Basic Pharmacology of Bovine Respiratory Therapy

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I graduated from veterinary medicine at Kansas State and practiced for about eight years in south central Kansas in a predominantly large animal practice. I returned then to the faculty, fully intending to take a little more work and go back to practice It didn't turn out that way, I kind of like the University life. I like what I am doing and so I have remained there. I try to keep in touch with veterinary practice in the field and appearing at meetings such as this is one of the ways that I attempt to do this so any of your questions, comments, or anything that you may be able to add to what I have stated, I would welcome. The topic "Respiratory Therapy" as you all are very much aware is not an easy one. It is not easy to accomplish in the field. It is not easy to accomplish from the speaker's standpoint of really deciding what is appropriate to mention within the limitations of time. I have chosen some topics to discuss with you that my reason for choosing is that you will not find them discussed in any great detail in any of the classical textbooks as such. I will spend very little time on antibacterial therapy with antibiotics and sulfonamides but we will touch on these sorts of things but I thought I would share with you some of the things that I had found in preparing for this talk that I felt were a little bit interesting.

First of all, the objective of any therapeutic regimen is an understanding of the entire subject. I firmly believe that before one can go about treating a disease you must understand the normal. We will spend a little time on the function, then one must understand altered physiology, altered function to really understand what the disease is. Lastly, when one gets to a decision on therapy, I think it is very, very important to decide ahead of time what your objectives are, what you really wish to accomplish and then make your decisions on what agent or agents one might use to accomplish your objectives. This is the approach which I am going to take today and I hope that you will bear with that. Our purpose then is to decide in drug therapy what drug or drugs, the mechanism that they are using to work, or in other words, why they work; then we are going to decide when one uses them and I think this is tremendously important. Lastly, how; I define how as a regimen. So we are going to discuss what, why, when and how. This is my philosophy on pharmacotherapy. Nothing really that original here. We will be spending our time helping with your knowledge of what's going on as we discussed previously. I think it is tremendously important in veterinary medicine because we must see signs and observe signs. Our patrons cannot talk, I feel that observations and your powers of observations are probably some of the most important aspects of a successful veterinary medical practice. I am a firm believer in common sense and I will try to allude to this in some of the situations. It is my opinion that these two attributes very, very much distinguish veterinary practitioners from our colleagues in human medicine. I think our powers of observation are much keener. I think they have to be, we have to rely on them to a greater extent and I think we use better common sense, good judgment in our practices. In veterinary pharmacotherapy, we always must wait and try to come up with our decisions relative to the agents we are using and balanced benefit versus risks. First of all, function. Respiration is controlled in the respiratory center which is found anatomically in the brain stem. It gets its positive drive primarily from two control sources, one is hypoxia, oxygen in the tissues is short and/or blood levels of carbon dioxide are elevated. Both of these are stimulatory to the respiratory center and give an increase to respiration in both rate and depth. We are interested, obviously, in an exchange of gases between lung and the blood. 1) separate respiration into three areas: one is the exchange of gases between the environment and the lung, 2) is the exchange of gases between the alveoli of the lung and the blood and lastly, terminal respiration or cellular respiration is where the cells use oxygen to form energy, biologically useful energy or ATP. There is a lot of complex physiological mechanisms involved here, one of them that we are interested in is, for example, a healthy respiratory mucosa. When the mucosa is healthy it produces a bathing layer of secretions which is of just right consistency. Normal respiratory mucosa produces secretions that are just right. If these secretions are too watery and too copious they flow backwards and end up in the alveoli and thus, interfere with gases exchanging. If they are too thick and ropy they cannot move at all and tend to build up in the respiratory passages. So we want the secretions the proper consistency. There are little cilia on these particular types of cells and they are motile and they help to move secretions up towards the pharynx. If the

secretions are the proper type and if the cilia are functional then the protective secretions will always be moved up to the pharynx and when this happens they can be passed to the outside. The autonomic nervous system plays a definite role in the function of the lungs. I have confined this schematic only to lung function, the sympathetic side dilates the bronchioles and may inhibit bronchiole glands. This is somewhat controversial and somewhat species dependent. I could find no specific statement as to its influence in the bovine. The parasympathetic side or the cholinergic side constricts the bronchiole, stimulates the bronchiole glands and increases the secretions of the tubular portion of the respiratory tract.

