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# THE VALUE AND LIMITATION OF PHARMACOKINETICS IN PREDICTING

## DOSAGE REGIMENS: EFFECTS OF SYSTEMIC DISEASE

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A great deal of recent literature has been devoted to the application of pharmacokinetic principles to the design of antimicrobial drug dosage regimens. There is a fundamental paradox evident when one tries to extrapolate much of these findings to the clinical setting. Most pharmacokinetic studies designed to determine drug dosage regimens are generally performed in healthy animals. However, the clinical target population ultimately receiving the drug is primarily comprised of diseased individuals. The clinical relevance of this dichotomy is not presently known. It is the purpose of this presentation to outline how systemic disease processes may affect pharmacokinetic predictions, to discuss how these changes might impact on the therapeutic efficacy, toxicity and tissue residues of antimicrobial drugs, and finally to present a powerful and economical system of pharmacokinetic modelling which can account for these disease-induced changes in the field situation.

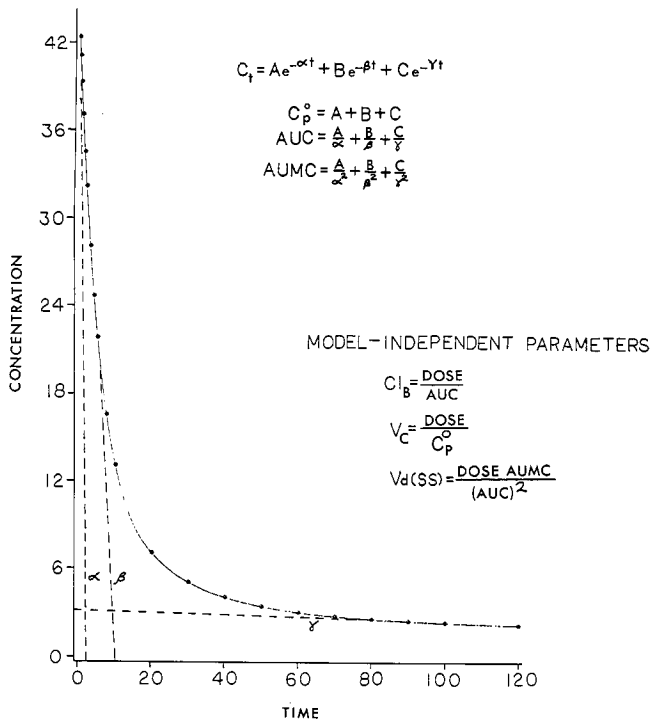
**Pharmacokinetic Principles:** When examining the effects of disease on drug disposition, pharmacokinetic experiments should be designed so that changes in drug clearance, distribution and absorption can be independently evaluated and correlated to physiologic processes. To optimally accomplish this goal, model independent procedures should be utilized where feasible (Jusko, 1980). The reasoning behind this assertion is that the information density of most pharmacokinetic studies is relatively low, that is only a limited number of pharmacokinetic parameters can be calculated from any one set of data. If one is interested in defining the precise values for all microconstants in a multi-compartment pharmacokinetic model, a great deal of data must be collected to insure that your model is correct. However, if one is primarily interested in determining the effects of a disease process on physiologically relevant pharmacokinetic parameters, then less data points per individual are necessary since these parameters can be calculated directly from the observed data with a minimal degree of assumptions. Two parameters are generally considered as being optimal to describe drug disposition in altered physiologic states. These are the total body clearance

( $Cl_B$ ) and the volume of distribution at steady state ( $Vd(ss)$ ). Both of these parameters can be directly calculated from the intercepts (A,B,C etc.) and exponents (alpha, beta, gamma etc.) of the standard polyexponential equations used to describe serum drug concentration-time profiles (Figure one). The value of these parameters are independent, a property not shared by some commonly employed model-dependent parameters, i.e.  $Vd(area)$ ,  $Vd(b)$ , and beta, which change as a function of elimination and distribution processes. Once when these parameters are determined, then the clinically relevant half-life ( $T_{1/2}$ ) can be calculated (Riviere et al., 1983).

$$T_{1/2} = \frac{0.693 \times Vd}{Cl_B}$$

This relationship clearly illustrates that the half-life of a drug is dependent on both elimination and distribution processes, implying that a disease-induced change in either of these components may alter the observed half-life. Since half-life is a primary determinant of the dose interval used in designing dosage regimens, both factors must be considered when looking at possible disease-induced changes in drug disposition.

