TECHNICAL REPORT for VETERINARIAN USE ONLY

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RxVitamins for Pets™

Liquid A Drops

Supplied in 15 ml dropper bottles

INGREDIENTS:

Active Ingredients: Vitamin A palmitate (*retinol palmitate*)……...2000 IU per drop

Inactive Ingredients: Extra virgin olive oil

Recommended Dosage(s):

General Use Dosing:……...445 IU/kg/day
1 drop per 4.5kg of body weight daily

Condition-Specific Dosing:……1000 IU/kg SID-BID

BACKGROUND INFORMATION:

In ancient Egypt, night blindness was described circa 1500 BC in the "Ebers Papyrus" No. 351. This written information may have derived from earlier medical sources dating back to 2500 BC. Although the Egyptians did not know of vitamin A or of the fact that a diet deficient in this vitamin would lead to a decline in the visual pigment rhodopsin (necessary for the function of the rods in the retina), night blindness (nyctalopia) was the first clearly-recognized nutritional-deficiency disease in recorded history.

The ancient Egyptians treated night blindness by instilling the juice of compressed liver onto the surface of the eye. It is likely that not enough of the vitamin A contained in the liver extract could be absorbed from the surface of the eye to cure the night blindness. However, if applied frequently enough, the drops of liver extract may have been absorbed through the nasolacrimal ducts and nasal passages in sufficient quantity to reverse the hypovitaminosis A. (19)

In modern history, vitamin A was identified as a fat soluble vitamin in 1913. Its chemical structure was elucidated in 1930. Researchers found that growing animals fed a diet that was deficient in vitamin A became unhealthy, demonstrating poor growth and reduced immune function. Animals fed a vitamin A deficient diet developed ocular inflammation and infection. These problems resolved almost immediately when the test subjects were given some cod liver oil or butterfat. (24).

Vitamin A is stored in the liver, which contains the highest amount of vitamin A of any organ. The liver contains 100 times the amount of vitamin A found in adipose tissue, and 10 times the amount of vitamin A found stored in the adrenal glands and in the testicles. Other tissues contain less vitamin A than these four organs.

SUMMARY of LIQUID A Drops APPLICATIONS:

1. **Dermatology** *(see page 2 for details)*

Applications for vitamin A and the synthetic retinoids in dermatology are primarily involved with the disorders of keratinization, which include:

- Vitamin A-responsive dermatoses
- Sebaceous adenitis
- Solar dermatosis of dogs and cats
- Feline chin acne
- Canine icthyosis

The anti-fibrinolytic effect of Vitamin A can improve wound healing in hyper-adrenocorticism or patients administered corticosteroids on a chronic basis. (29) (38)

2. **Ophthalmology** *(see page 6 for details)*

Vitamin A deficiency causes *nyctalopia* (night blindness) and xerophthalmia (dry eye). Supplementation with Vitamin A either parenterally or enterally will reverse these conditions if irreversible changes have not occurred by the time of repletion therapy. Topical Vitamin A ophthalmic drops can be used to symptomatically treat keratoconjunctivitis sicca (KCS) or ophthalmic irritation in general in the absence of hypovitaminosis A. (39). Topical vitamin A drops compared favorably to cyclosporin in the treatment of KCS. (15)

3. **Oncology** *(see page 7 for details)*

Vitamin A has been used in cancer therapy adjunctively to treat squamous metaplasia and squamous cell carcinoma. The synthetic retinoids have been used for Epitheliotrophic T cell lymphoma (mycosis fungoides).

4. **Immune Function** *(see page 7 for details)*

Vitamin A has been associated with improvement of immune function for colds and the flu, and has been found to be especially effective (anecdotally) when combined with the mineral zinc and the herb garlic for viral upper respiratory infections in human beings.

5. **Gastroenterology** *(see page 9 for details)*

Vitamin A has also been found to help with malabsorption disorders to help reduce intestinal inflammation by modulating suppressive regulatory T cells. (34)

1. DERMATOLOGY

The primary reason for the use of retinoids, both synthetic and naturally occurring in dermatology is their ability to regulate proliferation, growth and differentiation of epithelial tissues. Vitamin A (retinol) maintains healthy skin and epithelial tissue in general. Retinoids enhance wound healing by stimulating fibroblasts. Unfortunately, retinoids have not been found to be very efficacious in the treatment of neoplasms of the skin.