Next, I want to spend a little time on altered function and in this context I am not going to speak on specific diseases, you have had some excellent discussions of specific diseases. Anytime cells are insulted they react, and their protective reactions is inflammation. In this case, we are going to discuss bacteria and/or viruses, this could also include dust particles. Toxins can induce an environment that is destructive to the cell, you all are aware of this. These cells then can die and cell necrosis releases further cellular toxin. So we have a situation in which these toxins from bacterial and/or viral action cellular toxins can all gang up and produce inflammation of the lungs. At the same time we may encounter also a toxemia or other insults proceed in this direction. The classical representation of inflammation is heat, redness, swelling, pain and loss of function. All of these are important to our discussion today. The swelling in the edematous area in the lungs I think are quite straight forward as a pathological problem in gaseous exchange. When we encounter inflammation in the lung some of the outstanding signs would be swelling and edema, increased secretions, either thick or thin, and this predominantly is a function of time. Very early in the inflammatory response the secretions tend to be increased, copious and thin. Later on as the inflammatory process becomes more chronic they tend to thicken, giving the kind of secretions that we are all aware of in disease. Because of the swelling, edema and the increased secretions we get a decreased perfusion of blood and remember that the number 2 step in respiration is the exchange of gas between the alveoli in the lung and the blood. So if we are interfering with the gaseous exchange in the alveoli we are going to get a serious decrease in gaseous exchange, a hypoxia increased blood CO^2 and it may end up even severe enough to have a respiratory acidosis. Pathological respiratory secretions, the first excessive production, are very thin and watery, and unfortunately these migrate towards the alveoli. Their consistency is such that they cannot be moved towards the pharynx, there is just too much of them and they are too thin so they go towards the alveoli and this is a problem. Here they impede the gaseous exchange. Secondly, the thick ropy secretions in human medicine which is called sputum, is difficult to move to the pharynx and then again it impedes the air flow in the respiratory tree.

Anit-inflammatory drugs in my opinion are indicated in respiratory therapy. There are two general areas of mechanism that these drugs fit into. The first are the glucocorticosteroids. Their action here is stabilizing cellular membranes, enhancing cellular integrity, in other words, it is more difficult for the antimicrobial or the microbial toxins to bring out cell injury and cell insult. A classic here, of course, would be dexamethasone, and it is my opinion that if you are going to use steroids in respiratory therapy, they should be used early and they should be used very vigorously at a suggested dose, this can be altered to meet the needs of the animal, of 1/10th milligram per kg. Some would recommend a great deal less, I think this may be the upper limit. The second group of drugs that may be antiinflammatory are those drugs that inhibit the biosynthesis of prostaglandins. Aspirin is the classic, phenylbutazone, and I want you to mentally add dimethylsulfoxide, (DMSO) which has now been shown to be an inhibitor of the biosynthesis of prostaglandin and as such is a very important antiinflammatory agent.

