Approved and Unapproved Drug Use in Dairy Cattle

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The purpose of this presentation is to acquaint the members of this group with the veterinarian's role in treating lactating dairy cows. I'll first discuss the criteria used in selecting a course of therapy and then discuss drugs that are being used and why unapproved drugs are used for certain conditions. Selection of withholding times for unapproved drugs will also be examined.

Choosing the best antibiotic depends on several factors, all of which must be considered if optimal success is to be achieved. The primary concerns are the identity of the infectious agent, the nature of the disease process and the properties of the drug to be used.

Diagnosis of the disease is the initial step. The practitioner bases his diagnosis on the case history, the physical examination and possibly on the results of laboratory tests. He also considers the environment, management practices, the herd's vaccination history and the history of prior treatment attempts by the owner. For any drug to be used effectively, there must be a balance between the diagnostic and therapeutic efforts.

Determination of the causative agent(s) is the end result of the diagnostic effort. Sometimes the practitioner may only be able to narrow the possibilities to two or more bacteria after his initial examination. In this case a broad spectrum antibiotic or two antibiotics may be required. In other instances, he may know the bacteria's identity via a culture or other test. In this event, the practitioner can select an antibiotic which works more selectively against the known agent.

The next thing considered is the disease process. The disease process relates to the effects of the agent against the host's tissues and the effects of the body's defense mechanisms against the agent. Full understanding of the disease process requires the practitioner's knowledge of physiology, anatomy, bacteriology and pathology. It is imperative to select a therapeutic regimen that will enhance, not hinder, the body's defense mechanisms.

Once the practitioner has established the diagnosis and the identity of the infectious agent, he must also consider economics, the dairyman's experience and attitude, his own experience and the properties of the drugs themselves. As you will see, each of these will enfluence the selection of the antibiotic.

First, the treatment must be cost effective. Does the worth of the cow and the chance of success justify the cost of the proposed therapy? If more than one drug may be equally effective, which one would be more economical? These questions must always be addressed when a therapeutic program is being developed.

The experience and attitude of the dairyman are essential considerations. In many cases, the dairyman will be responsible for administering follow-up medication. Thus, the drug used must be one that he is capable of using correctly. Furthermore, we must consider his attitude towards withholding milk and slaughter withholding. Because the dairyman is ultimately responsible for withholding, veterinarians will not use some drugs for a client that cannot be trusted to comply with their instructions.

The practitioner's experience and knowledge also affect his decision. He will assess previous attempts against similar diseases and their success or failure. He also relies on the knowledge he has gained through his basic education, private readings and continuing education seminars. The practitioner's decision will also reflect his willingness to use, or not to use, unapproved drugs and to accept the responsibility for their use.

Finally, the properties of the different drugs must be considered. The basic goal of treatment is to select the appropriate drug and to administer it in such a way and for a time adequate to bring about a cure without causing side effects. In other words, we need to get the antibiotic to the site of infection and we need to maintain it there long enough and at a level high enough to eliminate the bacteria. To meet this goal, it is important to understand what happens to the drug once it is in the body.

The scientific study of pharmacokinetics relates to this movement of drugs within the body. By understanding the drugs' pharmacokinetics, basic chemistry, spectrum, bioavailability, mode of action and toxicity potential, we can more precisely develop a therapeutic program that has a chance to succeed.

Unfortunately, much of the required information is not included on the label or the package insert of many veterinary drugs. Often, the insert will only provide information on suggested doses, route of administration,

recommended uses and withdrawal times. This is certainly essential information, but we also need information concerning the drug's minimum inhibitory concentration (MIC) for different bacteria and the drug's chemical and pharmacokinetic properties. The MIC indicates the concentration of drug that is necessary to kill bacteria or to inhibit their growth. The other properties determine how the drug moves through the body.

Knowing the MIC of an antibiotic for different bacteria is invaluable. When we refer to the spectrum of an antibiotic, we are actually referring to the antibiotic's potential activity based on the MIC required to eliminate groups of bacteria. Some treatment failures that are blamed on bacterial resistance may really be the result of not achieving adequate tissue concentrations of the antibiotic. Therefore, the drug chosen must be capable of reaching a level in the infected organ that is high enough to eliminate the organism.

