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Review

Is body composition an important variable in the pharmacokinetics of anticancer drugs?

A review and suggestions for further research

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Introduction

Variability between individual patients in the therapeutic and toxic effects of anticancer drugs is one of the major problems confronting clinical oncology. Because of the narrowness of the therapeutic window that separates concentrations that are active from those causing unacceptable toxicity, any means to allow optimisation of drug exposure is worthy of consideration. Normalisation of drug dose using body weight or predicted surface area may be of only limited value in producing a consistent clinical outcome [24, 43]. It may be that characteristics other than body *size* are of prime importance in giving rise to between-patient variability in response. Body *composition* (body fatness) could be one such characteristic [1, 7].

The disposition of a number of agents has been studied in obese and non-obese subjects (for reviews see Abernethy and Greenblatt [1] and Cheymol [7]) and certain general conclusions have been drawn from the literature on non-cancer drugs. These conclusions are summarised in Table 1. For some drugs the apparent volume of distribution is altered in obese individuals (e.g. prednisolone) [32]. The hydrophilic or lipophilic nature of certain drugs is likely to be at least partially responsible for variation in distribution volume. Oxidative drug biotransformation is in general minimally changed by obesity, but there are significant exceptions (including prednisolone [1]). For a number of drugs, metabolic conjugation has seen shown to increase with increasing body weight [1]. Renal clearance of some agents is increased in obesity (aminoglycosides; procainamide) and this provides another mechanism by which body composition might influence drug pharmacokinetics. Furthermore, pathological changes associated with more severe obesity (e.g. in cardiac or hepatic function) might be important in the pharmacokinetics of certain antineoplastic agents in some cases. The relevant pathological features of severe obesity are described in Table 2.

Overweight and obesity (see below for definitions) are now prevalent in the developed world [37] and variation between individual patients in body fatness is very great [21, 37]. In the United Kingdom at present, approximately 40%–50% of adults would be defined as overweight or obese [37], and in the UK and throughout the developed world the prevalence of obesity is on the increase. Many patients with cancer are of course underweight, but relatively little attention has focused on possible effects of reduced body fatness on drug disposition.

There are therefore a number of reasons why variation in body fatness might influence the pharmacokinetics of antineoplastic drugs, but a literature search has revealed relevant empirical evidence for only seven agents used in cancer chemotherapy (Table 3; see below). The aims of this review are as follows:

1. To consider the empirical evidence that suggests that body fatness might influence the pharmacokinetics of anticancer drugs
2. To review the methods for the assessment of obesity used in these published studies and to discuss alternative methods available for measuring body composition (fatness, fat-free mass) of patients
3. To suggest areas in which subsequent research in this field might be most profitable

It is our impression that the majority of clinical oncologists and cancer pharmacologists are unfamiliar with the background to these questions, and we hope that a detailed discussion of this kind should stimulate debate in this potentially important area. Before considering these points we should make it clear that body composition is only one source of variability in drug exposure. Although the present review is designed to highlight on the possible role of body composition as a factor giving rise to variability in drug pharmacokinetics, it is not our intention to suggest that this is the only factor, or even the most important factor. The established causes of variability in drug pharmacokinetics

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Table 1. Mechanisms by which obesity can influence drug pharmacokinetics: examples of non-cancer drugs[a]

Mechanism	Effect	Examples/comments
Absorption	No effect described	Limited number of drugs studied
Distribution volume	Very large increase	Most benzodiazepines, thiopentone, phenytoin, verapamil, lignocaine
	Modest increase	Methylxanthines, aminoglycosides, vancomycin, ibuprofen
	Unchanged	Digoxin, procainamide, cimetidine
Protein binding	No marked effect described; possible increases in binding to α -acid glycoprotein	Little evidence available
Oxidative transformation	Minimal change in obesity, with a few significant exceptions where it increases	Exceptions include prednisolone, ibuprofen
Conjugation	Increase reported for selected drugs	Paracetamol, lorazepam, oxazepam
Acetylation	Results equivocal	Little evidence available
Clearance	Effects differ between drugs	No change for verapamil, lignocaine; possible increase for some renally cleared drugs such as aminoglycosides

[a] Summarised from Abernethy and Greenblatt [1] and Cheymol [7]

Table 2. Pathological features of severe obesity: effects on drug disposition[a]

Pathological feature	Effect
Hepatic fibrosis/fatty infiltration	Reduced drug oxidation
Cardiac hypertrophy and dysfunction: increased cardiac output and stroke volume	Perfusion and, hence, drug transport altered
	Effects on hepatic blood flow likely to alter elimination of some drugs
Increased glomerular filtration	Increased excretion of renally cleared drugs
Biliary tract disease	Alterations in hepatic transformation/excretion
Hyperlipidaemia, hyperlipoproteinaemia	Possible effects on protein binding
Other pathological features including hypertension, diabetes, atherosclerosis	Effects unknown but potentially important and likely to vary between drugs

[a] Summarised from Abernethy and Greenblatt [1] and Cheymol [7]

(including body size, renal and liver function, drug metabolism) are of course of prime importance and are discussed briefly, but the primary focus of the review is on body composition.

