Evaluation of Glucose Response to 3 Types of Insulin Using a Continuous Glucose Monitoring System in Healthy Alpacas

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**Background:** Persistent hyperglycemia is common in alpacas and typically requires insulin administration for resolution; however, little is known about alpacas’ response to different insulin formulations.

**Objectives:** To evaluate the effects of 3 insulin formulations on blood glucose concentrations and the use of a continuous glucose monitoring (CGM) system in alpacas.

**Animals:** Six healthy alpacas.

**Methods:** The CGM was installed in the left paralumbar fossa at the start of this crossover study and recorded data every 5 minutes. Regular insulin, NPH insulin, insulin glargine, and dextrose were administered to each alpaca over a 2-week period. Blood samples were collected for glucose testing at 0, 1, 2, 4, 6, 8, and 12 hours, and then every 6 hours after each administration of insulin or dextrose. Data were compared by using method comparison techniques, error grid plots, and ANOVA.

**Results:** Blood glucose concentrations decreased most rapidly after regular insulin administration when administered IV or SC as compared to the other formulations. The NPH insulin produced the longest suppression of blood glucose. The mean CGM interstitial compartment glucose concentrations were typically lower than the intravascular compartment glucose concentrations. The alpacas had no adverse reactions to the different insulin formulations.

**Conclusions and Clinical Importance:** The NPH insulin might be more appropriate for long-term use in hyperglycemic alpacas because of its extended duration of action. A CGM is useful in monitoring glucose trends and reducing blood collection events, but it should not be the sole method for determining treatment protocols.

**Key words:** Hyperglycemia; Insulin glargine; NPH insulin; Regular insulin.

Hyperglycemia is commonly associated with a number of disease states and stress in alpacas. As alpacas are relatively insulin resistant, a hyperglycemic state can persist for days until the primary condition is corrected. Insulin treatment is commonly instituted to treat persistent hyperglycemia in alpacas. There is little published information in this species on the glucose response to the various insulin formulations commercially available as most research has been performed with IV regular insulin. Subcutaneously injected human long-acting insulin (ultralente) depresses blood glucose for approximately 10 hours in alpacas, whereas the effects of IV regular insulin persist for approximately 45 minutes. Intravenous injection of regular insulin produced a nadir between 90 and 120 minutes, and depressed blood glucose for approximately 360 minutes.

Monitoring individual animal responses to insulin or dextrose treatment requires obtaining multiple blood samples to quantify blood glucose concentrations and trends. Repeated venipuncture and handling to obtain the necessary blood samples for glucose concentration measurements can cause discomfort and contribute to a stress hyperglycemia. Currently, veterinary hospitals that treat alpacas with these glycemic disorders use a variety of laboratory-based and point of care (POC) glucometers. Continuous glucose monitoring (CGM) systems have been used for many years in human medicine and have more recently been evaluated in several animal species. The CGM systems utilize a sensor implanted into the subcutaneous which transmits glucose concentrations to a receiver for evaluation by the patient or health care provider. To date, CGM systems do not appear to be routinely used in hospitalized alpacas and only 1 study of CGM use in camelids has been presented as an abstract, but no data have been published.

The first objective of this study was to evaluate various forms of insulin and administration routes (IV regular insulin, SC regular insulin, SC neutral protamine Hagedorn [NPH] insulin, and SC long-acting insulin) in healthy alpacas to establish baseline information and determine if adverse reactions occurred. The second objective was to evaluate a commercially available human CGM for use in alpacas.

**Materials and Methods**

**Animals**

Six apparently healthy, 2–2.5-year old, intact male alpacas from the Colorado State University (CSU) Department of
Clinical Sciences research herd were used for this study. The CSU Institutional Animal Care and Use Committee approved all procedures before conducting this research. The alpacas weighed between 59 and 82 kg and were in good body condition (3–3.5/5). The animals were maintained on a free choice grass hay diet before and during the study. A 16-g intravenous jugular catheter2 and the CGM system3 were aseptically placed in each alpaca at least 12 hours before drug administration to allow the animal to acclimate to the CGM apparatus, handling, and indoor facilities.

