

4-2022

## Assessment of the Effect of Acepromazine on Insulin Tolerance tests (ITT) in Dairy Heifers

Mya Catherine Orantes

Follow this and additional works at: [https://repository.lsu.edu/honors\\_etd](https://repository.lsu.edu/honors_etd)



Part of the [Animal Sciences Commons](#)

---

### Recommended Citation

Orantes, Mya Catherine, "Assessment of the Effect of Acepromazine on Insulin Tolerance tests (ITT) in Dairy Heifers" (2022). *Honors Theses*. 1153.  
[https://repository.lsu.edu/honors\\_etd/1153](https://repository.lsu.edu/honors_etd/1153)

This Thesis is brought to you for free and open access by the Ogden Honors College at LSU Scholarly Repository. It has been accepted for inclusion in Honors Theses by an authorized administrator of LSU Scholarly Repository. For more information, please contact [ir@lsu.edu](mailto:ir@lsu.edu).

Assessment of the Effect of Acepromazine on Insulin Tolerance tests (ITT) in Dairy Heifers

by

Mya Catherine Orantes

Undergraduate honors thesis under the direction of

Cathleen Williams, Ph.D.

School of Animal Sciences

Submitted to the LSU Roger Hadfield Ogden Honors College in partial fulfillment of the Upper  
Division Honors Program

April 2022

Louisiana State University  
& Agricultural and Mechanical College  
Baton Rouge, Louisiana

## Table of Contents

<b>Acknowledgments .....</b>	<b>3</b>
<b>Abstract.....</b>	<b>4</b>
<b>Introduction.....</b>	<b>5</b>
<b>Literature Review .....</b>	<b>6</b>
<b>Insulin Secretion.....</b>	<b>6</b>
<b>Glucose Metabolism.....</b>	<b>7</b>
<b>Insulin, Glucose, and Insulin Sensitivity.....</b>	<b>7</b>
<b>Insulin Tolerance Tests and Intravenous Glucose Tolerance Tests.....</b>	<b>8</b>
<b>Acepromazine with intravenous Glucose Tolerance Tests in Other Species .....</b>	<b>9</b>
<b>Acepromazine Functions and Mechanism of Action .....</b>	<b>10</b>
<b>Materials and Methods.....</b>	<b>12</b>
<b>Results .....</b>	<b>14</b>
<b>Figures 1 &amp; 2 .....</b>	<b>15</b>
<b>Figures 3 &amp; 4 .....</b>	<b>16</b>
<b>Figures 5 &amp; 6 .....</b>	<b>17</b>
<b>Figures 7 &amp; 8 .....</b>	<b>18</b>
<b>Discussion.....</b>	<b>19</b>
<b>References .....</b>	<b>21</b>

## **Acknowledgments**

I would like to acknowledge and graciously thank Dr. Cathleen Williams for being my incredible Thesis Director. Her teachings, advice, and encouragement truly carried me through every part of my research and writing. I must give my deepest appreciation to Steven Blair for providing me with a further understanding of this type of research, teaching me new methods of working with cattle, making every treatment day go smoothly, and assisting with the statistical analysis and my writing.

I'd like to give a special thanks to Dr. Charlie Hutchison, Mr. Dusty Schilling, Mr. Darryl Varnado, and Peni Wood for their warm welcome into the Southeast Research Station, and for providing us with facilities and food to get through our research. Last but not least, I would like to thank my Thesis Defense Committee, Dr. Cathleen Williams, Dr. Jennifer Ritchie, and Professor Nick Erickson, for taking the time to be a part of my thesis and for all of your brilliant comments and suggestions for assisting in my success.

## **Abstract**

In dairy calf research, it is vital to know and observe calves' energy utilization for long-term success in the dairy operation. Nutritional status is one large determinant of a calf's energy usage, while also being a major expense on the dairy farm. Calf growth and health are of utmost importance, and energy metabolism can be assessed in research for improving nutritional management strategies. Calves often have a fractious behavior in regards to human interaction, so chemical restraints like acepromazine, a commonly used sedative in animal medicine, are critical for research to keep the calf and the researcher safe. The object of this study was to determine if acepromazine affects the mechanism of insulin-induced glucose uptake. Ten Holstein calves were given either a bodyweight dose of acepromazine or saline via jugular vein catheter, followed by a dose of recombinant human insulin. Blood samples were taken at times -10 and 0 before insulin, and every 10 minutes for 60 minutes post insulin to measure the glucose curve of the calf. After 48 hours, the experiment was repeated with the treatment groups switched. Insulin stimulated a decrease in blood glucose levels in all calves; however, glucose concentrations did not differ between the two groups at any point during sampling. The administration of acepromazine did not alter the normal glucose response to insulin in dairy calves in this study.

## Introduction

An important aspect of dairy calf management is understanding the effects of nutritional management to maximize energy utilization and reduce the risk of deficiencies (2). Metabolic testing can provide the information to aid in this understanding. The insulin tolerance test (ITT) determines the body's sensitivity to insulin receptors by measuring and observing changes in blood glucose levels before and after insulin is administered (1). This test is commonly used for studies on ruminants and other species to further evaluate their nutritional status since insulin plays a large role in the body's overall metabolism.