Empirical evidence for influences of body fatness on the pharmacokinetics of antineoplastic drugs

Relevant evidence has been reported for seven drugs (Table 3). Six of the studies involved adult patients. In five of these, adult patients were categorised as either obese or non-obese on the basis of body weight relative to height, which was expessed as a percentage of "ideal body weight". In the other study a single patient was defined as obese on the basis of weight relative to ideal weight. The reference values for ideal body weight were taken from "ideal weight" tables drawn up for actuarial purposes [3]. Pharmacokinetic data have then been compared between groups of obese (>30% above ideal body weight) versus overweight (15%–30% above ideal body weight) or non-overweight individuals (<15% above ideal body weight), or in some studies the authors have analysed data using correlations of pharmacokinetic variables with percentage of ideal body weight (i.e. the ratio of actual weight/ideal weight ×100). In the only study of children considered herein, Zuccaro et al. [57] calculated a weight for height centile (using reference data of weight for height from the United States National Center for Health Statistics [35]) for each child and then compared the peak serum concentration of 6-mercaptopurine (6-MP) in children above and below the 75th centile of weight for height. Use of "weight for height" in childhood is analogous to the use of percentage of ideal body weight in adults.

In all of the studies considered herein except one [32], the dose was calculated on a unit surface-area basis. In the report by Milsap et al. [32] on prednisolone a fixed dose of 33 mg was given to each patient. Details of dosage for each drug are given in Table 3.

The discussion of the studies reviewed below will make it clear that most of the published data provide interesting indications of the effect of body composition on the pharmacokinetics of anticancer drugs but are not conclusive. Certain caveats are necessary at this point: (1) relatively small numbers of subjects were recruited in the studies and this resulted in comparisons between very small subgroups in many cases (Table 3); (2) comparisons between groups of widely varying relative weight or fatness will have tended to maximise the correlation coefficient in studies where pharmacokinetic parameters and relative weight were correlated; (3) patients were fairly heterogeneous in some of the studies cited; (4) in some cases, healthy volunteers rather than patients were studied; (5) in other cases, multiple drug therapy was being used and this may

Table 3. Studies on the influence of body composition on pharmacokinetics of anticancer drugs

Drug	Patient group, diagnosis	Sample size	Dosage	Index of body composition used	Main conclusion	Reference
Prednisolone	Adults, healthy volunteers	12	33 mg fixed dose	Weight relative to ideal body weight	Distribution into excess body weight reduced	[32]
Cyclophosphamide	Adults, breast cancer	16	150 mg/m^2 daily or 400 mg/m^2 daily, randomly assigned	Weight relative to ideal body weight	Clearance reduced in the obese	[39]
Ifosfamide	Adults, non-small-cell lung cancer	16	1.5 g/m^2 daily	Weight relative to ideal body weight	Increased relative distribution volume in the obese	[30]
Doxorubicin	Adults, variety of tumour types	21	50–70 mg/m^2 in single 1-h infusion	Weight relative to ideal body weight	Clearance reduced in the obese	[46]
Hexamethylmelamine	Adults, advanced ovarian cancer	31	115–200 mg/m^2 daily	Weight relative to ideal body weight	No effect	[13]
Methotrexate	Adult, osteosarcoma	1	9 and 10 g/m^2	Weight relative to ideal body weight	Unusually high steady-state volume of distribution and systemic clearance in an obese patient as compared with non-obese adults with osteosarcoma	[18]
6-Mercaptopurine	Children, acute lymphoblastic leukaemia	18	75 mg/m^2 daily	Weight for height centile	Lower peak serum concentration and AUC in children >75th centile, increased clearance and volume of distribution	[57]

have confounded the results; and (6) drug metabolites were measured in a few of the studies but not in every case. The authors of the reports identified these limitations and their conclusions were appropriately cautious. In no case did the authors recommend adjustment of drug dosage as a result of the research. All concluded that further studies were indicated.

Prednisolone

In the prednisolone study, Milsap et al. [32] compared drug disposition in eight obese and four normal-weight, healthy male volunteers. The uncorrected steady-state volume of distribution (Vss) was 20% greater in the obese subjects (mean, 44.1 vs 36.71 l), but when adjusted for body weight, the volume of distribution was lower in the obese group. The clearance of free drug correlated strongly ($r = 0.80$) with the degree of obesity (expressed as a percentage of ideal body weight) and was on average 41% greater in the obese group. Protein binding did not differ between the groups.

The authors discussed the potential importance of steroid metabolism in adipose tissue but preferred to implicate a relatively poor penetration of the drug into body fat. They also noted that enhanced prednisolone clearance could be explained by the effects of factors such as cardiac output, hepatic blood flow and liver size (all increased in obesity [1]).

Altered prednisolone dosage was not recommended in obese subjects in view of the small sample size and the evidence of enhanced sensitivity to adrenal suppression in the obese group [32].

Cyclophosphamide

Cyclophosphamide pharmacokinetics were measured in 16 patients with advanced breast cancer [39]. In all, 4 of the patients were at <20% of ideal body weight, 7 were 20%–30% above ideal weight, and 5 were >30% over ideal body weight. A significant positive correlation between body weight and elimination half-life was observed ($r = 0.62$) together with a significant negative correlation between body weight and cyclophosphamide clearance normalised to body surface area ($r = 0.58$) or ideal body weight ($r = 0.53$). However, neither body weight nor the ratio of body weight:ideal body weight correlated significantly with clearance. The apparent volume of distribution was not correlated with body weight.