FIGURE ONE. TRIEXPONENTIAL SERUM DRUG CONCENTRATION-TIME PROFILE



When designing experiments to measure these parameters in diseased animals, one must note that the sample timing may be altered as a result of a change in elimination half-life so that an experimental design optimal in normal animals may be totally inadequate to estimate disposition parameters in diseased individuals.

Disease effects on drug absorption should be evaluated using the standard methods employed in bioavailability studies (FDA, 1977). The extent ( $F$ ; AUC<sub>route</sub> AUC<sub>iv</sub>) and rate ( $K_a$ ) of the absorptive process should be compared in healthy and diseased animals. It is important that both of these parameters be estimated since the magnitude of rate constant  $K_a$  will affect the shape of the concentration-time profile of absorbed drug (Koritz, 1980), an event which would have impact on the ultimate dosage regimen employed. Such studies would necessitate a minimum of four experimental groups for each route of administration being considered; i.e. intravenous and extravascular studies in both healthy and diseased animals. The advantage of this type of experimental design would be that the effects of the disease process on other parameters of drug disposition would simultaneously be determined in the intravenous group. A novel model-independent system of pharmacokinetic analyses which may be extremely useful in this context is the linear system deconvolution technique (Veng-Pedersen, 1980). This mathematical modelling tool allows for a precise quantitation of disease effects on the drug concentration-time profile of the absorptive process without making detailed assumptions about abstract pharmacokinetic models governing drug disposition.

**Magnitude of Disease Effects:** Pathophysiologic processes which significantly alter either the clearance or distribution of an antimicrobial agent could have impact on dosage regimen construction. Very little work has been done on the effects of liver disease on the clearance of antimicrobial drugs. It would be expected that diseases affecting hepatic perfusion, parenchymal enzyme activity or albumin production could affect drug disposition. However, since most antimicrobial agents are eliminated primarily by renal routes, such disease processes may not have clinical significance. Drugs which may be affected by hepatic disease and which should be avoided in severe hepatic insufficiency include chloramphenicol, clindamycin, erythromycin estolate, lincomycin, oxacillin and tetracyclines. A major limitation in this field is the lack of a suitable liver function test which accurately reflects disease induced changes in drug handling capability (Jenner and Testa, 1981).

Renal insufficiency can have marked effects on antimicrobial agent disposition. This field, primarily composed of data generated from human studies, has recently been reviewed (Riviere

and Davis, 1984). The primary disease-induced change is a decrease in the renal clearance of drug which results in a reduced body clearance if the kidney is the primary route of elimination. Generally, this reduction is proportional to the decreased glomerular filtration rate as estimated by creatinine and inulin clearances, or serum creatinine concentrations. Drugs which are eliminated to a significant extent by the kidney include the aminoglycosides, sulfonamides, penicillins, cephalosporins, and tetracyclines. Note that a decrease in glomerular filtration will decrease the renal clearance of both parent drug and of polar drug metabolites undergoing hepatic biotransformation.

There have been a few experimental studies on the effects of renal insufficiency on antimicrobial drug disposition. The half-life of cephaloridine was up to three times longer in subtotally nephrectomized dogs compared to normals (Klausner et al, 1977). Likewise, experimental pyelonephritis in rats prolonged ampicillin elimination and altered the intrarenal distribution of drug compared to controls (Bergeron et al, 1982). Experimental renal disease also affected the disposition of gentamicin in dogs (Table One) (Riviere et al., 1981; 1984). Changes in aminoglycoside and cephaloridine disposition have toxicologic implications due to the narrow therapeutic window of these agents for producing nephrotoxicity.

**TABLE ONE: EFFECTS OF EXPERIMENTAL RENAL DISEASE ON GENTAMICIN PHARMACOKINETICS IN DOGS**

Disease	Creatinine Clearance (ml/min/kg)	Half-life (min)	Total body Clearance (ml/min/kg)	Vc (ml/kg)	Vd(ss) (ml/kg)
Normal	3.8 (0.9)	61 (8)	4.1 (0.6)	192 (7)	341 (24)
Nephrectomy	0.8 (0.2)	173 (20)	0.8 (0.1)	124 (22)	199 (19)
Glomerulo-nephritis	1.9 (0.6)	63 (16)	5.3 (1.2)	286 (42)	512 (25)

**Mean (SD)** Data from normal dogs in the author's laboratory (n=11). Nephrectomized dogs had 7/8 of the renal mass surgically removed (n=4).

