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# **An investigation into the mechanisms of action of Revalor-S and Optaflexx in growing steers**

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## AN INVESTIGATION INTO THE MECHANISMS OF ACTION OF REVALOR<sup>1</sup>-S AND OPTAFLEXX<sup>2</sup> IN GROWING STEERS

*D. K. Walker, E. C. Titgemeyer, J. J. Higgins, and B. J. Johnson*

### Summary

An experiment was conducted to evaluate the interaction between steroidal implantation and feeding ractopamine on nitrogen retention, blood metabolites, and messenger RNA (mRNA) expression. Six Holstein steers (initially weighing 509 lb) were implanted or not with Revalor-S (120 mg trenbolone acetate plus 24 mg estradiol-17 $\beta$ ), and all were fed no ractopamine for the initial 28 days and then 2 grams per steer daily of Optaflexx (200 mg/day ractopamine-HCl) on days 29 through 56. Implantation increased nitrogen retention. Optaflexx increased nitrogen retention in non-implanted steers, but did not significantly increase retained nitrogen in implanted steers. Implantation increased serum insulin-like growth factor (IGF)-I concentration. Optaflexx, however, numerically decreased serum IGF-I concentrations. Implantation numerically increased IGF-I mRNA in the longissimus muscle, but expression of IGF-I mRNA was significantly decreased when Optaflexx was fed. Both growth promotants increased nitrogen retention in steers, but, despite perceived differences in their mode of action, the combination yielded a less than additive response for nitrogen retention.

### Introduction

In the feedlot industry, enhancing efficiency of growth of finishing cattle is a major

objective. Improvements in growth have been achieved by use of steroidal implants. Steroidal implants such as Revalor-S that contain trenbolone acetate and estradiol-17 $\beta$  can improve daily gain and feed efficiency, which results, at least in part, from increased blood concentrations of IGF-I and local tissue production of IGF-I. Insulin-like growth factor-I affects postnatal muscle growth by increasing the number of satellite cells (which contain DNA), fusion of these satellite cells with existing muscle fibers, and muscle protein accretion.

Optaflexx is growth promotant that is new to the market in the United States. Optaflexx is the trade name for ractopamine-HCl, a  $\beta_1$  adrenergic agonist. Addition of Optaflexx to the diet can repartition nutrients away from fat deposition and to muscle accretion, thus improving daily gain and feed efficiency. Little research has been conducted with steers that have been implanted with Revalor-S and fed Optaflexx.

Implants and  $\beta$  agonists may improve growth by potentially different mechanisms. Previous research has shown that implanting steers with Revalor-S increases serum concentrations of IGF-I, and this effect is maintained for up to 150 days. Similarly, mRNA expression of IGF-I in the longissimus and the liver of steers implanted with Revalor-S is significantly increased by implantation. As a result

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<sup>1</sup>Revalor is a registered trademark of Intervet, Inc.

<sup>2</sup>Optaflexx is a registered trademark of Elanco Animal Health, Indianapolis, IN.

of these increases in IGF-I, daily gain and feed efficiency are improved. Insulin-like growth factor-I improves muscle growth by increasing protein accretion and by increasing the DNA content in the muscle, which is needed to sustain the increased protein accretion. Optaflexx has been shown to improve daily gain and feed efficiency in feedlot cattle, but the mechanisms involved have not been completely elucidated. For example, the impact of Optaflexx on IGF-I measures has not been documented.

The aim of our study was to evaluate effects of feeding Optaflexx to steers implanted with Revalor-S and, thus, evaluate some mechanisms of action for these growth promotants in an effort to predict if they might yield additive or synergistic responses. For our study, growing Holstein steers were used as a research model to provide some insight into the mechanisms by which these two growth promotants function.

### **Experimental Procedures**

Six Holstein steers (509 lb initial weight) were used in a split-plot design. Steers were housed in individual metabolism crates and were adapted to a corn-based diet for 1 week before the study. All steers had free access to water and received the same diet in equal proportions at 12-hour intervals during the experiment. The diet contained 62% dry rolled corn, 15% alfalfa hay, and 20% expeller soybean meal. Rumensin (30 mg/kg) and tylan (11 mg/kg) were added to the diet. The diet was formulated to supply excess metabolizable protein to the steers.

The main plot treatments were implantation with Revalor-S (120 mg trenbolone acetate plus 24 mg estradiol-17 $\beta$ ; Intervet, Millsboro, DE) or no implant. Three of the six steers were implanted on day 0. The subplot

treatment was feeding of 0 or 2 grams per steer daily of Optaflexx (providing 0 or 200 mg/day ractopamine-HCl; Elanco Animal Health, Greenfield, IN). None of the steers received Optaflexx during the initial 28 days of the trial, and then all steers were fed 2 grams per steer daily of Optaflexx, beginning on day 29 and continuing through the end of the trial.

