# General Session II

Pharmacology and the Practitioner

**Dr. Fred Wertman,** *presiding*

# A Practical Approach to Drug Dosage for the Practitioner: Introduction to the Use of Pharmacokinetics

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## Introduction

In recent years veterinary pharmacologists have become involved in the development of pharmacokinetic data for a large variety of drugs and chemicals commonly used in veterinary medicine. Unlike the human oriented pharmacologists who have an interest in this particular discipline, veterinarians are faced with a large number of species representing a variety of the biochemical and metabolic processes. In accordance with the usual trend, veterinary medicine tends to trail and perhaps mimic the progress experienced in human applications. We are currently emerging from a stage in which there was a great commitment to the development of pharmacokinetic data without much emphasis being placed upon the utilization of this data for clinical or other applications. This presentation is intended to depart from the process involved in developing pharmacokinetic data and focus upon the potential application.

It is of interest to note the various attitudes observed in students. After exposure to the discipline of pharmacokinetics in veterinary curricula, some see a powerful application of pharmacokinetics to the practice of veterinary medicine. Others fail to understand or appreciate its clinical application. Most practitioners see the mathematical derivations and believe there is no application for the general practice of veterinary medicine. They may see it as too time consuming to deal with individual cases. It is hoped that this presentation will provide evidence and justification for its application to clinical veterinary medicine, and perhaps some insight into those cases where it can be most valuable. The format includes the identification of five major areas in which data exists to justify the clinical application of pharmacokinetics in determining dosage. In each area a specific clinical case is described to demonstrate how pharmacokinetic data is applied. It should be understood that the examples used will not represent the total scope of application in each particular area.

There are five (5) areas in which the application of pharmacokinetics can be of benefit to the practitioner. These are:

A—Individualized dosage regimens
B—Estimating dosages for drugs not approved in various food animals
C—Economic assessment of multiple drug choices
D—Critical tissue distribution estimates
E—Estimating or projecting drug withdrawal times.

*A. Individualized Dosage Regimens—Case Analysis, Aspirin Dosage in the Bovine.*

Consider the circumstance where a valuable embryo transfer Simmental heifer (500 lbs) presents with elevated temperature (105°F), acute thoracic pain and labored shallow breathing. The diagnosis is acute pneumonia and one of the drugs of choice is a non-steroidal anti-inflammatory, e.g. aspirin[3]. An early therapeutic goal is to determine the dosage which will give you the desired therapeutic concentration of drug in the serum. The next goal is to maintain this therapeutic concentration as near steady state as possible. Your primary resource is the product label which recommends 1-3 boluses (240 grains) two to three times a day. This translates into 45 grams of aspirin, 2-3 times per day, or about 270 mg/lb/bwt total dose, depending upon which of the dosing variables you choose. Do you know from this label what the therapeutic concentration is? Are you sure what dosage it takes to maintain the therapeutic concentration? What dosing interval do you need to use? These and other

questions often confront the clinician. Applied pharmacokinetics[4] provide a means for estimating these values. For example:

Eq. 1

$$D_o = \frac{\bar{C} \times V_d \times T}{1.44 \times t_{1/2} \times F}$$

Where D is the dose to be administered, C is the average steady state level desired, $V_d$ is the volume of distribution, $\tau$ is the desired dosing interval, $t_{1/2}$ is the drug half-life and F is the fraction of the administered dose which can be absorbed. If it is easier to adjust the dosing interval rather than the amount of dosage, equation 1 is rearranged to read:

Eq. 2

$$T = \frac{F \times D_o \times 1.44 \times t_{1/2}}{\bar{C} \times V_d}$$

The variables for which you can solve include $D_0$ = dose, $\tau$ = dosing interval, or C = desired steady state concentration. In this case, solve the unknown for plasma concentration and set the other variables as dose = 270 mg/lb or 594 mg/kg q-8-H. The essential information we need for aspirin in the bovine is:[3]

| | | |
|---|---|---|
| half-life ($T_{1/2}$) | = | ½ hour |
| $V_d$ | = | 0.24 L/kg |
| % absorption | = | 70% |

**Thus**

$$\bar{C} = \frac{F(D)\ 1.44\ T_{1/2}}{V \times T}$$

**or**

$$\bar{C} = \frac{(0.7)\ (594\ mg/kg)\ (1.44)\ (.5\ hr)}{(0.24\ L/kg) \times 8\ hrs} = \frac{299.38}{1.92} = 155.92\ mg/L$$

**or**

$\bar{C}$ = <u>156 µg/ml</u> is the therapeutic concentration achieved with this dose.

