Feeding zilpaterol hydrochloride is associated with decreased dry matter intake shortly after initiation of feeding dependent on season and previous intake

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ABSTRACT: A database of daily feed deliveries for steers and heifers fed at 3 commercial feedyards in Kansas between January 1, 2010, and January 31, 2012 (n = 1,515 pens), was used to investigate the prevalence and extent of changes in DMI after initiation of feeding zilpaterol hydrochloride (ZIL) at 8.3 mg/kg (DM) for 20 d. Season affected the percentage of pens experiencing a decrease in DMI post-ZIL (P < 0.01), but there were significant (P < 0.01) season × sex, season × feedyard, season × pre-ZIL DMI, season × days post-ZIL, and season × period post-ZIL interactions. Average DMI decreased within 1 d after initiation of ZIL feeding in all seasons; however, this initial decrease was greater (P < 0.01) in the summer (–0.30 kg) and winter (–0.27 kg) than in the spring (–0.05 kg) or fall (–0.06 kg). The decrease in DMI averaged across all days post-ZIL was greater in summer than during other seasons for both steers and heifers, and the change in intake was greater in steers than heifers in all seasons but fall. Size of intake change within each season varied by feedyard and by season. The percentage of pens that had a large DMI decrease (≥0.9 kg/d) was greatest during the summer (33%), and the percentage of pens with no decrease was the least (15%); during the fall, 34% of pens had no DMI decrease and only 8% of pens had a large decrease in DMI. Intake before ZIL initiation affected size and prevalence of DMI decrease; with increasing pre-ZIL DMI, the percentage of pens with a decrease increased from 62% for pens with pre-ZIL DMI of less than 7.7 kg/d to 82% for pens consuming greater than 10.5 kg/d pre-ZIL (P < 0.01). Of those pens with greater than 10.5 kg/d pre-ZIL DMI, 27% had DMI decrease of greater than 1.4 kg/d compared to only 3% for pens consuming <8.7 kg/d pre-ZIL. The average dosage of ZIL consumed per animal with an average DMI of 7.3, 8.2, 9.1, 10.0, and 10.9 kg/d was calculated to be 61, 68, 76, 83, and 91 mg/animal daily, which may be related to the differences in DMI decrease. Pre-ZIL DMI contributed to DMI decrease during ZIL administration, but the increased occurrence and size of DMI decrease during the summer may indicate an additional physiological mechanism.

Key words: beta agonist, cattle, fatigued cattle syndrome, feedlot, heat stress, intake

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INTRODUCTION

Zilpaterol hydrochloride (ZIL; Zilmax) was approved for use in feedlot cattle by the U.S. Food and Drug Administration in 2006 and approved for use in combination with monensin sodium, tylosin phosphate, and melengestrol acetate in 2007 for increased rate of weight gain, improved feed efficiency, and increased carcass leanness in cattle fed in confinement for slaughter during the last 20 to 40 d on feed. Since the approval, there have been anecdotal reports from commercial feedyards of reduction in DMI in feedlot cattle beginning shortly after initiation of feeding ZIL; often, no difference in intake was detected, sometimes a small change was reported, and occasionally a substantial change of several kilograms was observed. In some instances, intake returned to pre-ZIL levels over time; in other cases, intake remained depressed.

Some studies have reported no effect of zilpaterol on DMI (Elam et al., 2009; Parr et al., 2011), while others have reported a decrease in DMI for cattle fed...
zilpaterol compared to control cattle (Montgomery et al., 2009a,b; Holland et al., 2010; McEvers et al., 2012b).

The objectives of the present study were to evaluate relationships between DMI before and after initiation of ZIL feeding in 3 commercial feedyards and to determine how this relationship is affected by season, sex, and pre-ZIL DMI.

MATERIALS AND METHODS

Animal care procedures were in compliance with the Guide for the Care and Use of Agricultural Animals in Agricultural Research and Teaching (FASS, 2010).