The nature of the renal disease process is also important as is evident from examining this Table. Although both subtotally nephrectomized and glomerulonephritis dogs have decreased creatinine clearances, gentamicin pharmacokinetic parameters are not directly predictable since the change in volume of distribution is different in both disease states (Riviere et al, 1981). It is of interest to note that in two sheep with

spontaneous renal disease, syndromes pharmacokinetically similar to experimental glomerulonephritis in dogs were seen (Riviere, 1982). These type of changes make the prediction of drug disposition in diseased individuals difficult at best. The effects on tissue residues would be critical since distribution as well as clearance changes would have major impact. Our laboratory has recently applied multivariate statistical procedures to these problems (Shy-Modjeska et al., 1983) in an effort to correlate changes in drug distribution and clearance to specific syndromes of renal insufficiency. It is hoped that this approach will allow us to identify disease specific patterns of changes in drug disposition parameters and identify clinical indices predictive of these syndromes in the field. In this case, the veterinarian would be alerted to watch for altered pharmacokinetics in individuals or groups of animals exhibiting signs of these disease states. This approach can easily be extended to other types of disease processes and management practices.

Renal insufficiency can also decrease the extent of serum protein binding which would increase the apparent volume of distribution. The rate and extent of hepatic biotransformation can also be affected. These multiple events may also result in complex disease-induced changes in drug disposition. An example of such a situation is the effect of renal insufficiency on sulfonamide disposition. The following changes in drug pharmacokinetics may occur: decreased clearance of parent drug and metabolites, decreased rate of hepatic biotransformation, and decreased extent of serum protein binding. These multiple changes make prediction of drug disposition difficult. Again, the area of greatest impact is the effects of subclinical renal disease on the tissue residue profile of drugs such as the sulfonamides since the disposition of both parent drug and metabolites at low levels are important.

Other disease processes can also effect drug disposition. Experimental studies in animals on the effects of disease on drug pharmacokinetics are rare and species differences may be criticle. Fever associated with endotoxemia has been documented to increase the volume of distribution of penicillin G in dogs (Baggot, 1977; 1980), of trimethoprim in pigs (Ladefoged, 1979), and of gentamicin in dogs (Pennington et al, 1975) and rabbits (Halkin et al, 1981). In contrast, endotoxin induced fever has also been shown to decrease the volume of distribution of gentamicin in horses (Wilson et al., 1983). Clearance of drug may also be decreased in this pathophysiological state as was demonstrated for sulphathiazole in pigs by Friis and Ladefoged (van Miert, 1980). This study also showed that drug clearance was dissociated from clinical estimates of renal function since inulin clearance was unchanged in this study, a finding conceptually similar to the changes seen in dogs with

glomerulonephritis given gentamicin. Endotoxemia has also been shown to either decrease or not change the oral absorption of sulfonamides in goats (van Gogh and van Miert, 1977; van Miert et al, 1976). Decreased absorption of ampicillin/ amoxicillin in calves given orally and intramuscularly has been reported (Groothuis et al, 1978). Endotoxemia has also altered the urinary metabolic profile of sulphafurazole in goats (van Miert, 1980). Finally, the volume of distribution and half-life of oxytetracycline were increased in pneumonic calves compared to healthy animals (Ames et al, 1983). This was correlated to increased lung tissue drug concentrations in the pneumonic animals.

Pregnancy has also been shown to significantly alter drug pharmacokinetics. Ampicillin volume of distribution and renal clearance were significantly increased in pregnant women compared to normal in a cross-over study (Philipson, 1977). Findings consistent to these have been reported for ampicillin in horses by our group (Traver and Riviere, 1982). In addition to these pregnancy induced changes, serum protein binding of sulfisoxazole was reduced in pregnant women (Dean et al, 1980). Changes in the state of hydration can also significantly impact on the volume of distribution and total body clearance of drugs as evidenced by a study of gentamicin in rats (LeCompte et al, 1981). The magnitude and nature of these changes are dependent upon the severity of the dehydration, its cause (i.e. vomition versus diarrhea) and its duration.

