Top 5 Substances that Affect Blood Glucose

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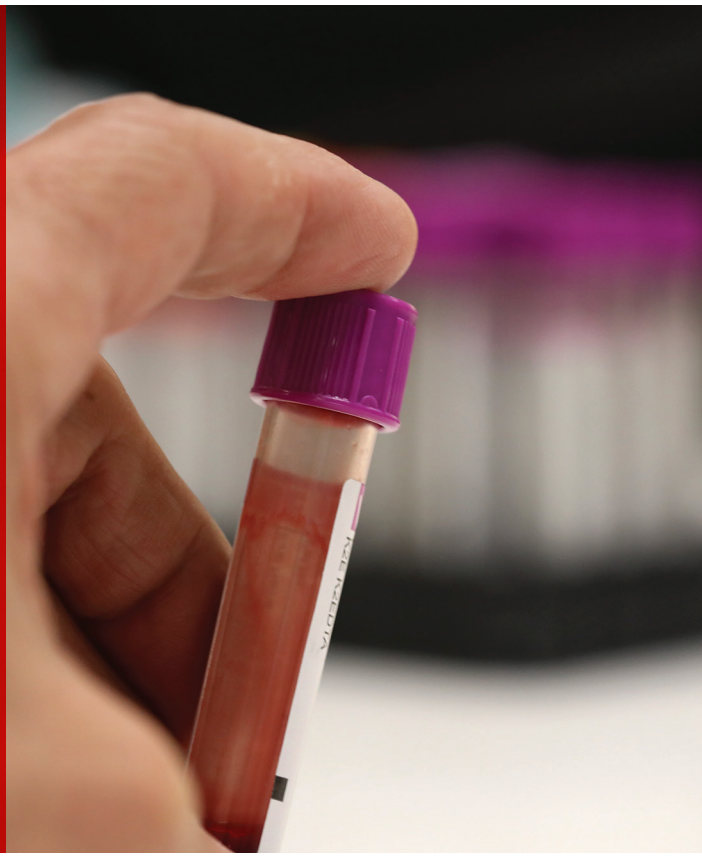

Glucose homeostasis requires that blood glucose be constrained within a narrow concentration. Homeostasis is accomplished through diverse physiologic mechanisms that work together to precisely regulate glycemia. Abnormalities in blood glucose (ie, hyperglycemia, hypoglycemia) occur when physiologic regulation is disrupted (eg, during disease states or metabolic disturbances). In some circumstances, medications and toxins may also affect blood glucose regulation; for example, many drugs produce glucose disturbances in humans and may cause similar disturbances in dogs and cats (see ***Drugs that Can Alter Blood Glucose in Humans***, next page).

Following are the author's top 5 substances that exert significant effects on blood glucose regulation in dogs and cats and the clinical situations in which they may be encountered.

1 Insulin

Insulin, secreted from β cells in the pancreatic islets of Langerhans, produces a potent hypoglycemic effect through its physiologic role as a hormone or when used as a replacement hormone to manage diabetes.[1] Insulin-induced hypoglycemia caused by naturally occurring disease is rare, but clinical disorders (eg, canine insulinoma) can occur.[2] In contrast,

TOP 5 SUBSTANCES THAT AFFECT BLOOD GLUCOSE

1. Insulin
2. Glucocorticoids
3. Xylitol
4. Growth Hormone
5. Progestins

DRUGS THAT CAN ALTER BLOOD GLUCOSE IN HUMANS*

Drugs that Induce Hypoglycemia

- Insulin
- Glucose-lowering drugs
  - –Biguanides
  - –Sulfonylureas
  - –Glucagon-like peptide-1 (GLP-1) analogs
- ACE inhibitors
- β blockers
- Antibiotics
  - –Quinolone antibiotics
  - –Chloramphenicol
- Disopyramide
- Ethanol
- Salicylates

Drugs that Induce Hyperglycemia

- Corticosteroids
- Quinolone antibiotics
- Antipsychotics
- β blockers
- Calcineurin inhibitors (eg, cyclosporine)
- Protease inhibitors
- Thiazide diuretics

*Hypo- or hyperglycemia has been reported as an adverse effect of many drugs used in human medicine. Some drug classes (eg, β blockers, quinolone antibiotics) appear on both lists because separate drugs within the class can cause hyper- and hypoglycemia. It is possible that these drugs exert similar actions on blood glucose in dogs and cats, although hypo- or hyperglycemic effects of many infrequently prescribed drugs are not well documented in these species.

