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Review

Normalisation of anti-cancer drug dosage using body weight and surface area: is it worthwhile?

A review of theoretical and practical considerations

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Introduction

Variation between individuals in response to chemotherapy is of great clinical significance, and variation in drug exposure is a major contributor to it. Reducing this variability in drug exposure is desirable so as to produce a more consistent therapeutic effect while at the same time minimising normal tissue toxicity. The principal strategy available for achieving this objective is the adjustment of drug dose with respect to body weight or predicted surface area.

However, empirical evidence of the failure of dose normalisation based on body weight or predicted surface area to achieve consistent drug exposure has been presented recently [21]. Moreover, the current methods of normalising drug dose can also be criticised on theoretical grounds. It is our impression that the majority of oncologists and cancer pharmacologists are in fact unfamiliar with the detailed background to dose normalisation. The aim of this review is to consider the empirical evidence for and against as well as the theoretical basis of the practice of normalising drug dose using body weight and predicted surface area. This subject is relevant to phase I studies and to therapeutic usage. The following questions are addressed:

1. What is the theoretical basis of dose normalisation using body weight and surface area?
2. What is the empirical evidence for (and against) dose normalisation using weight and surface area?
3. There are a great many formulae for the prediction of surface area from anthropometric data (height and weight), but only one formula is commonly used in clinical practice. Why is this particular formula in favour and what are its limitations?
4. Is predicted surface area of more value as a means of normalising doses between species (e.g. in the prediction of doses in patients based on optimal doses from animal models) than as a means of producing consistent drug exposure within a species (e.g. between individual patients)?

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Normalisation of drug dosage using predicted surface area: historical background

Scaling between species

Research on energy expenditure in animals and man carried out in the nineteenth and early twentieth centuries focused on the basal metabolic rate (BMR), which is the "minimal" rate of energy expenditure measured under standardised conditions. These data from several species were reviewed by Kleiber [29] in 1932, and he concluded that BMR increased with increasing body size but that the rate of change in BMR was slower than the rate of change in body size. In mammalian species ranging in weight from 0.15 (rat) to 679 kg (cattle), Kleiber [29] showed that the log of BMR plotted against the log of body weight produced a straight line with a slope of 0.75 and that most species aligned along it. This conclusion was supported by other investigators [1, 3], who extended the number of species for which data were available (from mouse to elephant), and the relationship between body weight and BMR in mammals has subsequently become known as the "mouse-elephant curve". Although absolute BMR varies between species, much of this variation is due to variation in body size, and if body size is normalised by expressing BMR per unit weight raised to the 0.75 power, then BMR is relatively constant between species (Table 1). That the appropriate exponent of body weight was 0.75, i.e. less than 1.0, is simply a reflection of the observation that BMR per unit body weight is lower in large animals than in small ones (Table 1).

A great many attempts have been made to review the data on mammalian BMR since 1932, and these have largely confirmed Kleiber's observations. It has also become clear that other physiological variables scale, on an inter-species basis, with a body weight exponent of less

Table 1. Minimal (basal) metabolic rates in different mammalian taxa

Animal	Body mass (kg)	Minimal metabolic rate		
		Absolute (KJ day^{-1})	Per unit mass (KJ $kg\ day^{-1}$)	Per unit mass (KJ $kg^{0.75}\ day^{-1}$)
Laboratory mouse	0.025	17	687	286
Laboratory rat	0.29	105	362	269
Dog	11.7	1,622	139	257
Man	70	7,006	99	289
Elephant	3,833	112,383	29	232

Various sources: Kleiber [29], Brody et al. [3], Benedict [1], Poczopko [37], Schmidt-Nielsen [44]

than 1.0 and close to 0.75. Water turnover rate, for example, appears to scale with a weight exponent of approximately 0.80 [4, 39]. Similar conclusions have been drawn with respect to cardiac output and glomerular filtration rate [39].