In the body, most drugs move from the blood stream into the tissues by passive diffusion across biomembranes. Several factors are involved when a drug crosses a biomembrane. First is contact time. Obviously, the longer that the drug is in contact with the membrane, the better is the chance for diffusion to occur. Secondly, we want a drug of small molecular size. Next, the drug should be lipid soluble because most biomembranes are lipid in nature.

Two other factors involved with diffusion of drugs are protein binding and the degree of ionization. These factors influence the amount of free drug which is available for diffusion. A low degree of protein binding is preferable because only the unbound portion of the drug is available.

The degree of ionization is also related to availability. Most drugs are either weak acids or weak bases. Because of this, the drug exists in both the ionized and nonionized forms. However, only the nonionized form is easily diffused. The ratio of ionized : nonionized drug depends on the pH-pKa coefficient.

The pH-pKa coefficient means that the proportion of the drug in the nonionized or available form depends on the dissociation constant (pKa) of the drug and pH of the medium. Thus, weak acids are more fully ionized when the pH is greater than the pKa and weak bases are more fully ionized when the pH is less than the pKa. For example, the pH of blood is 7.4 and the pH of milk is 6.6 to 6.8. We can then expect that drugs that are weak bases to dissociate more fully in milk than serum. In other words, the milk compartment will tend to trap basic antibiotics. This information is very important when choosing drugs for mastitis therapy and also explains why the serum concentration of some antibiotics is not a true reflection of the antibiotic's concentration in different body tissues.

Pharmacokinetic studies are very useful. A drug's pharmacokinetic values represent those intrinsic factors that characterize the drug's movement within the body. Because it is often difficult to determine actual drug concentration at the site of infection, knowledge of kinetic behavior can help to predict the drug's distribution to different organs. This information can tell us if we can reach the MIC for a specific organism and also helps to establish the dosage and dosage interval.

The last consideration of drug properties is bioavailability from the injection site. Most antibiotics achieve different serum concentrations when given by different routes. The dosage and dosage intervals are influenced by the rate of uptake into the circulation from the injection site when intramuscular (IM) or subcutaneous (SC) injections are given. Thus, the serum concentration and the duration of the drug will be affected by the route it is administered.

Final thoughts on therapeutics concern supportive therapy and drug interactions. Supportive therapy is often used in conjunction with antibiotic therapy. It is usually used to combat specific symptomatic problems. As with antibiotic therapy, the practitioner must evaluate the patient's condition and then assess the need for supportive drugs based on the parameters discussed previously.

Drug interactions must be fully understood and the potential advantages and disadvantages must be weighed if two or more drugs are to be used concurrently. Some drugs react with each other while still in the syringe or bottle while others react within the body. Interactions can be synergistic (enhancement) or antagonistic (inhibition). Drug combinations such as penicillin and streptomycin are synergistic while combinations such as penicillin and tetracycline can be antagonistic.

Practitioners use two or more antibiotics concurrently to achieve known synergistic effects, to treat mixed or multiple infections and as initial treatment for severe and undiagnosed infections. When using antibiotic combinations, the practitioner must be aware of possible antagonism, side effects and the possibility of changing the withdrawal times for one or both of the antibiotics.

In summary, the practitioner needs to consider many factors before initiating therapy. He must first arrive at a diagnosis and determine the causative agent. He must then select an antibiotic which will achieve a concentration at the site of infection adequate to inhibit or eliminate the bacteria. To do this he must be familiar with the drug's chemistry, spectrum and pharmacokinetics. He must also consider withdrawal times, the client's attitude and capability, his personal experience and the economics of the situation. Only after evaluating all of these parameters can the practitioner make the most responsible antibiotic selection.

Having discussed the decision process in therapy selection, I would next like to discuss some of the antibiotics that dairy veterinarians use, how these are used and why the practitioner may use antibiotics not approved for use in dairy cattle in certain situations. For this discussion, an "approved drug" will refer to one which is labeled for use in lactating dairy cattle. An "unapproved drug" is one which does not have label clearance for use in lactating dairy cows and which may or may not be approved for use in food-producing animals. A "prescription drug" means a drug that

is available only for use by or on the order of a licensed veterinarian. "Approved use" means that the drug is being used in accordance with label directions and "unapproved use" indicates that the drug is being used at a dose or in a manner that is not indicated on the label.

