Short Topics

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Factors Involved in Adverse Reactions to Bovine Biologicals

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Several bovine biologicals, while generally safe, occasionally are associated with adverse reactions. Vaccines have directly or indirectly induced diseases either by causing the disease they were intended to prevent or making the animal more susceptible to other infection. Biologicals can also induce anaphylaxis or hypersensitivities. Injection site reactions such as abscesses, swellings or granulomas can be directly or indirectly caused by bacterins or vaccines. Other conditions have also been related to use of biologicals.

Vaccine Induced Diseases

Vaccine induced diseases are usually caused by modified live vaccines. Attenuated BVD vaccines have been associated with causing mucosal disease,[1] bovine respiratory disease syndrome, and abortions.

Mucosal Disease

An animal with mucosal disease exhibits lesions throughout the alimentary canal. The calf is immunotolerant, shedding BVD virus while failing to develop neutralizing antibody. The pathogenesis of the disease is felt to be caused by exposure of the fetus to non-cytopathic BVD virus during mid-gestation.[2,3] The calf is born shedding virus, but received protective antibody from its dam's colostrum. If vaccinated with MLV-BVD after the passive titer falls below protective levels, the calf will develop mucosal disease lesions because of its inability to develop active immunity.

Bovine Respiratory Disease

Vaccination of incoming feedlot cattle with MLV-BVD vaccines has been associated with an increase in bovine respiratory disease.[4,5] The stress of shipping may cause an increase in cortisol levels suppressing the calf's immune system which can further be compounded by vaccination with MLV-BVD.[6] The immunosuppressed calf is less resistant to the effects of Pasteurella[7] or other organisms.

Virulent BVD

The animal that breaks with BVD following vaccination may already be incubating the infection from previous exposure or the vaccinal BVD virus may be marginally attenuated or contaminated with virulent BVD.[8] Field virus can enter the vaccine through the bovine cell line used for growing the vaccinal virus or from fetal bovine serum used to nourish the cell line.

All federally licensed biologicals are tested for viruses, bacteria, fungi and mycoplasma prior to release.[1] Occasionally the organisms, especially viruses, might not be detected through conventional testing methods.

Abortion

Susceptible dams run the risk of abortion from either vaccinating them with MLV-BVD or IBR vaccines or exposure to other vaccinates such as their nursing calf - which may be shedding the virus.[9]

Anaphylaxis and Hypersensitivities

Most veterinarians have experienced acute anaphylaxis following administration of a biological or other drug. The animal exhibits dyspnea due to laryngeal or lung edema which may lead to shock and, without treatment, death.[10]

Hypersensitivities to particular antigens can cause somewhat milder signs. These signs can be bloating, diarrhea, decreased milk production, nervousness, abortion and urticaria.[10] More common causes of these reactions are *Pasteurella* bacterins, leptospira,[10] other gram negative bacterins, or serum products. Less common causes of these bacterins, or serum products. Less common causes are modified live viral vaccines and miscellaneous components within the biologicals.

Case 1

Last year a practitioner related to me an incident about a rancher who had administered a combination clostridial-pasteurella bacterin and tetracycline to approximately 200 calves. The owner discontinued using the bacterin when problems were noted in the calves already treated. Another 100 calves received the tetracycline only. The veterinarian

was summoned to treat the affected calves. He described the 200 receiving the bacterin as very nervous, with diarrhea, approximately 20 were bloated and showing respiratory distress. These 20 were treated. One calf died immediately and a second one 8-12 hours later. This group of calves had loose stools and were off feed several days before returning to normal, while the calves not receiving the bacterin showed no untoward reactions.

Case 2

In March of 1984, a dairy owner consulted a veterinarian concerning a respiratory problem in his milking herd. At the suggestion of the veterinarian, the herd of 84 cows was vaccinated with inactivated IBR-PI_3-BVD vaccine. The following morning 12 cows had a watery diarrhea, decreased milk production, were off feed and had fevers ranging from 102° to 104°F. These cows gradually improved during the next week. Paired serum samples from the infected cows showed several sero-converting to IBR. Titers wouldn't be expected following one dose of inactivated vaccine. Speculation is that the cows were incubating IBR at the time of vaccination and were sensitized to that antigen. When vaccinated with highly concentrated IBR antigen, they developed a hypersensitive reaction.

Case 3

Approximately 40 dairy cows were vaccinated with an *E. coli* bacterin. The following day the owner reported their feed consumption was down 60%. The examining veterinarian reported that 12 had fevers ranging from 102.5° to 106°F. They were listless, had loose stools, decreased milk production and one had aborted. They were treated with aspirin. All but one was back to normal by six days post-vaccination.

Reports of abortion received following vaccination usually occur within hours to a few days post-vaccination. When a herd in various stages of pregnancy is vaccinated, those aborting are usually in late gestation. I recently had a case reported to me where 120-130 dairy cows were vaccinated with inactivated IBR-PI_3-BVD. Two cows aborted the next day and one a day later. All were in late gestation; one calf survived. The cows showed no other outward clinical signs. This type of reaction is too soon after vaccination to be caused by a vaccine induced infection. Most likely these abortions are caused by stress causing a cortisol release or hypersensitivity to the injected antigen. Possibly vaccination during the ninth month of gestation should be avoided.

