Therapeutics of Corticosteroids in the Bovine Animal and Problems Surrounding Their Use

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The corticosteroids have been used extensively in veterinary practice for the last 15 to 20 years. They have offered the practitioners of veterinary medicine a tool useful for blocking a portion of the pathological changes seen in infectious and metabolic disease. Unfortunately they have done little to advance the cause of specific disease therapy. I shall discuss the use of corticosteroids by veterinarians in some conditions in which they are widely employed and attempt to clarify their usefulness in some cases and their abuse in others.

First let us consider what the pharmacological properties of these agents are and which ones are most likely to be of therapeutic value (Figure 1). The ability of these agents to reduce an elevated temperature, to reduce inflammatory and allergic reactions, to stimulate the central nervous system, to increase the blood glucose levels and to improve the animal's demeanour have broad appeal to the practitioner.

Pharmacological Actions

1. Anti-inflammatory
2. Reduce Circulating Eosinophiles
3. Increase Circulating Neutrophiles
4. Cause Regression of Lymphoid Tissue
5. Reduce Circulating Lymphocytes
6. Stimulate Central Nervous System
7. Increase Appetite
8. Increase Blood Glucose
9. Increase Fat Mobilization
10. Increase Sodium and Water Retention (only those with mineralocorticoid tendencies)
11. Anti-pyretic
12. Anti-allergic

Figure 1. Adrenocortical steroids.

Veterinarians frequently question the dosage of corticosteroids employed in a particular treatment regime and wonder how the suggested dosage would change if he were to employ his "favourite" steroid for the same purpose. Most pharmacology texts have one or more tables relating the potency of these drugs for a variety of parameters (Figure 2).

The glucocorticoid and anti-inflammatory effect of the corticosteroid should be compared and the dosage of the drug to be used determined from the appropriate chart (i.e. if the drug is to be used in ketosis therapy consult the glucocorticoid potency). Of almost equal importance is the sodium retaining property of the drug. In almost all instances the practitioner should select one that does not cause sodium retention in order to avoid the problems of edema formation and fluid build-up that can be harmful to the animal.

Compound	Anti-inflammatory Potency	Gluco-corticoid Potency	Sodium Retaining Potency
Hydrocortisone	1.0[1]	1.0[2]	1.0[1]
Prednisolone	4.0[1]	5.5[2]	0.8[1]
Cortisone	0.8[1]	0.8[2]	0.8[1]
Triamcinolone	5.0[1]	≅25.0[3]	0.0[1]
Betamethasone	10[2] - 25.0[1]	≅25.0[3]	0.0[1]
Dexamethasone	10[2] - 25.0[1]	≅25.0[3]	0.0[1]
Flumethasone	≃75 - 100[4]	≃75 - 100[4]	0.0
Predef (Fluoro-prednisolone)	14.0[2]	50.0[2]	---

Figure 2. Relative Potencies of Corticosteroids.

Corticosteroids - Respiratory Tract Disease

Treatment of disease conditions of the respiratory tract has been subject to widespread steroid use and abuse. The antipyretic and anti-inflammatory effects of these compounds are sufficient inducement for many practitioners to routinely employ them in the treatment of viral and bacterial respiratory tract problems. The rapid drop in the animal's temperature, the improved breathing and overall improvement in demeanour would be most useful if they reflected a real improvement in the underlying disease problem. Unfortunately this is not the case and it makes assessment of the progress of the disease nearly impossible.

Perhaps it would be best to start by indicating instances where the corticosteroids are most likely to be of benefit. Few would argue with the proposition that respiratory tract disease having an allergic hypersensitivity basis (i.e. atypical pneumonia) should be treated using corticosteroids plus measures to remove the animal from the agent causing the problem. Another rational use for corticosteroids would be in the treatment of acute bacterial pneumonia where the pulmonary inflammatory response is so severe that the animal will suffocate before the antibacterial drugs have had time to act. Still another would be in the treatment of bacterial laryngitis or pharyngitis causing acute airway obstruction. (Dosages of corticosteroid in these acute life threatening situations

may be as high as five mg/100 lb. body wt. dexamethasone equivalent.)