One of the difficulties of using an inter-species scaling factor is that it is based on empirical observations: an adequate explanation of the mechanism responsible for the scaling of physiological processes does not exist. One explanation that has gained some currency is the "surface law", which argues that many physiological variables scale to body surface area. This was first suggested in 1839 [42], was raised to the status of a law by Rubner [41] in 1883, and is still widely believed. The rationale was that since heat loss is proportional to surface area, BMR would scale to surface area so as to maintain a constant body temperature. The balance of empirical evidence does not in fact support the "surface law". An inter-species scaling factor of 0.66 rather than 0.75 would be expected if the surface law were valid, since bodies with geometrically similar shape have surface areas that are proportional to the two-thirds power of body weight (i.e. $weight^{0.66}$). Since a mass of empirical evidence suggests that the appropriate scaling factor is significantly different from 0.66 and is actually 0.75 [44], the surface law must be rejected. Nevertheless, belief in the surface law provides the theoretical underpinning of the current practice of drug dose normalisation using body surface area.

Scaling within species

A few studies have focused on the scaling of physiological variables *within* rather than *between* species. These have produced evidence for a variety of scaling factors [26, 37, 48], all of which are less than 1.0 but some of which are closer to 0.66 than to 0.75. This issue is a complex one since the scaling factor may change within a species as development proceeds and body size changes [37, 48]. In human energy expenditure there is empirical evidence that the appropriate scaling factor is <0.60 within infancy, within childhood and during adulthood [9, 30].

In summary, a great deal of evidence supports the use of a scaling factor of <1.0 to normalise (adjust for body size) BMR, water turnover rate and, more recently, drug dosage. The appropriate scaling factor for adjustment *between* species is 0.75. The scaling factor for normalisation *within* a species is less clear but is certainly <1.0. A corollary of this is that differences in the optimal dose of anti-neoplastic drugs (either between or within species) should appear to be more constant when expressed on the basis of weight raised to the power of <1.0 rather than according to body weight (i.e. $weight^{1.0}$). There is in fact some evidence that this is the case [36], although the question as to what is actually achieved by normalising dose in this way remains open.

Normalising drug dose: use of body weight and surface area

Before reviewing how normalisation is carried out, we find it appropriate to consider what this can be expected to achieve. The most obvious consequence of normalising by surface area rather than by weight is that large individuals receive reduced doses relative to smaller individuals when dose is expressed per unit body weight (i.e. grams per kilogram). This general approach is consistent with the evidence reviewed above that the rates of many physiological processes are slower in large animals than in smaller ones. In comparative pharmacology the general principle that larger species require or tolerate smaller doses relative to body weight than do smaller species is well established [28].

The aim of normalising dose using surface area is therefore to reduce the relative dose as body size increases. If correct, this should avoid over-dosage while maintaining therapeutic activity. At this point it is necessary to recognise how this is effected, and this is best achieved using an example. One point that is not often realised is that normalisation of dose by surface area can have a very minor effect. To illustrate this, some examples are given in which the difference in dose given in grams per kilogram body weight is compared using two different approaches: dosing on a body weight basis versus dosing on the basis of predicted surface area. Consider a reference 5-year-old boy at any one of three combinations of weight for height (Table 2; data from the National Center for Health Statistics [18, 47]) dosed using surface area and body weight. If the dose used were 1 g/kg body weight, then all three boys would receive the *same* dose on a per-kilogram basis. If the dose were given at 1 g/m^2 surface area, then the actual dose per kilogram body weight would range from 0.042 to 0.039 g/kg, a range of only 7.6% (Table 2). This difference when the dose given is expressed per unit body weight is rather minor: the smallest (lightest) boy (code a, Table 2) receives a dose (grams per kilogram) that is only 7.6% higher than that received by the heaviest boy (code c, Table 2) if surface area is used. The question then arises, is this 7.6% difference in dose (0.042 vs 0.039 g/kg) significant or would dosing on a grams-per-kilogram body weight basis (with a variation of zero in the dose expressed as grams per kilogram) have achieved a similar result?