The minimum effective plasma concentration for aspirin in the bovine has been estimated to be about 30 µg/ml, thus we can see that at this dosage we are about 5x the therapeutic concentration.

Let's add a complicating factor, such as a shift in urine Ph from 6 to 8 units. The T½ of aspirin can change from ½ hour to 2.5 hours due to its active resorption in an acid urine. How does the clinician adjust an already excessive dose to take this into account? Using the same formula,

$$D_o = \frac{\bar{C} \times V_d \times T}{1.44 \times T_{1/2} \times F} \quad \text{or} \quad \frac{(30\ \mu g/ml)\ (.24\ L/kg)\ (8\ hrs)}{1.44 \times 2.5\ hr. \times .70},$$

we estimate a dose of **23 mg/kg.** Dosage adaptations can also be calculated when renal disease or renal failure becomes a problem (Table 1).

*B. Estimating Dosages for Drugs Not Approved in Food Animals: Case Analaysis, Carbenicillin in the Dairy Cow.*

Consider the case of a 20,000 pound (production) dairy cow with a suppurative joint lesion from which *Pseudomonas spp.* was isolated in pure culture. The drug of choice is carbenicillin.[6] The only dosage information available is in man and dog. Carbenicillin is poorly absorbed from the gastrointestinal tract. It is unstable in an acidic ph and must be administered parenterally. What information do we need? (Table 2)

| | | |
|---|---|---|
| Biologic half-life ($T_{1/2}$) | = | 2 hours |
| Volume of distribution ($V_d$) | = | 0.24 L/kg |
| Absorption (given I/V) | = | 100% |

The next decision involves the desired therapeutic concentration for the drug. Pseudomonas isolates from dairy cattle can vary in sensitivity to carbenicillin from 3.0 to 50 µg/ml. The clinical judgement we will use in this case is 10 µg/ml. How do we estimate a dose?

$$\text{Again, } D_o = \frac{\bar{C} \times V_d \times T}{1.44 \times T_{1/2} \times F} \quad \text{or} \quad \frac{(10\ \mu g/ml)\ (0.24\ L/kg)\ (12\ hrs)}{1.44 \times 2.0 \times 1.0}$$

$$D_o = 10\ mg/kg$$

If we wished to maintain a plasma concentration of 25 µg/ml, the dose would be increased to 25 mg/kg. (Note, dose and therapeutic concentrations do not always appear in parallel.)

*C. Economic Accessment of Multiple Drug Choices: Case Analysis of Minocycline, Tetracycline, and Oxytetracycline in the Dairy Cow.*[10]

There are many occasions in veterinary medicine when the economics of therapy come into question. The pharmacokinetic characteristics of a drug may allow a more accurate assessment of a drug of choice.

Presenting Case: 500 kg dairy cow with acute septicemic coliform mastitis.

Organism and Sensitivity:

*E. coli,* sensitive to most antibiotics

Drug Choice: Tetracyclines

Several factors are important. The rate and concentration achievable in plasma, as well as the serum/milk ratio should be considered.

TABLE 1. Use of antibiotics in patients with renal failure.