Invasive research on beef cattle is often difficult or labor-intensive due to their temperament. Beef cattle typically have fewer interactions with humans compared to dairy cattle, which tends to make them flee or have fearful/aggressive tendencies towards humans. Chemical restraints are one productive approach to research. Acepromazine is a commonly used sedative for animal management; the drug can be used to perform metabolic tests on beef cattle more efficiently and with less danger for the animal and the human. Acepromazine is a derivative of phenothiazine, and it acts as a dopamine receptor antagonist in the central nervous system, which causes sedation. Even though it is not often used in human medicine, it is frequently used in animals as a sedative, muscle relaxer, and antiemetic because of its low toxicity and fast-acting traits. (3)

Though beef and dairy cattle have different production purposes, they have identical bodily mechanics and systems. Dairy cattle were used in this experiment for the sake of efficient research. The purpose of the study is to determine if acepromazine will affect glucose or insulin sensitivities in dairy cattle.

## Literature Review

### Insulin Secretion

Insulin, a peptide hormone, plays a critical role in the regulation of human metabolism and glucose homeostasis. During digestion, the small and large intestines work to break down foods into simple nutrients to supplement the body. In this process, the intestines break down carbohydrates into glucose, a monosaccharide sugar that provides energy. The beta-cells, referred to as b-cells, from the pancreas secrete insulin in response to changes in ambient blood glucose concentrations to maintain glucose homeostasis (2). Glucose is taken up into these b-cells which triggers a signal cascade in the b-cell for insulin secretion (2). According to Mann et al (2), more recent studies suggest that the insulin-independent glucose transporters GLUT1 and GLUT3 are the main glucose transporters. Blood glucose increases after a meal and fluxes across the GLUT transporters, while it is also being phosphorylated to glucose-6-phosphate by glucokinase within the b-cell (2). Glucose-6-phosphate moves into the mitochondria to be metabolized to produce ATP. The ATP binds and closes the ATP-dependent potassium channel blocking potassium from exiting the b-cell, thus depolarizing the cell membrane (2). The L-type voltage-gated calcium channels are triggered to increase cellular calcium concentrations; this increase triggers a release of insulin and C-peptide from insulin-containing docked secretory vesicles which migrate towards the cell membrane (2).

Glucose-stimulated insulin release from b-cells is the primary mechanism of insulin regulation (2). The first phase of insulin response, acute insulin response to glucose (AIR<sub>glu</sub>), includes an immediate rise in insulin secretion due to insulin secretory vesicles already being docked and primed at the b-cell membrane, with a quick drop in insulin directly after. The second sustained phase is controlled by intracellular calcium levels and includes glucose

elevation which results from the recruitment of insulin secretory vesicles to the b-cell membrane (2).

## **Glucose Metabolism**

There are three different sources of glucose in the body. One is from intestinal absorption, where carbohydrates are digested to be broken down into glucose after a meal. Another source is glycogenolysis, which is the breakdown of the polymerized storage form of glucose called glycogen. The last source is gluconeogenesis, which is glucose being formed from lactate, pyruvate, amino acids like alanine and glutamine, and glycerol (12). Furthermore, glucose has multiple processes and outlets to go into. It can be stored in the form of glycogen. It can undergo glycolysis to become pyruvate which can either be reduced to lactate, transaminated to alanine, or converted into acetyl coenzyme A (CoA) (12). Acetyl CoA can be oxidized to CO<sub>2</sub> and H<sub>2</sub>O through the tricarboxylic acid cycle, converted to fatty acids for triglycerides, oxidized, or used for ketone body synthesis or cholesterol (12).

Glucose-6-phosphatase is the enzyme necessary for the release of glucose into the blood. Only the liver and kidneys have enough expression of glucose-6-phosphate to make a large contribution to the blood glucose concentration. These organs also contain the enzymes necessary for gluconeogenesis including pyruvate carboxylase, phosphoenolpyruvate carboxykinase, and fructose-1,6-biphosphatase (12).

## **Insulin, Glucose, and Insulin Sensitivity**

Any extra glucose in the blood not translocated by GLUT transporters to be stored in cells for energy will be stored in the liver, muscles, and fat cells, allowing the blood sugar



concentrations to decrease back to their baseline. Normally only high levels of blood sugar will stimulate the pancreas to release insulin. However, if an animal is given a dose of insulin injected into the bloodstream, it will cause the glucose levels in the blood to drop from their baseline and bottom out. In this scenario, the pancreas releases a different hormone known as glucagon which will cause the liver to break down stored sugar, glycogen, to be slowly released into the bloodstream until the blood sugar is back at the original blood sugar levels. Insulin and glucagon work together to sustain glucose homeostasis.

Reaven et al (13) performed glucose tolerance tests on male patients from the Medical Outpatient Clinic to study the relationship between glucose and insulin responses to oral glucose. The patients with impaired glucose tolerance (high blood sugar) had the highest mean insulin concentrations one and two hours after receiving glucose compared to patients with severe diabetes who had the lowest levels (13). This suggests that higher insulin sensitivity is more beneficial and allows the cells to work most efficiently in glucose and insulin metabolism. An insulin-resistant animal would have a low insulin sensitivity which could result in the cells no longer responding to insulin causing higher insulin and blood sugar levels (4). Despite the body's natural efforts, certain pharmaceuticals can affect the level of insulin sensitivity in an animal to correct the unbalance in the circulation.

