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FELINE health topics

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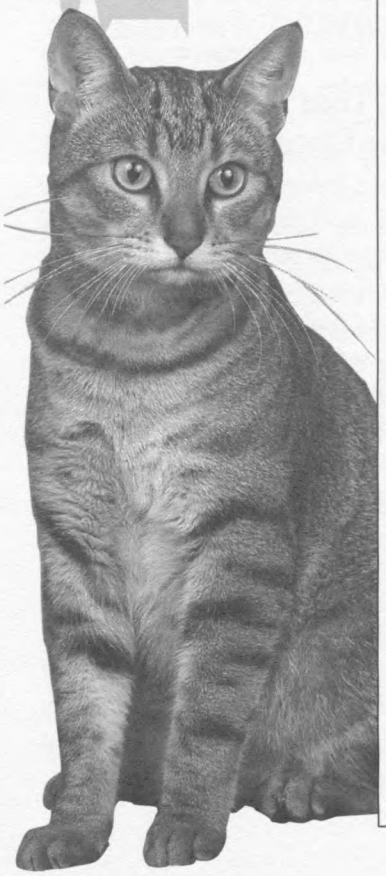
inside



Treatment of Feline Type 2 Diabetes Mellitus with Oral Hypoglycemic Agents

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Treatment of Type 2 diabetes in cats is aimed at attenuating the physiologic abnormalities by decreasing hepatic glucose output and glucose absorption from the intestine, increasing peripheral insulin sensitivity, and increasing insulin secretion from the pancreas.

In cats, the differentiation of these catagories is almost impossible prior to treatment; therefore, the clinician must rely on the response to oral hypoglycemic agents as a guide to whether the cat has sufficient beta-cell function to be managed with oral hypoglycemic agents. Oral hypoglycemic agents include the sulfonylureas (glipizide, glyburide, glimiperide), biguanides (metformin), thiazolidinediones (troglitazone), alpha-glucosidase inhibitors (acarbose) and transition metals (chromium, vanadium). Indications for oral hypoglycemic therapy in cats include normal or increased body weight, lack of ketones, probable type II diabetic, with no underlying disease (pancreatitis, pancreatic tumor), history of diabetogenic medications and owner willingness to administer oral medication rather than an injection. Reversal of glucose toxicity using a short course of insulin therapy prior to or in combination with oral hypoglycemic agents may improve the response to oral hypoglycemic agents. Diet should consist of low carbohydrate/high protein canned foods only.

Agents That Inhibit Intestinal Glucose Absorption

The alpha-glucosidase inhibitors impair glucose absorption from the intestine by decreasing fiber digestion and hence glucose production from food sources. These drugs were initially developed as "starch blockers" to control obesity in humans and may have application to the treatment of obese diabetic cats. Acarbose is used as initial therapy in obese pre-diabetic patients suffering from insulin resistance or as adjunct therapy with sulfonylureas or biguanides to enhance the hypoglycemic effect in patients with diabetes mellitus. Side effects include flatulence, loose stool and diarrhea at high dosages. One advantage of these medications is that they are not absorbed systemically and may be used in conjunction with other oral hypoglycemics or insulin. They are not indicated in patients of low body weight because of their effects on nutrition. The author has had experience with acarbose at a dosage of 12.5 mg/cat BID with meals; side effects, although rare if diet is adjusted, include semi-formed stool or in some cases overt diarrhea. The glucose lowering effect of acarbose alone is mild with blood glucose concentrations decreasing only into the 250-300 mg/dl

Treatment of Feline Type 2 Diabetes

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range. However, acarbose is an excellent agent when combined with insulin to improve glycemic control. Cats given acarbose will respond to a lower dosage of insulin and hypoglycemic episodes can be reduced.