GH = growth hormone

pharmacologic insulin preparations are the most potent hypoglycemic agents in routine clinical use.[1] Various modifications have been made to alter the pharmacologic properties of endogenously produced insulin, the mainstay for diabetes treatment in dogs and cats. These modifications, which have expanded the clinical efficacy of insulin preparations, may also produce severe hypoglycemia when administered inappropriately or after overdose. The endogenous hormone and all insulin preparations produce hypoglycemia via identical mechanisms, but pharmacologic modifications may cause the magnitude and duration of the hypoglycemic effect to be more pronounced.[3]

In most tissues, especially muscle and adipose tissue, insulin binds to specific insulin receptors on the surface of most cells.[4] After binding, receptor activation initiates a cascade of intracellular steps that culminates with the insertion of glucose transporters into the cell membrane and activation of cellular glucose uptake. In the liver, insulin serves as a regulator of glucose storage and production. Insulin activates glycogenesis and inhibits gluconeogenesis, both of which reduce blood glucose.[5] The hypoglycemic effects wane when blood insulin is low or absent.

2 Glucocorticoids

Glucocorticoids are a chemical class of hormones and synthetic drugs that includes cortisol, hydrocortisone, prednisone, dexamethasone, and less familiar hormones and drugs. They exert a wide range of effects on carbohydrate, protein, and lipid metabolism and are involved in regulation of inflammatory processes and the immune system.[6] The principal glucocorticoid effect on glucose homeostasis is promotion of hyperglycemia, which can be marked in the presence of supraphysiologic or pharmacologic glucocorticoid concentrations.[7]

Hyperglycemia caused by glucocorticoid excess can arise as a consequence of naturally occurring endocrine disorders or exposure to exogenous glucocorticoid substances.[8,9] Any condition that increases

adrenal production of glucocorticoids can produce hyperglycemia, including physiologic responses. In dogs, hyperadrenocorticism (ie, Cushing's disease) is the most common endocrinopathy associated with glucocorticoid overproduction and hyperglycemia.[10] In affected dogs, hyperglycemia occurs in the presence of excess plasma cortisol and other glucocorticoids, caused by adrenal hyperplasia or functional adrenocortical neoplasia.[11] Physiologic distress (eg, due to illness or fear) can result in hyperglycemia caused by activation of an adrenal hormone response (ie, stress hyperglycemia), which includes hypercortisolemia and elevations in catecholamines.[12] Stress hyperglycemia can occur during illness and is a common finding in otherwise healthy dogs and cats.

Exogenous glucocorticoids may also cause hyperglycemia.[13] Glucocorticoid preparations are among the most frequently prescribed drugs in small animal medicine. The potency of synthetic glucocorticoids, including prednisone and dexamethasone, is much greater than hydrocortisone. Thus, these preparations may produce substantial side effects, even when used at appropriate pharmacologic doses.[14] Hyperglycemia can develop as a side effect of oral, injectable, or topical glucocorticoid administration.[15]

Endogenous and exogenous glucocorticoids induce hyperglycemia by the same mechanism, referred to as insulin resistance.[16] Glucocorticoids reduce tissue sensitivity to insulin, which antagonizes the hypoglycemic actions of insulin. The insulin-resistant state is characterized by a subnormal biologic response to normal concentrations of insulin.[16]

