FACTORS AFFECTING RELEASE RATES AND BLOOD LEVELS OF HORMONES FROM STEROIDAL IMPLANTS

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ABSTRACT

Duration of anabolic activity and persistence of hormone release from implants needs to be considered in the design and implementation of implant programs for beef producers. Genetic potential to gain and deposit lean tissue in the carcass and the age of the animal may determine the optimal release (payout) rate of estradiol from an implant. Optimal release rates of TBA for cattle performance have not been studied. Implant excipient (carrier) has a pronounced effect on the release rates of hormones from ear implants. Payout of anabolic agents from silastic rubber-based implants generally is slower rate but persistence is longer compared to compressed pellet implants. Release rates of hormones from lactose-based implants appear to be faster than from cholesterol-based implants. Hormone release rate is slower in suckling calves than in older animals. There also may be an age or weight dependency on implant response by suckling calves. Combining estradiol and trenbolone acetate in the same implant results in persistently higher blood levels of estradiol and perhaps an extended growth response as compared to administering the same two agents in separate implants. More definitive information about the relationships between implant release rate, threshold concentrations of circulating hormones, and animal performance would help to fine tune implant programs.

INTRODUCTION

Beginning early in 1997, at least 19 anabolic steroidal implant products will be available for use in beef cattle in the United States. Hormone concentrations and indications for use are presented elsewhere in these proceedings. Implant programs should be designed to achieve predetermined performance and carcass merit goals. Length of anabolic activity or release (payout) rate of implants is one of several factors that need to be considered in the design of implant programs. The purpose of this paper is to discuss some of the factors that affect length of anabolic activity and circulating blood levels of anabolic steroids in cattle.

Optimal Payout Rates for Growth Promotion

In order to discuss the factors which affect payout rates of implants, it is beneficial first to examine rates of payout that maximize cattle growth. Wagner et al. (1979) titrated the dosage of estradiol for maximal rate of gain in feedlot steers; and they concluded from a four-site study that a payout rate of 55 mcg/d was the minimal dose required for maximal gain response. Hancock and Preston (1988), utilizing maximum reduction in plasma urea nitrogen (PUN) as the response criterion, concluded that an estradiol payout rate of 33 mcg/d was the optimum dose for maximum anabolic activity. More recently, however, Preston and Herschler (1992) reported that a greater payout rate (at least 174 mcg/d) of estradiol was required for maximum gain and efficiency of feedlot steers. One can speculate on the reasons for the discrepancy among estimates of optimal estradiol payout rates for feedlot steers between the studies of Wagner et al. (1979; 55 mcg/d) and Preston and Herschler (1992; at least 174 mcg/d). Nonimplanted steers in the study of Wagner et al. (1979) gained 1.04 kg/d; those in the Preston and Herschler (1992) study gained 25% faster (1.30 kg/d). Therefore, seems that cattle with a higher propensity to gain and deposit carcass lean tissue may require a higher daily release rate of estradiol. The minimum estradiol release rate (at least 174 mcg/d) to maximize gain proposed by Preston and Herschler (1992), is approximately that rate provided for a short period of time (60 d) by Synovex-S® (183mcg of E2/d, Table 2; Rumsey et al, 1992). Optimal release rates of trenbolone acetate (TBA) for maximum growth promotion have not been similarly studied.

Wagner (1983) titrated the optimal dosage of estradiol for rate of gain in suckling calves by using implants that released estradiol at rates ranging from 0 to 81 mcg/d. A six-trial summary indicated that a release rate of approximately 30 mcg/d provided maximum gain response. Presumably, young calves should require a lower dose of estradiol for maximum gain response than older, larger animals.

Measurement of Release Rates of Hormones from Anabolic Implants

Release rates of anabolic hormones from ear implants are generally biphasic (Figure 1) although some exceptions for TBA/estradiol combinations are discussed in a later section. Blood serum or plasma hormone levels of implanted animals are characterized by a high initial peak in the first 1-3 days, followed by a depletion curve that generally follows first-order kinetics. A theoretical threshold serum or plasma hormone concentration exists below which anabolic stimulation or growth promotion from an implant ceases. Threshold serum or plasma concentrations have not been elucidated for any of the anabolic hormones. The absence of this critical information has caused confusion in determining anabolic life of implants. For the example in Figure 1, if the true threshold concentration for the hormone depicted was 15 pg/ml (threshold "a"), then the implant would have an anabolic life of about 55 d. Conversely, if the true threshold concentrations were 10 pg/ml (threshold "b") or 5 pg/ml (threshold "c"), then the implant would have an anabolic life of about 80 or 140 d, respectively.