How many injectable and oral antibiotics are available for the systemic or parenteral treatment of lactating dairy cattle? I am aware of only eight—tylosin, erythromycin, procaine penicillin G, pen-strep, ampicillin trihydrate, dihydrostreptomycin, neomycin and several sulfonamides. All of these drugs, except for dihydrostreptomycin and ampicillin trihydrate, are available over-the-counter to dairymen. Table No. 1 lists these antibiotics, dosage information and withholding times.

In addition to parenteral antibiotics, there are several products available for intramammary or intrauterine administration to lactating cows. Table No. 2 lists these antibiotics. Note that only hetacillin and cloxacillin are prescription drugs.

By using these antibiotics according to label directions, the practitioner will ensure compliance with drug withholding regulations. However, some situations may require a marked increase of drug dosage, a different route of administration and/or more frequent administration. In these situations, following the label-approved directions may not produce the desired therapeutic effect. It is for this reason that the practitioner can find himself in a dilemma. On one hand, he must assume full responsibility for any drug he uses in an unapproved manner. This includes possible side effects and milk and meat residue violations that may occur from the unapproved use of the drug. On the other hand, the practitioner has a responsibility to provide the best and most scientifically sound therapy available. To provide this kind of care, the practitioner may use approved drugs in manners not printed on their labels.

In my opinion, there are several reasons for using approved drugs in unapproved manners. Because most of these drugs are readily available over-the-counter, they are frequently used by the dairyman without veterinary consultation. For that reason, they are frequently underdosed, overdosed, not given often enough or long enough and used to treat resistant organisms. Improper use of these drugs can then create several problems, two of the most important being the development of resistant bacteria and the prolongation of the disease.

Improper initial dosages, sub-therapeutic dosages and short duration of therapy can result in a condition where bacterial inhibition is not maintained. This leads to the formation of drug resistant mutant strains. The problem of drug resistant bacteria seems fairy common in our practice as witnessed by sensitivity testing and clinical experiences. To overcome bacterial resistance, it is necessary to use a different type of antibiotic or, in some cases, to use a higher dose of the same drug.

Recently published papers on the use of approved and unapproved antibiotics have given the practitioner vital

TABLE 1

Approved Antibiotics, Dosage Regimens and Withdrawal Times

Drug	Dosage	Interval	Route	Milk (hrs)	Slaughter (days)
Tylosin	2-4mg/kg	OD	IM	96	8
Erythromycin	2-4mg/kg	OD	IM	72	15
Penicillin	6000u/kg	OD	IM	48	5
Pen-Strep	4000u/kg	OD	IM	72	30
Sulfas	varies	OD	var.	var.	var.
Ampicillin	6-10mg/kg	OD	IM	48	6
D.H.S.	11 mg/kg	BID	IM	48	30
Neomycin	11mg/kg	OD	PO	48	30

TABLE 2

Approved Intramammary and Intrauterine Antibiotics

Drug	Dosage	Route	Milk (hrs)	Slaughter (days)
Penicillin	100,000 u/qtr	IMI	60	3
Hetecillin	62.5 mg/qtr	IMI	72	10
Cephapirin	200 mg/qtr	IMI	96	4
Erythromycin	300 mg/qtr	IMI	36	0
Cloxacillin	200 mg/qtr	IMI	48	10
Oxytetracycline	426 mg/qtr	IMI	96	4
Pen/Novobiocin	100,000 u/150 mg/qtr	IMI	72	15
Neomycin SO_4	1 to 2 g	IU	48	30

information on the uses of these drugs (2,4,5,7,9,11,12,13,14,15). Approved dosages, routes of administration and dosage intervals have often been shown to be ineffective and clinical experience bears this out. Table No. 3 includes several approved antibiotics that are used in practice and the dosages, intervals and routes of administration that can be used to increase the drugs' effectiveness.