**Continuous Glucose Monitoring System**

The CGM system used for this study was one of several commercially available for use in humans. These systems are designed to be used with a POC glucose meter for calibration of the CGM. This CGM system had an operating range of 40–400 mg/dL and a constant alarm that activated when glucose concentrations decreased to less than 55 mg/dL. For the study, the manufacturer provided instructions for “blinding” the system which allowed us to collect data without activating the alarm. The glucose readings were not displayed on the receiver and the data downloaded from the receiver had to be sent to the manufacturer for processing to obtain the glucose readings.

The CGM sensor was aseptically placed in the left paralumbar fossa of each animal (Fig 1). An approximately 10-cm square area in the dorsal paralumbar fossa was clipped and aseptically prepared. Sensor installation required minor modifications for installation in alpacas. Because of the thicker skin on alpacas, the installation needle containing the sensor wire could not be inserted under the skin without the use of a “guide.” A 20 g × 38 mm needle was used as the guide and was inserted into the SC space for approximately 2.5 cm and emerged at the insertion point for the CGM sensor wire. The CGM sensor wire was inserted into the needle and then the needle was removed leaving the sensor wire under the skin. The margins of the sensor included a self-adhesive pad which is sufficient for fixing the device on human skin. The alpaca fiber was only closely clipped and not shaved so the adhesive pad was also attached by using cyanoacrylate adhesive. We attempted to suture the adhesive pad to the first alpaca; however we discovered the cyanoacrylate adhesive was better at maintaining sensor placement and reduced the sensor and transmitter sagging which moved the sensor needle. After sensor placement, the transmitter was installed and the receiver activated. The receiver was attached to a neck band or halter on the alpaca to keep it within the required 1.5-m distance to the sensor/transmitter.

Following activation of the receiver, the CGM system required a 20-hour startup period after which the CGM system was calibrated according to the manufacturer’s instructions. A blood sample was collected via the jugular catheter (as described below) and tested twice on a POC glucometer4 and the 2 values were entered consecutively into the receiver. Calibration was also performed every 12 hours in the same manner using the average of 2 POC glucometer readings. Glucose readings from a POC glucometer were used for calibration rather than a laboratory chemistry analyzer as the manufacturer’s instructions recommended calibrating the CGM system within 5 minutes of obtaining a blood sample.

The manufacturer’s instructions recommended that the sensors be replaced based on several error codes or every 7 days so additional sensor installations were made approximately 10–15 cm ventral to the original location. The CGM receiver also had a rechargeable battery and the receiver had to be removed from the animal charged every 3–5 days. Recharging required up to 3 hours.

After the end of the data collection, the CGM data were downloaded to a computer and sent to the manufacturer for processing to obtain the values outside the normal operating range of 40–400 mg/dL. The manufacturer supplied the results in a Microsoft Excel spreadsheet which included animal identification, data collection times, and associated glucose concentrations. Data were recorded every 5 minutes by the CGM system.

**Point of Care Glucometer**

The POC glucometer used in this study had been previously evaluated and compared favorably to a laboratory chemistry analyzer.5 The POC glucometer was operated and calibrated according to the manufacturer’s instructions. Calibration was performed when a new container of test strips was utilized and when each collection period was approximately 3 hours. Blood glucose concentrations were measured by inserting a single-use glucose strip into the meter and applying a small volume of blood to the strip (collection described below). The POC glucometer and test strips were maintained and operated within a temperature range of 18–24°C, and the glucose operating range was 20–500 mg/dL. Glucose values less than 20 mg/dL were displayed as “LO” and values greater than 500 mg/dL were displayed as “HI” on the glucometer.

**Drug Administration and Sample Collection**

Three insulin formulations (short, intermediate, and long acting) and dextrose were administered to each alpaca according to the following schedule to allow for maximum washout while optimizing sampling with the CGM system. Insulin doses were selected based on published dosages3,7,23 and those commonly used at the CSU Veterinary Teaching Hospital as we wanted to determine the maximum expected glucose decrease and duration.