Several experimental methods have been employed to estimate release rates and(or) active life of anabolic implants. These include:

- Implant/explant studies
- Measurement of blood levels of anabolic hormones over time
- Metabolic measurements (e.g., PUN, nitrogen balance)
- Animal performance

Individually, these techniques provide valuable information, but they are somewhat limited in their ability to provide definitive measures of release rates and length of anabolic activity. Implant/explant studies provide a means by which to measure disappearance of anabolic hormones from an implant over time, but they provide only an average daily release rate over time. Measurement of blood levels of an anabolic hormone over time may better characterize a release curve, but this does not account for other circulating metabolites of the particular hormone measured. More importantly, threshold concentrations of circulating hormones, or concentrations below which anabolic stimulation or activity is not maintained, have not been established for beef cattle. Measures of nitrogen metabolism (e.g., PUN, nitrogen balance) are more sensitive measurements of anabolic activity, but they are not necessarily highly correlated with animal performance over time (e.g., Istasse et al., 1988). Animal performance (rate and efficiency of gain), particularly performance changes between interim periods in a study, may provide some insight into length of anabolic activity; but interim performance is highly variable and susceptible to environmental effects that may affect weighing conditions and resulting conclusions. Therefore, it seems that studies designed to measure length of anabolic activity or release rates of implants should incorporate as many as these techniques as possible.

Figure 1. Biphasic nature of hormone absorption from an ear implant.

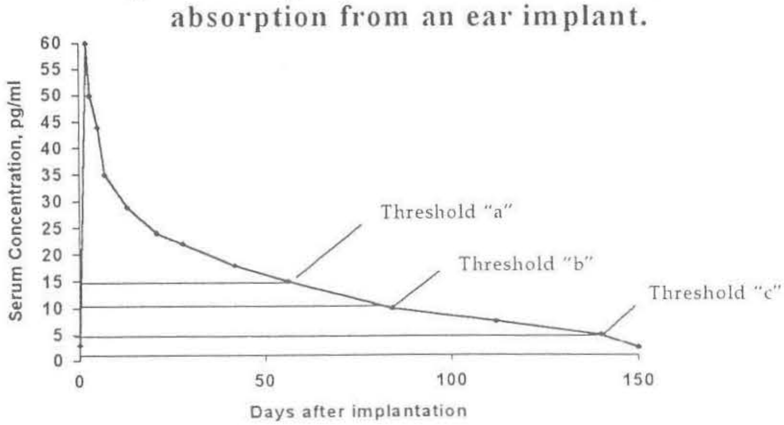

Table 1. Primary component of carriers for anabolic implants.

Implant	Carrier
Ralgro (36, 72 mg)	Lactose
Synovex (S, H, C, P)[a]	PEG[c]
Component (S,H,C)	PEG
Implus (S, H, C[b])	PEG
Revalor (S, H, G)	Cholesterol
Finaplix (S, H)	Lactose
Compudose	Silastic rubber
Encore	Silastic rubber

[a]S = steer, H = heifer, C = calf, P = Plus.
[b]Calf-oid.
[c]Polyethylene glycol.

Table 2. Effect of carrier on estradiol release rates over time.

Implant	Est. rate, mcg/d	Time, d	Reference
Silastic rubber[a]	66.0 (77)	146	Wagner (1983)
	53.5 (62.4)	196	
	52.7 (61.5)	208	
Compressed Pellet[b]	183	60	Rumsey et al., 1992
	23	60-150	

[a]254 cm implant. No. in parenthesis is estimate for a 3.0 cm implant.
[b]Synovex-S.

Factors Affecting Release Rates

Several factors have been implicated as having an effect on release rates of anabolic hormones from ear implants, including composition (solubility) of the excipient, age of the animal, mixtures of hormones contained in the implant, and implanting technique. These will be discussed individually.

Composition or solubility of the excipient. The excipient (also referred to as the implant support, matrix, or carrier) for various implant products differ in composition (Table 1); this may affect length of anabolic activity and(or) release rates of implants. Silastic rubber excipients are completely insoluble, whereas solubility of other excipients (lactose, PEG, or cholesterol) in compressed pellet implants vary. The difference in payout rate and length of payout between a silastic rubber implant (containing approximately 24 mg estradiol) and a compressed pellet implant (containing approximately 14 mg estradiol) is illustrated in Table 2. Estradiol release from the silastic rubber implant was characterized by a lower, but more prolonged release over time; initial estradiol release from the compressed pellet implant was higher initially, but release diminished more quickly with time.

Initially, lactose was used in compressed pellet implants because lactose is well absorbed by tissues and yields hard pellets (Istasse et al., 1988). However, its high degree of solubility may increase the hormone release rate and(or) reduce the length of anabolic activity compared to other carriers. Henricks et al. (1982) implanted heifers with 300 mg TBA in a lactose-based implant; they reported that 13.1 and 2.7% of the original TBA dose remained after 62 and 99 days, respectively. Similarly, unpublished data of Roussel-Uclaf showed that 9.1% of an original TBA dose remained in a lactose-based implant 107 d post-implantation. Conversely, 20% of a TBA dose remained in the implant 140 days after administration of TBA in a cholesterol-based implant in the ears of calves (Roussel-Uclaf, unpublished data). Istasse et al. (1988) compared implanting growing bulls once (18 wk before slaughter) with a cholesterol-based implant, versus implanting three times (18, 12, and 6 wk before slaughter) with a lactose-based implant. Each implant contained 200 mg TBA and 40 mg estradiol.