The subject of the use of antibiotics or sulfonamides in the therapy of respiratory problems and whether or not one should include coricosteroids in your regimen, I want to comment briefly about, knowing that this is a controversial subject. In the choice of antibiotic or antibiotics and/or using a sulfonamide I feel that the spectrum is of prime importance. In other words, that is of number one importance, and that is not unique and novel. The regimen that one outlines to use whatever drugs you choose is probably equally as important, and how you are going to administer it, intravenously, orally, intramuscularly or how. How often and for how long? My recommendations are that initial therapy in most cases will probably need to be intravenously, where ever that is practically appropriate. I think one of the problems is sometimes we do not attack this as vigorously as we should. Doses must be adequate. The reason that I state this is that we know that certain of the antibacterial products are recommended as being bacteriostatic, such as chloramphenicol and tetracyclines, but if the concentration of these agents are high enough, it has been adequately shown that chloramphenicol, tetracyclines and lincomycin can be bacteriocidal. I think a vigorous regimen is appropriate, get a high blood level early. Intravenous medication will accomplish this. As far as the sulfonamides are concerned I think that you need to remember that very high blood levels very early are important because of their mechanism of action. They are not effective against chronic types of disease or when the body defense mechanisms have been allowed to deteriorate and get worn out. If you are using a sulfonamide it should be very early. It has been my experience that in respiratory problems in cattle intravenous sulfonamides were always a very, very valuable tool for me and I would use them again today. Whether one should combine steroids in the regimen for treating respiratory problems in cattle I will give you my opinion, and obviously you may do as you see fit. In the

acutely ill shipping fever calf, I feel like corticosteroids are indicated. I think the regimen should be vigorous and given intravenously. These are not the dosage levels that are recommended for the shock patients but they are higher than one would use for an anti-inflammatory routinely or for treatment of an allergic sort of condition. These agents, in my opinion, are without toxicity. If they are limited to use in the first 24 to 36 hours, it is my opinion that at that time they should be discontinued. We know definitely, if the steroid therapy is prolonged, it is going to be detrimental to the best interest of the animal and there is adequate information in the literature from the field to suggest that the chronic use of corticosteroids along with antibacterial therapy is contraindicated. The patients will take longer to get well and there is a greater incidence of relapses, etc. However, I firmly believe and recommend that you give a try to very high doses in these acutely ill animals very early and then use your common sense and your own observations and judgement as to whether or not it needs to be repeated. Maximal action of dexamethasone, flumethasone group is going to last somewhere from 3 to 6 hours. If you are using the soluble prednisalones your maximal action will probably last 1 to 2 hours. The great controversy is which acts the quickest? I suggest to you from your standpoint you would not be able to notice a great deal of difference in the onset time. Studies have been shown in human medicine that between dexamethasone phosphate versus dexamethasone in the alcohol form, there is only a 10 minute difference and I would assume it is about the same in ours. So I would say that is not a limitation and whichever of the corticosteroids or the drugs are your choice, that is the one you should use but be vigorous. Dimethylsulfoxide is an interesting drug. It has been widely used in veterinary medicine for years even when we all had to get if from some other source and buy it as a solvent! A great many veterinarians are recommending using DMSO intravenously. I think it is very interesting.

I have always stated that I fell that the practicing veterinarian is probably the most innovative professional that there is in the world. I don't say that in any terms other than very complimentary. I think we should be proud of this. Most of the time our innovation is based on knowledge and observations and common sense and I think that is the combination that you can't beat. I am going to give you my idea about DMSO intravenously, say in a respiratory problem. We all know that, if you put DMSO on the unbroken skin, it is very rapidly crossed into the blood. We do a little experiment in our student laboratory where we have some of our students put some of this on the skin and then start telling us when they taste it and I think some of the earliest this year were around 10 seconds. The misconception is that if you mix a drug in DMSO that carte blanche it will go across the skin in the blood. That is not true, some does and some doesn't. It is even so unique that certain steroids will go across the skin in DMSO, others will not. I am not prepared to give you the list of which do and don't. A lot of veterinarians are using DMSO and the theory they are using is that it "drives" then a systemic antibiotic or sulfonamate into these inflamed tissues and gives you a higher tissue concentration, therefore, it is more efficacious. I am not sure that is true. My initial assumption or reaction is that it probably is not true. I do feel that you will see some beneficial actions in some of these but I would guess that the action is coming because DMSO is an antiprostaglandin, anti-inflammatory and this has been very definitely shown now. That is where the beneficial actions is coming from. It is an excellent anti inflammatory agent and when given intravenously at whatever levels you are used to using I think it would have this kind of action. There is some interesting work going on now relative to aspirin and its antiprostaglandin effect on anaphylaxis on inflammatory responses in respiratory problems and in cardiovascular problems in man. There is a lot of promise with this particular mechanism of aspirin in the future.