![Component of a continuous glucose monitoring system evaluated for use in alpacas](Image)

Fig 1. Components of a continuous glucose monitoring system evaluated for use in alpacas (left). Continuous glucose monitor sensor and transmitter attached to the left paralumbar fossa of an alpaca (right). A – Sensor and insertion device; B – Transmitter; C – Receiver.
Regular insulin (short acting, 0.2 U/kg IV) was given on day 1; dextrose (300 mg/kg of 25% dextrose, IV over 5–10 seconds) on day 3; NPH insulin (intermediate acting, 0.4 U/kg SC) on day 5 or day 8, regular insulin (0.2 U/kg SC) 3 days later (day 8 or day 11), and insulin glargine (long acting, 0.4 U/kg SC) 2 days later (day 10 or day 13). The sensor and IV catheter were removed 48 hours after administration of the insulin glargine (day 12 or 14), because of 2 alpacas inadvertently receiving NPH insulin IV rather than SC, the subsequent insulin doses were delayed as noted above. The dosing schedule was not randomized because of scheduling for recharging the CGM receiver battery and replacing the sensors but was developed based on estimated duration of insulin effects.

Jugular catheter blood sample collection was performed by a 3-syringe technique. Five milliliters of blood was collected into a 6-mL syringe containing 1 mL of heparinized saline (1 mL of 1:1000 heparin in 250 mL of 0.9% saline). Approximately 0.25 mL of blood was then collected from the catheter into a 1-mL syringe for testing the blood glucose. The heparinized saline/blood sample was injected back into the catheter and the catheter flushed with approximately 3–4 mL of heparinized saline. Blood samples were collected from the catheter at specific time intervals starting at 0, 1, 2, 4, 6, 8, 12, and every 6 hours thereafter following drug administration and every 12 hours for CGM calibration. After blood collection, the blood sample was immediately tested on the POC glucometer and result recorded.

After insulin treatment, if signs of hypoglycemia were observed (head tremors, excessive humming, and skittish behavior) or whole blood glucose was less than 20 mg/dL on the POC glucometer, the alpaca was to be administered an IV dextrose solution (5% solution) in a 60–100 mL bolus which was to be repeated if glucose remained less than 20 mg/dL or signs of hypoglycemia persisted. This dextrose dosage was used in a previous study and was adequate for increasing the glucose without causing hyperglycemia.

### Statistical Analysis

Statistical analyses were performed by MS Excel and Medcalc. Descriptive statistics were used to determine the nadir, peak response, and duration for the various insulin types as measured on the POC glucometer.

A Bland-Altman plot was prepared to assess agreement between the POC glucometer and the CGM concentrations using methods for multiple observations per test subject. The plot included the limits of agreement (LOA) between the 2 methods (mean difference ±1.96 standard deviations of the difference). In addition, by visually examining the layout of the data, systematic biases (mean difference) and proportional biases (positive or negative slope in the data) could be observed. Acceptance criteria were established based on a 3-tier LOA. As the effects of a large LOA would be more critical at lower glucose concentrations, we required an LOA of ±10 mg/dL at POC glucose concentrations ≤60 mg/dL, but allowed an LOA of ±50 mg/dL at POC glucose concentrations ≥300 mg/dL for acceptable results. An LOA of ±30 mg/dL was used for glucose concentrations between 60 and 300 mg/dL.

Deming regression analysis was performed as both comparison methods had potential measurement errors. The analysis examined for systematic error was represented by proportional and constant bias. Bias was identified when the 95% confidence interval (CI) for the slope did not include 1 (proportional bias) or the 95% CI of the y-intercept did not include 0 (constant bias).

Error grid plots were developed to evaluate clinical decision making if the CGM was utilized rather than the POC glucometer. A modified Clarke error grid was developed as the critical glucose limits in alpacas are different than those used in humans. Twenty percent limits were plotted around the perfect correlation line and treatment limits established at ≤60 mg/dL or ≥300 mg/dL. These limits were based on presumptive medical intervention for hypoglycemia or hyperglycemia outside these limits. The CGM would be considered acceptable if at least 95% of the POC glucometer readings were within zone A. This zone was defined as the region where the reading for both the CGM and POC glucometer was between 60 and 300 mg/dL, if the CGM reading was <60 mg/dL and the POC glucometer reading was also <60 mg/dL, and if the CGM reading was >300 mg/dL when the POC glucometer reading was also >300 mg/dL. Zone B was defined as CGM readings that would lead to inappropriate treatment for hypo- or hyperglycemia. Zone C was defined as CGM readings that would lead to inadequate treatment for either hypo- or hyperglycemia. Zone D was CGM readings that were opposite of the POC glucometer concentrations, leading to treatment of hypoglycemia rather than hyperglycemia or vice versa.

