

DR. MILLER: Thank you, Dr. Harvey. Our next presentation will be "Clinical Dose Determination" by Dr. Dwight Mercer. Dwight is a graduate of the University of Georgia, College of Veterinary Medicine, and he did his graduate work and received his Ph.D. under Dr. Tom Powers at Ohio State University. He had 12 years of service at the Food and Drug Administration and is now Director of the Research Program in the College of Veterinary Medicine at Mississippi State University. I've been told, not by Dwight but by someone else, that he likes to hunt, fish, and eat oysters -- not necessarily in that order. So, Dwight, I think we're ready to go.

DR. MERCER: Good morning and thank you, Bob, for that introduction; I appreciate that. I do like to hunt, fish, and eat oysters, and if the season's allowing it, I do quite a bit of it when I get a chance.

H. Dwight Mercer, DVM, PhD

Introduction:

In the mental preparation for a presentation of a topic with the complexities, variables, and personal preferences often encountered in clinical dosing, it was/is my intention to "tell it like it is" (to borrow a phrase from the well-known commentator) yet inject as much fairness and balance as my experience and knowledge will permit. Practicing veterinarians are a fiercely independent group of professionals. They demand and expect "room" for clinical judgement. They are not overly prone to being regulated, and will often "fall-back" to personal experience and preferences. AS a group, their primary source of information about drugs is still the drug company's detailmen. The practitioner commonly deals with the availability of new drugs and new information by trial and comparison, often reverting to tried and proven drugs, particularly if the economics are more favorable. He thus settles into a repertoire of drugs (average 15-20 drugs) that he is comfortable with and that, through experience, he can depend upon. He uses this group of drugs daily, on all species he encounters, and establishes his own judgements about the dose he uses and the effectiveness of that drug.

Given that this is a fair assessment of the practicing veterinarian, it is reasonable to project at least four levels of distinct interests in clinical dosing, all carrying their viewpoints, data bases and biases, yet none of which are non-participants in the issue of clinical dosing. These are:

1. Drug Development (The Drug Industry)
2. Regulatory Aspects (The Food and Drug Administration)
3. Academic Medicine (Clinical Pharmacologist)
4. Veterinary Practitioner (While being the primary user, often has the least involvement in the development of drug dosing regimens).

(Time nor space will allow me to address the over-the-counter and feed additive categories of drugs, which in their own right, pose numerous additional considerations). Using this perspective, let's see if we can use a single drug to illustrate some of the complexities of the clinical dose issue. Gentamicin is a good candidate for this exercise.

Drug Development Phase

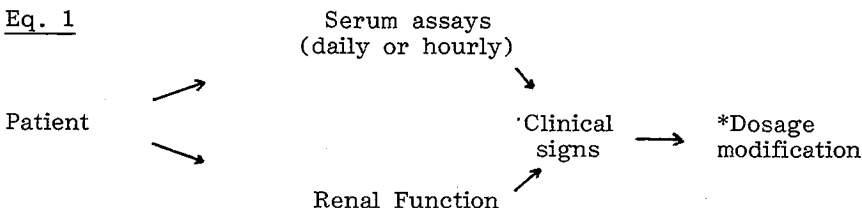
The dollars and time have been spent; the composition, chemistry, activity, pharmacology, toxicity, indications and recommended dosages are on the labels and package inserts. The product is limited to use in dogs, cats and horses. The dose in dogs and cats is 2 mg/lb given twice the first day, and once a day thereafter for 4-6 days. The precautions include a statement that says "dogs and cats with greatly impaired renal function be given one-half or less the dosage of gentamicin recommended for patients with normal renal function."

Regulatory Activities

Great amounts of manpower and expertise have been spent reviewing, negotiating, and finally approving this product. The label meticulously represents the supporting data.