Normalisation of dose to surface area begins to have a substantial effect only when differences in body size are much greater. For example, a boy 140 cm tall on the 50th centile for weight (code d, Table 2) has a predicted surface

Table 2. Body size and surface area and dose of anti-neoplastic agent

Individual	Code	Height[a] (cm)	Weight[a] (kg)	Predicted surface area (m^2)	Dose given[b]	
					Using surface area (g/m^2)	Equivalent dose (g/kg)
5-year-old boy	a	108	17.0 (5th centile)	0.72	0.72	0.042
	b	108	18.0 (50th centile)	0.73	0.73	0.041
	c	108	19.7 (95th centile)	0.77	0.77	0.039
Older boy	d	140	35.5 (50th centile)	1.18	1.18	0.033
Adult woman	e	152	47 (5th centile)	1.44	1.44	0.031
	f	152	60 (50th centile)	1.56	1.56	0.026
	g	175	91 (95th centile)	2.05	2.05	0.023

[a] Height and weight reference values taken from North American data [18, 47]
[b] Dose given at 1 g/m^2 predicted surface area

area of 1.18 m^2 from the Dubois formula. If the drug were given at 1 g/m^2 surface area, the dose in grams per kilogram would be equivalent to 0.033 g (Table 2). This is equivalent to a dose (grams per kilogram) 21% lower than that received by the younger boy (code b) in Table 2. The significance of a difference of this magnitude is unclear. However, it should be evident that if both boys were dosed at 1 g/kg body weight the difference in dose expressed in grams-per-kilogram terms would be zero, such that the effect of using surface area rather than body weight is to reduce the dose (in grams per kilogram) by 21% in the older boy.

Table 2 (codes e–g) also shows the effect (on dose per unit body weight) of normalising per unit surface area in three examples from adulthood. Normalising dose using surface area reduces the dose per unit body mass in the larger individuals, but the highest dose is only 35% greater than the lowest dose when these are expressed on a grams-per-kilogram basis. The significance of this difference is not obvious.

The greatest differences in body size are of course observed between children and adults, for example subjects a and g in Table 2. The dose per unit body mass given to subject a is almost twice that given to subject g. A difference in dose of this magnitdue clearly has the possibility of having greater clinical significance.

In summary, normalisation of drug dose in childhood can achieve little over the range of body size at any particular age but does have some effect where differences in body size are greater. This does not necessarily mean that normalisation using surface area *does* achieve the desired consistency of therapeutic effect and toxicity across a wide range of body size, only that it *may* do so. Empirical evidence on the success and failure of dose normalisation is necessary, and this is discussed below.

Prediction of surface area: the empirical basis

It is now standard practice in clinical medicine to use the Dubois height-weight formula [12] to predict surface area: Predicted Surface Area (m^2) = Weight $(kg)^{0.425}$ × Height $(cm)^{0.725}$ × 0.007184.

This particular formula, or means of predicting surface area derived from it (such as nomograms), has virtually monopolised the field since the 1950s. The Dubois equation is by no means the only equation for the prediction of surface area; countless others have been generated by different investigators sampling from different populations (for a review see Dubois [11]). The literature on the prediction of surface area is so extensive that it is difficult to cover. However, we shall attempt a brief review of this subject because the validity of the Dubois formula has been challenged [33], and we believe that the acceptance of it in clinical medicine owes more to custom and practice than to a clear demonstration of its benefits relative to other formulae.

The starting point must be the recognition that surface area is a difficult concept to define and is a variable that is extremely difficult to measure reproducibly. Skin surface area, for example, is not true surface area since the skin has many folds when seen on a small scale. Several different methods of measuring surface area have been used, and the general approach has been to derive formulae that predict surface area from measurements of height, weight and other factors (age, sex, race), sometimes in very small samples of subjects; the classic Dubois formula is actually based on a sample size of only nine individuals. An experimental approach to the direct measurement of surface area common to many studies, albeit one that has differed in detail between studies, involves an attempt to cover the body surface completely with a material (paper, cloth, masking tape and even lead plate have been used) and then to determine the surface area of the covering material by, variously, planimetry, geometric methods or gravimetric techniques.