A database of daily feed deliveries for steers and heifers fed between January 1, 2010, and January 31, 2012, at 3 commercial feedlots in Kansas (n = 1,515 pens of cattle; Table 1) was used to investigate the prevalence and extent of changes in DMI after initiation of ZIL feeding. Each daily feed delivery was divided by the number of animals in the pen and multiplied by diet DM to estimate per animal daily DMI. Because minor dietary changes were made periodically, each DMI value was adjusted to a common net energy (NEg) content by multiplying the daily DMI value by its corresponding NEg content and dividing by the average NEg content across the entire time period. Pre-ZIL baseline DMI was calculated as the average DMI for the 10-d period immediately before initiation of ZIL. Post-ZIL DMI was analyzed using daily DMI for d 2 through 9 after initiation of ZIL feeding and the average DMI within each of four 5-d periods of the 20-d ZIL feeding period. The average DMI across the 18 d before the 10-d pre-ZIL baseline was used to compare intake trends before initiation of ZIL feeding; the change in intake between the prebaseline and baseline DMI periods was used as a covariate in the models to correct for any preexisting trend in DMI.

A mixed model approach was used that included as fixed effects the main and interaction effects of sex (steer and heifer), feedyard (A, B, and C), season (fall, winter, spring, and summer), days after ZIL initiation (2–9), change in DMI before initiation of ZIL, and the interaction of baseline pre-ZIL DMI × season. Seasons were defined as follows: fall = September, October, and November, winter = December, January, and February, spring = March, April, and May, and summer = June, July, and August. The data were analyzed with days after ZIL initiation treated as repeated measures using an autoregressive covariance structure since data points observed closer together in time should be assumed to be more closely related than data points further apart in time. The MIXED procedure of SAS (SAS Inst. Inc., Cary, NC) was used to analyze the main and interactive effects of season, feedyard, sex, and previous DMI on change in DMI; the GLIMMIX procedure of SAS was used to evaluate the effects of those same variables on whether or not the pen experienced a drop in DMI. Effects were considered significant if \( P < 0.01 \) for the type III sums of squares.

Table 1. Description of the data used in the analysis for daily dry matter feed deliveries for cattle fed in 3 commercial Kansas feedlots between January 1, 2010, and January 31, 2012

<table>
<thead>
<tr>
<th>Item</th>
<th>( n ) (number of pens)</th>
<th>Average</th>
<th>SD</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feedlot</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>679</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>B</td>
<td>414</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>C</td>
<td>422</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Season</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Summer</td>
<td>399</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Fall</td>
<td>420</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Winter</td>
<td>338</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Spring</td>
<td>358</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steers</td>
<td>523</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Heifers</td>
<td>992</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Initial BW on zilpaterol, kg</td>
<td>–</td>
<td>517.2</td>
<td>36.3</td>
<td>396.8</td>
<td>641.8</td>
</tr>
<tr>
<td>Days on feed on initiation of zilpaterol feeding</td>
<td>–</td>
<td>132</td>
<td>29.2</td>
<td>74</td>
<td>283</td>
</tr>
<tr>
<td>DMI before initiation of zilpaterol, kg</td>
<td>–</td>
<td>9.55</td>
<td>1.46</td>
<td>6.45</td>
<td>20.57</td>
</tr>
<tr>
<td>Number of animals within each pen</td>
<td>–</td>
<td>134</td>
<td>64.7</td>
<td>50</td>
<td>447</td>
</tr>
<tr>
<td>Pens with DMI decrease, (^1) mean size of maximum decrease, kg</td>
<td>1,136</td>
<td>–1.35</td>
<td>1.29</td>
<td>0</td>
<td>–6.85</td>
</tr>
<tr>
<td>Pens with DMI increase, (^1) mean size of maximum increase, kg</td>
<td>379</td>
<td>0.67</td>
<td>1.29</td>
<td>0</td>
<td>6.56</td>
</tr>
</tbody>
</table>

\(^1\)Greatest divergence of individual daily DMI after initiation of feeding zilpaterol hydrochloride compared to the 10-d average DMI before the zilpaterol feeding period.
Season and dry matter intake affect intake response to zilpaterol