Agents That Improve Peripheral Insulin Sensitivity

Classes of oral hypoglycemics that are receiving attention in human medicine are the thiazolidinedione compounds. (Saltiel and Olefsky, 1996) Thiazolidinediones facilitate insulin-dependent glucose disposal and inhibit hepatic glucose output by attenuation of gluconeogenesis and glycogenolysis; troglitazone (Rezulin®), increases transcription and translation of proteins necessary for glucose metabolism. Some authors have suggested that use of this drug early in the course of NIDDM may slow progression of the disease. (Saltiel and Olefsky, 1996) Side effects of troglitazone are minimal and include transient mild decreases in WBC, platelets, and hemoglobin. (Berkowitz, 1996) No hypoglycemic reactions have been described. The author has limited experience with these compounds in cats; however, in humans insulin therapy can be discontinued in 15% of patients using troglitazone. Improvement in fasting BG, glycosylated Hb, and diabetic complications were noted in all patients and were significant when compared with placebo.

Compounds containing the transition metals, vanadium and chromium, have been shown to have insulinomimetic properties when administered in the drinking water of mice and rats suffering from experimentally-induced DM (Type I and Type II). A recent USDA study of 180 patients with NIDDM found that administration of 1,000 mg of chromium picolinate once daily resulted in amelioration of the classic signs of diabetes and normalization of blood levels of hemoglobin A1c. In Type II diabetes, constant suppression of blood glucose is achieved with vanadium. (Brichard, 1989) Studies have documented restoration of secretion of insulin in Type II diabetics treated with vanadium, suggesting reversal of "glucose toxicity." Oral vanadate causes a marked and sustained improvement in glucose homeostasis in NIDDM by exerting an insulin-like effect on peripheral tissues; furthermore, vanadium prevents the exhaustion of insulin stores in the pancreas.

Current research indicates that transition metals bypass the insulin-receptor and activate glucose metabolism within the cell. (Schecter, 1990) By acting at a post-receptor site, vanadium/chromium compounds are an ideal treatment for Type II DM which results from a lack of insulin receptor responsiveness. Unlike insulin, vanadium and chromium do not lower blood glucose concentrations in normal animals. Studies in our laboratory indicate that low doses (0.2 mg/kg/day) of oral vanadium will decrease blood glucose and serum fructosamine concentrations and alleviate the signs of diabetes (polydypsia, polyuria) in cats with early type II diabetes mellitus. Side effects include anorexia and vomiting initially; however, most cats showed no ill effects when vanadium therapy was reinstituted. Humans ingest vanadium as a solution in juice and chromium as a tablet; however, cats will ingest vanadium more readily in food once daily.

Agents That Inhibit Hepatic Glucose Output

Metformin belongs to the biguanide group of oral hypoglycemic agents. The biguanides inhibit hepatic glucose release and improve peripheral insulin sensitivity. (Kahn, 1990) Biguanides may be used alone or in conjunction with other oral hypoglycemic agents to treat Type II diabetes mellitus in human beings. (DeFronzo, 1995) One advantage of the biguanides is that they do not promote insulin release; therefore, there is little potential for the development of hypoglycemia when metformin is used as a sole agent. Furthermore, metformin does not cause progression of pancreatic amyloid deposition because it does not provoke insulin release. (DeFronzo,

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The ultimate purpose of the Cornell Feline Health Center is to improve the health of cats everywhere by developing methods to prevent or cure feline diseases, and by providing continuing education to veterinarians and cat owners. All contributions are tax-deductible.

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1995) In a recent large randomized parallel-group, double-blind control study, human patients with NIDDM underwent treatment with metformin alone or placebo. Compared with patients in the placebo group, the metformin group had lower mean fasting plasma glucose concentrations and glycosylated hemoglobin values. (DeFronzo, 1995) Side effects of the biguanides include lactic acidosis, nausea and diarrhea. Contraindications for metformin therapy in humans, and presumbly in cats, include concurrent renal disease, liver dysfunction, or cardiac disease. Experience with this drug as treatment for NIDDM in cats has been disappointing.