A repeated measures analysis of variation (ANOVA) was performed to compare glucose values under the different insulin and dextrose conditions. The CGM data were selected at a ±5 minutes range for the corresponding time period from the POC glucometer reading as the POC glucose reading was not obtained at exactly the same time as the CGM data were being recorded. The mean of these 3 CGM glucose concentrations per time point was calculated and used in the comparisons. A P-value <.05 was considered significant.

### Results

The alpacas had variable responses to the insulin forms and administration routes when the POC glucometer results were analyzed (Table 1). Intravenous administration of regular insulin decreased POC blood glucose most rapidly and SC insulin glargine had the slowest onset of response. The mean nadirs for the insulin formulations were not statistically different.

| Insulin Form | Route | Dosage (U/kg) | Nadir ± SD (mg/dL) | Mean Peak Response ± SD (hours) | Mean Duration <90 mg/dL ± SD (hours) |
|--------------|-------|--------------|--------------------|-------------------------------|-------------------------------------|
| Regular      | IV    | 0.2          | 45 ± 15            | 2 ± 1                         | 3.4 ± 1                             |
| Regular      | SC    | 0.2          | 42 ± 19            | 4.7 ± 0.9                     | 8.5 ± 1.9                           |
| NPH          | SC    | 0.4          | 45 ± 21            | 4.7 ± 0.9                     | 15.4 ± 6.2                          |
| Glargine     | SC    | 0.4          | 64 ± 29            | 12.5 ± 3.3                    | 10.5 ± 4.4                          |
Mean (±standard deviation) values ranged from 42 ± 15 to 64 ± 29 mg/dL.

The mean CGM values (Fig 2) were compared to their respective POC glucose values after insulin and dextrose administration. The CGM measured interstitial glucose concentrations every 5 minutes, therefore, standard deviation error bars for the CGM data were partitioned into 15-minute intervals to facilitate data analyses. The CGM glucose readings were usually lower than the whole blood POC glucose readings.

Fig 2. Continuous glucose monitor and point of care (POC) glucometer data for regular insulin IV and SC, NPH insulin SC, insulin glargine SC, and dextrose IV. The solid line with squares represents the POC glucose readings. The solid line without markers represents the continuous glucose monitoring (CGM) glucose data. Error bars for the CGM were calculated at 15 minute intervals. The * indicates where IV dextrose was given either due signs of hypoglycemia or POC glucometer reading of “LO” or 20 mg/dL.
except for the rebound glucose concentrations after the SC regular insulin administration. Data analyses were performed on POC and CGM glucose values where both values were available and within the meters’ operating ranges.

The Bland-Altman difference plot and Deming regression were performed using the POC and CGM glucose readings for all insulin types and dextrose (Fig 3). The Bland-Altman difference plot showed a wide range in the standard deviation (±1.96 SD = −27.9 to 63.6 mg/dL) with a mean of 17.8 mg/dL. When examining the difference plot using the 3-tier acceptance criteria, readings fell outside the low and midrange LOA. Examination of outliers did not determine a specific cause as the CGM read greater than or less than the POC glucometer on an approximately equal numbers of cases. The upper and lower LOA outliers were attributed primarily to 2 alpacas each and were randomly associated with insulin type or dextrose or just before the CGM sensor malfunctioned. Deming regression indicated there was a proportional bias as the 95% CI did not include zero, but no constant bias as the 95% CI included one.

The modified error grid showed that 90% of the glucose readings were within zone A, indicating the CGM was unacceptable for determining clinical decisions regarding treatment (Fig 4). Most values outside zone A were in the zone B area where the CGM reading was lower than POC reading and would have initiated possible treatment for hypoglycemia.

The ANOVA using repeated measures was calculated using the glucose concentrations obtained from all of the insulin formulations and dextrose administration, and the subject groups were identified as the 6 healthy alpacas. The POC and CGM glucose concentrations were not significantly different from each other (P = .53).