In general, predictive equations derived from different methods of measuring surface area are significantly different from each other [11], and there is some evidence of real differences in prediction formulae derived from different population groups (e.g. adults versus children) and disparate racial groups (summarised in [11]). Many different formulae for the prediction of surface area exist, but the Dubois formula has prevailed and usage of the other formulae has not survived. The reasons for the adoption of the Dubois formula rather than the alternatives that were available are not readily identifiable. In favour of the

Dubois formula is the observation that the nine subjects used to derive it were of diverse body shape: the sample included a 36-year-old cretin with the "physical development of a boy of 8"; a 12-year-old boy; a tall, thin adult man; and a short, fat adult woman. Secondly, the formula adheres to the principle of geometrical similarity – that shape remains constant as body size changes. The importance of adherence to similarity is that the formula should be applicable to individuals of widely differing size so long as the human form is geometrically similar across a wide range of body size. The Dubois formula was extrapolated, without the inclusion of additional subjects, such that it could be applied to children by Hannon [23].

There is empirical evidence that the Dubois formula predicts surface area with a systematic negative bias [33]. Mitchell and co-workers [33] made direct measurements of surface area in 237 subjects using a photometric technique that involved measuring the (photographically determined) skin surface area available for absorbing light while subjects were in a spread-eagle posture. Comparison of this "measured" surface area with predicted surface area from the Dubois formula showed that the two methods were highly correlated, but the predicted area was systematically lower than the measured area. Furthermore, the under-estimate was greater in smaller individuals, and the authors [33] suggested that the Dubois formula may be invalid when the predicted surface area is less than 1.3 m^2 (i.e. in children). Extrapolation of a predicted surface area below approximately 1.3 m^2 is therefore on shaky ground empirically. Given the assumption that individuals of different size (adult and children) are geometrically similar, then the extrapolation first suggested by Hannon [23] but now in routine clinical practice would be valid. However, this assumption must be in some doubt since shape is not likely to be independent of size [32].

There is also empirical evidence that supports the use of the Dubois formula [32]. Martin et al. [32] determined the surface area of 20 elderly adult cadavers by planimetry on paper tracings of dissected skins and compared the "measured" surface area with that predicted from the Dubois formula. They concluded that the predicted surface area did not differ significantly from the "true" surface area and recommended continued use of the Dubois formula. Since children were not included in this study, it remains likely that predicting surface area from the Dubois formula in children requires particular caution. Two nomograms for the prediction of surface area in childhood have been published in standard paediatrics texts [2, 15]. The "Hill/Boyd nomogram" published in *Nelson's Textbook of Paediatrics* [2] predicts surface areas identical to those obtained by application of the Dubois formula. The nomogram derived by Haycock et al. (cited in [15]) was based on an empirical study of surface area prediction in which infants and children were included. It predicts surface area *differently* from the Dubois formula, particularly in infants and children. Haycock et al. [15] concluded that at surface areas below 0.7 m^2 the Dubois formula under-estimates "true" surface area and suggested that their new nomogram should be used in infants and children. As indicated above, we believe that in current clinical practice in paediatric oncology the Dubois formula predominates.

One further point that is relevant to the application of the Dubois formula is the use of nomograms or calculating devices for the prediction of surface area. We draw attention to the observation of Turcotte [46] that nomograms printed in several standard texts were reproduced incorrectly from the original, leading to systematic under-estimation of surface area. We support the view that nomograms and calculating devices currently in use should be checked against the formula of Dubois and Dubois. In the course of preparing this review, we tested five nomograms from a variety of secondary sources and five "ready-reckoner" devices for calculation of surface area, all of which were in current clinical use in various trial protocols. Although the original source for the estimation of surface area was given on only one of the ten devices, all were based on the Dubois formula and predicted the same surface area over the wide range of combinations of height and weight tested.