RESULTS AND DISCUSSION

Of all pens that had a numerical decrease, the mean decrease (adjusted for all significant covariate factors) was 1.35 kg; of all pens that had a numerical increase, the mean adjusted increase in DMI was 0.67 kg. Of all the pens included in the data set, 10.3% had an adjusted numerical increase in DMI post-ZIL of greater than 0.45 kg and 15.2% had an increase of less than 0.45 kg. Season affected the percentage of pens experiencing a numerical decrease in DMI post-ZIL, but there were significant \( P < 0.01 \) season × sex, season × feedyard, season × day, and season × period interactions.

Average DMI declined within 1 d after initiation of ZIL feeding (Fig. 1); however, this effect was much greater on d 2 in the summer and winter than in the spring or fall. In all seasons, the decline in intake eventually plateaued (Fig. 2); in fall and spring, intake recovered slightly.

Change in intake was greater in summer than other seasons for both steers and heifers (Fig. 3) and the change in intake was greater in steers than heifers in all seasons but fall.

Feedyard C had a greater decrease in DMI vs. feedyards A and B, but the order of size of decrease between feedyards A and B varied by season (Fig. 4). Feedyard A had the smallest decrease in DMI during the spring, fall, and winter and had nearly no change in DMI when started on ZIL in the fall but actually had greater decrease in intake post-ZIL than feedyard B in the summer (Fig. 5). All 3 feedyards are within a 25-km radius so environmental conditions within season would not have

Figure 1. Mean change in daily DMI after initiation of zilpaterol feeding by day after initiation of zilpaterol feeding and season when zilpaterol feeding was initiated (season × day, \( P < 0.01 \)). Error bars = largest SEM across season within each day.

Figure 2. Mean change in daily DMI after initiation of zilpaterol feeding by 5-d period and by season when zilpaterol feeding was initiated (season × period, \( P < 0.01 \)). Error bars indicate largest SEM within period across seasons.
varied greatly among the feedyards. The 3 feedyards are managed by a single governing organization and the finishing diet and original sources of individual feed ingredients were similar among the feedyards.

The percentage of pens that had a large decrease in DMI (0.90–1.4 and >1.4 kg/d) were greater (18 and 15%; *P* < 0.01; Fig. 6) and the percentage of pens with no decrease was the least (15%) during the summer, while 34% of pens had no decrease in DMI during the fall.

As pre-ZIL DMI increased, percentage of pens with a decrease in post-ZIL DMI increased from 62% for pens with less than 7.7 kg to 82% for pens consuming greater than 10.5 kg (linear, *P* < 0.01; Fig. 7). Also, whereas only 2.5% of cattle consuming greater than 10.5 kg pre-ZIL had an increase in DMI of more than 0.45 kg, 37.8% of cattle with average DMI 7.7 kg had an increase in DMI of more than 0.45 kg (data not shown). The average dosage of ZIL consumed per animal with an average DMI of 7.3, 8.2, 9.1, 10.0, and 10.9 kg/d was calculated to be 61, 68, 76, 84, and 91 mg/animal daily, which may be related to the differences in decrease in DMI and warrants further investigation.

Summer months were isolated so that all feedyards, both steers and heifers, and all intake levels were adequately represented in the analysis. In pens started on ZIL during the summer months, greater pre-ZIL DMI resulted in a linear (*P* < 0.01) increase in the percentage of pens with >1.4 and 0.9 to 1.4 kg/d and a linear decrease in the percentage of pens with no decrease in DMI (Fig. 8). Of those pens with greater than 10.5 kg/d pre-ZIL DMI, 27% had DMI decrease of greater than 1.4 kg/d. Pens with greater pre-ZIL intake had a greater likelihood of having a decrease in DMI, and the size of the decrease was also greater.