3 Xylitol

Xylitol is a 5-carbon sugar alcohol used as an artificial sweetener in many commercial products (eg, chewing gum, drugs, candies).[17] Although safe for humans and most other mammals, xylitol induces severe hypoglycemia after ingestion in dogs.[17] Along with hypoglycemia, xylitol toxicity may cause hepatic necrosis that may progress to liver failure in some dogs, which may contribute to hypoglycemia via a separate mechanism.[18]

Xylitol appears to be a potent stimulator of insulin secretion in dogs; this effect has not been observed in other mammals.[19] The increase in plasma insulin induced by xylitol stimulates tissue uptake of glucose, leading to severe hypoglycemia. The mechanism that leads to hepatic necrosis, characterized by severely increased serum alanine transaminase (ALT) activity, is not completely known but may involve adenosine triphosphate (ATP) depletion.[20]

4 Growth Hormone

Growth hormone (GH; ie, somatotropin) is produced and secreted by the anterior pituitary.[21] In adulthood, GH is a component of the counter-regulatory response to hypoglycemia and stress.[22]

GH secretion disorders are uncommon causes of blood glucose disturbances in dogs and cats. The most frequently encountered clinical disorder of GH secretion is feline acromegaly.[23] Acromegaly in

POLL

Have you ever had a feline patient develop diabetes after treatment with methylprednisolone acetate?

A. Yes
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cats is caused by excessive GH secretion from a pituitary adenoma that causes hyperglycemia through induction of insulin resistance in muscle and adipose tissue.[23,24] Hyperglycemia can be severe, and affected cats often have diabetes mellitus on presentation for hyperglycemia treatment.[25]

5 Progestins

Progestins are a class of natural and synthetic compounds with actions that mimic those of progesterone.[26] Exposure to progesterone or progestins may produce alterations in blood glucose homeostasis in dogs and cats, although the circumstance under which the aberration occurs differs between the species. In dogs, progesterone and synthetic progestins stimulate GH secretion from mammary tissue, which contributes to insulin resistance in body tissues.[27] Progesterone-induced insulin resistance can be severe enough to induce diabetes mellitus in some pregnant dogs, which may resolve following pregnancy termination.[28,29] In countries where long-acting progestins are used to impede estrus cycling, treated dogs may develop hyperprogestinemia and, eventually, acromegaly as a result of persistent stimulation of GH release.[29]

In cats treated with megestrol acetate, a synthetic progestin, hyperglycemia or even overt diabetes mellitus may develop.[30] Progestin-induced hyperglycemia in cats does not have a clear link to elevated GH concentration, and the exact mechanism by which progestins induce carbohydrate intolerance in cats is unknown.[31]

GH = growth hormone

See page 66 for references.

Mirataz™
(mirtazapine transdermal ointment)

For topical application in cats only. Not for oral or ophthalmic use.

CAUTION: Federal law (USA) restricts this drug to use by or on the order of a licensed veterinarian.

Before using this product, please consult the product insert, a summary of which follows:

INDICATION: Mirataz™ is indicated for the management of weight loss in cats.

DOSAGE AND ADMINISTRATION: Administer topically by applying a 1.5-inch ribbon of ointment (approximately 2 mg/cat) on the inner pinna of the cat's ear once daily for 14 days. Wear disposable gloves when applying Mirataz™. Alternate the daily application of Mirataz™ between the left and right inner pinna of the ears. **See Product Insert for complete dosing and administration information.**

CONTRAINDICATIONS: Mirataz™ is contraindicated in cats with a known hypersensitivity to mirtazapine or to any of the excipients. Mirataz™ should not be given in combination, or within 14 days before or after treatment with a monoamine oxidase inhibitor (MAOI) [e.g. selegiline hydrochloride (L-deprenyl), amitraz], as there may be an increased risk of serotonin syndrome.