### **Insulin Tolerance Tests and Intravenous Glucose Tolerance Tests**

The Insulin Tolerance Test (ITT) measures the sensitivity of insulin receptors in the body by measuring blood glucose levels before and after insulin administration (1). It can determine the insulin resistance status from changes in the glucose values. This test is commonly used to determine the insulin-sensitizing efficacy of other compounds given to the animal. (1) The test is

performed by giving insulin intravenously while measuring glucose levels before and after the injection. A natural insulin-induced glucose curve will drop immediately after insulin is given and will plateau at a minimum value before the body will begin to release glycogen to increase the blood glucose to the baseline. An animal is insulin resistant if insulin given does not make glucose levels decrease to a low minimum. If an animal is insulin sensitive, the glucose levels will drop quite immediately in reaction to the insulin and will take more time to increase back to the original blood glucose baseline. Therefore, it can be determined with an ITT if a compound makes an animal more insulin resistant or sensitive if given this compound before the insulin injection.

The Intravenous Glucose Tolerance Test (IVGTT) is similar to the ITT in that it measures blood glucose levels; however, the IVGTT specifically measures a glucose-induced response on insulin, glucose, and sometimes C-peptide levels in the blood (9). Blood samples are taken every ten minutes for approximately 60-75 minutes. A bolus of glucose given intravenously immediately causes a spike in plasma glucose, insulin, and C-peptides, which then all steadily decline to return to their baselines within the next 60-75 minutes. (9)

The two tests, though requiring diligence and patience for effectiveness, are reliable ways to determine insulin sensitivity or resistance in an animal. They can stand alone or be coupled together to provide more understanding of the effects on the insulin and glucose relationship.

### **Acepromazine with Intravenous Glucose Tolerance Tests in Other Species**

Kamine et al (7) demonstrated one way to use the IVGTT to discover more about the metabolic mechanisms of circannual changes in body mass in Japanese black bears. Changes in blood biochemical values and glucose and insulin responses to IVGTTs during the active season

(August and early and late November) were investigated. Four adult female bears were anesthetized with 6 mg/kg tiletamine HCl and zolazepam HCl in combination with 0.1 mg/kg acepromazine maleate. Kamine et al (7) discovered no significant difference in basal levels of plasma glucose and serum insulin concentrations between groups. Though not specifically testing for the effect of acepromazine on these tests, they were able to use a small dose of acepromazine and make valid conclusions on the research at hand, which suggested that bears shift their glucose and lipid metabolism from the stage of normal activity to the hyperphagic stage stimulating lipogenic-predominant metabolism and accelerated glucose uptake (7).

Additionally, Ionut et al (8) investigated the direct effects of acepromazine on IVGTTs in dogs. Each dog was fasted 14 hours before treatment and underwent an IVGTT with or without a pretest administration of acepromazine maleate (0.1 mg/kg subcutaneous). The results showed there were no significant differences in the baseline plasma glucose, lactate, and insulin concentrations between dogs. Lower baseline free fatty acid concentration was found to be lower in acepromazine-treated dogs. There were also no differences in insulin sensitivity, insulin response to glucose, disposition index, or glucose effectiveness between dogs, pointing to the conclusion that acepromazine can be used as means of chemical restraint without interfering with the results of the glucose metabolism assessment (8).

### **Acepromazine Functions and Mechanism of Action**

Acepromazine can be administered via injection to the muscle, under the skin, or most commonly in the vein 45-60 minutes before an anesthetic event or as means of restraint (11). Though low toxicity, its most common side effect is lowering blood pressure. Cardiovascular collapse can but rarely occurs (11). Acepromazine is a short-acting phenothiazine that will stop

acting within 24 hours of administration, though the kidneys and liver may undergo effects for a longer duration. It should not be used on animals with significant heart disease, low blood pressure, severe dehydration, tetanus, and shock, and should be used with caution in pregnant animals and animals with liver disease, heart disease, clotting issues, or low platelets (11).

Acepromazine has effects on the entire central nervous system, more specifically at subcortical levels, and multiple other organ systems (3). It acts as a dopamine receptor antagonist in the CNS ultimately causing sedation, relaxation, and slower activity (3). It binds to dopamine receptors without activating them, inhibiting the actions of dopamine (3). It also acts as an antagonist on different postsynaptic receptors (subtypes D1, D2, D3, and D4 with different antipsychotic properties), serotonergic receptors (5-HT1 and 5-HT2 with anxiolytic, antidepressive, and anti-aggressive properties), histaminergic receptors (H1 receptors with sedation, antiemesis, and vertigo properties), alpha1/alpha2 receptors (antisympathomimetic, lowering of blood pressure, hypersalivation, incontinence, and reflex tachycardia properties), and muscarinic M1/M2 receptors (anticholinergic symptoms) (10).