Where then does the controversy exist in the treatment of respiratory tract disease? As we all know viruses play a prominent role in the etiology of bovine respiratory tract problems. It is generally agreed that corticosteroid administration reduces the animal's resistance to virus infections. Gross and Colmano (11) and Colmano and Gross (5) looked at the relationship between the plasma cortisteroid levels of chickens and their resistance to virus disease (Marek's Disease). High corticosterone levels were seen in conjunction with a high incidence and mortality due to this condition. Further to this point Dennet, et al. (6), demonstrated clearly the influence of corticosteroids in bulls on their ability to recover completely from IBR infections. These researchers showed that bulls that had elevated IBR titers but were negative to virus isolation rapidly became virus shedders when the disease was reactivated after a single dexamethasone injection (30 mg). The usefulness of this agent in detecting the carrier state of virus diseases becomes obvious. The above observations plus those of Colmano and Gross (5) showing that compounds that reduce plasma corticosterone levels, i.e. o.p. '-DDD and Metyrapone, reduce the incidence and severity of Marek's Disease makes the case against the routine use of corticosteroid in bovine virus disease quite strong. In fact it suggests that animals surviving viral disease plus corticosteroid therapy do so despite our efforts rather than because of them.

The question of their use in bacterial disease is not so clear cut (the diagnosis of respiratory tract disease with no viral component is in itself very difficult). Colmano and Gross (5) showed that high levels of plasma glucocorticoids were seen in conjunction with increased resistance to diseases such as *E. coli*. They proposed that glucocorticoids were an important part of the body defense mechanism. The relevance of this data however to the bovine situation is not clear. Schalm, et al. (16), showed that corticosteroids caused a marked increase in the plasma and milk neutrophile content when given to milking cows. The neutrophilia seen was of no protective value however in controlling subsequent coliform mastitis.

The detrimental or beneficial affects of glucocorticoids in bacterial disease are not as well defined as we would desire. Most authors agree however, that high levels of disease specific antibiotics should be given with glucocorticoids when the steroid is given in quantities large enough to cause a systemic anti-inflammatory response (17).

Corticosteroids - Abortion

Shortly after the introduction of the potent glucocorticoids into veterinary medicine reports of abortion in steroid treated cows began to appear. It is now known that most glucocorticoids given at high levels can act as abortifacients. The potent glucocorticoids dexamethasone and flumethasone appear to be among the most active parturition inducing agents.

Henry, et al. (12), demonstrated that cortisol and betamethasone could directly stimulate uterine activity. These authors suggested that the exogenously administered corticosteroids were mimicing the rapid rise in cortisol output by the fetal adrenals just prior to calving. The rise in corticoid output by the fetal adrenals is considered to be an important step in the initiation of calving. The administration of glucocorticoids to an animal does not always induce parturition. Cows carrying dead calves or calves with a pituitary-adrenal disfunction or cows in the first two-thirds of pregnancy are unaffected by these drugs (12). The use of corticosteroids as a means of control calving times has received considerable study from many authors (1,7,15). Jochle, et al. (13), concluded that this property of corticosteroids was not practical for use in the bovine. Corticosteroids were shown to reduce the normal movements of the calf as it becomes aligned in the birth canal prior to calving and also to lessen the relaxation of pelvic ligaments prior to parturition. Therefore although the calves born may be smaller (i.e. if calving is induced before term) there does not appear to be any lessening of calving difficulties (13). In addition most authors report a high incidence of retained placentas in cows in which parturition is induced with corticosteroids.

Bailey, et al. (1), used dexamethasone trimethylacetate, a longer acting corticosteroid, in his experiments. Calving occurred a longer period of time after drug administration (mean of 12 days as opposed to the two-four days seen in other studies) but these authors did not observe a significant increase in the incidence of retained placentas or calving difficulties.