There was a significant (*P* < 0.01) interaction between the effect of pre-ZIL baseline DMI and the size of

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**Figure 3.** Mean change in daily DMI after initiation of zilpaterol feeding for steers and heifers by season when zilpaterol feeding was initiated (sex × season, *P* < 0.01). Error bars indicate the largest SEM within sex across season.

**Figure 4.** Percentage of pens with a numerical decrease in DMI after initiation of zilpaterol feeding by feedyard and season when zilpaterol feeding was initiated (season × feedyard, *P* < 0.01). a–c Means within a season without a common superscript differ (*P* < 0.05).
Season and dry matter intake affect intake response to zilpaterol

The change in DMI and season (Fig. 9); however, in all seasons, the slope of the relationship was significant \( P < 0.01 \) and negative. During the summer, for each 1 kg/d increase in baseline DMI, post-ZIL DMI decreased 0.21 kg/d; conversely, during the fall DMI only decreased by 0.156 kg/d per 1 kg change in baseline DMI.

Some feedlots alter the time of feed delivery when pens of cattle are switched from the common finishing diet to the finishing diet containing zilpaterol. This change in feeding time may also perturb normal feeding behavior and negatively affect voluntary feed intake, and cattle with greater pre-ZIL DMI may have been affected to a greater degree by this potential change in time of feed delivery. Unfortunately, it was not possible to isolate and analyze for changes in time of feed delivery in the present data set.

From a production perspective, the observed reduction in DMI likely results in reduced gain and efficiency; Stock and Britton (1991) reported that a decrease in DMI of 0.23 kg results in a decrease of 0.05 kg ADG and 2% increase in the amount of feed required per unit of gain. The decreases in DMI in the present analysis were expected based on published data; however, the magnitude of the changes in some pens was not expected based on the literature. Korn et al. (2013) reported a range of intake changes from +0.45 to –0.68 kg for cattle fed ZIL at 8.3 mg/kg for 20 d vs. negative controls. There is divergence in the reported effects of zilpaterol on DMI, with reports ranging from small to moderate decreases in DMI (Baxa et al., 2010; Holland et al., 2010; Parr et al., 2011) to reports of greater decreases (Seramlin et al., 2010; McKevers et al., 2012a). South African researchers have reported reduced DMI of 6% in steers (Strydom et al., 2008) and 5% in cull cows (Strydom and Smith, 2010) fed ZIL at 6 mg/kg, although these reductions were not statistically significant. Vasconcelos

Figure 5. Mean change in daily DMI after initiation of zilpaterol feeding by season and feedyard (season \( \times \) period, \( P < 0.01 \)). Error bars indicate the largest SEM for each feedyard between the 4 seasons.

Figure 6. Percentage of pens with a decrease in DMI after initiation of zilpaterol feeding by size of decrease and season (season \( \times \) size of decrease, \( P < 0.01 \)). a–cMeans within a size of intake decrease group without a common superscript differ \( (P < 0.01) \).
et al. (2008) demonstrated a 0.40 kg reduction in DMI when ZIL was fed for 40 d at 72 mg/animal daily but no effect on DMI for cattle fed ZIL at 75 mg/animal daily for 20 d. Montgomery et al. (2009a) reported a ZIL × sex interaction for DMI; steers did not have a reduction in DMI during ZIL administration but heifers had a 0.52 kg reduction in DMI during the ZIL-feeding period. Kononoff et al. (2013) reported an interaction in DMI response to ZIL feeding with expression of the leptin gene; they reported no reduction in DMI when feeding ZIL to cattle with the CC allele, a reduction of 0.40 kg in cattle with the CT allele, and a reduction of 0.80 kg in DMI in cattle with the TT allele, indicating a genetic component to reductions in DMI in response to feeding ZIL.