## Materials and Methods

The methods used in this experiment were approved by the LSU AgCenter Institutional Animal Care and Use Committee. The research was performed at the LSU AgCenter Southeast Research Station in January of 2022 using ten 12-week-old Holstein dairy calves. The calves were randomly selected by age, and the experiment was completed using a randomized single switchback design, meaning half of the calves received acepromazine while the other half received a placebo saline dose on day 1, and the groups were switched on day 2. The research spanned two days with a 24-hour gap in between the days. Before the experiment, the calves were allowed to roam on normal pastures. To fast from grain supplementation, the calves were removed from their normal pens and grouped in a separate pen with access to water the night before and during each treatment. On day 1, each calf was weighed for record-keeping and drug dose calculations. Each calf had a 16-gauge x 3-inch catheter inserted into the jugular vein. The catheters were fixed with cyanoacrylate adhesive and athletic wrap. The catheter extensions were kept patent using a 6% sodium citrate solution. After all the catheters were placed, the calves were left undisturbed for one hour. A 0.02 mg/kg body weight dose of acepromazine was administered to 5 of the calves, while the other 5 calves designated as control received an equivalent dose of saline through the catheter. Thirty minutes later, the calves received a dose of recombinant human insulin in sterile saline (75mU/kg BW) at time 0. Blood was collected from the catheter at -10- and 0-minutes pre-insulin infusion and 20-, 30-, 40-, 50-, and 60-minutes post-insulin infusion. Blood samples were immediately tested in duplicate by being directly applied to a glucose test strip which was read by a pre-calibrated OneTouch Ultra handheld glucometer. Catheters were removed upon completion of the test. On day 2, the procedure was repeated; the previous control group received acepromazine while the acepromazine group from

day 1 received an equivalent saline dose. Glucose data were analyzed by analysis of variance (ANOVA) using the general linear model procedure of SAS software (SAS Inst., Cary, NC) in a switchback design with repeated measures. Factors in the analysis were calf, day, treatment, time, and appropriate interactions. Post analysis mean separation was performed across periods with the SLICE command of SAS. Treatment means were considered significantly different at  $P < 0.05$ .

## Results

Data were recorded on a paper spreadsheet during the time of the study. All data were analyzed using SAS analysis, which can be found in the charts below. The graphs were created using Google Sheets.

Insulin immediately caused a decline in blood glucose levels in all calves. On both treatment days, all glucose levels reached a low point (approximately 40 mg/dL) for ten minutes and began to steadily increase to approximately 50 percent of their original blood glucose levels 1 hour after insulin or saline were given. There were no significant differences ( $P > 0.05$ ) between the control or treatment group, or between treatment days one and two.

Figures 1, 2, 3, and 4 are graphical depictions of the glucose curve for the individual calves labeled by their tag number and were recorded from the glucometer during the time of treatment, whereas Figures 5 and 6 depict a comparison between the average glucose curves of each treatment group on either treatment day. Figures 7 and 8 show the mean glucose values with the directly correlating standard deviations calculated from SAS analysis. All standard deviation values remained low, meaning the coefficient of variation was never greater than 1.

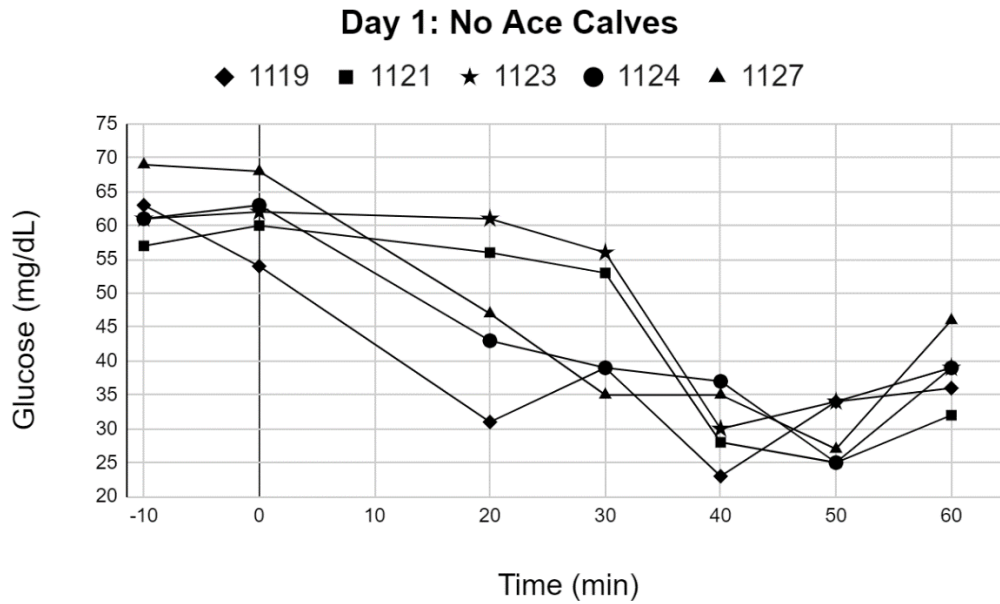


Figure 1. Blood glucose levels in response to recombinant human insulin given intravenously to 5 dairy calves treated with a saline dose (control) on the first treatment day. Saline was given at 0 minutes. Glucose levels decreased to a minimum amount at approximately 45 minutes for all calves and reached an average of 38.4 mg/dL at 60 minutes.