Agents That Promote Insulin Release From the Pancreas

The mechanism of action of the sulfonyureas is to increase insulin secretion and improve insulin resistance; however, some of these agents also cause an increase in hepatic glucose output. This leads to delayed hyperinsulinemia, weight gain, and atherscleorosis in human beings undergoing sulfonylurea therapy. Sulfonylureas, because of provocation of insulin release, may promote progression of pancreatic amyloidosis. In cats, glipizide has been used to successfully treat diabetes mellitus at a dosage of 2.5-5 mg BID when combined with dietary fiber therapy. The patient is evaluated weekly or every 2 weeks for a period of 2-3 months. If the fasting blood glucose decreases to less than 200 mg/dl, the glipizide should be continued a the same dosage and the cat reevaluated in 3-6 months. If the fasting blood glucose remains greater than 200 mg/dl after 2-3 months of therapy and the cat is still symptomatic (PU/PD, wt. loss), glipizide should be discontinued and insulin therapy or combination insulin/oral hypoglycemic therapy should be instituted. If the blood glucose remains greater than 200 mg/dl, the glipizide should be continued indefinitely and the cats should be rechecked in 3-6 months. Initial experience with glipizide as an oral hypoglycemic agent in cats has been disappointing. However, this may be related to patient selection rather than to overt failure of the drug. Cats with early type II diabetes are most likely to respond to any oral hypoglycemic agent. Side effects of oral hypoglycemics include severe hypoglycemia (rare in cats), cholestatic hepatitis, and vomiting. Gastrointestinal side effects, which occur in about 15% of cats treated with glipizide, resolve when the drug is administered with food. (Ford 1995) A new sulfonylurea, glimepiride (Amaryl) has recently been introduced in the human market; this compound has fewer side effects than glipizide. Furthermore, glimepiride may be dosed once daily.

Combining Oral Hypoglycemics With Insulin: Changes to and from Insulin

Agents that impair glucose absorption from the intestine (acarbose) or increase insulin sensitivity (vanadium, metformin, troglitazone) may be combined with insulin to improve glucose control. Vanadium has been shown to be beneficial in conjunction with insulin in rat and mice models of IDDM. (Schecter, 1992) In the case of "brittle diabetics" where small incremental changes in insulin dose may precipitate hypoglycemia, addition of a drug that enhances the action of insulin may lead to a reduction in the insulin dosage required to attain euglycemia. In humans, acarbose and metformin are commonly used in conjunction with insulin and other oral hypoglycemics (sulfonylureas) that cause insulin release. (DeFronzo, 1995) Caution should be used in combining any oral hypoglycemic agent with insulin as hypoglycemic reactions may occur. Changes from insulin to oral hypoglycemic agents or vice versa may be necessary in some diabetic cats. If a cat is particularly sensitive to insulin or exhibits transient diabetes because of reversal of "glucose toxicity," a change to an oral hypoglycemic should be considered. On the other hand, if a cat is being managed with oral hypoglycemic agents and ketosis develops, the oral hypoglycemic agents should be discontinued and the cat should be treated with insulin.

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TABLE 1: Oral hypoglycemic drugs used in the treatment of NIDDM in humans and cats.

Drug Trade Name	Dose	Frequency	Side Effect	Mech of Action
Chromium	1000 mg (H) 200 mg (C)	q 24 hr	None at this dose	Increases insulin receptor sensitivity
Glipizide	2.5-5 mg (C)	BID	Vomiting, hepatotoxicity	Insulin release
Glimiperide Amaryl®	1-4 mg (H) unknown (C)	q 24 (H) unknown (C)	As above but lower incidence	As above
Metformin Glucophage®	500-750 mg (H) 5 mg/kg (C)	BID	Anorexia, vomiting	Inhibits hepatic glucose output
Precose Acarbose®	50 mg (H) 12.5 mg (C)	BID with meals	Flatulence, soft stool	alpha-1 glucosidase inhibitor
Troglitazone Rezulin®	200-400 mg (H) 200 mg (C)	q 24 hr	Mild decreases in WBC, platelet, and Hb counts	Increases insulin receptor sensitivity
Vanadium	0.2 mg/kg/day (C)	q 24 hr in food or water	Anorexia, vomiting	Increases insulin sensitivity

American Association of Feline Practitioners Information Brief:

In response to inquiries regarding Fel-O-Vax®FIV — September 2002

Fel-O-Vax®FIV is an inactivated, dual subtype (based on strains of Petaluma subtype A and Shizuoka subtype D) feline immunodeficiency virus (FIV) vaccine. The adjuvanted whole virus vaccine was released in July 2002, and is produced by Fort Dodge Animal Health.