Continuous glucose monitor sensor error codes occurred randomly and it was difficult to determine the reason for the error. The sensor error codes were related to the sensor having failed or because of calibration issues (unable to be calibrated or not calibrating correctly). Once either of these codes was observed, the user was to attempt to recalibrate and if this failed, replace the sensor. Sensors failed 3 times for unknown reasons and 3 times for inability to calibrate (n = 1) or calibrate correctly (n = 2). Alpaca rolling was suspected for some of the failures as the alpacas were found to have straw along their dorsum.
The sensors were also designed to be replaced once a week in humans. We attempted to prolong this by resetting the receiver after 7 days in a pilot study; however, more data variability and sensor errors occurred after this time. For this study, we replaced the sensors at 7-day intervals if it was not replaced sooner because of an error code. Each alpaca had 2–3 sensors placed because of error codes or sensor expiration times. Receivers maintained battery charge for 4–5 days, so recharging was performed 6–12 hours before the next insulin administration as the receiver had to be removed from the animal.

Two alpacas required IV dextrose treatments because of clinical signs of hypoglycemia or “LO” readings on the POC glucometer. One alpaca was treated with IV dextrose 3 times after administration of regular insulin SC (at 4 hours after administration) and glargine insulin (2 treatments, at approximately 4 and 10 hours after administration). This alpaca reached the minimum detection limits for the CGM and had POC glucometer glucose nadirs of 20–30 mg/dL with all insulin formulations. The other alpaca was treated with IV dextrose at 4 hours after administration of NPH insulin because of the POC glucometer reading of 20 mg/dL; however, he did not show signs of hypoglycemia. All insulin forms induced mild increases of blood glucose above baseline values as the insulin was metabolized.

No other adverse reactions including injection site reactions were observed in any of the alpacas. Two alpacas were inadvertently administered 0.2 U/kg of NPH insulin IV rather than SC. Blood glucose responses were similar to that seen with regular insulin IV on nadir and duration of response until return to normal glucose concentrations (data not shown or included in calculations).

**Discussion**

The objectives of this study were to evaluate several insulin formulations and a CGM system in healthy alpacas. Insulin formulations evaluated are manufactured for use in humans but commonly used in animals. The absorption and metabolism vary among species, and have not been researched in alpacas. The alpacas responded to all formulations and routes of administration with the only adverse effects produced being hypoglycemia. The different durations of action were not unexpected except for the insulin glargine which we expected would have a longer effect on glucose. The CGM system worked well for monitoring trends in blood but does not function as a stand-alone glucose monitoring method as it required the use of a POC meter for calibration.

For this study, we only looked at single dosages of each insulin formulation. The dosages we selected are commonly used to treat hyperglycemic alpacas but produce variable results. The hypoglycemia that developed was not unexpected but 1 alpaca consistently reached the minimum detection limits of the CGM and POC glucometer. Similar significant hypoglycemic responses have occurred in alpacas utilized in a variety of studies (personal communication). The cause is unknown but might simply be attributed to individual genetic variations in metabolic pathways for set dosages. In addition, as the insulin dosages produced low glucose concentrations, the Somogyi rebound effect might have shortened the insulin duration. However, our data did not show a significant degree of a rebound hyperglycemia, so the effect on our results is unknown. A second source of variation in the glucose data could have been an insufficient washout period among insulin formulations. Because of the CGM sensors’ replacement schedules and project timeline, we designed the drug administration schedule to maximize insulin and dextrose washout periods, so were unable to randomize drug administration. Even though all alpacas returned to predrug administration glucose concentrations before the next drug administration, there could have been residual insulin and glucose resistance at the cellular level which could have affected the results. Finally, variables such as environmental factors and the exogenous dextrose administration could have altered response to the insulin dosages. We were unable to completely eliminate these variables as normal hospital activities and stall cleaning occurred near the alpacas and 2 alpacas had several fights during the study. No sensor or transmitter removal occurred during the fights, but events such as these could have affected both the CGM performance and endogenous glucose concentrations.

The causes for lack of differences in the duration of peak effect between the insulin glargine and NPH insulin are not known, but might be related to attributes of the insulin formulations or alpaca metabolic pathways and cellular receptor variations versus other species. Insulin glargine was developed using recombinant DNA technology resulting in a molecule that is a modification of the human insulin molecule. This peakless attribute of insulin glargine is preferred as it minimizes the variations in blood glucose concentrations in humans. Reports of insulin glargine use in other animal species produced more variable results with the insulin being peakless in dogs but not in cats and a ferret.