When fed at 1.5 times the approved concentration of 8.3 mg/kg, no significant change in DMI was observed, but when dosage concentration was increased to 10 times the approval concentration, there was a decrease in DMI (FDA, 2006). Robles-Estrada et al. (2009) and Avendaño-Reyes et al. (2006) reported no decrease in DMI for the entire feeding period when cattle were fed zilpaterol, but zilpaterol intake in these studies was 68 and 60 mg/animal daily, which would represent the lower 13% of the present data set; cattle in the present analysis with lesser pre-ZIL DMI had a lesser mean decrease in DMI, depending on season. Conversely, Lawrence et al. (2011) reported no reduction of DMI in cull cows consuming 143 mg ZIL/animal daily, which is much greater than any of the pens included in the present analysis. Other studies have also reported no effect of ZIL

Figure 7. Percentage of pens with a decrease in DMI after initiation of zilpaterol feeding by baseline (pre-zilpaterol) DMI. (Effect of pre-zilpaterol DMI: linear, \( P < 0.01 \), and quadratic, \( P = 0.81 \).) Means without a common superscript differ \((P < 0.01)\). Baseline DMI = mean DMI for the 10 d immediately before initiation of zilpaterol feeding. Shown above each column is the zilpaterol intake corresponding to DMI of 7.3, 8.2, 9.1, 10.0, or 10.9 kg.

Figure 8. Percentage of pens started on zilpaterol during summer months (June, July, and August) with a negative change in DMI after initiation of zilpaterol feeding by size of decrease and baseline DMI. (Effect of baseline DMI: DMI change < –1.4 kg: linear, \( P < 0.01 \), and quadratic, \( P = 0.03 \); DMI change –0.9 to –1.4 kg: linear, \( P < 0.01 \), and quadratic, \( P = 0.37 \); DMI change –0.45 to –0.9 kg: linear, \( P = 0.02 \), and quadratic, \( P = 0.45 \); DMI change 0 to –0.45 kg: linear, \( P < 0.01 \), and quadratic, \( P = 0.29 \); no DMI decrease: linear, \( P < 0.01 \), and quadratic, \( P = 0.88 \).)
Season and dry matter intake affect intake response to zilpaterol

Season and dry matter intake affect intake response to zilpaterol (Elam et al., 2009; McEvers et al., 2012b). The environmental conditions and time of year within the reported studies is not known and may have affected the DMI response to ZIL.

When steers were fed clenbuterol, DMI decreased 9%, whereas there was no decrease when ractopamine was fed (Strydom et al., 2008). Abney et al. (2007), Gruber et al. (2007), and Quinn et al. (2008) reported no decrease in intake when cattle were fed 200 mg/animal daily of ractopamine; however, Quinn et al. (2008) and Avendaño-Reyes et al. (2006) reported significant decreases in DMI in heifers and steers fed ractopamine at 300 mg/animal daily.

In both cattle and pigs fed ractopamine, there appears to be a dose-dependent response of DMI to β-agonist treatment. Although a dose-dependent DMI response to ZIL is also indicated in the present study, more research of a controlled nature, across feeding environments, on determining the contributing factors that cause a reduction in feed intake in zilpaterol fed animals is warranted. Quinn et al. (2008) saw no decrease in DMI at 200 mg of ractopamine/animal daily but did report a decrease in DMI at 300 mg. Strydom et al. (2008) reported no effect of ractopamine on DMI but reported 6.0 and 9.0% decreases in DMI for zilpaterol and clenbuterol. In that study, the ractopamine increased HCW by 7 kg whereas the zilpaterol and clenbuterol increased HCW by 14.4 and 15.9 kg, respectively, suggesting that potency for stimulation of lean growth is somewhat proportional to the resulting effect on DMI. A similar phenomenon is observed in pigs; ractopamine was associated with mild, nonsignificant decreases in intake when fed at 5 or 10 mg/kg but was associated with a 13.4% decrease in intake when fed at 20 mg/kg (Armstrong et al., 2004). Jones et al. (1985) similarly reported only a mild, nonsignificant decrease in intake when pigs were fed 0.25 mg/kg cimaterol but significant 7.4 and 8.7% reductions in intake when cimaterol was fed at 0.50 and 1.0 mg/kg.