Finally, a field study of emergency slaughtered ruminants (Nouws and Ziv, 1978) concluded that of 2886 animals examined, diseased individuals had a significantly greater incidence of elevated tissue drug residues of benzylpenicillin, dihydrostreptomycin and neomycin than did nondiseased individuals. A recent study in our laboratory (Riviere and Carver, 1984) indicated that hypothyroidism may have an effect on the tissue disposition of gentamicin in dogs. The terminal gamma phase serum elimination half life, normally approximately 30 hours in normal animals, was virtually nonexistent in three dogs with familial hypothyroidism. It is this pharmacokinetic phase which best correlates to tissue disposition of drug.

These samplings of reported studies, although not exhaustive, indicate the complexities of disease effects on drug disposition. Experimental models are not yet stable enough to make long term studies realistic. Additionally, the clinical relevance of these findings is not known since experimental models tend to only model a single disease process. If multiple events are occurring or if the expression of the disease is affected by management or therapeutic factors, direct extrapolation may not be possible. It is therefore imperative that studies be conducted to define the significance of clinical

disease on the parameters of drug disposition under field conditions. Experimental studies aimed at elucidating mechanisms may then be pursued.

**Disease Effects on Antimicrobial Drug Dosage Regimens:** As can be appreciated from the above overview, numerous disease processes can affect drug disposition in a complex fashion. These changes could easily impact on the efficacy, toxicity and residue profile in animal species of veterinary concern. What are these possible effects?

A decrease in the extent of absorption would effectively reduce the available dose of drug and thus would be equivalent to administering smaller doses. This would result in lower serum and tissue concentrations at all times. A change in the rate of absorption, if rate limiting, would have more serious implications since the body clearance of the drug and half-life would be altered. This would result in altered serum concentration-time profiles.

Changes in clearance and volume of distribution could have profound effects on the shape of the concentration-time profiles of antimicrobial agents administered according to guidelines developed in normal animals. To illustrate these, serum concentration-time profiles were simulated on a digital computer for gentamicin (Figure 2), sulfadimethoxine (Figure 3) and oxytetracycline (Figure 4). All are based on an open, two compartment pharmacokinetic model as described by Dr. Koritz in the preceding paper of this symposium. Parameters inputted were those derived after intravenous administration of a single dose of drug to normal dogs (gentamicin, sulfadimethoxine) or calves (oxytetracycline). Data is based on a compilation of average values from the literature and this laboratory (Baggot, 1977; Riviere, 1982; Riviere and Coppoc, 1981; Toutain and Raynaud, 1983; Nouws et al., 1983). These simulations are also most likely comparable in other species since the disposition pharmacokinetics are of a similar order of magnitude, i.e dogs, swine and small ruminants (Baggot, 1977; Richter et al, 1979, Wislon et al, 1983). The following values were utilized as input:

Drug	Half-life (minutes)	Vc (ml/kg)	Vd(area) (ml/kg)	ClB (ml/min/kg)
Gentamicin	61	195	350	4.0
Sulfadimethoxine	770	200	400	0.36
Oxytetracycline	345	225	950	2.0

Note that gentamicin has a rapid elimination half-life and a volume of distribution approximating extracellular fluid. Sulfadimethoxine has a similar distribution, however its half-life is prolonged due to a very low clearance. Oxytetracycline has an average rate of clearance but a large volume of distribution which prolongs the half-life. The drugs are dosed according to guidelines from the original sources which were based on achieving a "therapeutic window."

In relation to dose interval, gentamicin has the shortest half-life and thus never accumulated when given every eight hours. The figures follow through five cycles of drug administration and a terminal cycle where no additional drug is given. The gentamicin simulation is comparable to that observed in normal dogs given this regimen in our laboratory.