Normalisation of drug dose to surface area or body weight: empirical evidence for and against

The use of predicted surface area rather than body weight as a means of normalising drug dose had been established in oncology by the early 1960s. In addition to the theoretical requirement that drug dose should be reduced relative to body weight as body weight increases and the (erroneous) belief in the surface law discussed above, empirical evidence of the usefulness of predicted surface area was available by that time. Dawson [10] considered the relationship between dosage of a wide range of non-anti-neoplastic drugs and body weight in 1940. At that time, normalisation of drug dosage was carried out almost exclusively by adjusting dose to body weight rather than surface area. He reviewed evidence suggesting that smaller species are generally more tolerant of drug treatment than larger species when doses are calculated on a unit body weight basis and considered that the general principle that children require or tolerate larger doses than adults (when expressed per unit body weight) was well established. He concluded that adjustment of drug dose using a body weight exponent of <1.0 was justified on the basis of this evidence, but only as a general rule – adding the caveat that "In short, after all this discussion, the only principle of drug dosage which survives is that the dose must be adjusted to the individual patient".

Crawford et al. [8] in the (1950) report of an investigation that proved to be influential, proposed that surface area might be a more satisfactory index of drug requirements than body weight or age, particularly during infancy and childhood, when variation in body size is great. Crawford et al. [8] investigated the "recommended doses" of sulfadiazine and acetylsalicylic acid in infants, young children, adolescents and adults. They demonstrated evidence of consistent plasma concentration of the drugs within and between all four groups of patients when doses were prescribed on the basis of predicted surface area. They also reported the results of a clinical trial at the Massachusetts General Hospital, lasting 1 year, which involved prescrip-

tion of drug dose per unit surface area and appeared to suggest clinical advantages for the new regimen.

In 1958, Pinkel [36] reviewed the use of surface area as a means of normalising drug dosage in cancer chemotherapy. He collated data for various species on the "appropriate therapeutic dose" (MTD or maximum tolerated dose) of several antineoplastic agents – 6-mercaptopurine, mechlorethamine, methotrexate, actinomycin-D and tri-ethylene-thiophosphoramide – and demonstrated that MTDs were relatively similar across a wide range of variation in body size (mouse-adult-human) when expressed on a surface area basis but were very different when expressed on the basis of unit body weight. The rationale for the developing practice of using predicted surface area was therefore based on empirical evidence, although Pinkel offered a hypothetical basis for the observation that MTD tends to decline as body weight increases, which was that renal function, cardiac output, energy expenditure and "most physiological processes" scale with a mass exponent of <1.0 and approximately 0.67 (see above).

More recently, Grochow et al. [21] examined clinical and pharmacokinetic data from 306 adults receiving 9 antineoplastic drugs – brequinar, busulfan, dichloromethotrexate, hexamethylene-bisacetamide, menogaril, *N*-methylformamide, piroxantrone, taxol and trimetrexate – and attempted to relate variability in pharmacokinetic parameters (plasma clearance rate, volume of distribution, area under the curve) to variability in body weight, height and predicted surface area. In total, 96 correlation coefficients were calculated, but in only 5 of these did any of the measures of body size explain greater than 50% of the variability in pharmacokinetics. The authors concluded that normalisation of drug dose in adults to weight, height or surface area is of limited value and that surface area was no more useful than height or weight alone. However, they did suggest that for drugs in which exposure depends on renal clearance or cardiac output (both of which scale predictably with an exponent of <1.0), size or surface area may be more useful. Ratain et al. [38] have shown that the dosing of etoposide on the basis of body surface area predicts poorly for plasma concentration and area under the curve (AUC) and suggested a standard dose of 260 mg independent of patient size. Zuccaro et al. [50] demonstrated that the use of surface area for dosing of 6-mercaptopurine (6-MP) in childhood leukaemia did not achieve adequate consistency of therapeutic effect or toxicity, although variability in drug absorption and/or individual differences in drug metabolism may have contributed to this.

Other factors that give rise to variability in pharmacokinetics

These studies suggest that, in many cases at least, normalisation does not substantially reduce variability in drug exposure – implying that most of the variability that exists is the result of factors other than body size. Grochow et al. [21] suggest that at least part of the explanation might involve variation between patients in body composition (fatness).

