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Topical Reviews

Point-of-Care Glucose and Ketone Monitoring

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Early and rapid identification of hypo- and hyperglycemia as well as ketosis is essential for the practicing veterinarian as these conditions can be life threatening and require emergent treatment. Point-of-care testing for both glucose and ketone is available for clinical use and it is important for the veterinarian to understand the limitations and potential sources of error with these tests. This article discusses the devices used to monitor blood glucose including portable blood glucose meters, point-of-care blood gas analyzers and continuous glucose monitoring systems. Ketone monitoring options discussed include the nitroprusside reagent test strips and the 3-β-hydroxybutyrate ketone meter.

Introduction

Early and rapid identification of hypoglycemia and hyperglycemia as well as ketosis is essential for the practicing veterinarian as these conditions can be life threatening and require emergent treatment. Point-of-care (POC) devices such as portable blood glucose meters (PBGM) are widely used in veterinary practices to rapidly evaluate blood glucose at the cage side, allowing for immediate intervention. Additionally, the presence of blood and urine ketones can be evaluated through use of a 3-β-hydroxybutyrate (3-HB) ketone meter or ketone reagent strips.

Benefits of cage side monitoring using POC devices over laboratory measurements include portability, affordability, rapidity, and ease of use. These benefits are of paramount importance as they allow for frequent monitoring and patient-side decision making. Although the chemical laboratory analyzer is the gold standard method for measuring blood glucose and ketones, the length of time it takes for results is not practical for some patients. Furthermore, the very small volume of blood required for a POC device is especially advantageous for our canine and feline patients. The aim of this article is to provide an overview of cage side glucose and ketone monitoring.

Blood Glucose Monitoring

Glucose is the most abundant carbohydrate in mammals and the principal fuel for energy production.[1] Glucose concentrations in the blood are tightly controlled through complex regulatory and counter-regulatory hormones. Insulin is the predominant hormone responsible for regulating blood glucose concentrations but other important hormones include glucagon, cortisol, epinephrine, and growth hormone.[2] Glucose concentration is maintained within 53-117 mg/dL (2.9-6.5 mmol/L) in the resting state in dogs and 57-131 mg/dL (3.1-7.2 mmol/L) in cats.[3] Deviations of glucose concentrations from these ranges occur in numerous clinical diseases that affect carbohydrate metabolism.

Common causes of hypoglycemia in dogs and cats include sepsis, juvenile and toy breed hypoglycemia, insulinoma, hypoadrenocorticism, insulin overdose, xylitol intoxication, liver failure, and glycogen storage diseases. Clinical signs related to hypoglycemia include abnormal behavior, mental dullness, weakness, tremors, seizures, and death.[4] These signs are mostly due to inadequate glucose delivery to the brain, termed neuroglycopenia. The brain is an obligate glucose consumer, with only a limited ability to use local glycogen stores and protein as energy sources, and therefore relies on systemic glucose delivery to fuel its metabolism and function.[5,6] Neuroglycopenia leads to excess release of glutamate, a major excitatory neurotransmitter, from neurons following hypoxic ischemic brain injury. The elevated glutamate concentrations result in swelling of astrocytes[7] and intracranial hypertension. Prolonged hypoglycemia can therefore result in altered mental status that persists beyond the correction of hypoglycemia and may lead to cortical blindness and peripheral nerve demyelination due to generalized deficiency in energy substrate.[4] Normal blood glucose concentrations are essential for proper brain functioning. Therefore, prompt recognition and rapid correction of hypoglycemia through the administration of dextrose is essential.

Common causes of hyperglycemia include diabetes mellitus, pheochromocytoma, hyperadrenocorticism, iatrogenic (administration of medications such as glucocorticoids or dextrose containing fluids such as total parenteral nutrition), and stress hyperglycemia. Transient or stress hyperglycemia in sick veterinary patients can result from increased circulating glucocorticoids, catecholamines and insulin resistance.[8] Stress hyperglycemia has been documented to occur in animals with head trauma, blunt trauma, noncardiogenic pulmonary edema, congestive heart failure, and critical illness.[9-13] Mild elevations in blood glucose concentration are not generally associated with clinical signs. However, with severe elevations in blood glucose concentrations,

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Table
Factors That May Affect Glucose Concentrations Measured by a PBGM

Parameters	Effect on PBGM Measurement
Whole blood sample rather than plasma or serum	Decrease
Hematocrit	
Low	Increase
High	Decrease
PaO_2	
Low	Increase
High	Decrease
Mannitol	Increase
Dopamine	Increase

clinical signs can include increased thirst and urination, weight loss, polyphagia, and alterations in mental status and coma (Table). Since glucose contributes to the osmolality of the blood, it is capable of causing the movement of water between body compartments.[14] Hyperglycemia results in fluid shifting from the intracellular compartment into the intravascular space resulting in cellular dehydration. Glucosuria results when serum glucose concentrations exceed 180-200 mg/dL (10-11 mmol/L) and 260-310 mg/dL (14–17 mmol/L) in dogs and cats, respectively,[15] and can lead to significant urinary electrolyte and water losses, dehydration, and hypovolemia when there is an inadequate oral intake of fluids to compensate for these losses. In addition, hyperglycemia has been associated with detrimental effects including immunosuppression, proinflammatory and procoagulation effects, and modulation of the endothelium.[16-18] Therefore, patients with persistent and severe hyperglycemia should receive treatment with insulin therapy.