Due to the important role that vitamin A plays in maintaining healthy skin and epithelial cell function, the signs of deficiency as manifested cutaneously are similar to the signs of excess vitamin A. (33)

- Hyperkeratinization of the epithelial surfaces
- Hyperkeratosis of the sebaceous glands causing blockage of the ducts thus reducing secretion of sebum
- Seborrhea
- Firm papular eruptions with a firm center, either localized or generalized
- Haircoat problems
- Alopecia
- Scaling of skin
- Impaired wound healing
- Increased susceptibility to infection

Use of the synthetic retinoids has been subject to more veterinary studies than the use of naturally-occurring retinoids in veterinary medicine.

Diseases that have been found responsive to *isotretinoin* include:

- Schnauzer comedo syndrome
- Sebaceous adenitis (works best when used early in the course of the disease)
  For instance, Poodles, Vizslas and Shorthaired breeds
- Ichthyosis
- Feline acne
- Epitheliotrophic lymphoma
- Keratoacanthoma
- Sebaceous gland adenoma
- Sebaceous gland hypertrophy

Diseases that have been found responsive to *etretinate* include:

- Idiopathic seborrhea of Cocker and Springer Spaniels, Golden Retrievers, Irish Setters, and some mixed breeds.
- Sebaceous adenitis
- Ichthyosis
- Solar dermatitis in dogs
- Squamous cell carcinoma in dogs
- Follicular dysplasia (e.g.: Color dilution alopecia) (31)

There are two diseases in veterinary dermatology patients that improve when supplemented with the naturally-occurring retinoid, vitamin A.

A. <u>Vitamin A-Responsive Dermatoses</u> (32)

1. Cocker spaniels, Labrador retrievers, miniature schnauzers

a. Adult-onset, medically refractory seborrheic skin disease

- Marked follicular plugging and hyperkeratotic plaques with surface fronds especially prominent on the ventral and lateral chest and abdomen.
- Varying degrees of focal crusting, scaling, alopecia and follicular papules
- Cerumenous otitis externa present
- Generally dry, dull, disheveled easily epilated haircoat
- Rancid skin odor
- Mild to moderate pruritis

2. Gordon Setters

b. Adult onset, non-seborrheic, pruritis (especially over dorsum)

- Papular dermatitis in areas of pruritis
- Antibiotics resolves the papular dermatitis and lessens pruritis but relapses after cessation of antibiotic therapy
- Allergy testing inconclusive
- Skin biopsies show disproportionate follicular hyperkeratosis with vitamin A responsive dermatosis.
- Treatment with vitamin A resolves the rash and pruritis, and dog remains normal with continued vitamin A therapy
- Diagnosis by exclusion and response to vitamin A therapy

Dosage and maintenance (32)

- **Vitamin A (retinol) PO 1000 IU/kg sid** with a fatty meal or with fish oil.
- Improvement seen after 21 days
- Complete clinical remission in 8-10 weeks
- Lifetime therapy necessary or disease will return

B. <u>Sebaceous Adenitis</u>

The synthetic retinoid, isotretinoin has had some success in clinical trials of its usefulness for disorders of the sebaceous glands. There is a variability in response based on the affected breed. For instance, neither of the two synthetic retinoids have been shown to be successful in the Akita. In the poodle, studies have shown a variable response, and when poodles do respond, often the hair regrowth is abnormal in that the hair grows back straight versus "kinky".