TABLE 3

Examples of Unapproved Dosage Regimens

Drug	*Dose*	Interval	Route
Tylosin	13 mg/kg	BID	IV, IM
Erythromycin	13 mg/kg	BID	IM
Penicillin	22,000 u/kg	OD, BID	IM
Pen-Strep	8,000 u/kg	BID	IM
Ampicillin	22 mg/kg	BID	IV, IM
Penicillin	100,000 u	OD	IU

As you can see, we have increased the dosage for all of the drugs, we are giving four of them twice daily instead of once daily and tylosin and ampicillin can be used IV. Recent work does support these dosage regimens (2,4,5,7,12,14). It is my clinical opinion that when used at the listed regimens, these antibiotics are effective in treating certain bacterial infections that do not respond to the label-approved dosage schedules. When using these drugs at the higher dosages and increased frequencies, it may be necessary to increase the withholding times for both milk and slaughter.

I'd also like to mention that some of these approved antibiotics can also be administered via a route that is not label-approved. Examples include the use of oral sulfonamide solutions for intravenous administration and the use of injectable penicillin and pen-strep for intramammary and intrauterine infusions. Using approved drugs in these manners also places the responsibility for withdrawal times on the practitioner as well as liability for adverse reactions.

The next topic to discuss is the use of antibiotics that are not approved for use in lactating dairy cows. These drugs may or may not be approved for use in other food-producing animals. Obviously, the practitioner's liability and responsibility when using these unapproved drugs are greater than when using an approved drug in an approved manner. Before discussing some of these drugs and their uses, I'd first like to explain my understanding of the FDA's position on the use of drugs by veterinarians:

1) The veterinarian may prescribe or administer drugs in anyway his training and experience indicate;
2) The veterinarian may prescribe or administer any drug that he can legally obtain;
3) The veterinarian may repackage and dispense any drug that he purchases in bulk provided it is done in the course of his practice and there is a doctor-client-patient relationship;
4) The veterinarian can combine several drugs for administration at one time;
5) The veterinarian is totally responsible for the following acts:
   a) Using drugs for purposes not indicated on the label;
   b) Using dosages not specified on the label;
   c) Using unapproved drug combinations;
   d) Administering drugs not approved for use in animals.

As you can see, the practitioner is legally allowed to use unapproved drugs but he must assume full responsibility for their use. Why, then, do practitioners think it is necessary to use unapproved drugs in an age of lawsuits and consumer activism? I believe that the answer goes back to the statement that was made previously—the practitioner has an obligation to provide the best and most scientifically sound therapy that he possibly can.

Philosophical considerations aside, the fact remains that the dairy practitioner has a definite need for unapproved antibiotics. They are often the only antibiotics that some organisms are susceptible to. This is especially true for coliform mastitis and some bacterial pneumonias and uterine infections that do not respond to approved antibiotics. When treating these and other cases, there are several reasons why unapproved antibiotics are the ones of choice.

The first reason is bacterial resistance to approved antibiotics. Because unapproved drugs are not used as frequently and are not as available to dairymen, resistance to them is not as commonly encountered. Consider the practitioner's dilemma when called to treat an animal that the owner has treated for several days without response. The practitioner must decide if the antibiotic used by the dairyman was ineffective because it was improperly used or because the organism was resistant to it. If the veterinarian feels that the drug was ineffective because of resistance and that other approved antibiotics will not produce the desired effect, he may then feel obligated to use an unapproved antibiotic. The cow threatened by a severe, life-threatening illness poses a similar problem. In this circumstance, the practitioner must use the antibiotic that he believes will be the most effective and he must use it without delay. Based on his experience and judgement, an unapproved drug may be selected.

Another reason for using unapproved antibiotics is the limited spectra of the approved drugs. Penicillin, tylosin and erythromycin are primarily gram positive in action. Dihydrostreptomycin is primarily gram negative in action. Only ampicillin and the sulfonamides are broad spectrum in nature. Furthermore, achieving therapeutic concentrations of penicillin, ampicillin, dihydrostreptomycin and sulfonamides in some organs such as the udder is often very difficult. However, there are several unapproved antibiotics for which the MIC's against gram negative bacteria are readily attainable in the udder, lungs and uterus. Several of the unapproved antibiotics are also very effective against gram positive bacteria that are resistant to penicillin-type antibiotics which are commonly used for intramammery therapy.