The recommendations at this time to avoid inducing parturition is to avoid the use of corticosteroids in cows past 200 days of gestation. Also since a parenteral dose of 20-30 mg dexamethasone is usually required to induce calving in cases where steroids cannot be avoided they should be used at low levels (Figure 3). Hagg and Schiltz (10) demonstrated in their experiments that the intramammary administration of 10 mg dexamethasone (Figure 4) was sufficient to cause a number of treated cows to abort. Jochle, et al. (14), showed that 100 mg of progesterone daily administered for seven days (starting two days before the corticosteroid was given) could prevent

Compound	Abortifacient Dosage	Therapeutic Dosage	Time of Abortion After Treatment
Dexamethasone	10-20 mg	10 - 20 mg	1.5
Dexamethasone ester	20 mg	10 - 20 mg	10 - 15
Triamcinolone	30 mg	15 - 30 mg	10 - 15
Flumethasone sol'n	5 - 10 mg	2.25 - 5 mg	1 - 5

Figure 3. Corticosteroid Induced Parturition in the Bovine. (Jochle [14])

Drug	Dosage	Stage of Gestation (mean)	Abortion
Methylprednisolone	10 mg	241.0 days	0
Hydrocortisone	60 mg	241.8 days	0
Dexamethasone	10 mg	242.0 days	5
Control	0	241.6 days	0

Figure 4. Effect of Intramammary Corticosteroids on Maintenance of Pregnancy in Cows. Hagg and Schiltz (10).

the induced parturition. The fact that he was able to give the progesterone two days prior to the steroid drug is small consolation for the practitioner who has mistakenly given a glucocorticoid to a pregnant cow. It should however point to high levels of progesterone as the logical treatment when it is necessary to block corticoid induced parturition.

Corticosteroids - Ketosis

The glucocorticoids have found one of their most generalized uses in the treatment of bovine ketosis. Few practitioners would question the therapeutic rational surrounding this treatment or would question the fact that they do work.

Glucocorticoid administration causes a marked increase in the blood sugar level in both normal and ketotic cows (2) that usually lasts about 48 hr. Braun, et al. (2), examined the ability of a number of glucocorticoids to increase the blood sugar level and found dexamethasone and flumethasone to be among the most active.

The decision whether or not to use a corticosteroid in treating a case of ketosis however depends on: 1) the likely etiology of the condition; 2) the possibility of reactivating a latent viral or bacterial infection and 3) the fact that corticosteroids appear to cause a temporary marked reduction in the cow's milk output which may or mey not be beneficial. The fact that antibacterial therapy does not usually accompany ketosis treatment makes consideration of the likelihood of systemic infection following treatment most important although the levels of drug employed for this purpose tend to be lower (0.5-2 mg/100 lb. body wt. dexamethasone equivalent).

Some disagreement is evident as to the amount and frequency of the milk production drop caused by corticosteroids. Stockl (18) reported that his studies on ketotic and normal cows in Germany showed no evidence of decreased milk output subsequent to steroid administration. Carroll, et al. (4), and Braun, et al. (2), reporting on the situation in tYe U.S.A., demonstrated marked reductions in milk output following the use of these agents. It appears therefore for the North American situation that a milk production drop is likely to follow steroid therapy.

In the light of their research on the use of corticosteroids in normal and ketotic cows Braun, et al., made recommendations regarding treatment of

Decreasing Order of Preference:
1. 40% glucose iv + oral propylene glycol (8 to 10 oz. daily) 7-10 days oral
2. Glucose iv + corticosteroid im + oral propylene glycol (8 to 10 oz. daily) 7-10 days.
3. One glucocorticoid injection im repeated in 3-4 days.

Flumethasone and Dexamethasone were most useful in treating bovine ketosis.

