

Use of Body Surface Area to Calculate Chemotherapeutic Drug Dose in Dogs: II. Limitations Imposed by Pharmacokinetic Factors

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Anticancer drug dosages that specify the maximum dose and minimum dosing interval that are tolerated in a population of dogs are commonly recommended. Because the differences between the effective and toxic doses of most cancer chemotherapeutics is slight, it is important to achieve therapeutic concentrations in tumor tissues at the same time that concentrations in nontarget tissues are minimized. In order to determine the dosage regimen that will most likely accomplish these goals, similar drug concentrations must be achieved in all patients dosed according to a specific regimen. Dosing based on body surface area (BSA) is generally used in an effort to normalize drug concentrations. This is because it is well recognized that measures of many physiologic parameters that are responsible for drug disposition, including renal function and energy expenditure, can be normalized by use of BSA. However, there is substantial evidence that drug disposition is not always proportional to BSA. Differences in distribution, metabolism, and excretion pathways may preclude dose extrapolation among species or among individuals within a species based on BSA. Moreover, genetic differences in drug metabolism are well recognized in humans and in laboratory animals, and it is likely that similar differences exist among breeds of dogs. A review of the pharmacokinetic disposition of several cancer chemotherapeutics suggests that studies are needed to determine the most effective method to achieve equivalent anticancer drug concentrations in diverse veterinary patients.

Key words: Allometry; Cancer chemotherapeutics; Dosage regimen; Dose normalization; Drug excretion; Metabolism.

Plasma drug concentration data and the minimum concentration capable of inhibiting bacterial growth in vitro have been used for several decades to design dosage regimens that achieve optimum concentrations of antimicrobial chemotherapeutic drugs.^{1,2} Although in vitro assays designed to determine minimum effective antitumor drug concentrations can be used to accurately predict drug resistance, in vitro assays often do not correlate with in vivo sensitivity.^{3,4} Therefore, in contrast to antimicrobial drug regimens, most anticancer drug dosages are administered at the maximum tolerated dose and interval. Ideally, the method used to determine drug dosage should yield therapeutic concentrations in target organs and tissues, and minimize drug concentrations in tissues susceptible to toxicosis. This is vitally important when cancer chemotherapy is administered because the difference between effective and toxic doses of most anticancer drugs is slight. When clinical efficacy and toxicosis trials are conducted, it is also important that the dosage regimen minimizes differences in drug exposure in the study population. The method generally used to achieve these goals is the body surface area (BSA)-based dosage regimen. However, results from recent clinical trials in dogs suggest that this regimen may overdose small dogs.⁵

In several studies in humans, drug toxicosis was shown to be correlated to specific pharmacokinetic parameters.⁶⁻¹¹ Ratain and Vogelzang⁶ showed that human patients with vinblastine toxicity had significantly higher steady-state

blood concentrations of the drug. Similarly, the maximum steady-state doxorubicin concentration achieved with continuous infusions in human patients was significantly correlated with the nadir of leukopenia.⁷ Hematologic toxicities of carboplatin, doxorubicin, and 5-fluorouracil (5-FU) are clearly related to the area under the plasma drug concentration versus time curve (AUC).⁸⁻¹⁰ An increase in plasma clearance and a decrease in half-life are correlated to decreased 5-FU hematologic toxicity¹¹ and decreased vincristine neurotoxicity.⁶ Although in vitro studies have clearly indicated that tumor cell survival is dependent on the anticancer drug concentration in the culture medium and exposure time to the drug,¹²⁻¹⁵ it has been more difficult to determine the relationship between efficacy and pharmacokinetic parameters of anticancer drugs in patients due to multiple and diverse dosage regimens that achieve widely variable drug concentrations. A few studies have demonstrated that response is related to pharmacokinetic parameters. For example, short-term clinical response of human breast cancer patients was shown to be correlated to the peak plasma concentration of doxorubicin,¹⁶ whereas long-term response may be dependent on the AUC in plasma or target cells.^{17,18} Similarly, the efficacy of etoposide in small cell lung cancer in humans appears to be related to the maintenance of prolonged low blood concentrations of drug.¹² Although few pharmacodynamic or pharmacokinetic anticancer drug studies have been conducted in dogs, results of studies in humans suggest that a relationship between drug concentration and toxicity or efficacy is likely in animals. Therefore, it should be possible to determine a dose that is uniformly safe and effective on the basis of the pharmacokinetic profile of a drug.