Academic Medicine

Along comes a 10 kg dog with a urinary tract infection, culture positive for a coliform organism, sensitive to very few antibiotics (Gentamicin being one of these), with a BUN of 50 mg/%. The internal medicine specialist and the clinical pharmacologist swing into action. Renal compromise is likely, and gentamicin is the drug of choice (because of sensitivity). Ideally, and from a "best medicine" viewpoint, a monitoring profile model should be initiated, i.e.



*In human medicine and with certain toxic drugs, i.e., Digitalis glycosides, this model can be practiced on a routine basis. (3)

The renal compromise issue can be handled and the revised half-life of the drug calculated; e.g.

Eq. 2

$$t_{\frac{1}{2}} \text{ r.f.} = \frac{t_{\frac{1}{2}}}{\left[\left(\frac{\text{Cl creat obs}}{\text{Cl creat norm}} \right) - 1 \right] \times \text{Fe} + 1}$$

where $t_{\frac{1}{2}}$ is the normal value for the half-life of the drug, Cl creat obs is the creatinine clearance of this patient, Cl creat norm is the creatinine clearance value for a normal patient (120 ml/min), Fe is the fraction of the drug which is eliminated by the kidney and $t_{\frac{1}{2}} \text{ r.f.}$ is the half-life of this drug in this patient who is suffering from renal failure.

Given the necessary pharmacokinetic parameters for Gentamicin, one can recalculate the half-life, i.e., normal $t_{\frac{1}{2}} = 2.5$ hours, Fe = 90%, Vd = 0.25 L/kg

Eq. 3

$$t_{\frac{1}{2}} \text{ r.f.} = \frac{2.5}{\left[\left(\frac{.5 \text{ ml/min}}{120 \text{ ml/min}} \right) - 1 \right] \times .9 + 1}$$
$$t_{\frac{1}{2}} \text{ r.f.} = 24 \text{ hours}$$

The desired therapeutic concentration of Gentamicin is about 4-5 ug/ml,

whereas peak concentrations which exceed $12-15$ (4) ug/ml (2-3x) are associated with a higher incidence of toxic effects. Thus, with the use of a steady-state dosing equation;

$$\text{Eq. 4} \quad D = \frac{\bar{C} \times Vd \times \tau}{1.44 \times t_{\frac{1}{2}} \times F}$$

where D is the dose to be administered, \bar{C} is the average steady state level desired, Vd is the volume of distribution, τ is the desired dosing interval, $t_{\frac{1}{2}}$ is the drug half-life and F is the fraction of the administered dose which² can be absorbed, an accurate estimate of the appropriate dose can be calculated; e.g.

$$\text{Eq. 5} \quad \text{Dose} = \frac{5 \text{ ug/ml} \times 0.25 \text{ L/kg} \times 12 \text{ hours}}{1.44 \times 24 \text{ hrs} \times 1 \text{ (assume IV administration)}}$$

$$\text{Dose} = 0.43 \text{ mg/kg q } 12 \text{ H or } 0.86 \text{ mg/kg q } 24 \text{ H}$$

The recommended dose, as you will recall, was 2 mg/lb (or 4.5 mg/kg) given twice the first day, and once per day subsequently. Thus, the labelled dosage recommendations will not satisfy the needs of this patient and in fact is fairly certain to lead to a toxic response. Actually, if you look at table 1, you will note that, in man, the half-life of Gentamicin reverts to 2-4 days (48-96 hrs) in renal compromised patients, in which case, a quite severe reduction in dose and dosing interval would be essential. Please note that most antibiotics that depend upon glomerular filtration have (in most cases) extreme increases in half-lives.

Practicing Veterinarian:

Given the same case, and assuming no adverse idiosyncracies in his/her Gentamicin dosing schedule, and following the label directions for a renal compromised dog, the dose would be about 2.25 mg/kg once/day unless we can expect the practitioner to quantitate the term less on the label. It is reasonable to speculate that some clinical toxicoses from Gentamicin would be likely to occur in this instance.