Testing implications

- Cats vaccinated with Fel-O-Vax® FIV develop antibodies to the inactivated virus present in the vaccine.
- Currently available antibody-based FIV diagnostic tests (e.g., SNAP® Feline Combo, PetChek® FIV Ab plates, and Western blot) available in the United States and Europe cannot distinguish cats vaccinated with Fel-O-Vax® FIV from FIV-infected cats or from cats that are both vaccinated and infected.
- Negative FIV-antibody test results remain reliable (see the 2001 Report of the AAFP/AFM Advisory Panel on Feline Retrovirus Testing and Management at http://www.aafponline.org/about/guidelines.htm). But until tests that differentiate vaccinated cats from infected cats become readily available, it will be impossible to assess the significance of positive test results. (Is a positive-testing cat infected, vaccinated, or both?) Some consequences of this ambiguity:
  - The benefit of testing and isolating FIV-infected cats—the mainstay of reducing viral transmission—will be diminished if vaccinated cats are erroneously assumed to be non-infectious.
  - It will be impossible to ascertain the safety of adopting positive-testing cats into households with uninfected cats. Vaccinating all the residents prior to adoption may provide some protection, but it is unrealistic to expect all vaccinates to be protected.
  - Because infected cats—either healthy or ill—will be difficult to identify, the delivery of the specialized care they require will be significantly compromised.
  - Kittens born to vaccinated queens will likely test positive for passively acquired FIV antibody. According to studies conducted by the manufacturer, antibodies drop to levels that won't interfere with test results by the time kittens reach 8 weeks-of-age.
- Some shelters and other facilities designed to house strays often euthanize cats with positive FIV test results, so previously vaccinated uninfected cats may needlessly undergo euthanasia. Permanently identifying cats vaccinated with Fel-O-Vax® FIV (e.g., using a microchip or tattoo) has been suggested as a means of identifying vaccinated cats, thus sparing them from euthanasia. Yet previous vaccination does not rule out infection nor prevent the subsequent placement of infected cats.

It is crucial that clients are adequately informed about the vaccine's impact on future test results, and their decision should be reached only after careful consideration of both positive and negative implications.

Alternate test methods

Virus isolation (VI) has been suggested as another means of confirming or ruling out FIV infection, but VI has a multitude of limitations that make it impractical as a routine diagnostic tool in private practice settings.

Polymerase chain reaction (PCR)-based tests can potentially differentiate infected cats from vaccinates by identifying proviral DNA present in blood cells. Most, if not all, PCR-based assays available at the time of this writing present the following difficulties:

- Information regarding the sensitivity, specificity, and validation is largely lacking.
- Test reagents have not been standardized.
- Ability to detect various field strains to which cats might be exposed has been inadequately explored.
- Quality control within laboratories performing PCR-based FIV tests must be stringent if accurate results are to be obtained, yet mandatory quality control standards to which diagnostic laboratories must adhere are lacking.

PCR-based tests will become increasingly available to veterinarians, and it will be difficult to assess the reliability of test results until the shortcomings noted above are addressed. Refinements of PCR-based systems may resolve some of these

issues. However, at the time of this writing, a validated PCR test that will reliably identify all infected cats or that will distinguish infected cats from those vaccinated with Fel-O-Vax® FIV is not available to clinical practitioners. It should be noted that PCR test methodology cannot be modified for in-clinic use, and it is unlikely that a point-of-care test will be available in the foreseeable future.

Vaccine efficacy

FIV is commonly classified into five different subtypes (A, B, C, D, and E) based upon genetic variation within one section of the virus envelope gene. Subtypes A and B are the predominant subtypes in the United States. Substantial genetic variation exists both within and between the various subtypes (also called genotypes or clades). Experimental FIV vaccines reported thus far in the literature have demonstrated poor cross protection between subtypes (e.g., vaccines based on subtype A virus have shown decreased protection against subtype B challenge).