We have already mentioned histmaine as one of the toxins of inflammation, I suggest too, that it is an early toxin. Some work in equine would suggests that in the inflammatory response at least, histamine is really an early serious offender. The early inclusion of antihistamines has beneficial results. Histamine is a very strong bronchial constrictor and it will increase the water secretions. Again this bears out what I said earlier, that early in the inflammatory response the secretions are thin and watery. Histamine may very well be the primary offending agent. We have edema in the lungs tissues that is seriously impeding the movement of air and now we have bronchoconstriction. The bronchioles are smaller and all of this tends to be adverse as far as good gaseous exchange. Antihistamines, I feel, are useful in early respiratory therapy. If you are trying to use these later on in the course of the disease you will be disappointed. Because of this, I think some people have discarded them entirely. They will block histamines off the histamine receptors and as such then will be a bronchodilator and will tend to dry up these early, thin, watery types of secretions. I would caution you in that antihistamines should always be used intramuscularly and if you do give them IV cut the dosage way, way down and give it very slowly and the rest in the muscle. The reason that I recommend this to you is right here. We can reproduce this in the dog anytime we want to with pyrabenzamine, rapid intravenous injection. Every time the dog quits breathing you can see how abrupt it is, they don't gradually quit, they abruptly quit breathing. Fortunately, it is transitory. We are talking about somewhere in the neighborhood of 20, 25 seconds and we have had some of these go up to apnea of 60 seconds duration, but that is rare; it is usually less than 30 seconds. You can also see the blood pressure fall. Antihistamines are potent vasodilators, as the blood pressure starts back toward normal at about the same time that breathing starts back, so this suggests to me that it is very concentration-dependent and if you give it intramuscularly, you are not going to reach these offensive kinds of concentrations.

Expectorants - first of all, by definition expectorants increased the production of respiratory secretion. I think we have to qualify this a little bit, this dilutes a very thick ropy sputum. My point of emphasis to you would be that if early in the disease the secretions are already thin and watery and excessive, expectorants obviously are contraindicated. Later on when the secretions turn ropy and thick, I feel expectorants may be indicated so here again we talk about the how and the why and the what and the when. **With steroids the when is terribly important, with antihistamines I think the when is important, with the expectorants the when is very, very important.** So if we can dilute this old thick stuff out the cilia and the cough can remove these fluids and debris out of the respiratory tract, get more gaseous exchange and, obviously, this is beneficial to the health of these animals. Expectorant drugs, some of the classics that are most widely used are ammonium chloride, you can get all sorts of different dosages in the literature, 15 grams per day up to 45 grams per day. Glyceroglycolate is used as a muscle relaxant, sedative, hypnotic, intravenously in animals. Glyceroglycolate is an excellent expectorant at about 2 to 4 grams per day.