Representative samples of the diet, orts, feces, and urine were collected over 4-day periods for measuring nitrogen balance (a measure of lean-tissue deposition). Jugular blood samples were collected 2 hours after the morning feeding on days 0, 14, 28, 42, and 56 for analysis of glucose, urea, insulin, and IGF-I. Biopsy samples were collected from the longissimus muscle of each steer on days 0, 14, 28, 42, and 56. Semimembranous muscle and liver samples were collected from each steer after they were euthanized on day 56. Total RNA was isolated from muscle and liver samples for use in real-time, quantitative polymerase chain reaction (PCR) to measure the expression of IGF-I mRNA.

### **Results and Discussion**

Optaflexx significantly increased diet digestibility and significantly decreased nitrogen intake, fecal nitrogen excretion, and urinary urea nitrogen excretion (Table 1). Decreases in N intake were a result of slightly lower dietary N concentrations during the second half of the experiment. An increase in digestibility would lead to less fecal nitrogen loss. Total urinary nitrogen excretion was significantly decreased by Revalor-S and by feeding Optaflexx to control steers; it was not, however, affected by feeding Optaflexx to steers implanted with Revalor-S. Increases in diet digestibility and decreases in nitrogen excretion led to significant increases in nitrogen retention in response to Revalor-S as well as in

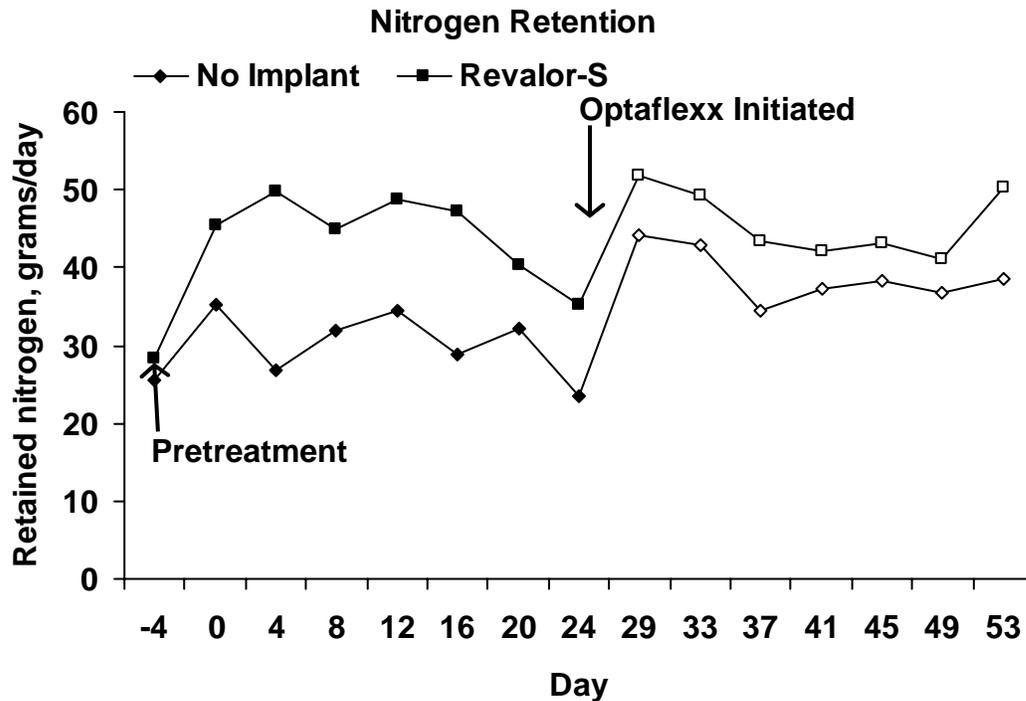
response to Optaflexx in non-implanted steers, but not in response to Optaflexx in implanted steers (Figure 1).

Plasma urea and glucose concentrations were not significantly affected by treatment (Table 2). Plasma insulin concentrations were not significantly affected by Revalor-S or Optaflexx, but numerically concentration decreased 66% in implanted steers when Optaflexx was fed, in contrast to an 8% decrease in non-implanted steers in response to Optaflexx. Implantation with Revalor-S significantly increased serum IGF-I concentrations. In contrast, Optaflexx led to numerical decreases in serum IGF-I concentrations in both control and implanted steers. During the final 28 days, when Optaflexx was fed, implanted steers maintained greater serum IGF-I concentrations than control steers did.