The CGM system was easy to install and use although modifications were needed to implant the sensor wire because of the alpaca’s skin thickness. This skin thickness and associated movements might have contributed to some of the variation and error codes we observed. The CGM sensor and transmitter are normally implanted into the abdominal region of humans, and human skin is thinner and relatively fixed as compared to alpacas. Studies of other CGM systems in small animals, swine, and equine species placed the sensor in the subcutaneous space in the lateral cervical region caudal to the ear, along the dorsum, or lateral thoracic wall caudal to the scapula. The neck and thoracic areas would have been an ideal implant location except that alpacas can easily scratch these areas with their hind feet, and the ventral skin on the neck is very thick (over
0.5 cm in males). Even with installing the CGM system in the paralumbar fossa, the system appeared to be robust for use in alpacas. The receiver was not waterproof but functioned appropriately in the dusty environment and despite being knocked off periodically during fighting.

The comparison of glucose distribution between the interstitial compartment and intravascular compartment fluids has not been documented in alpacas although they are equivalent in humans. In this study, there were no significant differences between the 2 systems, but the mean CGM (interstitial compartment) glucose concentrations were typically lower than the mean POC (intravascular) glucose concentrations after drug administration. Another source of variation in CGM glucose readings might have been caused by inflammation around the sensor. Inflammation in the area of a CGM sensor could potentially interfere with glucose circulation and sensor function over time. In Others studies, including this one, have not examined histologic changes around the sensor site but on gross examination, no inflammation or other reactions were observed.

A reliable POC meter should be used to calibrate the CGM and verify if insulin or dextrose treatments are required. This previous research found the glucose readings from POC meters can vary considerably based on sample tested and brand of glucometer. An ideal study would compare the CGM to a laboratory chemistry analyzer, however, calibration of the CGM must be performed with a POC glucometer because of the short-time period between blood collection, testing, and calibration. We chose a POC glucometer that performed adequately across the range of expected blood glucose concentrations.

This study found that the CGM should not be the only method for determining treatment for glucose abnormalities in camels. A POC glucometer that has been validated for use in camels is needed for calibration purposes and to verify glucose readings outside the operating limits of the CGM. The system has relatively expensive startup costs and the use of multiple sensors may also limit the usefulness in some patients. However, the ability to easily monitor glucose trends would be preferable to repeated venipuncture or disrupting intravenous fluid lines when an animal is on parenteral nutrition or other dextrose-containing fluids. Extreme hyperglycemic conditions as seen in some hospitalized alpacas can limit the use of the system until glucose levels decrease to <400 mg/dL to calibrate the system.

Finally, the different insulin formulations available produce variable responses in glucose concentration, and the data from this study can be used to assist in selecting a treatment regimen in hyperglycemic alpacas. Individual medical conditions will require monitoring for response to insulin treatment and modifications tailored to the individual patient at this time. Further evaluation of insulin formulations in hospitalized alpacas would be beneficial in addition to measuring endogenous insulin production in these animals.

This study found that alpacas respond to a variety of insulin formulations; however, the duration is variable from that observed in humans and other animals. The information provided here can be utilized by veterinarians to develop a treatment plan for severely hyperglycemic alpacas. A CGM system can be useful for monitoring trends in glucose concentrations in alpacas but should not be the sole method used to determine treatment for hypoglycemia or hyperglycemia.

Footnotes

*Tennent-Brown BS, Koenig A, Campbell R, et al. Real-time continuous glucose monitoring in neonatal camelids. In: 18th International Veterinary Emergency & Critical Care Symposium San Antonio, TX 2012:S19 (abstract)

**Intracath IV Catheter/Needle Unit, Becton Dickinson, Sandy, UT

Dexcom Seven Plus, Dexcom, Inc, San Diego, CA

E Precision Xtra, Abbott Diabetes Care, Inc, Alameda, CA

Microsoft Office Excel 2007, Microsoft, Redmond, WA

Novolin R, Novo Nordisk Inc, Princeton, NJ

N Novo Nordisk Inc

Lantus, Sanofi-Aventis U.S. LLC, Bridgewater, NJ

MedCalc, version 12.7.0.0, MedCalc Software, Ostend, Belgium

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Conflict of Interest: Authors disclose no conflict of interest.

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