The authors suggested that reduced clearance in the patients with greater body weight might have reflected reduced metabolism. However, drug metabolites were not measured. Clearance of cyclophosphamide occurs primarily via metabolism by hepatic cytochrome P-450, which has been reported to function at lower activity in (genetically) obese strains of mice relative to non-obese mice [14]. However, the application of rodent models of obesity to humans is problematic; a detailed discussion of this topic is provided by Abernethy and Greenblatt [1]. No correlation was observed between cyclophosphamide pharmacokinetics and either response or myelosuppression but this was not surprising, given that metabolite exposures were unknown.

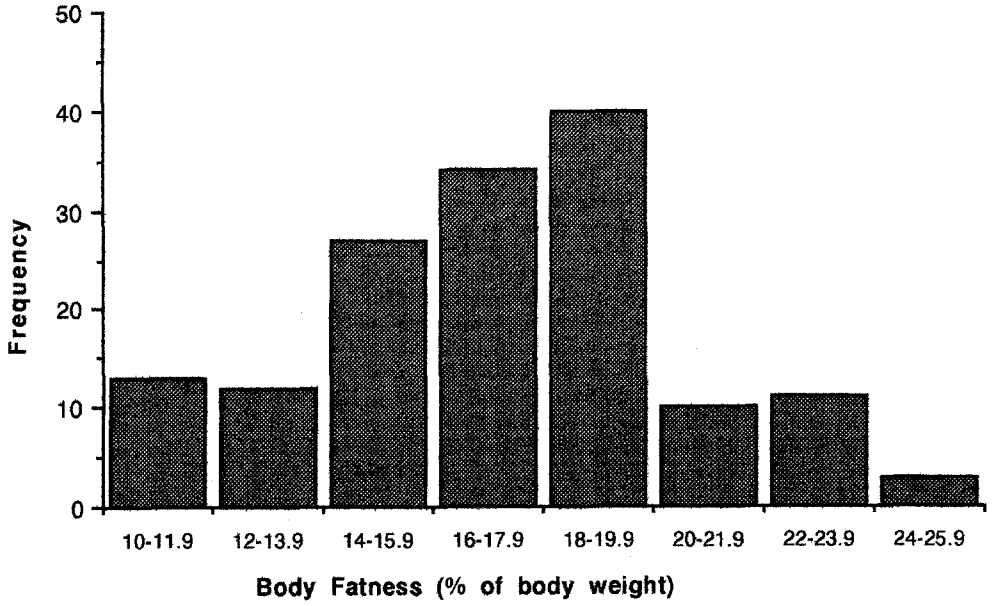

Fig. 1. Variability in body fatness of 150 adult men at the same relative weight. Data redrawn from Durnin [15]. The men ranged in height from 1.75 to 1.79 m and in weight from 70.0 to 71.9 kg. The relative weight (percentage of ideal weight) was therefore almost identical in all cases, but the body fatness (expressed as a percentage of body weight) ranged from 10% to 25%

Ifosfamide

In a study of 16 patients with carcinoma of the bronchus (4 obese, defined as >20% above ideal body weight; 12 non-obese), Lind et al. [30] reported an increased elimination half-life in the obese group. The average terminal elimination half-life was 6.4 h in the obese group as compared with 5.0 h in the "control" group. Prolongation of the elimination half-life arose from an increased volume of distribution (Vd β) in the obese group (mean, 42.8 l) versus the non-obese group (35.5 l). The plasma half-life correlated significantly with the ratio of body weight : ideal body weight (i.e. was higher in individuals at greater relative weight). Normalisation of Vd β for ideal body weight produced a strong positive correlation with the ratio of body weight : ideal body weight, implying enhanced distribution of ifosfamide into "excess" body weight. Clearance was similar between the groups, irrespective of the means of expressing it (milliliters per minute; milliliters per minute per kilogram body weight; milliliters per minute per kilogram ideal body weight). The authors discussed the point that the report by Powis et al. [39] on the related drug cyclophosphamide produced different conclusions with respect to clearance and volume of distribution but were unable to explain fully the disparity – physicochemical differences between cyclophosphamide and ifosfamide may have been responsible [30].

Doxorubicin

Pharmacokinetics were studied in 21 adult patients with a variety of tumour types [46]. Patients were divided into three groups on the basis of percentage of ideal body weight: normal (<115% of ideal body weight, n = 7); mildly obese (115%–130% of ideal body weight, n = 7); obese (>130% of ideal body weight, n = 7). The area under the concentration-time curve (AUC) was 2 times greater in the obese group than in the normal-weight group, and clearance (milliliters per minute) was reduced accordingly, with the volume of distribution (V_{SS}) remaining unchanged. The β-phase elimination half-life (up to 48 h) was 20.4 h in the obese group vs 10.6 h in the normal-weight patients. The observed clearance and elimination half-life of doxorubicin in this study were linearly correlated with the percentage of ideal body weight (r = 0.75, clearance; r = 0.62, half-life). Furthermore, the mean residence time of the drug was approximately double the predicted values in the obese patients. AUC and half-life values for the doxorubicinol metabolite were the same in the obese and normal-weight groups.

The authors argued that doxorubicin was likely to have minimal distribution to adipose tissue, whereas the unaltered doxorubicinol concentrations observed (and also 7-deoxyglycone metabolite concentrations) indicated that the obvious metabolic pathways could not be responsible for the effects on parent-drug pharmacokinetics. The authors felt that no conclusion could be drawn in relation to the effects of elevated doxorubicin in obese patients because of the relatively small numbers of patients involved and the use of additional drugs in combination. Further studies were indicated.