The iodides, both the inorganic and the organic, I am sure you are all aware, have been suggested as expectorants. The human literature tells us that this is the drug group of choice for its expectorant action. Sodium iodide, potassium iodide, 30 milligrams per pound for one treatment, this is as suggested in the 20% sodium iodide solutions, organic iodides, you can find all sorts of recommendations for the levels to be used and they will fall somewhere in the neighborhood of 6 milligrams per pound per day for about 5 days. I would suggest to you that in respiratory problems of an infectious disease nature that one limits the duration of any type of iodide therapy to just a few days. There is some work being done now to show that iodides, used chronically, will inhibit the production of certain antibodies and have been shown to inhibit phagocytosis. It is very obvious that in treating these conditions with eigher antibiotics or sulfonamides we rely very heavily on the body's own mechanisms to ultimately conquer the disease. If you think antibiotics and sulfonamides are magic in curing these diseases, you are missing boat because the animal's own defense mechanism ultimately must "cure" the disease, the drugs don't. There are certain drugs that have been shown to stimulate this ciliary activity. I would have to state I have no idea how important this is in respiratory therapy but you might be interested in knowing some of these. Potassium iodide, I could not find this reference for sodium iodide, but I have to assume it would be equally effective. Sodium iodide, of those agents you usually would be using when you need this kind of action, would probably be the agent here. The prednisolone group also is capable of stimulating ciliary activity and remember this is the motility, the beating action that helps move these fluids back out of the respiratory tree into the pharynx where the animal can get rid of them. Cholinergic blockers-these drugs block acetylcholine off its receptors, it blocks excessive parasympathetic action. The classic here is atropine, and I only list it as the prototype, there are many other agents that are effective here and might be used. If you block this parasympathetic-cholinergic action, what you are really doing is blocking the constriction of the bronchioles, you are blocking the stimulation of secretions and so the ultimate effect will be bronchiole dilation and drying up of some of those secretions.

Other groups that are known to be bronchodilators, the adrenergic, include epinephrine which is the classic here used in human medicine for the treatment of asthma. Isopropranenol is even a more effective bronchodilator than epinephrine. Dimethylated xanthines are excellent bronchodilators, theophilin and its organic counterpart, organic theophilin, which we know of as amynophyllin is an excellent bronchodilator if you feel a patient is really needing a bronchodilation. Caffeine will accomplish this but it is very, very weak. I don't know whether you have ever witnessed this. In the community that I practiced in, a lot of these people from somewhere in their own heritages or whatever were used to treating newborn calves with very strong coffee. I had never tasted strong coffee till I moved to this community. It is a CNS stimulant, we know, but it might also be giving these babies some beneficial action as a bronchodilator. Then as we mentioned just a moment ago, the atropine group is a bronchodilator. There are occasions when one wants to increase respiration, we talked about drying up secretions, we talked about protecting the cells of the respiratory tract, we talked about bronchodilation. Sometimes you may want just to stimulate both the rate and depth of respiration. The respiratory center in the brain stem is part, obviously, of the central nervous system and will react to certain central nervous system stimulant drugs. The respiratory center stimulant that I have chosen to discuss here, first of all, is Dopram which is a very potent respiratory antileptic. I think you should be aware that from a pharmacolgical standpoint Dopram is very specific for the respiratory center. But no more so than is peniline tetrazone, the current trade name, Emzol. Dopram has an additional advantage in that it stimulates the vasomotor center which also is adjacent to the brain stem area. So with Dopram you will get the beneficial effect and it stimulates respiration, both rate and depths, and you will also get stimulation of the cardiovascular system via its stimulatory effect on the vasomotor center and I think it is obvious to all of us that there are certain patients that both of these actions are going to be beneficial. Emsol is the classic of this particular group. The only comment that I would have here is that it is efficacious. There is no question about that, you must recognize that if you compare these two, Dopram has a greater effect on the cardiovascular system. Metrazol has a greater effect on the higher center. Metrazol is a potent cerebral stimulant. That can be either good or bad. It can be bad in that it has a greater tendency if you are not careful and if overdosed, to produce convulsions as compared to Dopram. Caffeine sodium benzoate is the salt

form that is soluble in water so we can use it parenterally. It is a respiratory center stimulant. I would have to say that its efficacy is less than either Dopram or peniline tetrazole.