The following hypothetical disease conditions were simulated. They are of a similar severity to those reviewed above. First, the total body clearance was reduced by two-thirds to a value one-third of normal with the volume of distribution held constant. This results in a tripling of elimination half life. In dogs, this would correspond to a glomerular filtration rate of 1.2 ml/min/kg (4 ml/min/kg normal). Detecting this degree of renal insufficiency in a population of animals would be difficult since serum creatinines would only be marginally elevated (approximately 1.1-1.5 mg/dl) as would the serum urea nitrogen (approximately 20-35 mg/dl). This degree of "sub-clinical" renal insufficiency could be caused by a number of common disease processes, examples of which include exposure to nephrotoxic drugs or environmental toxins, septicemia, massive diarrhea with prolonged episodes of dehydration, nephrotoxic plants or immunological processes. In swine and poultry units, exposure to ochratoxin, some heavy metals, nephrotoxic drugs, or plants such as pigweed could produce this degree of renal insufficiency.

The second simulated disease state is one where only the volume of distribution of the drug is doubled, with clearance remaining unchanged. This results in a doubling of elimination half-life and is similar in magnitude to the experimental studies reviewed above. The final case is one in which only the volume of the central compartment, representing well perfused organs, is decreased by one-half. This scenario could result from an acute fluid loss (i.e. vomiting) or a disease induced reduction in blood flow to these organs (i.e. early phase of endotoxemia).

FIGURES TWO - FOUR. SIMULATED SERUM DRUG  
 CONCENTRATION-TIME PROFILES IN THREE DISEASE STATES.  
 All concentrations are in mcg/ml.

GENTAMICIN

SIMULATED SERUM DISPOSITION CURVES

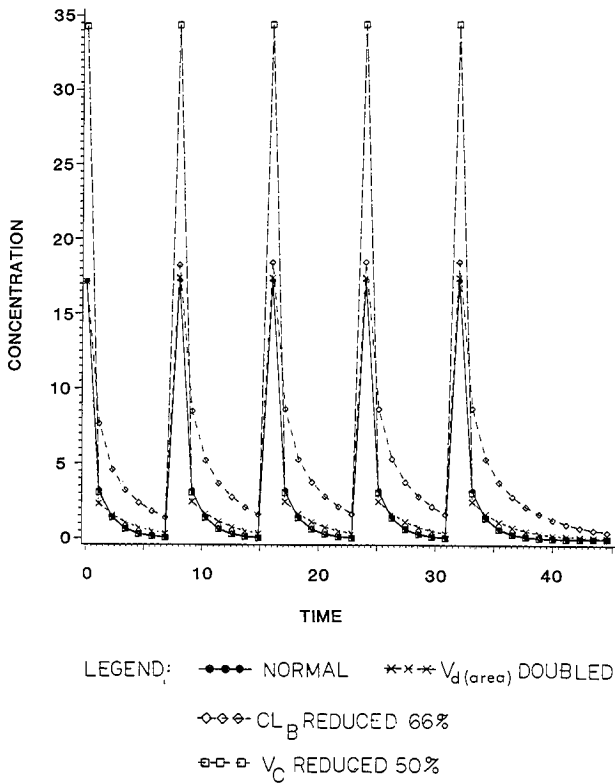


FIGURE TWO. 3 MG/KG EVERY 8 HRS.