Hexamethylmelamine

The only "negative" finding identified in our review of the literature on body composition and drug pharmacokinetics was a study of hexamethylmelamine (HMM) [13]. In 31 patients with advanced ovarian cancer, pharmacokinetics of HMM and its metabolites were measured. Patients were classified into three groups on the basis of weight

relative to ideal weight: fat ($n = 6$), normal ($n = 14$) and thin ($n = 11$). All of the pharmacokinetic parameters measured (AUC to 6 and 12 h, peak plasma level, α and β elimination half-life) showed considerable variability between patients, and the authors found little evidence of any influence of age, concomitant administration of other anticancer drugs or fatness. The drug was given orally and, since oral absorption of HMM is extremely variable [12], this may have confounded the results. Alternatively, HMM pharmacokinetics may not be influenced by body composition.

Methotrexate

An anecdotal case has been presented in which an obese adult patient (184% of ideal body weight) with osteosarcoma exhibited unusual pharmacokinetics after receiving high-dose methotrexate (9–10 g/m^2) as compared with control values otained from the literature [18]. The Vdss value (0.398 l/kg) and systemic clearance (0.0956 l h^{-1} kg^{-1}) were slightly elevated with respect to the literature values for adult osteosarcoma patients, but the terminal β-phase half-life (9.29 h) was normal. The authors suggested that changes in Vdss and clearance may offset each other in obesity, leaving the elimination half-life unchanged. Renal clearance was not specifically measured but this may have influenced clearance (measured CrCl clearance was >150 ml/min). The authors proposed that obese individuals might require larger doses of methotrexate to achieve serum levels comparable with those attained by lean patients. Although they stressed that on the basis of a single case, no specific dosage recommendation could be given regarding the use of high-dose methotrexate in obesity, they suggested that both renal function and methotrexate serum concentrations be monitored in obese individuals. Since such measurements are routinely made in high-dose methotrexate therapy with leucovorin rescue, it should not be difficult to accrue further data. Until then, one should clearly be cautious about the significance of this individual case.

6-Mercaptopurine

In the treatment of childhood acute lymphoblastic leukaemia (ALL), 6-mercaptopurine (6-MP) has a critical role in the maintenance of remission [26]. Variability in the pharmacokinetics of 6-MP does lead to clinically significant differences in outcome (relapse), and there is some evidence that variation in body fatness might contribute to this [57]. Zuccaro et al. [57] demonstrated larger distribution volumes (liters per kilogram), lower serum (nanograms per milliliter per hour) AUC values and lower peak serum concentrations (nanograms per milliliter per hour) in heavier children (above the 75th weight-for-height centile) than in lighter children (below the 75th centile). All of these parameters varied by a factor of around 2 between the groups, and there was a negative correlation between AUC and weight-for-height centile ($r = -0.75$; $n = 18$). Zuccaro et al. [57] argued that variation in oral bioavailability (absorption) between patients, known to be important in the maintenance of remission in ALL [56], was not responsible for the observed variation in pharmacokinetics. This implies that heavier children may be "underdosed" and may thus be at increased risk of relapse. In fact, the only available evidence on the prognostic significance of relative weight in childhood ALL suggests that low weight might have *adverse* prognostic significance, but this requires confirmation [44]. One further caveat concerns the variability in pharmacokinetic data obtained when repeat measurements were carried out by Zuccaro et al. [57], which suggested that reproducibility (both within and between patients) was relatively poor. It is established that other factors such as drug absorption and, particularly, drug metabolism are of primary importance in determining interpatient variability in the response to 6-MP [29], but it is possible that body composition could also play a role.

Assessment of body composition

Before we consider the methods available for assessing body composition, two points must be made. Firstly, assessment of body composition has until very recently depended on a model in which the chemical composition of the body is made up of two components: fat mass (FM) and fat-free mass (FFM). These two components do not exist anatomically but are a theoretical construct based on chemical analysis. The FM consists of material that could be extracted by an appropriate lipid extraction method, i.e. represents all of the lipid in the body, and has a density of 0.90 g/cm^3. The FFM comprises everything else (e.g. bone, blood, muscle) and is therefore relatively heterogeneous anatomically but is assumed to be relatively homogeneous in terms of chemical composition, having a density of 1.10 g/cm^3. If the body is assumed to comprise only two components and if these components have specified and constant density, then if the whole-body density is measured the FM and FFM can be solved for. The two-component model has classically depended on underwater weighing [50], employing the Archimedes Principle to determine body density. This is still regarded as the "gold standard" for the assessment of body composition in the absence of direct chemical analysis of cadavers.

The second point that must be made concerns the distinction between quantitative measurement or estimation of body composition (FFM and FM) in individuals and a less direct approach that employs indices that are correlated with FFM and/or FM. This is of some practical importance since these indices, such as weight for height, weight relative to ideal weight at a particular height or body mass index (weight/height^2) are easier to employ in clinical settings but are not *measurements* of FFM and FM. Rather, they are *correlates* of body composition. Relative weight is *correlated* with FM (high relative weight tends to indicate high body fatness), but weight indices of this kind can be confounded by a number of factors (other than body fatness) that influence body weight. A large solid tumour burden, for example, will increase relative weight [51], as will a high FFM: bodybuilders have high relative weights but relatively low fatness due to a relatively large muscle

bulk; weight for height of children with solid tumours can be confounded by tumour bulk [51].