Drug concentrations are dependent upon several interrelated processes that include absorption from the site of administration, distribution and storage in tissues, enzymatic and nonenzymatic metabolism, and excretion. In order for BSA-based dosing to be valid, these processes must be correlated to BSA. In the following sections, the pharmacokinetic processes for several anticancer drugs commonly used in dogs are described. Some of these processes

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are clearly not size-dependent. The available pharmacokinetic data are often limited to species other than dogs; however, this information provides insight regarding the likelihood that the pharmacokinetic disposition of the drug is proportional to metabolic rate or BSA. It should be noted that BSA-based dosing became established because certain studies indicated that drug elimination was proportional to metabolic rate for different species. These early studies did not compare metabolic rates among breeds within a species. Moreover, the effects of age and disease may render pharmacokinetic processes size-independent. Because variable drug exposure may cause toxicity in dogs, a critical evaluation of current anticancer drug dosing schemes is needed. It is likely that BSA-based dosage regimens are appropriate for some anticancer drugs; however, evidence presented in Part I¹⁹ of this review illustrates that the formula used to estimate BSA may be inaccurate. For those drugs having pharmacokinetic processes that are not proportional to BSA, use of any BSA formula is likely to result in toxicity.

Pharmacokinetic Processes and the Effect of Body Size

Absorption

Almost all drugs are absorbed by passive diffusion; therefore, drug absorption is a function of the physicochemical properties of the drug rather than physiologic processes. To our knowledge, the surface area for diffusional absorption has not been shown to change in proportion to metabolic rate or BSA. The extent of drug absorption in dogs of different body size should be similar regardless of whether the drug is administered on the basis of body weight or BSA. However, drug bioavailability may be affected by the presence of neoplastic or inflammatory cell infiltrates in the bowel or liver. The effect of disease on the bioavailability of chemotherapeutic drugs has not been reported in dogs; however, malabsorption syndromes in people with intestinal lymphoma or after treatment with anticancer drugs or radiation have been described in several experimental and case reports.^{20–23} It is likely that these factors also influence absorption of orally administered drugs such as cyclophosphamide and methotrexate.

Distribution

Although chemotherapeutic drug toxicity may be demonstrated to correlate with drug concentrations in plasma, toxicity is ultimately a result of concentrations in tissues. Drugs may distribute to any 1 or several tissues and body fluids. Drug distribution is a complex function of tissue perfusion, cell membrane permeability, and drug affinity for plasma and tissue proteins. Most drugs enter cells by diffusion; however, some chemotherapeutic drugs, including melphalan, are transported by specific carrier proteins.^{24,25} Carrier-mediated transport is generally saturable and dose-dependent. Little is known about differences among numbers or affinities of transport proteins in different species or breeds.

Protein-bound drug in blood is generally pharmacologically inactive because protein-bound drugs do not diffuse across membranes. Therefore, the drug concentration in the

blood, number of protein binding sites, affinity of the binding sites for specific drugs, and competition for these sites between concurrently administered drugs and endogenous molecules determines the amount of drug that is free to enter tumors and exert a pharmacologic effect. The degree of plasma protein binding varies significantly among drugs. 5-FU does not bind to plasma or tissue proteins in humans,²⁶ whereas melphalan is 90% bound to albumin; with one-third bound irreversibly by alkylation.²⁷ With multiple dosing of melphalan, plasma drug concentrations increase, presumably until binding sites are saturated. Although the degree of protein binding in dogs is not known, one may expect 5-FU tissue concentrations to be linearly correlated to dose or plasma concentrations. Conversely, melphalan tissue concentrations are unlikely to be correlated to dose unless plasma protein binding sites are saturated. Most bound drugs are associated with albumin, the most abundant protein in plasma. However, drug binding affinity is often greater for globulins and lipoproteins. For example, on a mole per gram basis, vincristine and vinblastine adsorb 10-times more extensively to α and β globulins than to albumin *in vitro*.²⁸ Some drugs, including mitoxantrone and the vinca alkaloids, bind persistently to blood cells as well as to plasma proteins.^{28–31} Although there is considerable homology among plasma proteins of different species, a difference in binding affinity *in vitro* has been described for a number of drugs, including cisplatin (CDDP).³² To our knowledge, differences in binding affinities among different breeds within a species have not been examined. No evidence exists that binding affinities or the proportion of drug bound are correlated to metabolic rate or BSA. For example, vincristine has been shown to be approximately 70% and 60% bound to proteins, leukocytes, and platelets in human patients and dogs, respectively.²⁸ Similarly, approximately the same percentage of mitoxantrone (80%) is bound nonspecifically to plasma proteins and blood cells in both humans and dogs.^{29,30} Therefore, one should expect the extent of distribution of these drugs to be similar in these species and not to scale with BSA. Moreover, if differences in the binding affinities or proportions of drug that are bound to plasma proteins or blood cells exist among breeds of dogs, this could result in size-independent differences in drug distribution.