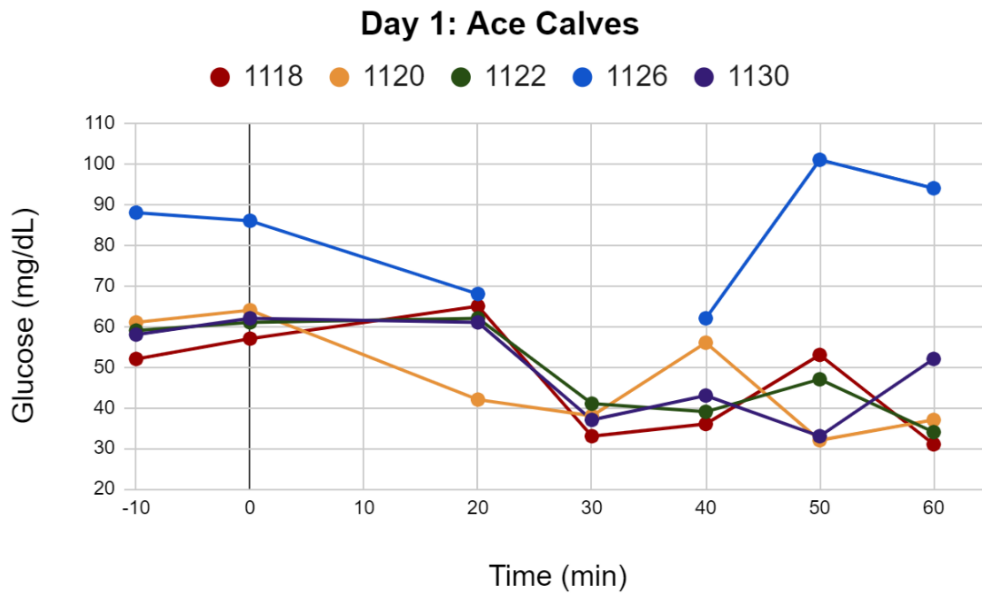


Figure 2. Blood glucose levels in response to recombinant human insulin given intravenously to 5 dairy calves treated with acepromazine on the first treatment day. Acepromazine was given at 0 minutes. Glucose levels decreased to a minimum at approximately 42 minutes for all calves and reached an average of 49.6 mg/dL at 60 minutes. Glucose failed to be measured at 30 minutes for calf 1126 due to glucometer errors.



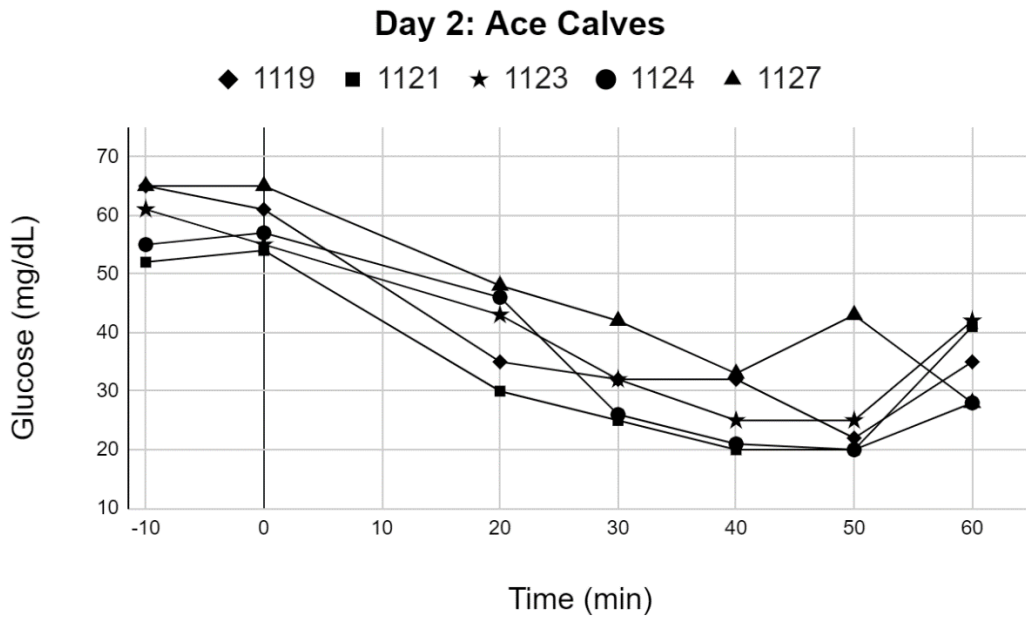


Figure 3: Blood glucose levels in response to recombinant human insulin given intravenously to 5 dairy calves treated with acepromazine on the second treatment day. Acepromazine was given at 0 minutes. Glucose levels decreased to a minimum at approximately 48 minutes for all calves and reached an average of 34.8 mg/dL at 60 minutes.