Beta-adrenergic agonists stimulate numerous physiological changes in the body, many of which may possibly be tied to the negative DMI response reported herein. In young steers infused with cimaterol, heart rate and circulating NEFA and lactate concentrations were

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**Figure 9.** Relationship between ultimate change in DMI post-zilpaterol vs. baseline DMI before initiation of zilpaterol feeding for cattle fed zilpaterol during fall (September, October, and November), spring (March, April, and May), summer (June, July, and August), and winter (December, January, and February). Fall: DMI change = −0.156 × (pre-zilpaterol DMI) + 1.30; effect of pre-zilpaterol DMI: \( P < 0.01, R^2 = 0.09, n = 381 \). Spring: DMI change = −0.167 × (pre-zilpaterol DMI) + 1.26; effect of pre-zilpaterol DMI: \( P < 0.01, R^2 = 0.10, n = 338 \). Summer: DMI change = −0.21 × (pre-zilpaterol DMI) + 1.26; effect of pre-zilpaterol DMI: \( P < 0.01, R^2 = 0.08, n = 350 \). Winter: DMI change = −0.217 × (pre-zilpaterol DMI) + 1.52; effect of pre-zilpaterol DMI: \( P < 0.01, R^2 = 0.17, n = 266 \). Pre-zilpaterol change in intake was included as a covariate within each season.
elevated within 6 h after initiation of infusion (Byrem et al., 1998); NEFA and lactate were also released from the hind limb where the cimaterol was infused within 12 h after infusion. Liver glycogen stores are reduced by 48% within 15 min in pigs fed salbutamol vs. control pigs (Warriss et al., 1990b); liver glycogen stores remained at or below 50% of controls through slaughter (Warriss et al., 1990a). Administration of clenbuterol resulted in dramatic, rapid, and transient increase in blood glucose and NEFA in lactating cows (Stoffel and Meyer, 1993), calves (Blum and Flueckiger, 1988), and pigs (Dunshea et al., 1993). Although blood glucose was not different in pigs fed salbutamol (Warriss et al., 1990a), blood lactate at slaughter was elevated 46% vs. controls.

Feeding zilpaterol at 7.5 mg/kg caused elevated heart rate in cattle within 1 d postfeeding (FDA, 2006); heart rate and blood pressure were elevated in dogs and monkeys after infusion of ractopamine (FDA, 1999). Human asthma patients treated with high doses of albuterol had 167% increases in plasma lactate (Rodrigo and Rodrigo, 1984) and also is limited by preference of the liver for propionate over lactate as a gluconeogenic substrate (Baird et al., 1982; Blum and Flueckiger, 1988; Stoffel and Meyer, 1993). Although blood glucose was not different in pigs fed salbutamol (Warriss et al., 1990a), blood lactate at slaughter was elevated 46% vs. controls.

Infusion of exogenous lactate decreases voluntary food intake in monkeys (Baile et al., 1970) and rats (Racotta and Russek, 1977; Nagase et al., 1996), and elevation of blood lactate by infusion of either epinephrine or isoproterenol resulted in dramatic reduction in voluntary food intake in rats (Racotta et al., 1984). The mode of action of lactate-stimulated intake depression is not understood but may be related to hepatic oxidation of fatty acids. Allen et al. (2005) theorized that gluconeogenesis is suppressed during periods of elevated blood glucose; intravenous infusion of glucose in lactating cows reduced glucose output from and lactate uptake by the liver (Baird et al., 1980). Circulating glucose is often elevated after administration of β-agonists or other catecholamines (Blum et al., 1982; Blum and Flueckiger, 1988; Stoffel and Meyer, 1993). Because lactate is a key intermediary in the conversion of a significant amount of propionate, which ultimately proceeds through gluconeogenesis (Leng et al., 1967), and because L-lactate may contribute to a significant proportion of total glucose output by the ruminant liver (Reynolds et al., 1988), it is conceivable that accumulation of circulating lactate due to metabolic alteration by catecholamines could result in the same negative feedback inhibition. In addition, the ability of the liver to convert L-lactate to glucose can be overwhelmed by excessive load of circulating lactate (Naylor et al., 1984) and also is limited by preference of the liver for propionate over lactate as a gluconeogenic substrate (Baird et al., 1980; Donkin and Armentano, 1995). If, at the time of β-agonist initiation, cattle are consuming a predominantly grain diet and have greater than average intake, resulting in a substantial amount of propionate being absorbed and given preference for conversion via gluconeogenesis in the liver, an accumulation of blood lactate seems plausible, resulting in rapid signal for satiety.