Nonetheless, because of the success of the synthetic retinoids in the treatment of this disease, vitamin A is now used as a less expensive alternative that can work as well. The oral **vitamin A dosage used is for small to medium sized dogs is 10,000 IU BID; large breeds (Akitas, Standard Poodles) 20,000 IU BID**. **(1000 IU/kg BID)** At these doses

vitamin A rarely causes keratitis conjunctivitis sicca (KCS), but it is suggested that tear film production be routinely monitored by Schirmer Tear Test (STT). Concurrent use of trimethoprim-sulfa drugs is contraindicated, as this may potentiate the possibility of developing KCS. (41)

C. Cushings Disease and Wound Healing

Chronic elevated corticosteroid levels in the blood, due either to a disease such as hyperadrenocorticism or iatrogenic disease from medication will affect the course of wound healing due to the fibrinolytic effect of the glucocorticoids. It is thought that vitamin A mediates this by means of the destabilization of lysosomal membranes. (29) (38) It has been suggested that surgical patients who are diagnosed with hyperadrenocorticism or who are on steroids concurrent with surgery receive vitamin A supplementation. Dose ranges cited by surgeons anecdotally are from **vitamin A 5000 IU to 20000 IU per day (1000 IU/kg qd)** while on steroids until the wound has healed. Preconditioning with enteral dosing of vitamin A for 2-4 weeks prior to elective surgeries can reduce total duration of surgical wound healing.

D. Chronic Seborrhea/Pyoderma

Synthetic retinoids (etretinate) have in the past been used for this condition when the case is appropriate, but this medication is no longer available in the United States. In a patient with this diagnosis who is also pruritic, it is important to rule out allergies before supplementing with the naturally occurring retinoid, vitamin A. The dose that is considered to be both safe and effective for this condition by dermatologists is **vitamin A 1000 IU/kg/day PO.**

E. Solar Dermatosis

This problem of excessive exposure to sunlight occurs most commonly with white pigmented dogs. Treatment is multimodal, incorporating **vitamin A PO at 1000 IU/kg/day** for 3 months, then M-W-F; d alpha tocopherol (vitamin E) 200-400 IU BID; sodium ascorbate (vitamin C) 250-500 mg BID; waterproof sunscreens with an SPF of at least 30; oral NSAIDs; oral antibiotics for 30-60 days; a canine bodysuit to protect against solar radiation to help reduce total solar exposure. If after this therapy there are still remaining areas of inflammation that have not resolved, the use of Solareze (3% diclofenac gel) once daily is recommended. Other topical options if the Solareze does not help would be 5% imiquimod (Aldara), 0.2-0.5% tretinoin (Renova) creams or 0.1% tacrolimus ointment (Protopic) (40)

F. Feline (Chin) Acne (severe refractory cases)

Feline acne is considered to be a keratinization disorder of the hair follicle, associated with glandular hyperplasia. Treatment consists of treating secondary bacterial infections with the appropriate antibiotic(s) for 2-3 weeks. The hair on the chin is clipped, and warm compresses are applied. Compresses can contain witch hazel solution, human acne pads can be used, or shampooing with benzoyl peroxide, sulfur-salicylic acid or ethyl

lactate shampoos can be used daily to every few days. Other topicals that have been suggested include: Mupirocin ointment or cream, 2.5% benzoyl peroxide gel which can be irritating occasionally, 0.01%-0.025% tretinoin cream or lotion, 0.75% metronidazole gel, clindamycin, erythromycin or tetracycline containing topicals.

For severe and refractory cases, systemic vitamin A or isotretinoin therapy may be effective. (21)

G. Feline Solar Dermatosis

Caused by damage by sunlight (actinic) to white haired skin in cats. With repeated damage, the sunburn will progress to preneoplastic lesions (actinic keratoses, squamous cell carcinoma in situ) and over time, frank squamous cell carcinoma will ensure. Older white cats and indoor white cats that "sunbathe" are at highest risk. The ear tips and margins are commonly affected, but lesions may also develop on the nose, lips or eyelids.

Treatment consists of avoidance of peak hours of sunlight, sunscreen with an SPF of 30 or greater containing titanium dioxide can be applied to the ear tips. Contact with the eyes is to be avoided with sunscreens. It has been suggested that beta carotene, 30 mg BID PO per cat may help resolve pre-neoplastic lesions, but is not effective if frank squamous cell carcinoma has been diagnosed.