Lastly, camphor, I mention this out of nostalgia. I used to use an awful lot of camphorated oil with glycol in it in treating my respiratory condition patients. You hear this argued a great deal today. Is that efficacious or is it not? I think about the only comment I would have here is that at least my patient smelled like I had been treating him! Lastly, a very interesting condition that I thought I would pass on to you if you subscribe to Animal Nutrition and Health you have seen this, but I think it is very intriguing. Workers at Washington State, I believe, are working with the condition they call acute bovine pulmonary edema or commonly called "the fog fever". This occurs in animals that have access to an overload and then an environmental change and all sorts of things. This ends up as an emphysematous condition and can be life threatening. They are working with the etiology of this and their proposed mechanism is that amino acid triptophan with certain ruminal microorganisms is converted first to indole-acetic acid and then with certain other microorganisms is further converted to 3-methylindole and it is the 3-methylindole that is the offending agent in producing fog fever. Interestingly enough, if they challenge cattle with triptophan intravenously, indole-acetic acid parenterally, there is no fog fever but if they challenge these animals with 3-methylindole they will all show both clinical and pathological signs of fog fever. They can feed high levels of triptophan *in vivo* and consistently reproduce this clinical entity. Now the interesting part about this is if you feed these animals Rumensin you will prevent this condition. Rumensin widely categorized, can be called an antibiotic and it does influence certain of the microflora in the rumen and you are familiar with that as it's feed additive ability to increase feed efficiency.

I would like to summarize then and conclude my presentation by going back to my initial premise and challenge you in your everday work to enhance your knowlege, which you are doing by attending a meeting such as this. Be more aware that you do have excellent powers of observation and use them. Use common sense and when this applies to drugs you ask yourself what drugs, how I am going to give them, when, and then you weigh the benefit to the animal versus the risk to the animal and possibly following this kind of a regimen and outlining your objectives it may be of some help to you in your practice.

Discussion

Dr. Bechtol: One of the biggest problems I have is controlling respiratory disease and in trying to set up a program, so I will go through some quick management type things and program and open up for questions when the rest of the panel gets through. When we receive a lot of cattle we like to expose them to hay directly off the truck, fill them up on hay, then go on to a ration of choice; we prefer feed bunk, or bunk apron, or use racks but they expose lots of hay for long periods of time, we just want to expose them to hay for 2-3 days or maybe just one depending on the size of the herda and type of problem, because some cattle just eat hay, do not eat the ration, and they don't go to the bunk when they need to. Expose to fresh ration at all times. We don't like them to feed too much, 2 times a day or maybe 3 in the summer (early morning, late afternoon, and do a spot check). Bunk space — 15-18 inches at the start, 8-12 inches on finishing (Texas Panhandle usually crowds cattle, only using 8-9 inches), so 15-18 inches is better for these light cattle. They should be eating 3% of their body weight first 5-8 days, have 10 day as far as changing rations, and have them on feed by 20th day.

We can change this a little. This is a program where we usually start on 50-60% concentrate; now we have a 65% concentrate ration — 10-12% crude protein, now up to 15% crude protein. Use hay for management, not nutrition; expose to bunk, get started on ration. I don't like to use silage in starting ration, but in the Texas Panhandle they have to use silage (at a minimum, trying not to get over 10-12-15% silage as a starting ration). This goes along with constant feeding technique, I don't like to use urea in starting rations, and I don't like to use rumensin in starting rations, but some nutritionists in the area like to expose their cattle to some in the ration, and some are getting acclimated to the situation, but I don't like to use rumensin at all. We try not to use too many antibiotics, but for problem cattle we use antibiotic program (AS 700), approved neomyocin product of a 300-350 level, most of us use 700 level for the first 5-10 days, tapering off to 350 for 7-10 more days, then off. I do not like 28 day programs, as feed yards can only handle so much ration, by 28 days on feed, if not adjusted to consumption level, day 31 you get a break problem. So for 7-10 days use a high level, then 7-10 days an intermediate level, and then take cattle totally off it.

There is good data supporting a higher level than the 700 level (oxytetracycline and chlortetracycline). Used as high as 2 grams for the first 3-5 days, then 1 gram for the next 5 days, then 500 mg., then off. Do not come off too abruptly.

Another product that's been pushed aside somewhat is Neoterra Feed Grade — 250-500 mg. Neomycin, 500-750