Hydrophilic drugs that are minimally protein-bound can be assumed to distribute to fluid compartments. Patients with tumor-induced effusive disease can, therefore, be expected to have altered distribution of hydrophilic drugs compared to those patients with no evidence of pleural or peritoneal effusion. Dose normalization of highly plasma protein-bound drugs such as CDDP may also vary with disease states that alter plasma protein concentrations. In dogs that are hypoproteinemic as a result of tumor-induced glomerulonephritis or protein-losing enteropathy, or hypoalbuminemic secondary to tumor-induced cachexia, blood loss, or effusion, a larger proportion of the drug may be pharmacologically active or cleared from the body. These pathologic states should be of greatest concern to clinicians who are using drugs that demonstrate extensive protein binding. For example, a change in binding from 90% to 80% will double the amount of pharmacologically active drug, whereas a drug that is 60% bound would have

to have its binding reduced to 20% to do the same. Moreover, because most drugs bind to proteins by reversible equilibrium reactions, administration rates may influence distribution volumes of some drugs by changing the proportion of drug that is bound to proteins. For drugs that enter cells by diffusion, higher initial plasma concentrations associated with bolus administration may favor distribution, whereas slow infusions may favor distribution of drugs that cross cell membranes slowly.

Drug distribution may also be profoundly altered by the drug vehicles cremophor EL and polysorbate 80. These solvents cause degranulation of mast cells in the dog, resulting in hypotension, decreased cardiac output, and cutaneous reactions.^{31–36} Although other species also demonstrate this reaction, the response in dogs is considered more severe.

Excretion

The concentration of a drug in blood over time (AUC) is a function of the total clearance by all eliminating organs. Dose normalization is based on the assumption that equivalent concentrations and AUCs in plasma and tissues will result in equivalent efficacy and toxicity. Therefore, BSA-based dosing assumes that clearance of a drug is proportional to BSA. Excretion of anticancer drugs occurs primarily by glomerular filtration and biliary secretion, and factors that influence these excretion pathways will indirectly influence the relationship between clearance and BSA.

Excretion of many water-soluble drugs and metabolites occurs via glomerular filtration. Similar allometric equations have been generated for glomerular filtration rate (GFR) and metabolic rate using data from species that differ widely in body mass^{37,38}; therefore, GFR should be correlated to BSA. Smaller mammals should require proportionately greater doses of drugs that are excreted by this route compared to larger mammals because smaller mammals have proportionately greater GFRs. Although this has been confirmed to be true for several drugs across a wide range of body masses among species (rat, dog, horse),³⁹ this relationship has not been shown within a given species.

The rate of filtration of a drug depends on the fraction of the drug in plasma that is not protein-bound, because the glomerular membrane is almost impermeable to plasma proteins. For example, platinum compounds differ in aqueous stability and protein binding, and therefore, differ predictably in elimination rate. The labile chloride ligands of CDDP are readily replaced by water molecules, resulting in a positively charged aquated species that binds to plasma and tissue proteins, as well as to DNA.⁴⁰ In contrast, protein binding of carboplatin is limited because the bulky cyclobutane dicarboxylic acid moiety must be first removed.⁴¹ As a result of extensive protein binding, the elimination half-life of CDDP is approximately 70 hours compared to a 2-hour half-life for carboplatin in humans.⁴² Because unbound platinum clearance has been shown to be correlated to creatinine clearance,⁴³ one would expect BSA to be an appropriate basis for dosing these drugs. However, the half-life of CDDP in dogs (120 hours) is not shorter than that in humans.⁴⁴ This suggests that the rate-limiting factors for clearance of CDDP may be species-dependent differences

in protein binding affinity. Whether unbound platinum clearance is proportional to BSA for members of a single species is not known. A preliminary pharmacokinetic study of CDDP in dogs indicated that clearance was more closely correlated to body weight than to BSA (Frazier, unpublished data). Other anticancer drugs, including vincristine and doxorubicin, are excreted to some extent by glomerular filtration as parent drugs and metabolites; however, it is likely that metabolism is the rate-limiting step for clearance of these drugs.^{45,46}