# SULFADIMETHOXINE

## SIMULATED SERUM DISPOSITION CURVES

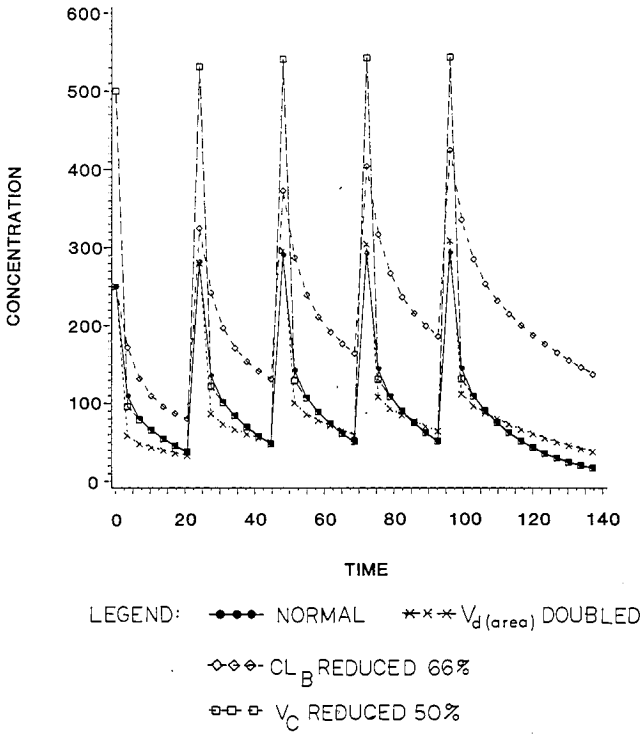
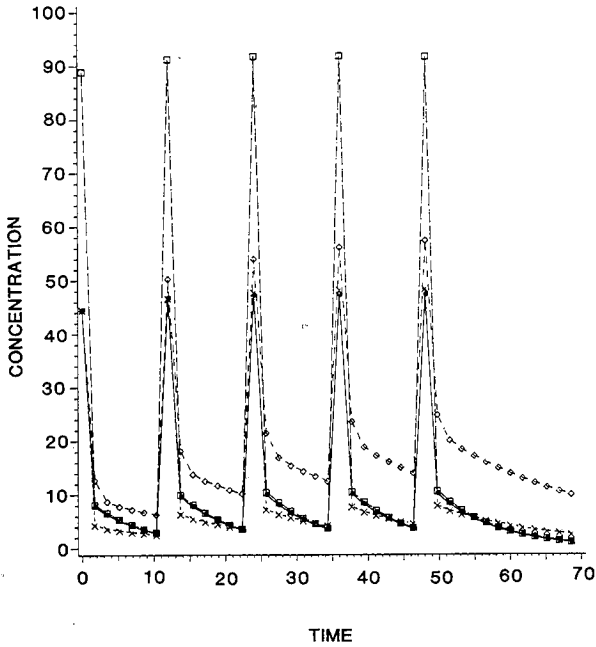


FIGURE THREE. 50 MG/KG EVERY 24 HRS.

# OXYTETRACYCLINE

## SIMULATED SERUM DISPOSITION CURVES



LEGEND: ●—● NORMAL    \*—\*—\*  $V_d(\text{area})$  DOUBLED  
◇—◇—◇  $CL_B$  REDUCED 66%  
□—□—□  $V_C$  REDUCED 50%

FIGURE FOUR. 10 MG/KG EVERY 12 HRS.

It should first be noted from examining these graphs that a reduction in the volume of the central compartment only alters the peak serum concentrations of drug but does not otherwise effect the profile. Since peak serum concentrations are relatively restricted to the central compartment, this disease induced change would not probably affect therapeutic efficacy or toxicity unless the toxic action were directed against a receptor located in this compartment. The half-life is not affected.

The other two disease conditions, both more likely to occur in a field setting, do significantly change the shape of the serum concentration-time profile. Reduction in total body clearance by two-thirds results in accumulation of sulfadimethoxine and oxytetracycline since these compounds are now being dosed using intervals which in the presence of disease are shorter than the half-life. Only in the case of gentamicin is the dose interval longer than half-life with the result that significant accumulation does not occur. However, with all three drugs, the area under the curve (AUC) and trough serum concentrations are significantly elevated compared to normal which could result in toxicosis. This situation has been observed in or laboratory. Another important effect would be the prolonged terminal rate of elimination of sulfadimethoxine and oxytetracycline in food animals. After only five cycles of drug administration, one can appreciate from these simulations that a prolongation of withdrawal time would be necessary.

The effects of a change in volume of distribution are more complex. If one only looks at the first cycle of drug administration (similar to a single dose study), the primary differences compared to normal are slightly decreased serum concentrations. This effect is pronounced with sulfadimethoxine due to its low rate of clearance. However in the multiple dose situation, the effect observed is prolongation of the elimination half life induced by the reduction in the volume of distribution. This overshadows the dilution effect expected with an increased volume and seen in the single dose situation. This effect is accentuated when drug accumulates in subsequent cycles of drug administration. Stated in another fashion, the increase in volume reduces the fraction of an administered dose eliminated during each dose interval. This can be conceptually viewed as a "sink" phenomenon. Accumulation is evident if the drug is dosed at an interval shorter than its elimination half life. Since this is not the case with gentamicin, the effect is not observed. The primary implication is to tissue residues since this scenario would accentuate their occurrence. Additionally, since the volume of distribution is actually a proportionality factor relating the serum concentration of drug to the total amount of drug in the body, the relationship of this serum concentration to corresponding tissue residues is altered in the diseased animal.