As a condition of licensure, the United States Department of Agriculture (USDA) requires manufacturers to determine vaccine efficacy based upon results of laboratory studies. Accordingly, 45 eight week-old specific pathogen free kittens were randomized into two groups: 25 were vaccinated with Fel-O-Vax® FIV three times three weeks apart while 20 kittens served as non-vaccinated controls. Approximately one year later, both groups were challenged intramuscularly with a subtype A virus that differed by 10% in a portion of the envelope gene from the subtype A virus used in the vaccine. The preventable fraction (defined as the proportion of cats protected by vaccination in excess of the proportion that is naturally resistant) was calculated to be 0.82 (82%).

Challenge models that accurately reflect "real world" exposures to infectious agents are difficult to design and control, expensive, and involve large numbers of cats. In addition, they often require several years of data collection to obtain meaningful results. Laboratory challenges of the kind required by the USDA provide necessary and valuable information, but for reasons of practicality and expense, they may not reflect vaccine performance in the field. Although these efficacy figures are encouraging, it is possible that fewer than 82% of vaccinated cats will be protected from the vast array of FIV genetic variants to which they may be exposed in nature. Therefore, while reasonable to expect that some cats vaccinated with Fel-O-Vax® FIV will be protected from infection, others certainly will not.

Conclusion

The absence of tests that distinguish cats vaccinated with Fel-O-Vax® FIV from infected cats, coupled with questions regarding the vaccine's ability to induce protection against all the subtypes and strains of FIV to which cats might be exposed, makes the decision to recommend use of this product far from straightforward. It is crucial that clients are adequately informed about the vaccine's impact on future test results, and their decision should be reached only after careful consideration of both positive and negative implications. If the decision ultimately falls in favor of vaccination, cats should test negative immediately prior to receiving Fel-O-Vax® FIV.

Type 2 Diabetes

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Oral hypoglycemics are becoming increasingly popular for use in cats with Type 2 diabetes mellitus. Sulfonylureas are the most common class of drugs and glipizide has been used at a dosage of 5 mg BID PO to manage diabetes in cats for several years. Newer drugs, such as acarbose, may be used as adjunct therapy with other oral hypoglycemics and diet. Metformin and the thioazolodidiones have been recently studied in cats and may show promise particularly if combined with insulin or dietary therapy. Diet, utilizing low carbohydrate, high protein formulations, may be key to successful management of diabetes in cats.

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What's NEW in Feline House Soiling, Spraying and Fighting

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There have been several exciting advances in our ability to reduce anxiety in cats. This is important because anxious cats spray and fight with one another. They may also aggress against people or house soil.

With the help of the Cornell Feline Health Center, we studied the effects of two different medications on spraying. This was a double blind crossover experiment. Each of 18 cats was treated with one drug for 4 weeks. After a wash-out period of one week, the cat was treated with the other drug (AB or BA order). The owners recorded the number of sprays per day. They were instructed to use a paper towel to determine sprays if the spray wasn't visible to the naked eye. Cleaning was done with an enzymatic cleaner, Anti-Icky-Poo®. At the conclusion of the drug treatment, spraying incidents/day were recorded for a further two weeks. The two drugs tested were clomipramine (5 mg/cat/day orally) and cyproheptadine (2 mg/cat/day orally). Clomipramine is a tricyclic antidepressant, the main mode of action of which is blockage of serotonin reuptake. This functionally increases serotonin in the synapse. In contrast, cyproheptadine is a drug with multiple actions. It is an anti-androgen, as well as an appetite stimulant, an antihistaminic and a serotonin antagonist. The results were very clear cut. Prior to treatment, the cats sprayed 10/wk. The spraying rate fell to 3/wk in those cats treated with clomipramine and rose to 17/wk in those treated with cyproheptadine. We had assumed that cyproheptadine, which has suppressed spraying in an intact male cat and mounting in a castrated male cat would decrease spraying in males. The increase was unexpected, but supports the hypothesis that clomipramine acts directly to reduce spraying through serotonergic pathways rather than non-specific sedation.

In a second study, we investigated the effect of clomipramine (5 mg/kg orally) on aggression toward other cats. Ten cats (the aggressor of each pair) have been studied so far. There has been a profound decrease in aggression with no behavior modification or change in management of the cats.