In one study, rate and efficiency of gain were similar between treatments even though steers receiving a lactose-based implant were implanted three times. However, in a three-trial summary, Bartle et al. (1992) found no difference in performance of feedlot steers administered 140 mg TBA plus 28 mg estradiol in either a lactose-based or cholesterol-based implant, and fed for 140 to 168 d.

Age of animal. Release rates of implants may be slower in suckling calves than older animals. Rumsey et al. (1992) reported that approximately 25% of the original dose of estradiol benzoate and progesterone remained after 60 d in a compressed pellet implant (Synovex-S®) following administration to yearling feedlot steers. Ritchie et al. (1990), however, reported that approximately 50% of the original dose of estradiol benzoate and progesterone remained 83 d after implanting suckling calves with Synovex-C®, and that approximately 25% of the original dose remained 172 d after implantation (Table 3). The calculated estradiol payout rate from d 83-172 (21.4 mcg/d of E2, Table 3) is very close to the 30 mcg/d release rate estimated by Wagner (1983) to be optimal for gain of suckling calves. The reason for this difference in absorption rate for suckling calves and yearling calves has not been elucidated. However, Gill et al. (1986) detected no benefit from reimplanting suckling calves in a two-trial summary that averaged 241 d in duration. Similarly, Corah et al. (1996) reported no benefit from reimplanting suckling calves with Synovex-C in a summary of four studies that were conducted for periods of 172 to 188 d. Although the study by Gill et al. (1986) was conducted over the winter with fall-born calves, it seems doubtful that reduced blood flow to the ear as a result of cold ambient temperatures is a major factor; studies by Ritchie et al. (1990) and Corah et al. (1996) were conducted on spring-born calves. There may also be an age or weight dependency on reponse to suckling implants of estradiol and progesterone (Corah et al., 1996), and zeranol (Greathead, 1984).

Mixtures of hormones contained in the implant. Combinations of either TBA, testosterone propionate, or progesterone with estradiol in the same implant may extend the absorption time of estradiol in ruminants (Heitzman et al., 1977; Riis and Suresh, 1976; Harrison et al., 1983). Nevertheless, blood levels of TBA do not appear to be altered as a result of combining TBA with estradiol in the same implant. Heitzman et al. (1981) implanted steers with either 20 mg estradiol, 140 mg TBA, or 20 mg estradiol plus 140 mg TBA in separate implants or combined in a single implant. Rate of gain was faster ($P<.05$), and feed conversion was improved for steers implanted with the combination implant vs those administered the same dosage of hormones in separate implants. Further, plasma estradiol concentrations for steers receiving the combination implant were significantly higher than controls for 91 d; administration of estradiol in a separate implant significantly elevated plasma estradiol for only 28 d. The authors concluded that physically mixing the hormones resulted in a slower and more sustained release of estradiol from the implant. Similar results of elevated estradiol levels for an extended period of time in steers implanted with a combination of estradiol and TBA (Revalor-S®) can be found in reports by Hickman et al. (1994) and Johnson et al. (1996).

Whether elevated blood levels of estradiol over time was the result of delayed release is not clear because residual hormone in the implants was not measured in any of the studies discussed in this section. Nevertheless, blood concentrations of estradiol remained elevated for an extended period of time when administered in the same implant with TBA. Implanting with an estrogenic implant following a combination estradiol/trenbolone acetate implant thereby may be of limited value.

Table 3. Payout rate of estradiol benzoate/progesterone implants[a] in suckling calves

Item	83 d	172 d
No. steers	28	25
Age, d	89	0
EB payout, %	50.5	76.9
avg. mcg E2/d	43.8	21.4[b]

[a]Synovex-C. Adapted from Ritchie et al., 1990.
[b]From 83 to 170 d.

Implanting technique. One major source of variation in implant response is implanting technique. Improper placement (anywhere other than in the middle one-third of the ear) or crushing of implants upon administration likely will result in more variable absorption rates, increased demonstration of secondary sexual characteristics (e.g., bulling, elevated tailheads, etc.), and variable performance.

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QUESTIONS & ANSWERS

Q: Might differences either between seasons or between calves and yearlings in blood circulation to the ear alter payout of an implant or is payout limited by release of the chemical from the carrier and independent of blood circulation? Calves often lose part of their ear from frostbite but yearlings don't seem to.

A: Why is implant release rate slower in calves? Vascularization may be less in calves and blood flow to the ear probably may be lower, especially during cold months. Hormone release probably is related to vascularization and blood volume. That might explain some differences.