An additional problem with the use of relative weight indices is that individuals of the same relative weight can vary very substantially in body fatness [15] (Fig. 1). For example, Figure 1 illustrates a range in body fatness (percentage of body weight) of 10%–25% in adult men at the same relative weight. Relative weight is therefore a crude *index* of fatness/obesity rather than a precise *measure* of fatness in individual patients. This is relevant to the present review because all of the existing published studies on body composition and pharmacokinetics of anticancer drugs (Table 3) have employed indices that express body weight relative to height (in most cases the same index was used) rather than actual *measurements* of body composition (FFM, FM) and, thus, the potential for confounding effects is great. For example, increased distribution of any drug into "excess" body weight (i.e. weight in excess of ideal body weight) is usually assumed to mean preferential distribution into body fat but could actually represent distribution into excess FFM rather than excess FM.

Obese individuals tend to have a larger FFM as well as a larger FM than do non-obese individuals, and since FFM and FM were not measured in the studies reviewed herein an alternative explanation for some of the observed results cannot be ruled out, i.e. observations of increased distribution into excess body weight may be due not to differences in *fatness* between patients but to differences in FFM. In animal studies using theophylline, an increased distribution of the drug into "excess" body weight was observed, but this was subsequently identified (by dissection and drug analysis) as being due to increased distribution in the "excess" FFM, not body fat, of the obese animals [1]. We choose this extreme example to illustrate the point that the precise, quantitative measurements of pharmacokinetic parameters in the studies reviewed herein were not matched by precise and quantitative measurements of the factor being tested for an influence on pharmacokinetics, namely, body fatness. Rather, fatness was inferred using relatively crude indices. In the study of prednisolone disposition reported herein [32] the authors noted an inability to identify the nature of the reduced distribution into excess body weight. Such an effect could have been due to a failure of the drug to distribute into excess FM or excess FFM.

Methodology for the assessment of body composition

Detailed reviews of this subject are available [10, 23, 31] and the topic will not be discussed in great detail in the present review. We will concentrate on techniques that are simple and can be employed in clinical use with relative ease (at the bedside, for example) and at low cost. These criteria include total body water, bioelectrical impedance, and skinfold thickness for the prediction of body density. Near-infra-red interactance (NIR) is a potential "bedside" method that is based on assessments of peripheral body fat [31]. Measurements are usually made on the upper arm and used to infer total body fatness. This particular method has not yet been validated, and some initial assessments have been disappointing [33]. One major source of error arises from the dependence of NIR on measurements of fatness in one region of the body only, with extrapolation to total body fat. Recent developments in technology have provided new techniques, including magnetic resonance imaging and dual-energy X-ray absorptiometry [19]. The new methods permit development beyond the two-component model to allow construction of a model of the body that consists of three or four components (whereby the fat-free mass is separately quantified as water, mineral and protein). These new techniques show great promise but have not been fully evaluated. Moreover, they are in general not readily suitable for use at the bedside and therefore will not be considered in this paper.

Measurement of skinfold thickness

Measurement of the thickness of subcutaneous adipose tissue with calipers at standard sites (usually four sites: biceps, triceps, suprailiac, subscapular) can be used to predict body density and, hence, using the two-component model, FFM and FM. Prediction is based on empirically derived regression equations that relate the log of the sum of four skinfolds to body density [16] (measured by underwater weighing). In the hands of a trained observer the method is very precise [10] and meets our criteria of simplicity, ease of use and low cost. As the regression equations are age- and gender-specific, the appropriate equation must be chosen, and particular problems exist with the validity of this approach in children and the elderly. In both groups the basic assumptions of the two-component model are invalid (constant composition and density of the FFM), and the equations that predict density from skinfold thickness are based on rather small sample sizes [45]. One source of potential error that may be applicable in patients with cancer is that the skinfold thickness method depends on the relationship between subcutaneous adiposity and total body fat being similar to that in the original healthy population upon which the predictive equations are based. It is possible that in a number of clinical settings in oncology the fat distribution of patients may be abnormal, and the relationship between subcutaneous adiposity and total body fat may therefore be disturbed. The practical significance of this source of error is unknown at present.

Measurement of total body water

The two-component model states that the FM by definition contains no water: all water is contained in the FFM. Since the water content of the FFM is *relatively* constant at approximately 73% [23], the FFM (and the FM, by difference) can be estimated as follows: FFM (kg) = total body water (kg)/0.73.

Total body water is routinely determined by isotope dilution techniques using water "labeled" with deuterium (^2H), tritium (^3H), or oxygen-18 (^{18}O). The isotopic label is given orally as a single drink, and once this has thoroughly mixed ("equilibrated") in body water (usually within 4–6 h) a sample of body fluid (saliva, urine, plasma or serum) is

obtained so as to determine the enrichment of the tracer and, hence, the degree of dilution in total body water. The technique is therefore readily employed "at the bedside", but analysis of the stable isotopes deuterium and oxygen-18 is more problematic since this requires access to a mass spectrometer or infra-red spectrophotometer [31]. Tritium is analysed more conveniently by liquid scintillation counting. That tritium is a radioactive isotope severely restricts its use in humans, but this is less of a practical problem in patients with cancer (especially in adults) than in other groups of patients.