Specifically, at equivalent serum concentrations, one would expect a higher level of residues in the diseased animal compared to the healthy one.

Caution must be exercised when interpreting simulations. First, only a single pharmacokinetic parameter is being altered. In the field, multiple parameters are probably changing as a result of the disease, i.e. a reduced clearance and an increased volume of distribution. The effects would be accentuated since elimination half-life would be sextupled. Secondly, concurrent disease processes may be occurring. Finally, many experimental studies are conducted using only a single dose of drug yet multiple doses are clinically employed. As evidenced by these simulations, interpretation may be different with multiple doses.

**Implications:** The effect of these changes on the design of dosage regimens must be viewed in terms of toxicity, efficacy and residues. If toxicity is correlated to total amount of drug in the body, then altered clearance and volume changes could significantly increase the risk of drug toxicity. Serum drug concentrations in this case would thus exceed the upper limit of the therapeutic window. If the animal is being treated for a soft tissue infection, therapeutic efficacy may actually increase since higher serum concentrations of drug are present when clearance is reduced and the ratio of tissue to serum drug concentrations is increased with the altered volume of distribution. Note that these effects may be counteracted by pharmacodynamic factors related to the disease process (drug inactivation by organisms or binding to purulent material, altered tissue pH in the presence of infections, reduced oxygen tensions, decreased host defences, etc.)

The implications to residues in food animals are more serious since both clearance and volume changes result in accumulation. In the case of a sulfonamide in the presence of renal disease, one would likely encounter a decreased clearance of drug coupled with an increased volume of distribution, a combination which synergistically would prolong elimination half life and enhance accumulation. Altered metabolic profiles would complicate the situation further. If the disease were diagnosed, then the dosage regimen could be appropriately adjusted (see Riviere and Davis, 1984). The only other possible mechanism to remedy this situation would be to perform pre-slaughter drug analyses, and if drug were detected then the withdrawal time could be lengthened until no drug were detected. This would be efficacious if elevated serum concentrations were a result of reduced clearance. However, if a volume of distribution change occurred, serum drug concentrations may no longer accurately reflect tissue residues. An alternative would be to monitor urine concentrations of drug, the premise of FSIS's Live Animal Swab Test (LAST). However,

disease processes also change the relationship of urine to tissue concentrations, a finding reported by Bergeron et al (1982) and Nouws and Ziv (1978) and observed in our laboratory. In the study involving antibiotic residues in slaughtered ruminants, urine concentrations did not always correlate to renal tissue concentrations and further, renal concentrations did not always correlate to muscle concentrations. In fact clearance from muscle tissue was often faster than kidney tissue clearance, an observation which would complicate the interpretation of FSIS's Swab Test on Premise (STOP).

**Comments and Suggestions:** It is evident from this analysis that systemic disease may have a major impact on the pharmacokinetics of antimicrobial drugs in animals. The limited number of studies conducted indicate that such effects probably occur in the clinical setting. It is also obvious that individual animal variation in pharmacokinetics, in severity of disease expression, and differences in disease pathophysiology all contribute to making a **priori** prediction of these changes difficult yet necessary. Classical pharmacokinetic analysis as presented above is powerful in identifying and describing the effects of disease on pharmacokinetics, however, such studies are not practical to implement on an individual basis in clinical veterinary practice. The only economical approach is that used in human clinical pharmacology where dose regimens are tailored to the individual patient by monitoring drug concentrations at specified times and comparing them to predicted values based on estimates obtained in healthy animals. This approach has been advanced by Dr. Lloyd Davis in veterinary medicine (Davis et al, 1980). In terms of antibiotics, this approach in both human and veterinary medicine has only been extensively employed to monitor aminoglycosides in an effort to avoid toxicity. With the increase in availability and decreased cost of drug assays, coupled with more sophisticated microbiological techniques (MIC determinations), the monitoring of drug concentrations on an individual patient basis in companion animal practice may become widespread.