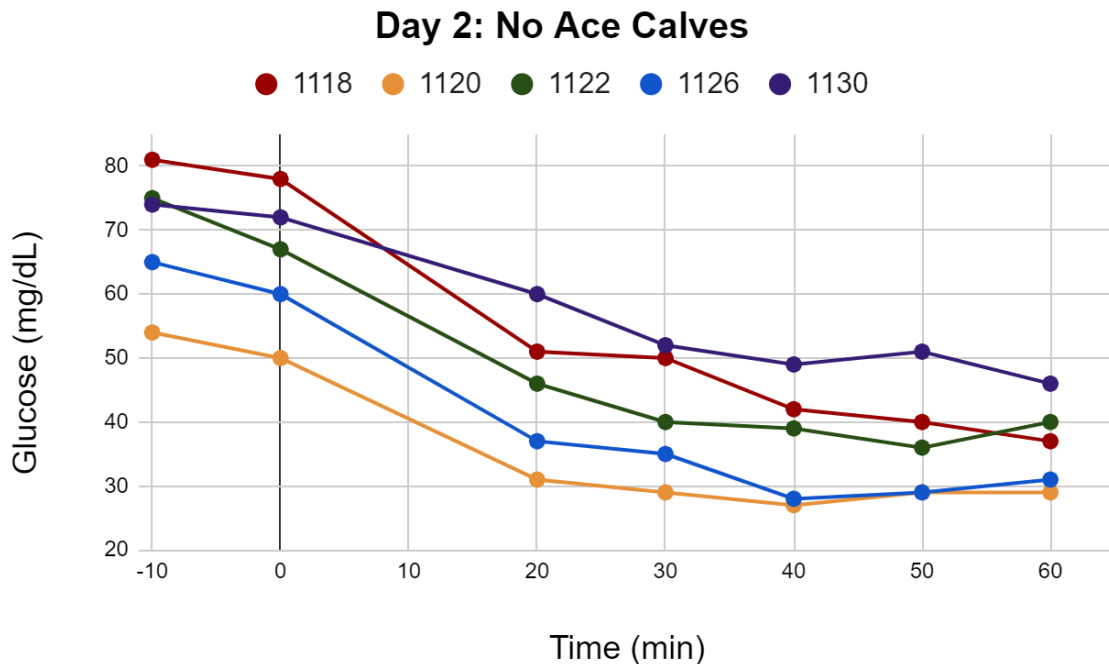


Figure 4. Blood glucose levels in response to recombinant human insulin given intravenously to 5 dairy calves treated with a saline dose (control) on the second treatment day. Saline was given at 0 minutes. Glucose levels decreased to a minimum at approximately 48 minutes for all calves and reached an average of 36.6 mg/dL at 60 minutes.

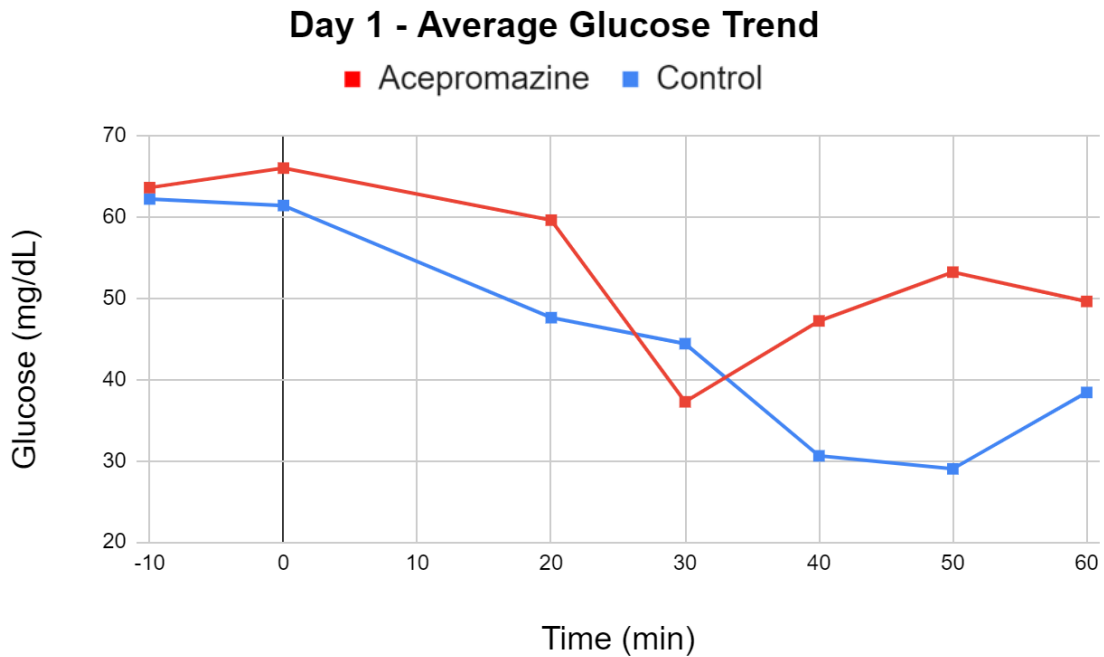


Figure 5. Average glucose trend for the two treatment groups on treatment day 1. The treatment group that received acepromazine reached a minimum glucose concentration approximately 15 minutes before the treatment group that did not receive acepromazine. There was no effect of day or treatment ( $P > 0.05$ )