Figure 5. Ketosis Treatments. Braun, et al., (2).

ketosis (Figure 5). In decreasing order of preference they were: 1) Glucose (500 to 1000ml) i.v. + propylene glycol 8-10 oz. for seven - ten days. 2) The above + one injection of a corticosteroid and 3) Two injections of corticosteroid (the second three to four days after the first).

Corticosteroids - Mastitis

The property of corticosteroids of reducing inflammation in mammary tissue has been used in veterinary mastitis therapy for many years. The rational appears sound if one accepts that they do indeed work and the usefulness of a rapid reduction of mammary gland swelling, to reduce tissue damage and fibrosis as a result of the infection.

Two major considerations are relevant in mastitis therapy: 1) the effect of local inflammation on the mammary gland itself and 2) the effect of toxins liberated by the infectious process in the udder on the whole body system. Local administration (intramammary) administration of glucocorticoids to reduce swelling and inflammation was examined by Carroll, et al. (3). They studied a DMSO-flumethasone mixture on experimentally-induced mastitis and found the combination to be of little or no value in reducing udder swelling and inflammation. Ficarelli and Vezzani (8) noted in a preliminary report on their findings that DMSO 90% plus corticosteroids and antibacterial drugs give a favourable treatment response. Unfortunately these workers do not appear to have published the follow-up data in their experiments. The value of local corticosteroid therapy in reducing mammary gland swelling and inflammation is therefore still very much in doubt as to its effectiveness.

Since the glucocorticoids are not in themselves antibacterial and may indeed reduce the mammary gland's resistance to infection, antibacterial drugs appropriate to the causative organism must always be used with the corticosteroid. Most mastitis preparations today contain adequate quantities of antibacterial drugs and therefore seem capable of counteracting any unfavourable response due to the presence of the steroid.

Occasionally one encounters cows with acute coliform mastitis in which there is evidence of severe toxemia due to endotoxins released by the organisms in the mammary gland. The animals are usually quite depressed, pyrexic and show evidence of severe cardiovascular change and dehydration. Corticosteroids (up to 10 mg/100 lb. body wt. dexamethasone equivalent) have been shown in some

cases to produce a marked improvement in the animal's over-all condition. This improvement however is frequently reversed in 12-24 hr. and the animal's condition may again deteriorate. However in some instances the improvement seems sufficient to get the cow back on the road to recovery. The ability of corticosteroids to counteract the affects of bacterial endotoxins has been reported by Thomas and Smith (15) and can be employed in acute coliform mastitis as an adjunct to antibacterial and fluid therapy.

Corticosteroids - Udder Edema

Corticosteroids that do not cause sodium or water retention in the kidneys have been used in the control of udder edema in the bovine. Compounds such as dexamethasone are said to increase the filtration rate in the kidney (17) and thereby increase the fluid and electrolyte losses, when given in conjunction with a diuretic (i.e. chlorthiazide). This is one of the few instances when these compounds really cause a marked improvement in response of the animal to treatment. Unfortunately they cannot be used in cows prior to calving, a time in which udder edema is frequently a severe problem in heifers.

Summary

As suggested above, the glucocorticoids have been used in a wide variety of diseases and for an equally wide variety of reasons. There are few instances when it can be said with certainty that they are definitely needed. Despite their widespread, almost routine, application in some respiratory disease problems and mastitis there are few real indications for their use. The possible significance of these agents in regulating bovine parturition has also been studied but has not been found to be practical at this time. The treatment of ketosis and the control of udder edema using glucocorticoids has been shown to be a sound therapeutic practice. The possibility of inducing parturition in cows if given prior to calving or reactivating a latent infectious process tend to limit their usefulness.

The best thumb rule to follow with corticosteroids is to use them as an adjunct to therapy only when there is reasonable chance that they will be effective and when prior experience shows that the response that is supposed to occur, does occur. Anything less than a favourable response that is clearly visible to the practitioner and owner and that derives from use of the drug based on sound therapeutic principles is poor veterinary practice and a waste of your client's money.