The assumption of a constant water content of the FFM gives rise to error where the water content of the FFM varies between individuals and where there are systematic changes in hydration of the FFM (e.g. during pregnancy [10, 31]). In fact, it is becoming increasingly obvious that the assumption of a constant water content of the FFM is an oversimplification. In healthy adults the variability in FFM hydration between subjects is of sufficient magnitude to produce errors of practical significance in body composition studies [20, 27]. Furthermore, hydration of the FFM is not constant during infancy and childhood but shows systematic changes (a decline in the water content of the FFM is characteristic of infancy and childhood [17, 27]). Estimation of the FFM and FM in the paediatric setting is therefore somewhat complicated. Furthermore, it is likely that in disease states, including cancer, hydration of the FFM may be altered: Cohn et al. [9] have suggested that in patients with wasting disease the water content of the FFM is higher than expected (due to loss of body cell mass with relative expansion of the extracellular fluid, ECF).

Bioelectrical impedance

Bioelectrical impedance (BEI) depends on the differential resistance of the FM and FFM to a weak (800 μA, 50-kHz) electrical current. As the technique is safe, rapid and non-invasive and the apparatus is relatively inexpensive, this does represent a suitable method for use "at the bedside". Body height^2/resistance is highly correlated with fat-free mass [47], but the validity of the technique has been called into question. The accuracy and precision of BEI is unacceptable to some investigators [10], and further problems arise from the equations chosen to predict FFM from measured resistance: several equations exist, reflecting the observation that the relationship between height^2/resistance and FFM alters with age, differs between the sexes and may vary between populations [47]. Use of an inappropriate predictive equation can lead to systematic error in the estimation of FFM [11]. One further problem with impedance is that since the electrical signal is conducted by body water (and associated electrolytes), any disturbance in body water can confound the measurement [11]. Different predictive equations are used in different types of impedance apparatus, and it is advisable that the software employed by these devices be validated by comparison with one of the more established methods, preferably prior to more widespread adoption of the methodology in groups of patients with cancer. The basis of the comparison between "new" and "old" methods is extremely important and this is discussed below.

Differences between methods of assessment

Studies have repeatedly demonstrated that all of the methods of assessing body composition are highly correlated [23, 31]. However, since correlation is an index of *association* rather than a test of agreement between methods [4], it is not safe to assume that the various methods outlined above actually *agree*, and evidence of real differences in predicted fatness between methods of assessment has been reported (e.g. in younger adults by McNeill et al. [34] and Fuller et al. [20]; in the elderly by Reilly et al. [45]). The most appropriate means of determining *agreement* between methods concentrates on differences between methods at the individual level and is described by Bland and Altman [4]. Furthermore, the *validity* of a new method should not be tested using correlation with an established method [4], although this process has unfortunately become established in body composition research.

The possibility of differences between methods should therefore be kept in mind in the design of studies that attempt to identify the influence of body composition on drug pharmacokinetics; all experimental subjects should be studied using the same methodology, although this does not rule out employing more than one technique in each subject.

In some settings in oncology, particular physiological/pathological features of the clinical problem may confound the method of assessment that is employed. All methods require accurate measurements of body weight, but should this be adjusted when the tumour burden is large? This may be of particular importance for certain childhood malignancies [51]. Cohn et al. [9] suggested caution in the use of total body water in certain groups of patients with cancer because of the possibility of a relatively large variation in the water content of the FFM. Cohn et al. [9] also concluded that measurement of total body potassium (a laboratory technique for the assessment of body composition) was problematic in patients in whom substantial muscle wasting had occurred because muscle is relatively rich in potassium.

It should also be emphasised that the *absolute validity* of any method of assessment cannot be established in studies of human body composition since this would require chemical analysis of the cadaver. Slaughter/chemical analysis is routinely carried out as a means of establishing the validity of assessment techniques in animal studies [42], but this is obviously not possible in the clinical setting. It is therefore standard practice to compare between methods, often with measurement of density (by underwater weighing) serving as the reference method or "gold standard" so as to provide a means of determining the *relative validity*. However, underwater weighing techniques would be feasible in only a few clinical settings in oncology. It should also be pointed out that the assumption that underwater weighing is a "gold standard" perhaps places too much faith in the basic assumptions of the two-component model [10, 19].

Implications for future research

Drugs that may be of interest

All of the drugs for which some evidence of an influence of body composition on pharmacokinetics exist (Table 3) seem worthy of further attention. Research on related agents may also be profitable. In addition, drugs that are known or suspected to be particularly lipophilic or hydrophilic are likely to have volumes of distribution that vary systematically with body composition and are therefore of potential interest in this context. Anticancer drugs vary widely in terms of hydrophobicity/hydrophilicity [54]. For example, nitrosoureas are extremely hydrophobic in character, whereas carboplatin is hydrophilic. Others are amphipathic, combining structural features of both types – examples would include anthracyclines and ether lipids. Drugs to concentrate on should also include those for which a variation in drug outcome cannot be explained by known variables.

Given the relative paucity of data available, we feel it would be appropriate to investigate a range of anticancer drugs for the effects of body composition. This review has concentrated on what may be considered to be "normal" variation in body fatness and possible effects on drug pharmacokinetics, but more severe variation in fatness leading to pathological effects (e.g. effects of morbid obesity on renal, hepatic or cardiac function; see Table 2) may also be of relevance in some clinical situations and therefore deserves greater attention.