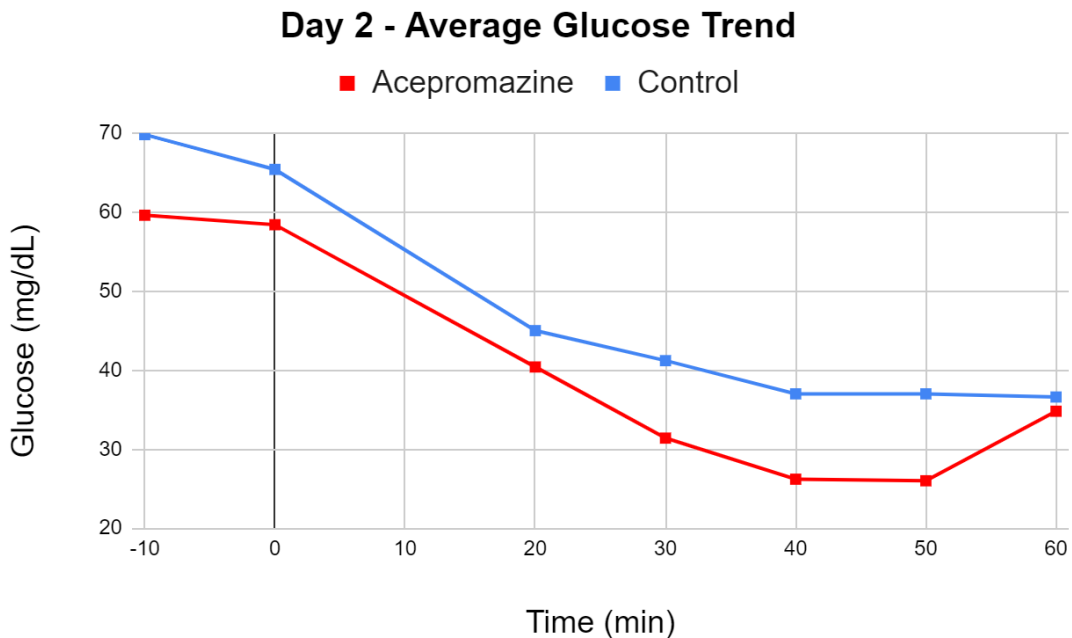


Figure 6. Average glucose trend for the two treatment groups on treatment day 2. The treatment group that received acepromazine reached a lower glucose concentration than the treatment group that did not receive acepromazine. Both groups' glucose concentrations decreased at a similar rate. There was no effect of day or treatment ( $P > 0.05$ ).

## Statistical Analysis of Days Combined

Treatment Group	Time (minutes)	Mean Glucose Value	Standard Deviation
Control	-10	66.00	8.59
Control	0	63.40	8.26
Control	20	46.30	10.99
Control	30	42.80	9.21
Control	40	33.80	8.04
Control	50	33.00	8.03
Control	60	37.50	5.80
Acepromazine	-10	61.60	10.37
Acepromazine	0	62.20	9.15
Acepromazine	20	50.00	13.22
Acepromazine	30	34.00	6.04
Acepromazine	40	36.70	13.97
Acepromazine	50	39.60	24.51
Acepromazine	60	42.20	19.60

Figure 7. SAS calculated mean glucose values and standard deviations for each treatment group every 10 minutes for 1 hour. The treatment group is the combined average for the group at a certain time measurement for both experiment days. All standard deviation values remained lower than their correlating mean value, making the standard deviations low.

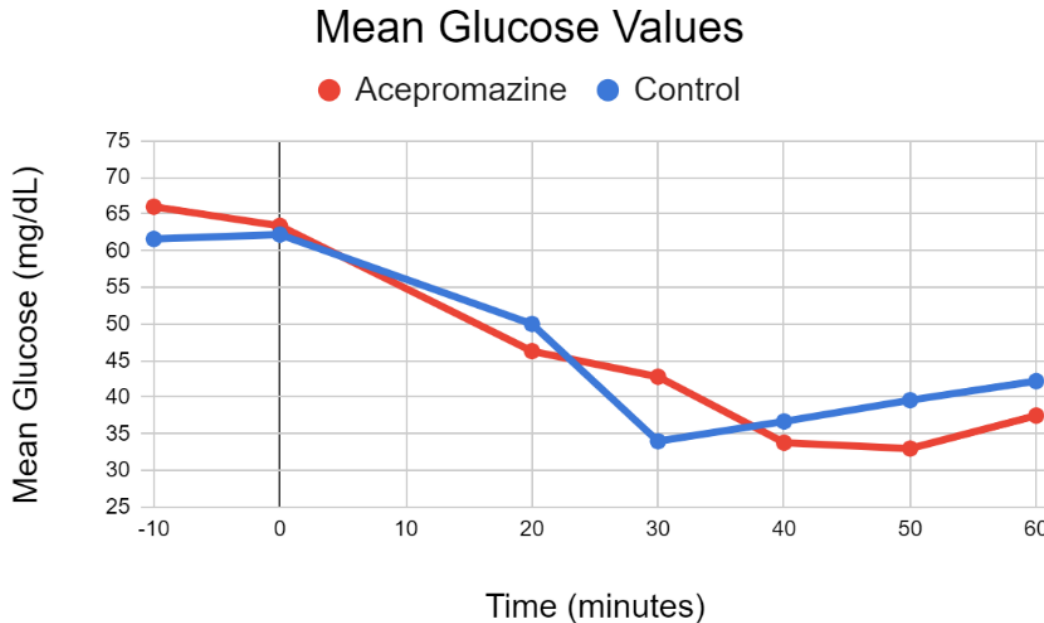


Figure 8. Mean glucose values in response to acepromazine compared to the mean glucose values in response to saline (control). This chart shows the combined average for the groups on both days. Acepromazine caused no significant changes in mean glucose values ( $P > 0.05$ ).