The synthetic retinoid, acitretin (5-10 mg/cat qd) may be effective for non-neoplastic actinic lesions in some cats. Vitamin A may be used as an alternative treatment for these actinic non-neoplastic lesions. (22)

2. OPHTHALMOLOGY

Vitamin A *deficiency* leads to nyctalopia, xerophthalmia and hyperkeratinization of the cornea. (40) Vitamin A has been found to be effective as a topical ophthalmic for "dry eye" in human clinical trials for patients who have dry eye but do not have hypovitaminosis A. Physiologic levels of vitamin A cause keratinizing epithelia in ophthalmic tissue to differentiate into secretory epithelia, thus maintaining normal ocular tear film. (39)

A human study involving 25 patients with primary Sjogren's syndrome (SS) (the approximate equivalent of KCS in the dog) and 15 controls found that the fat soluble vitamins (A,D and E) played a role in immune-modulation. Patients with SS who had extra-glandular manifestations of the disease were found to have a decrease in Vitamin A levels as compared to controls. Vitamin A levels were positively correlated associated with Schirmer's test values. (37)

A study compared the efficacy of vitamin A (retinyl palmitate) with cyclosporin A eye drops for the treatment of dry eye syndrome in 150 human patients with diagnosed dry eye disease. It was found that both the vitamin A eye drops and the topical cyclosporin A 0.05% drops led to significant improvement in blurred vision, tear film, Schirmer's tear test scores and cytologic findings in patients with dry eye syndrome ($P<0.05$) compared to the control group that was treated with preservative-free artificial tears alone. (15)

Ocular Herpesvirus and Vitamin A

Starr (36) evaluated the use of parenteral vitamin A combined with triamcinolone in the treatment of experimentally induced herpetic keratitis in the rabbit. It was found that the high dose vitamin A (875 times greater than the RDA for rabbits) reduced the severity of the herpetic keratitis, but the low and moderate doses did not. The vitamin A did not affect immunity nor virus recovery. Although the rabbits treated with the high dose of vitamin A showed the best response in this study, the rabbits who were not infected with the herpes virus but who received the high dose of vitamin A, had significant weight loss over the other groups. No symptoms of xerophthalmia were observed, but due to the toxic effects of the vitamin A on the weight loss of the rabbits, the authors recommend the use of topical vitamin A for this problem.

3. ONCOLOGY

The retinoids have been found to have an anti-neoplastic effect that has been described as multi-factorial. Retinoid receptors complex with certain "proto-oncogenes" that ultimately can downregulate neoplastic cell proliferation at the same time as it upregulates normal cell maturation and differentiation. The loss of normal retinoid receptor expression on cells has been associated with malignant transformation.

Retinoids also will enhance Langerhans Cell proliferation and their production of Interleukin 12 (IL-12). IL-12 has potent anti-tumor and anti-metastatic effects. The Langerhans cells are the main epidermal cellular mechanism for immunomodulation. (46)

A number of animal studies have reported inhibition of tumor growth by oral administration of retinol or retinyl esters. Using relatively higher doses in mice ~ 500 IU/kg, the oral administration of retinol decreased growth of transplanted human breast cancer cells. (6) Another study in rodents administered oral retinol found that 20% of test subjects had complete remission, and a partial remission in the other 80% of subjects. (12)

In human clinical trials with oral retinol or retinyl esters (retinyl palmitate) studies have measured the inhibition of acute non-lymphocytic leukemia and found an improvement in the disease-free interval in patients that had been treated in the past for lung cancer. Human phase two studies have been conducted using oral vitamin A combined with chemotherapy. Oral doses in these human studies ranged from 30,000 to 300,000 IU/day. These studies suggested that oral vitamin A combined with chemotherapy and/or radiation had improved outcomes. (1)

Squamous cell carcinoma (SCC)

The synthetic retinoids have been found to be effective in some patients with solar-induced squamous cell carcinoma. Pre-neoplastic lesions of this disease (squamous metaplasia) have been shown to be sensitive to etretinate; early superficial lesions responded to a combination of Isotretinoin and local hyperthermia. No studies have been performed using the naturally occurring retinoid, vitamin A. (18) (17)

Intracutaneous Cornifying Epithelioma (ICE) (Keratoacanthoma)

Vitamin A deficiency is characterized by increased keratinization, which is an integral part of the pathology of this benign epithelial proliferation arising from superficial

epithelium between hair follicles. Only one case in the cat appears in the literature.