Suggestions on methodology

A number of previous studies (Table 3) have produced evidence that body composition (or at least relative body weight) can influence the pharmacokinetics of antineoplastic drugs. One concern, however, is the reproducibility of the pharmacokinetic measurements. Zuccaro et al. [57] found systematic variation in the pharmacokinetics of 6-MP but noted also that the reproducibility of their measurements within individual patients dosed on different occasions was relatively poor. If variability within patients in pharmacokinetics is generally high, then this may imply that factors such as body composition are relatively unimportant since body composition is unlikely to change over short periods. Clearly, reproducibility of the pharmacokinetic measurements is a pre-requisite for studies of the effects of body composition. Where possible it might be appropriate to focus initially on agents that are given intravenously or have reproducible bioavailability following oral administration.

It may be useful to reiterate the main points discussed earlier in this review in relation to study design. Thorough evaluation of the role of body composition in relation to pharmacokinetic variability between patients will demand relatively large samples of patients drawn from fairly homogeneous patient populations, along with detailed measurements of the pharmacokinetics of the drug given and relevant metabolites. Meeting these criteria is clearly not easy.

The studies summarised in Table 3 demonstrated variability in pharmacokinetics, but no study has yet reported that variation in body composition has a clinically significant influence on what might be seen as drug exposure *outcomes*: toxicity and antitumour activity. We suggest that investigations into the influences of body composition on both pharmacokinetics and clinical outcome are indicated.

One further recommendation on the question of body composition methodology is that future research should employ *measurements* of body composition (FM, FFM) in individual patients. The use of *indices* of body fatness, such as relative weight, has been valuable in identifying possible effects of body composition. We feel that more detailed research investigations in this area now require actual *measurements* of FM and FFM rather than proxies of these variables, without the extra "noise" introduced by use of the proxy. The choice of which particular method to employ (skinfolds, impedance, total body water or one of the other methods) is probably less important than the decision to use a measurement of body composition rather than an index of it. The "bedside" methods described above need not be impractical in clinical use, although we accept that indices such as percentage of ideal body weight are simpler to calculate and therefore have practical advantages in the clinical setting. Body composition research in other areas has been limited by the failure of investigators to describe fully the methods used and, in particular, the predictive equations employed (e.g. see the discussion of differences in impedance software above). If such problems are to be avoided in research on body composition and anticancer drug disposition, we suggest that the following practices be adopted: (1) methods employed should be described in detail (e.g. the side of the body employed and the software utilised in impedance studies), (2) potential errors in the assumptions of the methods should be considered in each case and (3) body composition data of individual patients should be presented where possible.

Variation in body fatness: some predictions

Body fatness is extremely variable between individuals and there is no "normal range" as such [23]. Despite this, wide variability between individuals exists and some general trends are apparent. We will discuss these briefly because they give rise to predictions relating to where variation in body fatness might make a difference in terms of drug pharmacokinetics and clinical outcome.

In the developed world, overweight and obesity are on the increase, and many groups of cancer patients will contain a wide variation in body fatness, including in some cases a high proportion of relatively fat individuals (breast cancer, for example [30, 38]). There are relatively few data on the body composition of different groups of patients with cancer. A survey of 836 breast cancer patients at the Mayo Clinic reported that 53% were >30% above their ideal body weight [38]. Within any large group of even fairly homogeneous patients with cancer there is therefore likely to be wide variation in body fatness and within-group comparisons will thus often be valuable.

Since cachexia and underweight are common in many settings in oncology, variation in body fatness and FFM will be great within patients (during the course of the disease) and between groups of patients. As undernourished patients *tend* to have reduced FFM as well as reduced body fat, an unusually low percentage of body fat cannot be assumed in cachectic patients. Little is known about the effects of underweight on the pharmacokinetics of anticancer drugs. Poor nutritional status (underweight, specific nutrient deficiency) is known to impair a range of physiological and biochemical functions (e.g. enzyme activity [48]) and could therefore have important implications for variability between patients in drug pharmacokinetics, but a detailed discussion of this area is beyond the scope of this review.

There are also substantial between-group differences in body fatness. Perhaps the greatest of these is gender differences. Although there is some overlap in the distributions, females generally have higher body fatness (percentage of body weight) than do males throughout life. These differences exist from birth and throughout childhood [17, 25] but become particularly marked only approaching and during puberty. Large differences between the sexes exist in adulthood [23]. The mean percentage of body weight that is fat is generally greater in females than in males, but this disguises differences between the sexes in absolute body composition. For example, in absolute terms, adult males can have a larger FM as well as a larger FFM than do adult females. There are also differences between the sexes in the composition of the FFM [8], but the practical significance of these in relation to drug disposition in unclear. With any drug whose pharmacokinetics varies systematically with body fatness, differences between the sexes might therefore be expected, although there are of course other between-sex differences that are even more important in this respect. For many drugs, age-related influences on these variables would exceed the effect of body composition differences between the sexes.

Variation in body fatness between individuals is also age-related. There is a general trend to increased relative body fatness (weight of fat as a percentage of body weight) in old age, and in many individuals there is also an increase in the *absolute* amount of total body fat present in old age. The FFM shows a marked decline in old age in both sexes, primarily via loss of muscle mass [49]. Again, although fatness is by no means the only difference between young and old individuals, it is one possible source of variability in the pharmacokinetics of antineoplastic agents, and we would therefore predict that for any drug for which body composition is relevant to variation in pharmacokinetics, differences between groups of patients at different ages might be expected. This is not to ignore age-related variation in renal and liver function, which for many drugs would be of greater significance than age-related variation in body fatness.