| | Principal Mode of Excretion or Detoxification | Appropriate Half-Life in Serum | | Proposed Dosage Regimen in Renal Failure | |
|---|---|---|---|---|---|
| | | Normal | Renal Failure* | Initial Dosage† | Give Half of Initial Dose at Interval of |
| Penicillin G | Tubular secretion | 0.5 hour | 6 hours | 6 gm IV | 8-12 Hours |
| Ampicillin | Tubular secretion | 1 hour | 8 hours | 6 gm IV | 8-12 Hours |
| Carbenicillin Ticarcillin | Tubular secretion | 1.5 hours | 16 hours | 4 gm IV | 12-18 hours |
| Methicillin | Tubular secretion | 0.5 hour | 6 hours | 6 gm IV | 8-12 Hours |
| Cephalothin | Tubular secretion | 0.8 hour | 8 hours | 4 gm IV | 18 hours |
| Cephalexin Cephradine | Tubular secretion & glomerular filtration | 1 hour | 15 hours | 2 gm orally | 8-12 Hours |
| Cefazolin | | 2 hours | 30 hours | 2 gm IM | 24 hours |
| Kanamycin | Glomerular filtration | 3 hours | 3-4 days | 15 mg/kg IM | 3-4 days |
| Amikacin | Glomerular filtration | 2.5 hours | 3 days | 15 mg/kg IM | 3 days |
| Gentamicin | Glomerular filtration | 2.5 hours | 2-4 days | 3 mg/kg IM | 2-3 days |
| Tobramycin | Glomerular filtration | 2.5 hours | 3 days | 3 mg/kg IM | 2 days |
| Vancomycin | Glomerular filtration | 6 hours | 6-9 days | 1 gm IV | 5-8 days |
| Polymyxin B | Glomerular filtration | 5 hours | 2-3 days | 2.5 mg/kg IV | 3-4 days |
| Colistimethate | Glomerular filtration | 3 hours | 2-3 days | 5 mg/kg IM | 3-4 days |
| Tetracycline | Glomerular filtration | 8 hours | 3 days | 1 gm orally or 0.5 gm IV | 3 days |
| Chloramphenicol | Mainly liver | 3 hours | 4 hours | 1 gm orally or IV | 8 hours |
| Erythromycin | Mainly liver | 1.5 hours | 5 hours | 1 gm orally IV | 8 hours |
| Clindamycin | Glomerular filtration and liver | 2.5 hours | 4 hours | 600 mg IV or IM | 8 hours |

* Considered here to be marked by creatinine clearance of 10 ml/minute or less.
† For a 60 kg adult with a serious systemic infection. The "initial dose" listed is administered as an intravenous infusion over a period of 1-8 hours, or as 2 intramuscular injections during an 8-hour period, or as 2-3 oral doses during the same period.
‡ Aminoglycosides are removed irregularly in peritoneal dialysis. Gentamicin is removed 60% in hemodialysis.

For Example:

| Drug Choices | Milk/Serum Ratio | Desired Conc. | T½ |
|---|---|---|---|
| Minocycline | 1.58 | 2 µg/ml | 9 hours |
| Tetracycline (aqueous) | 1.25 | 2 µg/ml | 6 hours |
| Oxytetracycline (aqueous) | 0.75 | 2 µg/ml | 4 hours |

*It is worth noting that there is a wide variation in half-life values for oxytetracycline in the literature [1, 8, 10]. Obviously things such as dose, vehicle, age, and methodologies have great impact on pharmacokinetic values.

Dose and Route:

20 mg/kg intravenously (determined empirically), estimating that this dose would produce serum concentrations of at least 5 $\mu$g/ml.

Cost/Cow: Based upon 500 kg cow at dose of 20 mg/kg.

Minocycline – total dose – 10 grams per day – @ $38.60/gm = $368.00

Tetracycline – total dose – 10 grams –t.i.d. – @ $4.48/gm = $44.80 x 3 = $134.40.

Oxytetracycline – total dose – 10 grams –b.i.d. – @ $5.68/gm = $56.80 x 2 = $113.60

It should be obvious that the cost of the drug and the desired therapeutic concentration of 5 $\mu$g/ml may not be reasonable except in special circumstances, e.g., very valuable dairy animal. Some compromise must be reached. The question is how this should be done. Clinically this may simply involve cutting the dose in half and guessing.

There are better ways to manipulate dose to acquire a desired steady-state therapeutic concentration, e.g.:

Desired drug concentration in milk =0.5 $\mu$g/ml and wish to maintain this concentration at an average steady state: Remember our formula!

$$\bar{C} = \frac{F\ (D_o)\ 1.44\ T_{1/2}}{V_d \times T}$$

We wish to calculate the dose required for minocycline to maintain an average steady state concentration of 0.5 $\mu$g/ml in milk. The milk/serum ratio = 1.58 for minocycline, therefore, we need to establish a serum concentration of 0.375

Therefore:

$$D_o = \frac{\bar{C} \times V_d \times T}{F \times 1.44 \times T_{1/2}}$$

$$D_o = \frac{.000375\ \text{mg/ml} \times 500\ \text{ml/kg} \times 24\ \text{hours}}{1.0 \times 1.44 \times 9\ \text{hours}}$$

$$D_o = 0.4\ \text{mg/kg}$$

TABLE 2. Pharmacokinetic values for carbenicillin, carfecillin, ticarcillin and BL-P 1654 administered intravenously to lactating cows.