## Discussion

Administration of 0.02 mg/kg body weight dose of acepromazine did not alter the insulin or glucose responses to intravenous recombinant human insulin in dairy calves. These results are aligned with other assessments on insulin and glucose responses in other species. Kamine et al (7) concluded there were no significant differences in basal levels of plasma glucose and serum insulin concentrations between the active season and hibernation season in Japanese black bears. The bears were anesthetized with a combination of sedatives including 0.1 mg/kg of acepromazine maleate, which suggests that acepromazine was used safely and did not cause any major changes in the insulin and glucose responses. Additionally, Ionut et al (8) specifically investigated the effects of acepromazine on IVGTTs and found no significant differences in insulin sensitivity or the insulin response to glucose suggesting acepromazine can be used as a chemical restraint without interfering with the insulin and glucose mechanisms. Because of the pairing relationship of ITTs and IVGTTs, their research can be applied to assist in concluding this study.

Acepromazine did not make the dairy calves less sensitive to insulin. Therefore, it can be concluded that acepromazine can be used as means of chemical restraint in dairy calves without interfering with their insulin and glucose metabolism. Acepromazine will be helpful for further researchers to perform safe and efficient testing on temperamental dairy cattle to further understand and maintain the nutritional status of the animals. More pertinently, this study can be applied to research on beef cattle since they tend to be more temperamental than dairy cattle and commonly require different restraint techniques. The results of this study could also potentially be applied to other temperamental livestock species, although baseline levels of glucose will differ.

There are possible factors that could have affected the insignificance of the results. During the time of treatment, the glucometers had multiple errors when calculating blood glucose levels due to imperfect insertion or uncleanliness of the glucose strips. This might infer that the results of all blood glucose values could have been more precise if a more accurate glucometer was used. Also, it is possible that the calves fasted for a longer amount of time before Day 2 treatment compared to Day 1 treatment, which could explain why some calves' blood glucose levels plateaued for a longer amount of time at their minimum values on Day 2 shown in Figures 3, 4, and 6.

Further research can be done to explore the effects of acepromazine in other livestock species as they tend to require chemical restraints in comparison to household species, and all livestock species need their nutritional status monitored and upkept for the success of farm industries. This would include further the conclusion that acepromazine's mechanism of action does not interfere with insulin/glucose mechanisms of action. Other research could be done on other pharmaceuticals as means of chemical restraint that may work more efficiently, have a longer half-life, or have less long-term effects on the subjects.

## References

1. 2022. Insulin Tolerance Test (ITT). Melior Discovery. <https://www.meliordiscovery.com/in-vivo-efficacy-models/insulin-tolerance-test-itt/>
2. Mann, E., M. Sunni, M. Bellin. 2020. Secretion of Insulin in response to diet and hormones. Pancreapedia: Exocrine Pancreas Knowledge Base. doi: 10.3998/panc.2020.16
3. 2005. Acepromazine. National Library of Medicine. <https://pubchem.ncbi.nlm.nih.gov/compound/Acepromazine>
4. 2019. Gunnars, K. Insulin is an important hormone that controls many bodily processes. Healthline.
5. De Meyts, P. 2000. The insulin receptor and its signal transduction network. Endotext [Internet].
6. 2021. Watson, S., How insulin works. WebMD. <https://www.webmd.com/diabetes/insulin-explained>
7. Kamine, A., M. Shimozuru, H. Shibata, T. Tsubota. 2012. Changes in blood glucose and insulin responses to intravenous glucose tolerance tests and blood biochemical values in adult female Japanese black bears (*Ursus thibetanus japonicus*). *Jpn J vet Res.* 60(1): 5-13.
8. Ionut, V., E. L. Kirkman, R. N. Bergman. 2004. Investigation of the effect of acepromazine on intravenous glucose tolerance tests in dogs. *Am J Vet Res.* 65(8): 1124-7. doi: 10.2460/ajvr.2004.65.1124.
9. Hahn, R. G., S. Ljunggren, F. Larsen, T. Nyström. 2011. A simple intravenous glucose tolerance test for assessment of insulin sensitivity. *Theor. Biol. Med. Model.* 8:12. doi: 10.1186/1742-4682-8-12.
10. 2007. Acepromazine. Drugbank. <https://go.drugbank.com/drugs/DB01614>
11. Gollakner, R. Acepromazine. VCA Animal Hospitals. <https://vcahospitals.com/know-your-pet/acepromazine>
12. 2020. Melmed, S. Hypoglycemia. Williams Textbook of Endocrinology. <https://www.sciencedirect.com/topics/medicine-and-dentistry/glucose-metabolism>
13. Reaven, G., R. Miller. 1968. Study of the relationship between glucose and insulin responses to an oral glucose load in man. *Diabetes.* 17(9):560-9. doi: 10.2337/diab.17.9.560.