Concluding remarks

The question of the influence of body composition on the pharmacokinetics of anticancer drugs has recently received increased attention for two principal reasons. Firstly, there is some empirical evidence that body composition is an important variable in the pharmacokinetics of certain anticancer drugs [13, 18, 32, 46]. Secondly, recent evidence has suggested that normalisation of the dosage of antineoplastic drugs using either body weight or predicted surface area is actually of very limited value in producing consistent drug exposure [24, 43]. Attention is now being focused on factors other than body size/surface area that might give rise to variation in pharmacokinetics [24, 28, 43, 52]. For a number of anticancer drugs, body composition may well be one such factor, although for many agents the importance of variability in body composition relative to variability in factors such as renal or hepatic function (and drug metabolism) may well be limited.

A current example whereby body composition may be relevant is the calcium channel blocker verapamil, which is being evaluated as a modulator of multidrug resistance. The ability to achieve and maintain active drug levels to inhibit the P-glycoprotein efflux pump while at the same time avoiding adverse cardiac effects is critical. Earlier studies have shown that the apparent volume of distribution of verapamil was greater in obese (858 l, $n = 11$) as compared with normal-weight (310 l, $n = 11$) patients, and some differences were maintained in the weight-corrected volumes[2] (7.0 vs 5.1 l/kg).

The ultimate aim of identifying and quantifying the factors that are responsible for variability in pharmacokinetics is the adjustment of drug dosage so as to produce a consistent therapeutic effect while at the same time minimising toxicity [28, 36, 41, 52]. A longer-term aim of research on the effects of body composition on the pharmacokinetics of antineoplastic drugs must therefore be the development of straightforward, user-friendly schemes for the adjustment of drug dosage based on assessments of body composition. Although not without problems [28, 41, 52], useful schemes that adjust the dosage of antineoplastic agents based on assessment of other physiological parameters (notably renal and hepatic function) are presently in common use for a number of drugs including methotrexate, cisplatin, carboplatin, cyclophosphamide, bleomycin, amsacrine, doxorubicin, daunorubicin, vinicristine and vinblastine [5, 6, 28]. There are of course a number of factors other than hepatic and renal function that give rise to variability in pharmacokinetics between patients, notably variability in drug metabolism; 6-MP and amonafide are good examples of this [29, 40]. We do not suggest that body composition is relevant to the pharmacokinetics of all anticancer drugs or that it is more important than these other factors. Our hypothesis is simply that body composition may be relevant to a number of anticancer drugs and that, for some drugs, the effects of body composition are perhaps going unnoticed at present. During the final preparation of this manuscript, Kobayashi and Ratain [28] also commented briefly on the possible role of obesity in the individualisation of cancer chemotherapy and draw conclusions similar to ours.

That six of the seven published reports (Table 3) of empirical evidence linking body fatness with variability in pharmacokinetics demonstrated a "positive" result (i.e. an apparent influence of fatness on pharmacokinetics) might

reflect publication bias in favour of positive results. Alternatively, the observation of, for example, an unusually long elimination half-life of a drug in obese patients may have stimulated those making the observation to undertake the studies reported herein. The absence of such observations for other drugs could mean that body fatness has a relatively limited role or that effects of body composition either have not been noticed or are subtle.

In the six studies reviewed herein (Table 3) that identified an apparent effect of body composition on drug pharmacokinetics, the authors did not make any specific recommendation in relation to the adjustment of drug dosage. In general they indicated a need for additional work. At present any guideline on the adjustment of drug dosage to body fatness would be premature, but it seems likely that further research will lead to such an endpoint for at least some antineoplastic drugs. It should be emphasised, however, that an observed correlation between pharmacokinetic behaviour and body composition in patients with widely different features (e.g. normal versus obese) may not necessarily translate easily into a dosing model for the oncology patient community at large. However, it is possible that a simple dosing equation or rule of thumb could be developed that might be applicable to all patients or to particular groups of patients.

Clearly, unless there were very obvious indications that such studies would be important for the clinical outcome, it would be difficult to justify extensive de novo pharmacokinetic studies on agents that are in routine use and for which the drug disposition patterns are well understood. However, using the convenient "bedside" techniques for body composition assessment described above, it would be possible to incorporate body composition measurement into early clinical trials of new anticancer agents where pharmacokinetic studies would be carried out routinely. Measurement of pharmacokinetic parameters is being used with increasing frequency to relate drug exposure to clinical outcome [28, 54, 55]. Moreover, population pharmacokinetic strategies [53] are being evaluated as a possible means of individualising drug dosage, and body composition could be incorporated as one of a number of variables that can be built into a Bayesian approach.

The potential value of body composition measurement in predicting pharmacokinetics and clinical outcome would ideally be assessed in large prospective trials. In practice, however, this might be difficult to achieve except in the context of prospective studies aimed at dose individualisation on the basis of pharmacokinetic measurements. It seems more likely that an early indication of a possible role of underweight, overweight or obesity would be detected by clinical and pharmacokinetic observation in early phase I and phase II studies, and this might then lead to the development of dose adjustment strategies for subsequent routine use. These would be modified further by subsequent clinical experience. It seems evident that such strategies would have to be both clear and simple to gain acceptance by busy oncologists.

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