic cytochrome P-450, is lower in genetically obese rats than non-obese rats, although the levels of hepatic cytochrome P-450 are similar [16]. In humans the clearance of some drugs that undergo hepatic oxidation, including diazepam [5], ibuprofen [3] and prednisolone [32], is decreased in obese compared to non-obese individuals, while the clearance of other drugs that undergo hepatic oxidation, including antipyrine, theophylline [24, 38], caffeine [9], and phenytoin [4], is unaffected by obesity.

No correlation was found between the therapeutic or the myelosuppressive effects of treatment and cyclophosphamide pharmacokinetic parameters. This is not surprising, since cyclophosphamide is itself non-cytotoxic and is converted by hepatic metabolism to cytotoxic species [40]. The rate of hepatic oxidation of cyclophosphamide appears to have little effect on the response to cyclophosphamide in humans [40]. It is possible that delayed elimination of other anticancer drugs that are directly cytotoxic and are cleared by the liver could lead to a need for dose reduction or a longer interval between courses for drugs in patients with increased body weight.

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