Renal and hepatic function are of course important parameters that are often taken into account in clinical practice in oncology. Renal or hepatic dysfunction can lead to delayed drug elimination and increased toxicity. A standard text indicates that patients with renal impairment receive reduced doses of methotrexate, cisplatin, carboplatin, cyclophosphamide, bleomycin, streptozotocin, etoposide, hydroxyurea and deoxycoformycin, while patients with hepatic dysfunction are given decreased doses of amsacrine, doxorubicin, daunorubicin, vincristine and vinblastine [6]. Carboplatin is cleared almost completely by glomerular filtration, and pharmacokinetic studies with this agent have led to the construction of simple dosage formulae that allow the clinician to select a desired level of thrombocytopenia [13] or plasma carboplatin AUC [5] based on the measurement of glomerular filtration rate alone.

One further parameter that is an important determinant of individual differences in drug pharmacokinetics in oncology is of course inter-individual differences in drug metabolism. This is a large and rapidly expanding area and detailed discussion of it is beyond the scope of this review. A brief consideration of one example is justified so as to reinforce the point that body size/surface area is by no means the only parameter that gives rise to variability in drug pharmacokinetics. A good deal of evidence is now available of marked inter-individual variation in the pharmacokinetics of 6-MP, which is the mainstay of "maintenance" chemotherapy in childhood acute lymphoblastic leukaemia. Variability in the clinical effect of 6-MP is not only of academic interest but is critical to differential outcome [22, 24, 25, 31]. The origin of this marked variability is not fully understood, but inherited variation in thiopurine methyltransferase (TPMT) activity is likely to be responsible [31]. A genetic predisposition to high or low TPMT activity would appear to give rise to differences in 6-MP pharmacokinetics between patients [31]. Clearly, then, although surface area can be useful in dose adjustment, there will be many drugs for whose dosage it will not be helpful. Each case must be assessed on its own merits.

Normalisation of drug dosage between species

Extrapolation of drug dosage in animal models to the clinical setting is the starting point in phase I trials. This process can be seen as an inter-species scaling of drug dose. Freireich et al. [16] presented evidence in 1966 that in several species (mouse, hamster, rat, rhesus monkey, dog, man) the MTDs of a number of anti-neoplastic agents were relatively similar when expressed per unit surface area. This therefore provided a practical application for inter-species scaling: it was suggested that the starting dose in phase I trials could be predicted from the MTD in animal models using the same dose per unit surface area. The incorporation of a "safety factor" of one-third the MTD per unit surface area in the appropriate animal model was recommended.

Homan [27] confirmed and extended the data on comparative pharmacology of anti-neoplastic agents collected by Freireich et al. [16] and Schein et al. [43] for a total of

37 anti-neoplastic drugs. There is therefore a good deal of empirical evidence in favour of the practice of extrapolating doses between species using inter-species scaling. On a theoretical basis the approach is justifiable due to the strong evidence of a scaling factor of approximately 0.75 between species for various physiological parameters (see above) and, indeed, a reanalysis by Travis and White [45] of data collected by Freireich et al. [16] and Schein et al. [43] concluded that body weight raised to the three-quarters power was the most appropriate scaling factor. It should be noted, however, that this is (statistically) significantly different [34, 45] from an approach based on body weight raised to the two-thirds power (the "surface law") as suggested by Freireich et al. [16].

One further caveat is necessary: this approach to the inter-species normalisation of drug dose is somewhat crude since it takes relatively little account of particular between-species differences in pharmacokinetics or pharmacodynamics that are not simply related to surface area. A recent example is the marked disparity in the metabolism of iododoxorubicin to 4′-iodo-4′-deoxy-13-dihydrodoxorubicin due to the absence of an aldo-keto reductase in mice that is very active in man [17]. The reservation concerning between-species differences in pharmacokinetics and pharmacodynamics was made by Mordenti [34], who carried out another re-evaluation of the influential Freireich et al. [16] data. Determining doses for one species based on data from another is facilitated by the principles of inter-species scaling. Although this is useful, the result can be seen only as an approximation. More refined schemes for transferring doses between species incorporate consideration of the detailed pharmacokinetic and pharmacodynamic differences between species [7, 14, 20, 35, 40]. This issue is of great practical significance as it represents a means to estimate suitable starting doses for phase I trials and to permit efficient but safe dose escalation as recommended by Collins and others [7, 14, 19, 20, 35, 40].