The dilemma facing the food animal practitioner is how to economically implement a similar program in modern large scale confinement or feedlot operations. Clearly, monitoring of drug concentrations in individual animals is not economically or practically feasible (i.e. animal handling, identification, etc.). However, there are some alternatives which may be implementable. Generally in a herd/flock situation, disease is **not** an individual animal event but rather groups of animals are all affected with the same infectious syndrome, i.e. all have pneumonia, enteritis or a septicemia caused by the same etiologic agent. In fact, the veterinarian's diagnosis is on a herd basis. All animals are seldom examined. In intensive swine or poultry units, affected individuals may be selected and submitted to a diagnostic laboratory for slaughter and necropsy. Based on these

results, a specific treatment will be tailored to the herd/flock situation. Indications for drug usage are written and approved in this context. Therefore, any pharmacokinetic scheme which must address these field conditions must be formulated on a herd/flock basis. This scheme must also be able to handle the concurrent disease processes and different management situations encountered in the field. Interindividual and interherd/flock variability in drug disposition parameters must be identified, quantitated and accounted for.

This situation appears tailored to the application of the recently developed pharmacostatistical techniques termed population pharmacokinetic analysis (Sheiner and Beal, 1980, 1981, 1983; Beal and Sheiner, 1982; Sheiner, 1982). Bowen (1982) has also suggested that this approach be studied by veterinary academia relative to the use of drug combinations in food animals. This system of analysis, embodied in the **NONMEN (NONlinear Mixed Effects Model)** computer program developed by Drs. Sheiner and Beal at the University of California at San Francisco, is based on studying pharmacokinetics in the target population rather than in the individual animal. To accomplish this, a limited number of samples are taken for drug analysis from a large number of individuals in a field situation. Single samples from an individual are even useful in this system. It was developed for human medicine so that samples collected in the process of routine patient care could be used to model drugs in the place of expensive planned experiments. The resulting data collected is often more representative of the target population. Variability between patients becomes an asset to this type of procedure since the population error structure can be explicitly modelled as the analysis is conducted. This is accomplished by evaluating the patient's (or herd/flock's) physiologic and disease (and management) status simultaneous to conducting the pharmacokinetic analyses. Both sets of data are then analysed simultaneously and the pharmacokinetic and statistical model parameters determined at one time. The variability between individuals is thus explicitly modelled as is the effect of specific diseases.

We suggest that the following procedure could be considered for implementation in food animal medicine. Classic pharmacokinetic studies would provide the general model which describes drug disposition in the normal individual and "hints" as to the nature of disease-induced changes in drug disposition. The relationship of physiologically relevant pharmacokinetic variables ( $V_d(ss)$  and  $Cl_B$ ) to measurable clinical/pathologic parameters would then be determined in a population pharmacokinetic study. This step would most economically be conducted in the setting of clinical efficacy trials by collecting a few blood samples for drug analysis from all of the animals in the trial. Multivariate statistical techniques would

first be applied (Shy-Modjeska et al; 1983) to identify relevant correlations. These relationships would then be inputted into the NONMEN program and relevant pharmacokinetic and statistical model parameters determined. This step would thus improve upon the pharmacokinetic models developed in the preclinical phases. Since these studies would be conducted in animals with various disease processes in the efficacy trials designed to determine approved uses, relationships to relevant disease processes would be established. This type of procedure would automatically account for disease effects, therefore, the dosage regimens constructed using these models would not again have to be adjusted. By including terminal serum and/or urine analyses, regimens designed to optimize efficacy and minimize toxicity and residues could be developed. In subsequent use of the drug, monitoring of drug concentrations would serve to enlarge the data base, further refine the underlying pharmacokinetic model, and identify new disease conditions where model predictions do not hold. Any "error" in the model can be correlated to additional clinical or management parameters and the model readjusted. This process would be powerful in identifying those disease conditions where drug disposition is significantly altered from normal, and would identify clinical correlates useful to predict these situations. The veterinarian would then be alerted to clinical syndromes where dosage guidelines must be adjusted and he would be provided with data to appropriately adjust withdrawal times to avoid residues. STOP and LAST tests could then confirm his assumptions. In the developmental phases, population pharmacokinetics could also be employed to identify situations where these screening tests generate false positive or negative results.

This approach using pharmacokinetic studies in normal and diseased animals, to define the preliminary model, coupled with population studies conducted simultaneous with efficacy trials, may be the most economical and optimal approach to designing pharmacokinetically-based dosage regimens for antimicrobial agents in diseased animals.

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