Although these tumors respond well to surgical excision, patients who have this disease often will present with multiple tumors that are continuously forming, thus necessitating multiple surgeries on the same animal.

The use of the vitamin A-related synthetic retinoids has been reported to be successful in treating this problem, although long term therapy is necessary, and lesions may reoccur upon cessation of retinoid therapy. Etretinate has been found to be more successful in treating these lesions than isotretinoin. (41) (11)

Canine Cutaneous T Cell Lymphoma

(Mycosis fungoides or Epitheliotrophic T Cell lymphoma)

The synthetic retinoids isotretinoin and etretinate have been used successfully in canine and human T-cell cutaneous lymphomas. Withrow, 2001 reports several studies in dogs with cutaneous lymphoma improving after multiple months on the retinoids. Withrow notes that in his experience it takes at least 2 months to see a response to this medication. (43)

4. Vitamin A and Immune Function:

Vitamin A helps to maintain the integrity of all mucous membranes, which are the body's first line of defense against the invasion of pathogens and antigens. Vitamin A deficiency leads to increased keratinization of mucosal tissue, resulting in alteration of the mucosal linings of the respiratory and gastrointestinal tracts. In hypovitaminosis A, mucus-producing cells are replaced by keratin-producing cells. Mucus secretions are reduced, and the mucous membranes become tough and relatively inflexible, thus increasing the chance that pathogens may gain entry into the body, resulting in disease. Supplementation with vitamin A reverses this keratinization of epithelial tissue.

Human patients deficient in vitamin A are more susceptible to contracting infectious diseases and have higher mortality rates in general. Infections tend to deplete vitamin A stores, so an individual who may be borderline in vitamin A sufficiency could become vitamin A deficient during disease, which could create a downward spiral into frank hypovitaminosis A.

Infectious diseases of humans that are associated with vitamin A deficiency include measles, chicken pox, respiratory syncytial virus (RSV), AIDS and pneumonia. Measles infections in children have been treated adjunctively with 2 treatments of high dose vitamin A (200,000-400,000 IU), if given within 5 days of the onset of clinical signs. In humans, vitamin A supplementation has been shown to significantly reduce infant mortality in measles patients by at least 50%. (5)

The measles virus is very closely related to the virus that causes Canine Distemper (CD). As a result of the documented benefits of Vitamin A supplementation for children with measles, Greene 2006, has suggested that vitamin A, in combination with intravenous vitamin C therapy can be supportive to patients with CD when treated early in the course of infection. (8)

Dietary Sources of Vitamin A

Vitamin A is considered by many veterinary nutritionists to be the most important vitamin. Vitamin A is added almost universally to animal diets. Plants do not contain vitamin A. Green and orange plants contain pro-vitamin A in the form of the β-carotene.

The vitamin A activity of β-carotene is more than that of other carotenoids, but it has only half the potency of pure vitamin A. Vitamin A is one of the most variable nutrients in the diet. This is because concentrations of the carotenoids in plants vary widely according to geographic location, maturity, method of harvest, amount and type of processing length and conditions of storage and exposure to high temperature, sunlight and air.

Nutrient Interactions

The absorption and utilization of vitamin A is dependent upon adequate intake of dietary fat, protein, vitamin E and zinc. Vitamin E enhances the body's use of vitamin A. Intake of large amounts of vitamin E decreases vitamin A stores in the body. High doses of vitamin E can help to counteract hypervitaminosis A. Zinc and protein are required to produce retinol binding protein, which is responsible for the transportation of vitamin A from the liver to the systemic circulation in humans. These two nutrients work synergistically in many of the same physiological processes that are involved with vitamin A metabolism. Concurrent supplementation with Vitamin D has been observed to potentiate the development of the skeletal exostoses associated with hypervitaminosis A in humans. (7)

Retinoids and Vitamin A Activity

Vitamin A derivatives, whether naturally occurring or synthetic, and which have vitamin A activity are called "Retinoids". Vitamin A is known as "retinol". Retinol is metabolized into retinaldehyde (AKA: "Retinal") and retinoic acid. Retinal is primarily involved with vision and reproduction; retinoic acid is involved with growth and differentiation.