In his excellent review of the prediction of the human toxicity of anti-cancer agents from animal data, Grieshaber [20] emphasised the value of a "compound directed" approach. According to this concept there should be no hard and fast rules underlying inter-species comparisons. Factors such as the intended clinical route and schedule, mechanism of action and species differences in pharmacokinetics are paramount. Although this approach has been used successfully to initiate clinical studies at a starting dose higher than that which would normally apply, the majority of agents nevertheless enter phase I trials at one-tenth or one-thirtieth of the dose lethal to 10% of the study population (LD_{10}) or at one-third of the TLD (toxic dose low) using the inter-species scaling factors for surface area [17, 20].

Overall conclusions

Normalisation of dose between species

A great many physiological variables scale predictably between species with a weight exponent of 0.75. There is also some evidence that optimal or maximum tolerated drug doses tend to scale in the same way between species. This provides a useful guide for the extrapolation of drug dosage in animal models to starting doses in phase I clinical trials in oncology. The approach does have its limitations but has generally proved to be safe.

Normalisation of dose between patients

On a theoretical basis, normalising drug dosage to surface area can be expected to achieve relatively little within groups of individuals of broadly similar size. When body size does vary greatly. i.e. in infancy and childhood and particularly *between* childhood and adulthood, normalisation reduces the relative dose as body size increases. This achieves a significant normalisation of dosage relative to body size but may not necessarily lead to consistent therapeutic effect and toxicity. Normalisation of dose using surface area could therefore be of limited value in this respect but is unlikely to have adverse effects. We do not suggest that the practice of normalising dose using surface area be abandoned or that routine use of fixed doses is indicated; rather, we simply advise a more realistic attitude to the limitations of dose normalisation using body size or surface area.

What next?

In routine clinical use, surface area is usually predicted from a single equation derived from nine subjects in the early part of this century. There are doubts as to the validity of this particular formula, and its theoretical basis (the "surface law") is flawed. Adoption of this formula by the clinical community perhaps owes more to custom and practice than to rational consideration of the problem. In view of this observation and of the recent evidence of the failure of dose normalisation (by body weight or surface area) to produce consistent exposure to a number of anti-cancer drugs [21, 38, 50], we should perhaps be prepared to view the whole question of normalisation of drug dosage more critically. Both the specifics of the Dubois formula and its derivation as well as the general concept of normalising dosage using surface area are limited.

Drug pharmacokinetics appear largely unexplained by variability in body size/surface area. There is therefore an argument in favour of modifying the design of dose-response studies in oncology such that collection of information on the factors that *do* give rise to such variability is a high priority. When complete, such studies would provide the data necessary for the design of doses "tailored" to individual patients.

We conclude that it is now appropriate to reconsider what dose normalisation is actually achieving in practice and to concentrate greater effort on the factors (other than simply body size and surface area) that make a more significant contribution to variability in pharmacokinetics and pharmacodynamics, since these are likely to have greater influence on the variation in clinical effect. These factors include genetically determined inter-individual variation in drug metabolism [31], physiological variation between

patients (in renal or hepatic function, for example), variability between patients in drug absorption and, possibly, variability between patients in body composition [21]. The conclusion of Dawson [10] in 1940 that "the only principle of drug dosage which survives is that the dose must be adjusted to the individual patient" is as relevant today as it was in 1940.

Of course it is common practice among clinical oncologists to give a fixed dose (usually based on surface area) and to modify this according to the toxicity observed [49]. While this pragmatic approach has utility, it should be emphasised that although increased doses are frequently reduced when unacceptable toxicity (usually haematological) is seen, doses will not commonly be adjusted upwards in the absence of such toxicity. Thus, whereas over-treatment may be avoided, under-treatment will generally remain uncorrected.

Any contribution that detailed pharmacological investigations can make to what is largely a pragmatic business could lead to significant improvement in dose individualisation. However, such strategies must stand the tests of practical robustness and genuine clinical value. We hope that the issues raised in this review will contribute to the origin of strategies that improve dosing in cancer chemotherapy.

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