| | Carbenicillin | | Carfecillin | | Ticarcillin | | BL-P 1654 | |
|---|---|---|---|---|---|---|---|---|
| | Mean ± 1 SD | Mean ± 1 SD | Mean ± 1 SD | Mean ± 1 SD | Mean ± 1 SD | Mean ± 1 SD | Mean ± 1 SD | Mean ± 1 SD |
| Dose mg/kg | 8.8 ± 0.4 | 26.7 ± 0.3 | 8.7 ± 0.3 | 21.8 ± 0.7 | 8.7 ± 0.6 | 26.0 ± 0.2 | 8.4 ± 0.2 | 22.2 ± 1.4 |
| No. of cows | 4 | 3 | 4 | 2 | 4 | 3 | 4 | 3 |
| Kinetic value | | | | | | | | |
| A°, ug/ml | 29 ± 15 | 107 ± 15 | 49 ± 27 | 218 ± 60 | 43 ± 27 | 225 ± 109 | 91 ± 41 | 144 ± 79 |
| B°, ug/ml | 1.6 ± 0.2 | 7.0 ± 3.1 | 2.6 ± 1.1 | 6.7 ± 0.4 | 1.4 ± 0.4 | 25 ± 23 | 17 ± 14 | 3.6 ± 1.8 |
| a, $min^{-1}$ (x $10^{-3}$) | 27 ± 2.0 | 26 ± 6.0 | 48 ± 22 | 30 ± 8.0 | 46 ± 17 | 46 ± 33 | 83 ± 43 | 10.2 ± 4.7*** |
| , $min^{-1}$ (x $10^{-3}$) | 9 ± 2.2 | 7.5 ± 0.5 | 4.4 ± 2.3 | 0.57 ± 0.04*** | 12.7 ± 3.3 | 9.7 ± 2.0 | 8.3 ± 1.9 | 3.3 ± 0.02** |
| $k_{12}/k_{21}$ | 0.38 ± 0.14 | 0.29 ± 0.03 | 2.1 ± 0.8 | 7.5 ± 1.8*** | 0.52 ± 0.31 | 0.59 ± 0.51 | 0.95 ± 0.30 | 0.20 ± 0.01* |
| $v_1$, 1/kg | 0.24 ± 0.03 | 0.24 ± 0.04 | 0.22 ± 0.14 | 0.10 ± 0.01 | 0.19 ± 0.07 | 0.12 ± 0.06 | 0.09 ± 0.02 | 0.17 ± 0.09* |
| $v_{dss}$, 1/kg | 0.33 ± 0.06 | 0.30 ± 0.05 | 0.66 ± 0.34 | 0.84 ± 0.18 | 0.28 ± 0.07 | 0.19 ± 0.07 | 0.16 ± 0.06 | 0.21 ± 0.10 |
| $C1_B$, 1/min/kg(x $10^{-3}$) | 5.52 ± 0.47 | 4.34 ± 0.4*** | 5.56 ± 1.5 | 1.74 ± 0.33** | 5.32 ± 0.52 | 2.92 ± 0.10*** | 2.5 ± 0.14 | 1.38 ± 0.09** |
| t½, min | 122 ± 24 | 97 ± 13 | 184 ± 101 | 739 ± 26*** | 65 ± 24 | 121 ± 48* | 83 ± 18 | 304 ± 138** |
| 0 hormal milk AUC 600 min / AUC° serum, % | 4.6 ± 2.3 (n=11) | 3.7 ± 0.9 (n=4) | 6.2 ± 3.0 (n=12) | 1.4 ± 0.4*** (n=6) | 5.7 ± 2.3 (n=7) | 3.5 ± 0.9 (n=7) | 7.6 ± 3.4 (n=9) | 6.0 ± 5.4 (n=7) |
| 0 mastitis milk AUC 600 min / AUC° serum, % | 12.0 (n=1) | 5.9 ± 2.8 (n=6) | 25.0 (n=1) | Not done | 11.4 ± 5.6 (n=5) | 11.4 ± 2.9 (n=3) | 41.4 ± 13.0 (n=7) | 12.0 ± 3.3 (n=4) |

* = P 0.05; ** = P 0.01; *** = P 0.005 significance of differences when the mean kinetic values obtained with the two dose levels are compared.
n = number of quarters.
From Nouws, Ref. 6.

Total dose/day minocycline = 0.40 mg/kg x 500 kg = 200 mg
Cost = $7.72/day

If the desired steady state concentration in milk were to be 2 μg/ml, this would require a dose of 1.85 mg/kg or 925 mg/day which would be about $35.00/day.