HUMAN WARNINGS: Not for human use. Keep out of reach of children. **Wear disposable gloves when handling or applying Mirataz™ to prevent accidental topical exposure.** After application, dispose of used gloves and wash hands with soap and water. After application, care should be taken that people or other animals in the household do not come in contact with the treated cat for 2 hours because mirtazapine can be absorbed transdermally and orally. However, negligible residues are present at the application site and the body of the cat at 2 hours after dosing. In case of accidental skin exposure, wash thoroughly with soap and warm water. In case of accidental eye exposure, flush eyes with water. If skin or eye irritation occurs seek medical attention. In case of accidental ingestion, or if skin or eye irritation occurs, seek medical attention.

PRECAUTIONS: Do not administer orally or to the eye. Use with caution in cats with hepatic disease. Mirtazapine may cause elevated serum liver enzymes (See **Animal Safety** in the product insert). Use with caution in cats with kidney disease. Kidney disease may cause reduced clearance of mirtazapine which may result in higher drug exposure. Upon discontinuation of Mirataz™, it is important to monitor the cat's food intake. Food intake may lessen after discontinuation of mirtazapine transdermal ointment. If food intake diminishes dramatically (>75%) for several days, or if the cat stops eating for more than 48 hours, reevaluate the cat. Mirataz™ has not been evaluated in cats < 2 kg or less than 6 months of age. The safe use of Mirataz™ has not been evaluated in cats that are intended for breeding, pregnant or lactating cats.

ADVERSE REACTIONS: In a randomized, double-masked, vehicle-controlled field study to assess the effectiveness and safety of mirtazapine for the management of weight loss in cats, 115 cats treated with Mirataz™ and 115 cats treated with vehicle control were evaluated for safety. The vehicle control was an ointment containing the same inert ingredients as Mirataz™ without mirtazapine. The most common adverse reactions included application site reactions, behavioral abnormalities (vocalization and hyperactivity), and vomiting. **See Product Insert for complete Adverse Reaction information.** To report suspected adverse events, for technical assistance or to obtain a copy of the SDS, contact Kindred Biosciences, Inc. at 888-608-2542. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at **http://www.fda.gov/AnimalVeterinary/SafetyHealth**.

EFFECTIVENESS: The effectiveness of Mirataz™ (mirtazapine transdermal ointment) was demonstrated in a randomized, double-masked, vehicle-controlled, multi-site field study involving client-owned cats of various breeds. Enrolled cats were ≥ 1 year of age and had existing documented medical history of ≥ 5% weight loss deemed clinically significant. The most common pre-existing conditions included renal insufficiency, vomiting, and hyperthyroidism. Some cats had more than one pre-existing condition. Cats were randomized to treatment groups in a 1:1 ratio of Mirataz™ to vehicle control. A total of 230 cats were enrolled and received either Mirataz™ (115 cats) or a vehicle control (115 cats) containing the same inert ingredients without mirtazapine. The cats were 2.8-24.6 years of age and weighed 2.1-9.2 kg. The dosage was a 1.5-inch ribbon (approximately 2 mg/cat) mirtazapine or vehicle ointment administered topically to the inner pinna of the cat's ear. A total of 177 cats were determined to be eligible for the effectiveness analysis; 83 cats were in the Mirataz™ group and 94 cats were in the vehicle control group. The primary effectiveness endpoint was the mean percent change in body weight from Day 1 to the Week 2 Visit. At Week 2, the mean percent increase in body weight from Day 1 was 3.94% in the mirtazapine group and 0.41% in the vehicle control group. The difference between the two groups was significant ($p<0.0001$) based on a two-sample t-test assuming equal variances. A 95% confidence interval on the mean percent change in body weight for the Mirataz™ group is (2.77, 5.11), demonstrating that the mean percent change is statistically different from and greater than 0.

STORAGE: Store below 25°C (77°F). Multi-use tube. Discard within 30 days of first use.
HOW SUPPLIED: Mirataz™ is supplied in a 5 gram aluminum tube.
MANUFACTURED FOR:
Kindred Biosciences, Inc.
1555 Bayshore Highway, suite 200
Burlingame, CA 94010

NADA 141-481, Approved by FDA
Made in USA.
NDC 86078-686-01
REG-MTZBS-008 Rev. 26Apr2018
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