Finally, several products which were once available for use in lactating dairy animals are now unapproved. Oxytetracycline and nitrofurazone are two good examples. These broad spectrum drugs are still very useful.

The drugs listed in Table No. 4 comprise a partial listing of

TABLE 4
Unapproved Drugs That May Be Used for Lactating Dairy Cows

Chloramphenicol (Rx)*	Gentamicin
Nitrofurazone (Rx)*	Spectinomycin
Lincomycin	Oxytetracycline
Polymixin B	Ampicillin Na (Rx)*

*(Rx) means the drug is available only as a prescription drug.

unapproved antimicrobials which may be used in dairy practice. There are other antibiotics and combinations of products that are being used, but these are the ones with which I am most familiar. Please note that only three of these drugs are available on a prescription only basis, so their distribution and use may not be under a veterinarian's supervision.

Cloramphenical is used in a variety of ways. The oral form of the drug is most commonly used. Chloramphenicol is often the drug of choice for gram negative infections. The drug is given IM, IV and SC to treat coliform mastitis and other severe infections that don't respond to conventional forms of therapy. It is also used as an intramammary infusion for chloramphenicol susceptible *Staphylococcus, Streptococcus non-agalactia* and coliform mastitis. Chloramphenicol is also used for intrauterine therapy.

Nitrofurazone solution is a broad spectrum product that is sold for topical use and for treating infertility in mares. There has been some concern over the drug's possible carcinogenic effects. In dairy cattle, nitrofurazone solution is used intravenously to treat coliform mastitis and is used for intramammary and intrauterine therapy. Nitrofurazone is often mixed with other drugs for administration into the uterus and udder.

Spectinomycin is used primarily against gram negative and *Pasteurella* spp. infections. It has also been shown to be effective against *Staphylococcus aureus* strains that are resistant to penicillins, chloramphenicol, oxytetracycline and erythromycin (2). The drug's toxicity potential is very low and development of resistance to it is very slow. Spectinomycin is available as an oral product for treatment of pig scours and as injectable products for use in small animals or turkey poults. Both forms of the drug can be given parenterally for treatment of mastitis, pneumonia, septic metritis, etc. The oral form is used alone or in combination with nitrofurazone for intramammary and intrauterine treatment of susceptible organisms. A product containing lincomycin and spectinomycin is used by some practitioners for treating mastitis and pneumonia.

Once approved for use in lactating dairy cattle, oxytetracycline is still widely used. As a matter of opinion, I am sure that many dairymen do not realize that it is not labeled for use in their lactating cows. Oxytetracycline is a broad spectrum antibiotic with good tissue distribution characteristics. It is used IV, IM and SC to treat mastitis, uterine infections, hardware disease, etc. Some practitioners also use the injectable form for intrauterine therapy and some others use a powdered form for treatment of post-partum uterine infections.

Polymixin B is a narrow spectrum antibiotic that is used mainly against gram negative infections. Because the drug can be very toxic when used parenterally, many practitioners only use it for intramammary infusion. Besides its effectiveness against coliform mastitis, polymixin B also protects against the side effects of the endotoxins which are released by gram negative bacteria. It is endotoxin release during coliform mastitis that causes the severe systemic signs associated with the disease. European work indicated that the drug was effective in reducing swelling and in improving the clinical condition of the cow with coliform mastitis when infused into the udder (15). Polymixin B is available as an injectable product or as a polymixin B and neomycin solution for oral use.

Gentamicin is a broad spectrum antibiotic that is used for treating mastitis and uterine infections of dairy cows. It is effective against coliform mastitis and several of the bacteria which can infect the reproductive tract. Because the injectable form is very expensive, its use in adult cows is usually limited to intramammary and intrauterine infusions. Gentamicin is labeled for the intrauterine treatment of mares and as a small animal injectable. An over-the-counter product is sold for use in poultry.