Retinoic acid receptors on regulatory sites in keratin genes directly affect keratinization. Retinoic acid may influence growth by acting on the hair root. Cutaneous epithelium has a specific nuclear receptor for retinoic acid. (10)

The synthetic retinoids include tretinoin (Retin-A™, Ortho) which is used topically in humans to treat acne, as well as other dermal issues, isotretinoin (Accutane™, Roche) and etretinate (Tegison™, taken off the US and Canadian markets in 1998 due to toxicity concerns, but available in other countries, globally). There are a number of veterinary studies exploring the uses and effectiveness of isoretinoin and etretinate. A newer synthetic retinoid, acitretin (Soriatane™, Micromedex) is a metabolite of etretinate and was designed to replace etretinate, but is very expensive for veterinary use.

Summary of the Functions of Vitamin A

The functions defined for vitamin A within the body are (25) :

1. **Vision**
- Visual pigment rhodopsin transformation into nerve signal and vision
- Vitamin A deficiency leads to night blindness (nyctalopia)

2. **Growth**
- Insufficient vitamin A affects appetite and subsequently affects growth

3. **Cellular Differentiation**
- Retinoids activate or inhibit gene transcription, dependent upon the target cell type.
- Retinoids induce differentiation by binding to the specific retinoid nuclear receptor, RAR (retinoic acid receptor) and RXR (retinoic acid X receptors) which then (with several steps prior) bind with nuclear DNA, thus inducing gene transcription leading to cellular differentiation.
- These receptors are members of the steroid/thyroid/Vitamin D receptor super family, and thus influence and are influenced by these hormones and vitamins. (46)

4. **Morphogenesis**
- Natural retinoids function as signaling molecules vital to embryonic development of the heart, lungs, eyes and epithelia.
- Retinoids induce normal development of the fetus at physiologic levels but will induce fetal abnormalities with large doses or with hypovitaminosis A.
- Exogenous vitamin A supplementation is considered a teratogen and is absolutely contraindicated during pregnancy or in reproductively active animals.

5. **Immune Response**
- The natural retinoids have profound effects on the maturation and differentiation of lymphoid cells.
- With hypovitaminosis A, the primary immune response to protein antigens has been found to be reduced in rats, but no impairment was found for the second, anamnestic response.
- Vitamin A deficiency impairs the immunological response to certain viruses (e.g.: Measles virus); vitamin A repletion restores this response.
- Vitamin A has long been known as the “anti-infective” vitamin because of its ability to improve the rate of recovery from infectious diseases. Vitamin A stimulates white blood cell function and increases antibody response to antigenic challenge. Individuals with vitamin A deficiency have an impaired ability to mount effective antibody responses. Hypovitaminosis A results in decreased levels of helper T-cells. (24)

6. **Bone development**
- Vitamin A is important for growth, maturation and remodeling of the bone.
- Hypovitaminosis A decreases osteoclastic activity and impedes bone remodeling, causing long bones to be deformed. Affected animals are usually clinically painful and lame.
- Hypervitaminosis A causes premature closure of the epiphyseal plate resulting in decreased length and thickness of long bones. (14)

SIGNS of VITAMIN A DEFICIENCY

Dogs
Anorexia, body weight loss, ataxia, xerophthalmia, conjunctivitis, corneal opacity and ulceration, skin lesions, metaplasia of the bronchiolar epithelium, pneumonitis and increased susceptibility to infections. Young, growing dogs will develop defective remodeling of the cranial foramina which produces a stenosis of the cochlear nerve followed by degeneration of the cochlear neurons resulting in deafness. Experimentally, a similar degeneration was found in both the trigeminal and optic nerves. (25)