These results are very good news for feline practitioners. We have two drugs of proven efficacy for spraying, both of which appear to be superior to amitriptyline and buspirone and less dangerous than diazepam which can induce hepatotoxicity. We have used paroxetine (2.5 mg/day P.O.) and found it effective, but likely to cause constipation and in a few cats the serotonin syndrome.

It is good veterinary medicine to treat spraying but it would be even better to prevent it. One cat per household is preventative, but cat lovers are tempted to add more cats because each deserves a home. Vic Spain, a veterinary epidemiologist formerly at Cornell, studied over 1500 cats adopted from a large western New York shelter. He found that those males who were neutered early were much less likely to spray, to be hyperactive, and to be aggressive to veterinarians, but they were more likely to hide.

Good news for feline practitioners. We have two drugs of proven efficacy for spraying, both of which appear to be superior to amitriptyline and buspirone and less dangerous than diazepam which can induce hepatotoxicity.

Spraying has been the subject of a study performed by the University of California, Davis behavior group. They found that spraying by spayed females can be treated successfully by improving litter hygiene. Owners were instructed to use clumping litter, to scoop daily, to provide a litter box per cat plus one (three boxes for two cats), and to clean sprayed areas with Anti-Icky-Poo®, an enzyme cleaner. Almost all female cats stopped spraying, but almost none of the males did. Those cats that continued to spray were treated with fluoxetine (0.5 mg/kg/day orally). If spraying rate did not decline in 14 days, the dose was increased to 1 mg/kg/day. Fluoxetine resulted in a significant reduction in spraying (>70%) from 8.6 sprays/wk to 0.4 sprays/wk after 2 months of treatment. No serious side effects were noted.

Feliway®, the feline cheek gland pheromone, has been shown to reduce spraying, although the results in the United States show less effectiveness (75% reduction) than the European ones (90-99% reduction). There are two new pheromonal products not yet available in the U.S. One is a plug-in vaporizer version of

Feliway® that would eliminate the labor of identifying and cleaning the sprayed area with water or alcohol (not Anti-Icky-Poo). Another combination of cheek gland secretion, Felifriend®, is also available to reduce aggression by cats.

Veterinary behaviorists and feline practitioners must be alert to detect new products for cat owners. Some of these include toys such as the Delidome® that releases plastic balls on a schedule programmed by the owner. The balls have a hole through which small treats will be released if the cat pushes the ball around. The owner can record a message that will be played at the time the balls are released. Red lights flash too, so that deaf cats will be notified of the availability of treats. This is a good toy for obese cats because it increases exercise and can be set for early a.m. to reduce night time meowing.

Other products such as a flushing litter pan await the test of time. So far, the loud fans and flushing seem to frighten cats. The Littermaid® self-cleaning litter box does seem to be used by most cats. It can be very helpful for the caretaker who does not like to clean the box (the husband of a pregnant cat-loving wife, for example).

There seems to be a new litter invented monthly. We have seen citrus based, pine based, and cedar based litters come and go, and wheat based litter come and be accepted by some cats. Although cats seem to use shredded newspaper, the pellets of Yesterday's News are not popular. Few cats would use a pebble litter through which urine would run onto a disposable diaper. Recently, litter pearls or crystals have appeared and been sold by several of the large litter manufacturers. Dr. Jacque Neilson, a board certified veterinary behaviorist in Portland, Oregon, performed a two-choice preference test between a crystal litter and a clumping litter (Purrfect Cat Litter) at her local shelter. The cats had an overwhelming preference for the clumping litter. The cats only used the crystals once. She observed why when she added a few teaspoons of water to the litter. The litter turns hot and hisses as gas is released. This probably frightens or even hurts the cat as he or she squats over the hot spot. The crystals are good at detecting blood in urine because they turn red.

The take home message is that spraying should soon be a rare problem and easily treated, and that house soiling can arise when owners try new products that look good but do not feel or sound good to the cat.

Adapted from Dr. Houpt's presentation at the 14th Annual Fred Scott Feline Symposium.

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