The equivalent numbers for tetracycline at the desired 2 μg/ml concentration would require 1.24 mg/kg three times per day or 1860 mg total dose = $8.30/day. The equivalent numbers for oxytetracycline at the desired 2 μg/ml concentration would require 4.58 mg/kg twice daily or 4580 mg total dose = $26.00/day.

*D. Critical Tissue Distribution Estimates: Case Analysis, Uterine Wall Infection in the Bovine.*

As veterinary medicine moves into the computer era, it is reasonable to forecast a need to become more efficient and economical in the choice and dosing of clinical patients. As pharmacologists, we have often wondered if it would not be more appropriate to estimate dosage on the basis of the tissue and the target site of an infection. We are approaching (if not already there) a time when, given the information regarding the critical distribution estimates of a drug, dosing can become a function of the tissue site, as well as the tissue concentration needed.

In a recent study reported by Bretzlaff, et al., ([1] [2]) involving a pharmacokinetic study with oxytetracycline, they have reported some critical plasma-to-tissue ratios in genital tract tissues of post-partum cows. This data would now allow us to calculate a precise dose of drug for a specific tissue site of infection (Table 3).

Tissue-to-plasma Ratios for Oxytetracycline:

| Caruncles | Endometrium | Uterine Wall | Ovaries |
|---|---|---|---|
| 0.95 | 1.33 | 1.88 | 1.04 |

TABLE 3. Concentrations of OTC in plasma (ug/ml), and genital tissues (ug/g), and plasma-to-tissue ratios of OTC concentrations in postpartum cows after 8 hours of constant IV infusion of OTC at a rate predicted to give a plasma plateau concentration of 5 ug/ml.

| Item | Cow 17 | Cow 18 | $\bar{X}$ | SD |
|---|---|---|---|---|
| Plasma (ug/ml) | 4.96 | 4.13 | 4.54 | 0.59 |
| Intact uterine tissue (ug/g) | 4.11 | 3.45 | 3.78 | 0.47 |
| Caruncles (ug/g) | 5.36 | 4.21 | 4.78 | 0.81 |
| Endometrium (ug/g) | 3.59 | 3.23 | 3.41 | 0.26 |
| Uterine wall (ug/g) | 2.65 | 2.19 | 2.42 | 0.32 |
| Ovaries (ug/g) | 4.45 | 4.28 | 4.36 | 0.12 |
| Plasma: intact uterine tissue | 1.21 | 1.20 | 1.20 | 0.01 |
| Plasma: caruncles | 0.92 | 0.98 | 0.95 | 0.04 |
| Plasma: endometrium | 1.38 | 1.28 | 1.33 | 0.07 |
| Plasma: uterine wall | 1.87 | 1.89 | 1.88 | 0.01 |
| Plasma: ovaries | 1.11 | 0.96 | 1.04 | 0.11 |

From Bretzlaff[2]

Presenting Case: 500 kg cow with fulmanating infection of the uterine wall.

Assumptions: Oxytetracycline is the drug of choice; wish to use the drug intramuscular, and need to maintain a steady state level of 1 μg/gm of infected tissue. Thus, we would need to maintain 2x the desired tissue level, or about 2 μg/ml in the serum.

Necessary pharmacokinetic parameters:

$T = 12$ hours (recent estimation) [2]
$V_d = 0.80$ L/kg
$F = 80\%$

Methodology:

$$D_o = \frac{\bar{C} \times V_d \times T}{F \times 1.44 \times T_{1/2}}$$

$$D_o = \frac{2\ \mu g/ml \times 800\ mg/kg \times 12\ hours}{.80 \times 1.44 \times 12\ hours} = \frac{19.2}{13.82}$$

$D_o = 1.38$ mg/kg B.I.D.

The tissue ratios did not change in cows with diseased reproductive tracts, ([2]) therefore our estimates should hold true in the diseased animal.

The label recommended dosage for oxytetracycline in the bovine is 3-5 mg/lb/BWT per day.

*E. Estimating or Projecting Drug Withdrawal Times: Case Analysis, Carbenicillin in Dairy Cows*

A few years back we published a general classification scheme for consideration of drug residue potential on the basis of pharmacokinetic profiles.[5] I find these criteria very useful particularly if the drug in question has had any pharmacokinetic studies done in the target specie or any other species. These criteria involved classifying drugs into types depending upon pharmacokinetic values. Since I recently presented the details in a talk at the Food Animal Conference at Ohio State, I will only refer to the example that fits carbenicillin.