Cats
Weight loss, serosanguinous exudate around the eyes, muscle weakness, Squamous metaplasia of the these tissues in the following order: Conjunctiva, salivary glands, endometrium of the uterus, and respiratory tract. Subpleural cysts lined with squamous epithelium without bronchial communication, metaplasia of the trachea and bronchi; Conjunctivitis, xerosis with keratitis and vascularization of the cornea (xerophthalmia), photophobia, delayed pupillary response to light, formation of cataracts, extensive infectious sequelae common in lung and salivary glands, marked hypoplasia of the seminiferous tubules, absence of spermatocytes, pancreatic acinar tissue loss of zymogen granules, retinal changes associated with loss of visual pigment, reproductive and developmental disorders including abortion, resorption of fetuses, premature birth, hairless kittens, and cleft palates. (25)

SAFETY OF VITAMIN A

Carnivores circulate retinyl esters in plasma, unlike other mammals whose vitamin A circulates bound to retinol binding protein (RBP). This is believed to allow carnivores in general, and dogs and cats specifically, to possess a much higher tolerance to developing toxicity to both the natural and synthetic retinoids.

Acute Hypervitaminosis A most commonly is caused by ingesting naturally-occurring sources such as the liver from certain animals who highly concentrate vitamin A in their liver, such as Polar Bears, sharks and sled dogs. Cats who are fed diets consisting mainly of beef liver will, over time develop chronic hypervitaminosis A. In 1857, the artic explorer Elisha Kane experienced "vertigo, diarrhea and their concomitants" after feasting on polar bear liver. Fifty years later another example of acute vitamin A intoxication happened to the arctic explorer Mawson. He had to struggle 520 km back to his base station after losing all of his food supplies in a crevasse. He existed entirely on the meat and livers of dead huskies. On the trip back to base camp he suffered loss of hair, skin desquamation, vomiting, diarrhea and skeletal pains. His partner died. It has been estimated that 100 gms (~3 oz) of husky liver could contain as much as 1,000,000 IU of vitamin A. (35)

Symptoms of this acute toxicosis include:
Abdominal pain, nausea, vomiting, anorexia, headache, dizziness, fatigue, irritability, generalized desquamation, cheilitis, hair loss, hepatomegaly, splenomegaly, tenderness of the long bones, edema, hemorrhagic manifestations (petechia, epistaxis), increased

intracranial pressure creating bulging fontanelle in infants, elevated serum alkaline phosphate, calcium and liver function tests. The symptoms of abdominal pain, through irritability will begin within 4 hours of ingestion of a toxic dose, followed in several days by the remaining symptoms starting with generalized desquamation. Resolution of symptoms with cessation of the toxic ingestion will resolve within a week if the patient does not expire prior. (35)

a. Maddock, 1949 described the pathology associated with feeding a group of 5 greyhound puppies 8 weeks of age. Vitamin A was fed at the level of 300,000 IU/kg of body weight 6 days weekly. This vitamin A supplement was administered by mouth for 22 days. At this point in time the desired effect of producing pathology was not observed. This group of researchers from the Department of Pathology at the Harvard Medical School then fed these dogs by gavage, rinsing the dosage down with corn oil or olive oil, and continued this for another 45 days for a total of 67 days of feeding this high level.

   By day 30, the appetites of these dogs was seen to decline, which corresponding with dramatic weight loss. The 2 female subjects seemed to respond more quickly to the adverse effects of the hypervitaminosis A than the 3 males. Signs observed included shivering, sensitivity to touch, pain, diarrhea, unable to use hind legs, licking forepaws a lot. Tenderness was observed over all of the epiphyses. Changes were seen on radiographs and on histopathology of the epiphyses consistent with the findings of hypervitaminosis A. The paper describes in detail the gross and microscopic pathology observed in these five experimental subjects. Mild exophthalamos was the only ocular lesion described in 2 of the 5 dogs, after 55 days on the high dose of vitamin A. No other ocular pathology was noted. The researchers commented that dogs appear to have a lessened susceptibility to the effects of high doses of vitamin A. (47)

b. Akinosho, 1971 described the clinical signs and histopathology of ocular tissue in a group of 6 rabbits weighing 1 kg each, who were injected with an oil-based solution of 1,000,000 IU of vitamin A once daily for 10 days. After 10 days the experimental subjects were sacrificed and histopathology and histochemistry were performed on corneal and conjunctival tissues. Clinically, they measured a 30% weight loss in the treatment group after 10 days who were also observed to be less active than the control group. Bilateral ear collapse was seen in 100% of the treatment group after 7 days of injections.