A second clinical example can be used to illustrate another circumstance that the practicing veterinarian and those in academic medicine face almost on a daily basis. Estimating dosages of drugs that while indicated, are not specifically approved (7) in food animals. Chloramphenicol is a good candidate for this exercise.

Presenting Case: Acute septic mastitis in a valuable 500 kg dairy cow in which an E. coli, sensitive only to chloramphenicol has been isolated. The essential pharmacokinetic parameters in the bovine for this drug are:

$$t_{\frac{1}{2}} = 3.5 \text{ hours}$$

$$Vd - 1.33 \text{ L/kg}$$

Drug Choice
Chloramphenicol

Serum/Milk Ratio
1.0

Desired conc
5 ug/ml

Rationale: Looking for maximum achievable plasma levels of the drug and to maintain a steady state concentration.

Dose and Route: Since Chloramphenicol⁽⁷⁾ is not approved for use in food animals, the dose has to be calculated to meet preestablished clinical criteria, e.g., to maintain an average steady state concentration of at least 5 ug/ml in the udder.⁽⁸⁾

Methodology:

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

$$D_o = \frac{0.005 \text{ mg/ml} \times 1330 \text{ ml/kg} \times 8 \text{ hours}}{1.0 \times 1.44 \times 3.5 \text{ hours}}$$

$$D_o = 10.5 \text{ mg/kg t.i.d.}$$

A 500 kg cow would then require 5250 mg x 3 = 15750 mg (15.7 gm) of Chloramphenicol per day, given intravenously.

Cost/Cow: 500 kg cow treated t.i.d. would require 15 gm of drug at 4.05/gm = \$60 per day, which is reasonable for a valuable cow that may be producing 20,000 lbs of milk/year. A major responsibility now resides with the veterinarian to be sure that this animal does not enter the food chain in a reasonable period of time.^(5,6)

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 pharmacologist, 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 ratio's 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.

Tissue-to-plasma Ratio's for oxytetracycline:

Caruncles
0.95

Endometrium
1.33

Uterine Wall
1.88

Ovaries
1.04

Presenting Case: 500 kg cow with fulminating 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 ug/gm of infected tissue.

Necessary pharmacokinetic parameters:

$$t_{1/2} = 12 \text{ hours (recent estimation)}^{(2)}$$

$$V_d = 0.80 \text{ L/kg}$$

$$F = 80\%$$

Methodology:

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

$$D_o = \frac{2 \text{ ug/ml} \times 800 \text{ ml/kg} \times 12 \text{ hrs}}{.80 \times 1.44 \times 12 \text{ hours}} = \frac{19.2}{13.82}$$

$$D_o = 1.38 \text{ mg/kg B.I.D.}$$

The tissue ratio's 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.

This little exercise has been but a sampling of the number of clinical examples one could use to demonstrate the complexities of clinical dosing. The neonate vs. the geriatric patient, obese vs. dehydrated patients, diseased vs. normal, human drugs vs veterinary drugs (and their common cross-overs) are but a few more that could be cited. However, I believe the points have been made.

Summary Observations:

1. The drug industry can not afford nor find the clinical materials needed to study all the dosing variables encountered in clinical medicine.
2. The regulatory agencies must visualize and adopt the methodology needed to expand the scope of drug approvals rather than narrowing the spectrum.
3. Acamadecians have the tools and are using and teaching students the science of drug dosing.
4. The practitioner will continue to use his clinical judgements in selecting and using the drugs available to him and those needed to meet his client's needs.

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	Tubular secretion	1.5 hours	16 hours	4 gm IV	12-18 hours
Ticarcillin	Tubular secretion	0.5 hour	6 hours	6 gm IV	8-12 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	Tubular secretion	1 hour	15 hours	2 gm orally	8-12 hours
Cephradine	& glomerular				
Cefazolin	filtration	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 or 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.

Table 2. 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⁾

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