Injection Site Reactions

Abscesses or granulomas can occur with any injection, but they have more potential developing following use of adjuvanted or irritating products. If bacteria enter an inflammed injection site, there is an increased chance an abscess will develop. Most of these are noticed two to three weeks post vaccination or at slaughter. The most common isolate in cattle appears to be *Corynebacterium pyogenes.*

Case 4

Owner vaccinated 160 cows with an *E. coli* bacterin I.M. in the thigh. Starting one week post vaccination swellings developed at the injection sites. Over the next six weeks a total of 140 cows developed reactions. *C. pyogenes* was recovered from all abscesses cultured. A partial bottle of vaccine was sterility tested and found negative for bacteria and fungi. Poor vaccination technique was probably the cause of this problem.

Sterile abscesses can develop if the biological forms a depot in the tissues. The body reacts by treating the vaccine as a foreign body and walls the injection site off with granulation tissue. Following removal of the vaccine by macrophages and other cells, the sterile abscess usually regresses.

Other Reactions

Neonatal Isoerythrolysis can be caused by vaccinating with anaplasmosis vaccine. RBC antigens contained in the vaccine may stimulate anti-RBC antibodies. These antibodies are passed to the newborn calf through the colostrum. If the calf inherited an incompatible blood type, N.I. can result. These reactions can be avoided by vaccinating the cows while open so that any anti-RBC antibodies that develop will be at a decreased level at parturition.[11 12]

Killed *Pasteurella* bacterins have demonstrated a lack of efficacy and in some cases have been associated with an increase in disease incidence[13] and severity of lung lesions. This probably is due to lung macrophages phagocytizing antibody coated *Pasteurella* organisms, which results in death of the macrophage, and tissue damage.[14 15]

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Abstracts

Recent advances in antimicrobial drugs: The penicillins

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The pharmaceutic industry has been successful in preparing penicillins that overcome the therapeutic limitations of penicillin G: gastric acid instability, restricted antibacterial spectrum, and susceptibility to enzymatic inactivation. Penicillins are highly effective and are safe first choice antibiotics in human and veterinary medicine. The discovery of the penicillin nucleus (6-aminopenicillanic acid) ushered in the era of semisynthetic penicillin chemistry that has provided veterinary medicine with the isoxazolyl (e.g., cloxacillin) and aminopenicillins (e.g., ampicillin and amoxicillin). In view of the importance of *Pseudomonas* spp (otitis externa, metritis, and occasionally mastitis), it is surprising that ticarcillin has not been developed for animal use. Many fewer penicillins are used in veterinary medicine than in human medicine. The difference reflects the special features of veterinary practice: absence of specialist hospital indications, restricted use of sensitivity testing before therapy, and of course, cost considerations. Recent advances in penicillins will result in the development of novel animal health products.

Mode of action of penicillins—Penicillins inhibit enzymes responsible for the synthesis of the bacterial cell wall that is a mucopeptide layer of polysaccharide strands interlinked with short peptide bonds. During growth, autolysins disrupt the lattice to provide acceptor sites for new material. In healthy cells, autolysis and new cell wall deposition are in balance. Enzyme inhibition results in the classic penicillin effect: inhibition of cell wall synthesis, defective cell wall, formation of spheroplasts, osmotic lysis, and cell death.

Selecting therapeutic concentrations: Minimum inhibitory concentrations vs subminimum or supraminimum inhibitory concentrations

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Although antimicrobial agents have been used for therapy in veterinary medicine for over 35 years, many questions regarding proper dose, proper dose interval, (i.e., continuous vs intermittent therapy), and the proper duration of therapy persist. Therapy is often initiated on an empirical basis, i.e., based on information derived from or guided by experience; this occurs when therapy is initiated before obtaining culture results. Some consider antimicrobial therapy an art rather than a science.

High serum antimicrobial concentrations are assumed to have an additional advantage by increasing the amount of drug that diffuses into the various body tissues and fluids. The drug concentration at the infection site is assumed to be of major importance in predicting the drug's efficacy.

The drug diffusibility from the blood to the extra vascular tissues is dependent on molecular size, lipid solubility, drug pK, environmental pH, and the extent of protein binding. Certain specific factors that are a property of the tissue or fluid compartment also exist, e.g., the actual amount of penicillin in CSF can be decreased by an active biological pump. Therefore, CSF penicillin concentrations at any time are a function of penicillin's diffusibility into CSF and also a function of the rate at which penicillin is actively pumped out of the CSF. The choroid plexus is similar to the proximal convoluted tubule of the kidney which actively transports organic acids.

Evidence for the biological pump was established by revealing (1) that penicillin was capable of moving out of the CSF against a concentration gradient, (2) that the pump could be inhibited competitively by p-aminohippuric acid and probenecid, and (3) that the pump was saturable, i.e., there was a transfer maximum.

Principles of clinical pharmacokinetics of antimicrobial drugs

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The term pharmacokinetics was introduced by Dost in 1953 to describe that field of pharmacology concerned with the study of the rates of drug absorption, distribution, metabolism, and excretion as well as the pharmacodynamics of drug action. Since then, the importance of the contributions of pharmacokinetics have been increasingly recognized in drug design, drug therapy, and development of dosage regimens. However, basic pharmacokinetic studies are generally conducted in healthy animals and the effects of disease on various pharmacokinetic parameters are not investigated. Therefore, dosage regimens derived from these studies may not be appropriate for diseased animals. Clinical pharmacokinetics, on the other hand, are concerned with the study of the effects of disease and other variables (e.g., age pregnancy) on the pharmacokinetics of drugs in animals. Information obtained from clinical pharmacokinetic studies allows practitioners to modify dosage regimens developed in healthy animals to optimize delivery of antimicrobial agents to the site of action at a concentration sufficiently high and of adequate duration to exert a beneficial effect.