Ampicillin Na is similar to ampicillin trihydrate which is approved for use in lactating cows. The major advantage of this form is the higher and more rapid serum concentrations that it produces. The drug is sold for use in horses.

It is my opinion that the unapproved antibiotics do fill a void in veterinary therapeutics. Several of these antibiotics are the only cost effective drugs available for the treatment of coliform mastitis. Others have been invaluable for treating pneumonias, uterine infections, *Staphylococcus* mastitis and other diseases that do not respond to approved antibiotics. Because of their positive contributions, I anticipate that the use of unapproved antibiotics will continue in necessary situations despite the problems with establishing drug withdrawal times.

There are several ways a practitioner can select a withdrawal time when using an unapproved drug or an approved drug in an unapproved manner. Knowing the drug's pharmacokinetic properties and tissue distribution is very important. For instance, we know that the aminoglycoside antibiotics (gentamicin, neomycin) tend to accumulate in the kidneys for prolonged periods after parenteral administration. Therefore, a long slaughter time is required. We also know that the aminoglycosides are poorly absorbed from the udder. We can use this knowledge to guide us in determining both milk withholding and slaughter withholding after intramammary use.

The literature does contain information which can be used as guides for selecting withdrawal times (2,7,9,13,14,15). For example, chloramphenicol has been shown to persist in kidney and muscle tissue of calves for 21 days and for 36 hours in milk following intramuscular administration. Gentamicin has been found in kidney tissue for over 100 days and in milk for 108 hours. This type of data is very useful and is available for other unapproved drugs. However, it is necessary to use this information only as a guideline and not as the absolute minimums.

More specific information on withholding can be found for several drugs. Spectinomycin is used in England and that country requires a five day slaughter withdrawal and 48 hours milk withholding. Chloramphenicol is used in several

foreign countries and a nine day slaughter and 96 hour milk withholdings are required. When oxytetracycline was approved in this country, a 96 hour milk withholding was required. Again, these are not absolute values. Differences in testing techniques and the sensitivity of the test will influence these times.

When high doses of approved antibiotics or combinations of drugs are used, the label requirements for withholding are usually extended. However, it is advisable to have a milk sample checked before the milk is sold. Checking the milk samples from cows treated with unapproved antibiotics is also recommended. The Delvotest P can be used on the farm or in the office and most milk processors will provide this service to their producers.

Because the practitioner is legally responsible for the withholding information that he gives to the client, it is essential to allow more than adequate time. In addition, a milk sample should be checked if feasible. These steps will help to ensure that the milk and meat are not adulterated with potentially harmful antibiotics. Illegal drug residues affect us all. The milk processor and the dairyman both suffer economic hardship. The veterinarian not only faces the risk of a civil lawsuit, but may also jeopardize his opportunity to use drugs freely. Finally, the consumer deserves to purchase milk and dairy products that are free of adulteration. To this end, both the dairyman and the veterinarian must use drugs responsibly.

Another comment on withholding is that preventing antibiotic residues should be a moral as well as a legal obligation. Several of the drugs that we have discussed cannot be detected with current testing techniques. Does a negative test result mean that a particular antibiotic is not present? Of course not. It only means that it is not being detected. This must not be a license to cheat. Moreover, there are many other types of drugs which are given to dairy cows. Some of these drugs do have withholding information on the label, but other do not. Even though these substances probably cannot be detected in milk, we are still obligated to keep milk that may contain these drugs out of the food supply.

Finally, there must be adequate communication between the practitioner and the dairyman. The practitioner must be certain that the dairyman completely understands the use of the antibiotic and the time required for withholding both milk and meat. Preferably, these instructions should be presented to the dairyman in written form and the animal should be identified as having been treated. The important point to remember is that there must be communication and trust between the dairyman and this veterinarian.

In summary, we have discussed how the practitioner selects a course of therapy and which properties of the drug determine its potential usefulness against different bacteria. These properties also aid in determining dosage, interval and route of administration. The rationale for using unapproved drugs and approved drugs in unapproved manners was examined and examples of these drugs and uses were cited. Finally, selection of withdrawal times was discussed.

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