Anticancer drugs are also secreted via organic acid and base pathways in both the kidney and liver. Renal proximal tubule secretion occurs by active basolateral transport against an electrochemical gradient or by passive movement across the basolateral membrane at electrochemical equilibrium. Although limited diffusion occurs, drug elimination in bile is primarily via active secretion. BSA-based dosing assumes that the rate of transport by these active and passive processes is correlated to metabolic rate. The rate of drug secretion depends on the rate of delivery of the drug to the site of transport (tissue perfusion), the affinity of the proteins involved in active transport compared to the affinity of plasma proteins for the drug, the degree of saturation of carrier proteins, and the rate of transfer of the drug across the cell membrane. Therefore, BSA-based dosing implies that each of these factors is correlated to body mass or that the net influence of these factors results in a rate of secretion that is proportional to body mass. Examples of anticancer drugs that are eliminated by secretion pathways include the platinum compounds, which are secreted to a limited extent in bile and by renal tubular cells.⁴⁷ Similarly, 5-FU and its metabolites are eliminated by active renal tubular secretion as well as by glomerular filtration.¹¹ Biliary secretion is the major route of excretion for vincristine in dogs, rats, and humans⁴⁵ and for doxorubicin and its metabolites in rats and dogs.⁴⁶ Mitoxantrone is eliminated primarily in the bile of rabbits, dogs, rats, monkeys, and humans.^{48–51} These studies also indicate that the rate of excretion for a given drug differs among species and there is no evidence that the rate of secretion for any 1 pathway is proportional to body mass. For example, only 24 hours are required for biliary secretion of 50–60% of a total dose of mitoxantrone in dogs compared to more than 120 hours required for biliary elimination of 50% of a dose in rats.^{48–50} To our knowledge, the relationship between rate of secretion and body masses within a given species has not been examined.

Obviously, disease states that alter renal or hepatic perfusion or carrier proteins, altered secretion of bile acids, concurrent exposure to drugs that compete for protein carriers, or altered renal or hepatic perfusion due to cremophor or polysorbate 80 administration may alter elimination rates. For example, excretion rates of several compounds are known to change in parallel with excretion rates of bile acids.⁵² Additionally, it has been suggested that decreased elimination of high doses of vincristine may be a result of damaged hepatocyte microtubules involved in biliary transport.⁵³ If this is true, prolonged or high doses of vincristine may decrease biliary elimination of concurrently administered drugs, such as doxorubicin, as well. The increased toxicity noted when L-asparaginase and vincristine are giv-

en concurrently in people may also be a result of impaired biliary secretion of one or both drugs.⁵⁴

Metabolism

The rate-limiting step for drug excretion is often metabolism. Extensively metabolized drugs are often metabolized by several different pathways in an individual, a species, or a class of animals. For example, doxorubicin may be metabolized by aldo-keto reductase, cytochrome P450 reductase, xanthine oxidase, or cytochrome C reductase, depending on the species. Doxorubicinol, aglycones, sulfate, and glucuronide conjugates have been described in humans,⁵⁵ whereas rats produce little doxorubicinol due to low aldo-keto reductase activity.⁵⁶ The primary metabolite produced by the dog, doxorubicinol, is formed by widespread cytoplasmic reductase enzymes that appear to have different affinities (K_m) and maximum rates (V_{max}) for the substrate in different tissues and species.^{55,56} Concentrations of these enzymes are greatest in the liver, with lesser amounts in the kidney, heart, and skeletal muscle. The affinity of the enzyme for doxorubicin is greater in human liver and kidney than in corresponding tissues in dogs, rats, and mice, whereas the maximum rate of reductase activity (V_{max}) is greater in the canine liver than in livers in humans or rodents.⁵⁶ Enzyme affinity and activity are obviously not proportional to the body mass of members of different species. Greater clinical toxicity observed in small dogs compared to large dogs with BSA-based dosing⁵ suggests absence of a correlation between the rate of metabolism of doxorubicin to form doxorubicinol and body mass of members of a single species as well. Genetic differences in humans result in quantitative and qualitative differences in cytochrome P450 isozymes⁵⁷ that are known to influence drug toxicosis,⁵⁸ and it is likely that isoforms of enzymes also exist between genetically diverse breeds of dogs. It is possible that differences in enzyme affinities and activities among tissues of different breeds also contribute to differences in doxorubicin-induced toxicosis. Moreover, induction of specific isozymes may increase metabolism of doxorubicin and invalidate dose normalization among individuals within a given species.⁵⁹ Further studies are needed to elucidate the relationship between enzyme affinity and activity for these various pathways and body mass of dogs.