Glucose may be measured on whole blood, serum or plasma. However, there are some discrepancies in the measurements obtained through the different blood components. Plasma glucose concentration is reported to be approximately 12%-13% higher than that obtained from whole blood because the water content of the erythrocytes (73%) is lower than that of plasma (93%). As glucose is freely diffusible between plasma and erythrocytes, the greater water content of the plasma provides an osmotic gradient leading to a higher glucose concentration.[1] This hypothesis is supported by a recently published veterinary study, where serum and plasma glucose concentrations measured on a PBGM developed for use in people was more accurate as compared with whole blood PBGM measurements.[19]

Once blood is sampled, blood glucose should be rapidly analyzed because glycolysis will continue in blood cells In Vitro, thereby falsely reducing the measured glucose concentration.[20] Leaving blood at room temperature without separating the serum or plasma reduces the concentration of glucose by 5%-10% every hour. This process is accelerated in the presence of leukocytosis and erythrocytosis.

The source of the blood sample (arterial, venous, or capillary) may also affect the measured glucose concentration. Venous samples give slightly lower values than capillary samples, regardless of whether they are measured on whole blood or plasma, as the glucose is taken up by the cells. In fasted animals, this difference does not have a significant clinical effect.[1] However, in a postprandial state, blood glucose concentration measured on an arterial sample may be as much as 32 mg/dL (1.8 mmol/L) higher than on a venous sample in people.[1] In both dogs and cats, capillary blood glucose measurements obtained from the ear using lancing devices were compared with venous samples. The differences in blood glucose concentrations between the samples were so small that they were unlikely to affect clinical decision making.[21,22] Based on the currently available information in the veterinary literature, it is reasonable to assume that capillary, venous, or arterial samples will provide clinically similar blood glucose measurements, assuming that the site is adequately perfused. If blood flow to the sampling site is compromised, as may be the case in an animal with shock, the blood glucose concentration in that limb will likely be lower and not be reflective of systemic circulation, and a central venous or arterial blood glucose measurement should be done. This finding was recently confirmed in a study of dogs and cats with aortic thromboembolism. In this study, a blood glucose measurement obtained from an affected limb was 30 mg/dL (1.7 mmol/L) or 16 mg/dL (0.9 mmol/L) lower in the cat and dog, respectively, as compared to a central venous or nonaffected limb peripheral venous blood glucose measurement. Interestingly, these blood glucose difference cut-offs were 100% sensitive and 90% specific in cats, and 100% sensitive and specific in dogs, for a diagnosis of aortic thromboembolism.[23]

POC Devices to Measure Glucose

Portable Blood Glucose Meters

PBGMs are handheld devices with the sole function of measuring glucose. There are many PBGMs from various manufacturers available on the market. Some devices may only be available in certain countries while others are available globally. PBGMs were originally designed for humans with diabetes mellitus to monitor their capillary blood glucose at home. In veterinary patients, venous blood is most commonly used for in-hospital blood glucose monitoring, whereas capillary samples may be used in diabetic pets for at-home blood glucose monitoring.[24] Blood may be collected into plain, EDTA, or lithium heparin tubes for use with a PBGM.[25-27] However, blood glucose measurements on fluoride anticoagulated blood underestimated the actual blood glucose concentration when evaluated using the SureStep (or Gluco Touch) (SureStep LifeScan Inc, Milpitas, CA, USA) portable blood glucose meter.[25,26]

Glucose Measurement Methodology

PBGMs are designed to measure glucose on whole blood. Using a fixed volume of blood, some PBGMs lyse the red blood cells and analyze the amount of glucose in the volume of lysate whereas other PBGMs use a series of absorbent pads to separate the cellular portion of the sample from the serum or plasma portion. This allows only the serum or plasma to react with the enzymatic reagents. PBGMs using whole blood lysate results must therefore be corrected to serum or plasma measurements, generally through the application of an internal algorithm.

The 2 main enzymatic reactions used by PBGMs in the detection of glucose are glucose oxidase and glucose-1-dehydrogenase.[28] The most commonly used method is the glucose oxidase reaction between the test strip and the glucose in the blood.[24] In this method, glucose oxidase is a catalyst for the oxidation of glucose to gluconic acid and hydrogen peroxide. The amount of hydrogen peroxide produced is proportional to the glucose concentration in the blood sample. The change in hydrogen peroxide concentration can be measured by using a color change as an indicator (photometric technique) or via the production of an electrical current (amperometric technique) (Fig 1). In the glucose-1-dehydrogenase technique, glucose is converted to gluconolactone using a coenzyme to convert nicotinamide adenine dinucleotide (NAD) to the reduced form (NADH). The NADH concentration is measured and is proportional to the blood glucose concentration.[29]