Messenger RNA is the product of gene expression and is the first of many steps in producing a protein. Measuring mRNA expression of a gene is not a direct measure of the protein produced, but it typically is related to production of the protein. Insulin-like growth factor-I mRNA expression in the longissimus muscle followed the same pattern as serum concentrations of IGF-I (Table 2). Implantation with Revalor-S led to numerical increases in IGF-I mRNA expression, but IGF-I mRNA expression in longissimus muscle was significantly decreased by Optaflexx.

During the final 28 days, when Optaflexx was fed, implanted steers maintained greater IGF-I mRNA expression than control steers did. Implantation with Revalor-S resulted in numerical increases in IGF-I mRNA expression in semimembranosus muscle tissue on day 56 (Table 3). Revalor-S also led to numerical increases in IGF-I mRNA in the liver on day 56 (Table 3), which agrees with the higher serum IGF-I concentrations that implanted steers maintained throughout the study. Because the liver is the primary source of blood IGF-I, the relationship between liver mRNA expression and serum concentrations of IGF-I was expected.

The results gathered from this experiment show that Revalor-S or Optaflexx can improve growth in lightweight, growing Holstein steers, as shown by improvements in nitrogen retention. Administering a combination of the two, however, did not enhance nitrogen retention beyond that observed for the implant alone. The two growth promotants demonstrated different modes of action; Revalor-S increased serum concentrations and mRNA expression of IGF-I, whereas Optaflexx led to decreases in these parameters. Although our steers were not typical of finishing cattle that would receive Optaflexx (they were much smaller and more recently implanted), the use of these animals allowed an evaluation of the mechanisms of action of the two growth promotants.



**Figure 1. Effects of Revalor-S and Optaflexx on nitrogen retention over time in Holstein steers.** Filled symbols represent times when Optaflexx was not fed, whereas the open symbols represent times when Optaflexx was fed. Each value represents an average of nitrogen retained over four days. SEM = 1.4.

**Table 1. Effects of Revalor-S and Optaflexx on nitrogen balance and diet digestibility in growing steers**

Nitrogen, grams/day	Days 0 to 28 No Optaflexx		Days 29 to 56 2 g/d Optaflexx		SEM
	No Implant	Revalor-S	No Implant	Revalor-S	
Dietary intake <sup>a</sup>	143.2	140.4	139.6	135.6	3.9
Fecal <sup>a</sup>	35.2	35.4	29.1	29.9	2.9
Urinary <sup>b</sup>	77.2 <sup>z</sup>	60.8 <sup>x</sup>	71.2 <sup>y</sup>	60.2 <sup>x</sup>	4.0
Retained <sup>b</sup>	30.4 <sup>x</sup>	44.6 <sup>z</sup>	39.0 <sup>y</sup>	45.9 <sup>z</sup>	1.4
Dry matter digestibility, % <sup>a</sup>	76.9	77.7	79.0	80.2	1.9

<sup>a</sup>Effect of Optaflexx,  $P < 0.05$ .

<sup>b</sup>Effect of Revalor-S  $\times$  Optaflexx interaction,  $P < 0.05$ .

<sup>x,y,z</sup>Means having different superscript letters within a row differ,  $P < 0.05$ .

**Table 2. Effects of Revalor-S and Optaflexx on blood metabolites and IGF-I mRNA expression in Holstein steers**

Item	Days 14 and 28 No Optaflexx		Days 42 and 56 2 g/d Optaflexx		SEM
	No Implant	Revalor-S	No Implant	Revalor-S	
Plasma glucose, mM	4.81	4.64	4.72	4.36	0.2
Plasma urea, mM	4.60	4.24	4.30	4.02	0.3
Serum insulin, ng/mL	0.50	0.40	0.46	0.14	0.1
Serum IGF-I, ng/mL <sup>a</sup>	443	593	359	545	93
Longissimus mRNA					
IGF-I, arbitrary units <sup>b</sup>	516	838	218	453	181

<sup>a</sup>Effect of Revalor-S,  $P < 0.05$ .

<sup>b</sup>Effect of Optaflexx,  $P < 0.05$ .

**Table 3. Effects of Revalor-S on mRNA expression in semimembranosus muscle and liver**

Tissue	No Implant	Revalor-S	SEM
	--- IGF-I mRNA, arbitrary units ---		
Semimembranosus muscle	956	3,288	792
Liver	37,252	78,554	19,536