Because drugs are often metabolized by multiple pathways, it may be more appropriate to consider the relationship of the overall rate and extent of catabolism to metabolic rate or BSA for dose normalization. Across species lines, considerable evidence exists that extent and rate of metabolism are not closely correlated to metabolic rate or BSA. For example, mitoxantrone, like doxorubicin, is metabolized by different pathways in different species.^{30,48,60–62} One would expect mitoxantrone to be more rapidly excreted in rats and rabbits than in dogs if BSA-based dosing is appropriate; however, the rate of biliary excretion is greater in dogs than in rats and rabbits, and approximately 50, 40, and 25% of mitoxantrone is excreted in the form of metabolites in dogs, rats, and rabbits, respectively.^{30,48,50,60–62}

Because half-life represents the net effect of distribution, metabolism, and excretion pathways ($t_{1/2} = 0.693 \text{ VD/Cl}$

where $t_{1/2}$ is half-life, VD is apparent volume of distribution, and Cl is clearance), it may be a better indication of the value of BSA-based dose normalization than are comparisons of specific pathways. For many anticancer drugs, the half-life does not correlate to metabolic rate or BSA. For example, the elimination half-lives of vincristine in the rat (70 minutes) and dog (75 minutes) are similar.⁴⁵ Similarly, the half-lives of mitoxantrone in monkeys, dogs, and humans (approximately 8, 28 and 37 hours, respectively) are not proportional to body mass.^{27,44,63} Relationships between body mass and drug half-lives within a species have not been thoroughly examined. Comparisons of drug half-lives among different patients should be viewed with caution, however, because administration protocols of drugs may affect pharmacokinetic parameters such as half-lives and AUC. For example, drug accumulation occurs when vincristine is administered more frequently than every 16–21 days in human patients due to the prolonged terminal elimination half-life (85 ± 9 hours).⁶⁴

Some drugs, such as cyclophosphamide and (dimethyl-triazeno) imidazole carboxamide (DTIC), require metabolic activation for antitumor activity. For these drugs, both the rate of formation of the active metabolites and the excretion rates of the parent compounds and metabolites should be considered for dose normalization. Mellett et al⁶⁴ demonstrated that a linear correlation existed between cyclophosphamide dose on a BSA basis in mice, hamsters, rats, dogs, monkeys, and humans and the plasma cyclophosphamide AUC. Because the AUC is dependent upon all factors that affect the plasma concentration of drug, including excretion, metabolism, and binding, it appears that the net effects of these functions are correlated to BSA. However, cyclophosphamide is metabolized to at least 2 cytotoxic metabolites by enzymatic processes in the rat^{66,67} and nonenzymatic metabolism in humans,⁶⁸ and the data of Mellett et al⁶⁴ reveal nothing about the correlation between excretion of these metabolites and BSA. The metabolite 4-hydroxycyclophosphamide, formed by mixed-function oxidase activity, exists in a steady-state with the a cyclic tautomer aldophosphamide. These compounds can be deactivated enzymatically. Alternatively, phosphoramidate mustard can be formed nonenzymatically from aldophosphamide, a reaction that is accelerated in the presence of albumin.⁶⁸ Although there is approximately 80% homology in their amino acid sequences,⁶⁹ bovine serum albumin is only one-third as effective as human serum albumin in catalyzing formation of phosphoramidate mustard. Cytotoxicity has been suggested to result from intracellular generation of phosphoramidate mustard, whereas those cells exposed only to the primary circulating metabolite, 4-hydroxycyclophosphamide, are spared. Qualitative or quantitative differences in the ability of canine serum albumin to catalyze the formation of phosphoramidate mustard as well as differences in cytochrome P450 isozymes in various breeds could alter dose normalization of cyclophosphamide for dogs.