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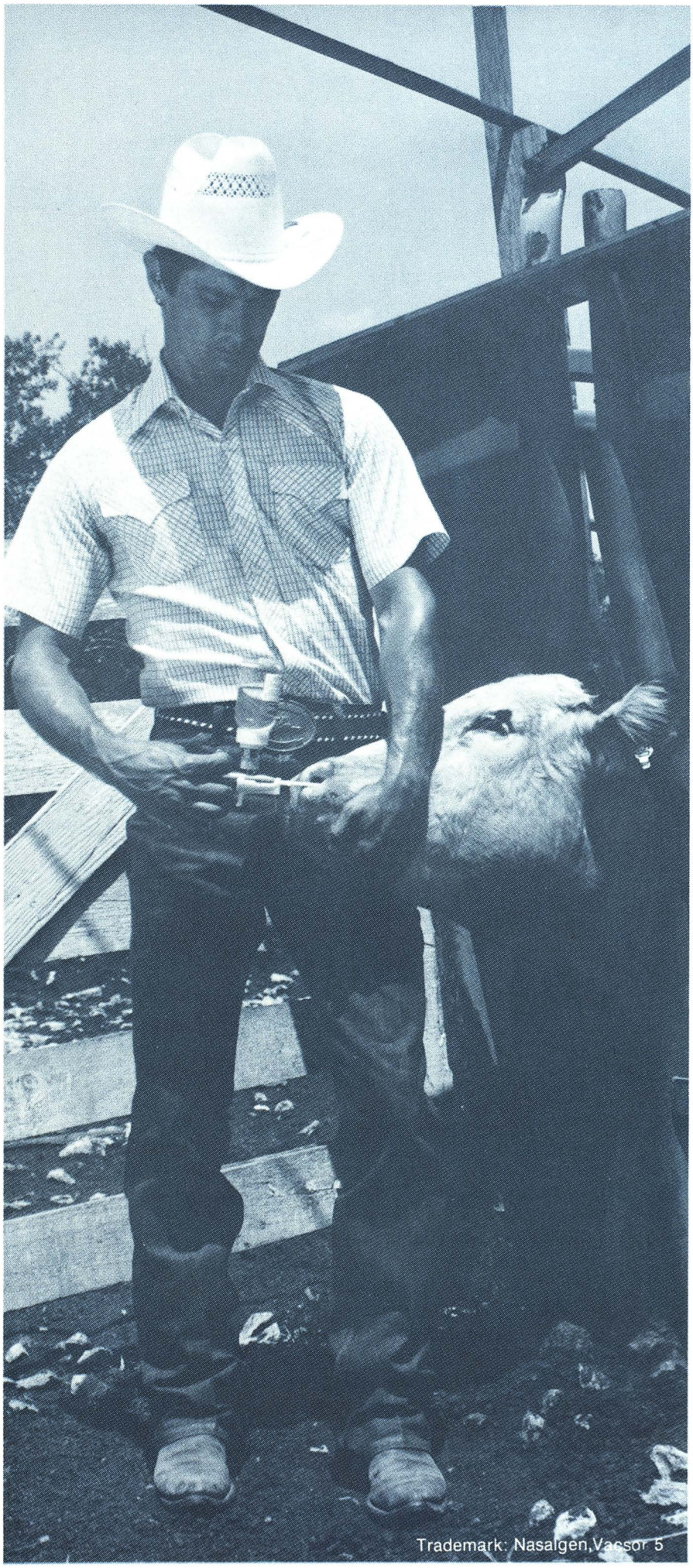

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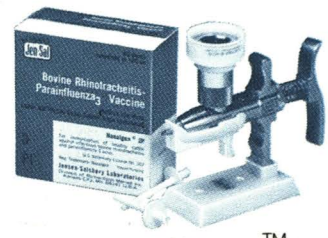

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