*Type I Drugs—Low risk for extended residues*

1. Rapid absorption rate constant ($k_{ab}$).
2. High degree of absorption (> 90%). Absorption of drugs from aqueous solutions is rapid and almost complete.
3. Low volume of distribution ($V_d$) (organic acids), <0.2-0.25 liter/kg.
4. Short biological half-life ($t_{1/2}$ < 1 hr)—for example, penicillins and cephalosporins.
5. One or two compartment model drugs.
6. Low affinity for tissues.

An example of the deliberation process for drugs which may fall in this category include some of the newer beta-lactam antibiotics such as carbenicillin, carfecillin, ticarcillin, and BL-P1654. Table II taken from a current reference by Nouws ([6]), et al., demonstrates several important relationships for drugs for which adequate residue data have not been developed. Ampicillin has been

approved for certain uses in the bovine with an established withdrawal time of *6 days*. Milk withdrawal has been established at 4 milkings. When you compare the T½, volumes of distribution, clearance rates, and tissue penetration ($K_{12}$, $k_{21}$) ratios, many of the beta-lactam antibiotics have very similar pharmacokinetic profiles, and thus similar withdrawal times (Table 4) ([6 7 9]). If I have to estimate a withdrawal time for any of these drugs that have been used in a food animal, I use a rule of thumb of doubling the known withdrawal times, or those that have been estimated.[7] This means that for carbenicillin when used for a pseudomonas infection in a dairy cow, I would estimate a *12 day* withdrawal and a *96 hour* milk discard time. In general, Type I drugs will be virtually eliminated within a 10 day period. With regard to excessive dosing, I generally double the withdrawal time. You can see from actual data in Table 4 that this withdrawal time would be more than adequate.

TABLE 4. Calculated withdrawal times in hours for beta-lactam antibiotics in tissues of normal dairy cows after a single intramuscular injection of several products. (At an arbitrary detection limit of 0.01 or I.U./ml tissue fluid).

| Antibiotic Product | Dose[a] | Muscle Drip | Serum | Kidney Cortex |
|---|---|---|---|---|
| Sodium penicillin G (E) | 9.0 | 12 (14)[b]<br>15* | 12 ( 14)[b] | 14 ( 16)[b]<br>18* |
| Sodium ampicillin (F) | 10.1 | 13 (17) | 14 ( 18) | 18 ( 24) |
| Sodium amoxycillin (H) | 8.9 | 9 (12) | 13 ( 17) | 15 ( 20) |
| Sodium cephapirin (J) | 8.5 | 10 (13) | 11 ( 14) | 14 ( 18) |
| Sodium cephacetrite (L) | 8.5 | 11 (13) | 11 ( 12) | 15 ( 17) |
| Procaine penicillin G (A) | 9.3 | 41 (51)<br>41* | 45 ( 55) | 63 ( 81)<br>69* |
| Penethamate hydriodide (B) | 9.0 | 19 (21) | 43 ( 46) | 48 ( 66) |
| Procaine penicillin G (C) | 6.9 | 33 (44) | 38 ( 51) | 51 ( 73) |
| Procaine penicillin G (D) | 6.5 | 34 (40)<br>33* | 33 ( 39) | 44 ( 54)<br>51* |
| Ampicillin trihydrate (G) | 12.5 | 76 (89) | 87 (104) | 117 (145) |
| Amoxycillin trihydrate (N) | 13.0 | 74 (81) | 73 ( 80) | 97 (104) |
| Benzathine cephapirin (K) | 8.3 | 21 (43) | 76 (117) | 105 (155) |

(b) Calculated withdrawal time in hours by substituting the drug concentration ratio between tissue and serum (R), mean C and of the drug in serum in Equation 6. The extreme values are given in brackets (see material and methods).

* Calculated withdrawal time in hours by substituting the tissue parameters from Table 3 into Equation 6.

(a) Dose in I.U. (x 1000) or mg/kg live weights.

From Nouws & ZIV, Ref. 6.

## Conclusion

**With the advent of microcomputers to handle the mathematics involved in pharmacokinetics, along with the continuing development of rapid analytical methodologies for many clinical drugs, it is entirely reasonable to expect a great expansion and application of pharmacokinetics to clinical veterinary medicine within this decade. It is my hope that practitioners will begin to invest in acquiring the available knowledge which will allow more precise dosage estimations in those specific cases where the need is obvious.**

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