Although the rate of bioactivation of DTIC has not been examined in the dog, studies in mice, rats, and humans suggest that this rate may be proportional to metabolic rate and BSA.⁷⁰ The peak concentration of the active monomethyl-triazine metabolite in the mouse is 10-times greater than in the rat or in humans after receiving equivalent BSA

doses.⁷⁰ The half-life of activation in the mouse and rat is 6–8 and 2–3 times greater than in humans (12, 35, and 75–90 minutes, respectively). By comparison, the metabolic rates (cal/kg/hour) are 5.3–9.2 and 3.1–4.3 times greater in the mouse and rat, respectively, than in humans.^{71,72} Additional studies are needed to determine the relationships between clearance of the active metabolite and bioactivation and body mass for a single species.

No evidence exists that the rates of nonenzymatic degradation of drugs, such as melphalan, or metabolites, such as 4-hydroxycyclophosphamide and aldophosphamide, are correlated to BSA. Melphalan is nonenzymatically degraded to 2 hydrolysis products and at least 3 metabolites in dogs, and clearance is independent of renal or hepatic function.⁷³ This was demonstrated by Page and colleagues,⁷⁴ who indicated that dose-limiting toxicity in dogs was more closely correlated to body weight than to BSA.

Finally, BSA dosing may be appropriate for some drugs. Actinomycin-D is not metabolized, is minimally plasma protein-bound, and is excreted by biliary secretion in the rat, monkey, and dog.⁷⁵ When expressed on a body weight basis, body surface area doses are more than 3-fold greater in the rat than in the dog. Administration of actinomycin-D at 0.6 mg/m² BSA resulted in higher initial plasma and tissue concentrations in the smaller animals but nearly equivalent drug exposure over time (concentration $\times$ time [$C \times T$]) in 11 tissues measured over 5–6 days. It should be noted that actinomycin-D distributes slowly to tissues (distribution half-life = 3 hours) and the elimination half-life from tissues was approximately equal for the 3 species. Neither toxicity nor efficacy were determined in that study. It may be presumed that these factors would be determined by drug exposure over time in target and nontarget tissues; however, high initial concentrations could predispose to increased toxicity. That study indicated the importance of evaluating tissue concentrations of drugs, where possible. Other drugs that are distributed more rapidly than actinomycin-D may achieve higher tissue concentrations that are proportional to higher plasma concentrations.

Conclusion

In conclusion, drug clearance may differ among species or among patients within a species due to variations in absorption and distribution resulting from differences in gastrointestinal physiology, tissue volume or blood flow, transport protein–drug affinity, plasma protein, or tissue binding. Excretion may differ in proportion to GFR or the quantity or quality of metabolizing enzymes. It is clear that genetically determined differences exist in metabolizing enzymes in humans and it is likely that these differences also occur in genetically diverse breeds of dogs. BSA may be an appropriate basis for dosing drugs that are eliminated intact by glomerular filtration or degraded nonenzymatically, with glomerular filtration being the rate-limiting factor for excretion. Drugs that are metabolized by enzymes having identical specificities and affinities in diverse species or within a given species may also be presumed to have the same exponential relationship to body weight for these species; however, these exponential relationships may not be accurately described by the currently used BSA formula.

BSA dosing may be appropriate only if the rate and extent of drug distribution is equivalent for all breeds or is correlated to metabolic rate. Multiple drug therapy is often indicated for cancer patients, and drug interactions may influence dose normalization. Many therapeutic agents stimulate enzymes that are responsible for metabolism of drugs. Conversely, other drugs may inhibit enzyme systems. A drug may displace another from the receptor at its site of action or from a plasma or tissue protein. A drug may also influence renal excretion or intestinal absorption of another drug. Finally, clinicians must remember that any relationship between BSA and drug pharmacokinetics may be weakened by the effect of disease on drug disposition.

Although several studies have shown a correlation between drug dose on a BSA basis and plasma AUC when data are plotted for several species, studies have failed to address whether this relationship persists for all breeds within a species. Furthermore, studies have focused on parent drug concentrations over time in plasma, when concentrations of active metabolites in tissues may be the more critical factor for dose normalization. Future studies are needed to address distribution, metabolism, and excretion pathways of anticancer drugs in animals. Studies in experimental animals should be designed to include comparisons of pharmacologic effect and drug exposure over time ($C \times T$) in both serum and tissues. Statistically valid studies of allometric relationships between clearance of cancer chemotherapeutics and body weight are likely to yield exponential relationships that differ from the BSA equation currently used.

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