Leptin is pivotal in intake regulation in all mammals (Ingvarsen and Boisclair, 2001) and is greatly elevated in cattle proportionate to total percentage body fat and plane of energy; circulating NEFA levels are not affected by body fat content but are greatly elevated during the undernourished state due to body fat mobilization (Delavaud et al., 2002). Cows with greater DMI and BW have greater circulating leptin concentrations (Liefers et al., 2003), and Nkrumah et al. (2005) reported a correlation between greater circulating leptin and both DMI and time spent feeding. Konigsson et al. (2008) reported that cattle in negative energy balance and losing weight during lactation had greatly elevated circulating NEFA concentrations with no change in leptin levels, indicating that leptin is more a function of dietary energy and total body composition rather than short-term transient measures of fat mobilization. Lipolysis is stimulated by elevated leptin; leptin is not stimulated by lipolysis (Fruhbeck et al., 1997; Shimabukuro et al., 1997). On the contrary, leptin is depressed in fasting animals, during which time NEFA are elevated due to lipolysis, and leptin returns to normal within 2 h of refeeding (Chelikani et al., 2004). This indicates that that circulating leptin is tied to nutritional state, not circulating lipids. These findings suggest the unlikelihood that the intake reduction observed in the present analysis and in previous studies is associated with rapid mobilization of fat stores caused by β-agonist initiation. Notably, Kononoff et al. (2013) reported that the genotype for the transitional SNP 25 LEP R25C, commonly referred to as the leptin gene, which is associated with greater rate of fat accumulation in cattle, modified the DMI response to zilpaterol inclusion. Cattle with the CC genotype (leaner growth) demonstrated no change in DMI during zilpaterol administration, cattle with the TT genotype (greater fat deposition) had a 0.8 kg decrease in daily DMI, and cattle with the CT genotype (intermediate rate of fat accretion) had intermediate (0.4 kg/d) decrease in daily DMI. Unfortunately in that study there was no indication of the time frame after administration of zilpaterol when the decreases in DMI became apparent.

Respiratory alkalosis (low blood pH) is a normal sequelae observed during acute heat stress in birds and mammals (Teeter et al., 1985; Bouchama and DeVol, 2001). Increased respiration rate and volume result in increased expiration of CO2; this loss of CO2 results in low blood pH and reduced the responsiveness of arteries to norepinephrine (Ryan and Gisolfi, 1995). At elevated ambient temperatures (>25°C), respiration rate and panting scores increase with increasing body fat content, dark-
ness of hide color, and previous treatment for respiratory disease (Brown-Brandl et al., 2006). The mild and transient reductions in DMI in cattle fed zilpaterol during the spring and fall may be attributed to temporal changes in blood lactate. However, during periods of mild or acute heat stress, especially in cattle with elevated body fat content such as those approaching harvest, it is conceivable that treatment of cattle with a catecholamine such as zilpaterol may exacerbate the extant respiratory alkalosis through elevation of blood lactate, resulting in a greater and more sustained reduction in voluntary intake.

**Conclusions**

The likelihood of pens having decreased intake and the size of the drop in intake after initiation of zilpaterol feeding is greatest during the summer and least during the fall. Pens with greater feed intake before initiating zilpaterol feeding are more likely to experience a decrease in intake after initiating zilpaterol feeding, and the size of the decrease will likely be greater. Increasing dosage of zilpaterol consumed may contribute to the decrease in intake, but the increased likelihood and size of the intake decrease during the summer may indicate the presence of an additional physiological mechanism.

**LITERATURE CITED**