   There was no observable difference in the appearance of the corneas of the treatment group compared to the control group. Some of the treatment group showed slight development of exudate and conjunctival dryness. None of the control group manifested these changes. No sign of inflammation was observed in the experimental group.

   Histopathologically, there was corneal epithelial thinning in the experimental group. The goblet cells of the conjunctiva of the experimental animals were reduced in numbers and irregularly shaped and non-uniform in size. Histochemically, significant changes were observed between the two groups. There was loss of basophilic staining in the experimentally treated eyes. This is the first time these changes have been

reported in rabbits. (44)

c. The author of this technical monograph (Silver) has been unable, after an exhaustive search of the veterinary literature, to find a comparable study of the ophthalmic effects of hypervitaminosis A in dogs or cats.

d. From the Merck Veterinary Manual, 1998: "Hypervitaminosis A occurs in cats fed excess vitamin A, usually diets consisting only of liver. This results in excessive exostoses, most prominent in the cervical and thoracic spine. Clinical signs include neck pain and rigidity and thoracic limb lameness. Vertebral lesions are evident on radiographs. Reduction of dietary vitamin A prevents further exostoses but does not significantly reduce the lesions already present. (45)

Chronic Hypervitaminosis

A became more common after vitamin A was popularized as a dietary supplement in the 1940's and 1950's. (20) (28) (35)

Symptoms of chronic toxicosis include (but are not limited to):
Skeletal malformations, spontaneous fractures, internal hemorrhage, anorexia, slow growth, weight loss, skin thickening, dryness, desquamating rash, xerosis, cheilitis, blepharospasm, epistaxis, hair loss, bone and joint pain, pruritis, insomnia increased blood clotting time, reduced erythrocyte count, enteritis, congenital abnormalities, conjunctivitis, fatty infiltration of the liver, hepatomegaly and reduced function of the kidney and liver. (35)

a. Hypervitaminosis A is been described in cats fed a diet exclusively of liver. The primary clinical findings for hypervitaminosis A in the cat include extensive bridging exostoses and enthesophytes, most prominent in the cervical and cranial thoracic spine. The exostoses may extend to the entire spine, ribs, pelvic and thoracic limbs. Enthesophytes may also form around limb joints, especially shoulder causing increased sensitivity of the joints. (16)

b. Skeletal changes in the early stages of the disease will cause the cat to show clinical evidence of pain. Over time lesions ankylose causing neck stiffness, with head held low and directly in front of the body, and abnormal posture. Compression of spinal roots occurs when the exostoses spread to intervertebral foramina. Signs indirectly associated with hypervitaminosis A in the cat are lethargy, depression, irritability, poor grooming, lameness, kangaroo-like sitting position matted haircoat, change of voice, constipation, increased water intake, decreased appetite, weight loss over several months, and gingivitis. (13) (30).

c. Cline et al. (1997) measured the changes in the tibia bones of adult dogs by computer tomography after feeding a diet containing 7500 IU/kg daily of vitamin A for a year. No adverse changes in the bone were observed. The authors concluded that a dietary concentration of 7500 IU/kg/day was not detrimental to normal bone health in adult dogs for a year, and that canines appear less sensitive to excess vitamin A in the diet than some other mammals. (4)

Reduced Vitamin A Toxicity in Dogs and Cats

Dogs and cats metabolize vitamin A differently than other species. Research has found that cats and dogs do not depend on retinol binding protein (RBP) to transport vitamin A in plasma. Instead, they transport vitamin A as the retinyl ester (mostly retinyl stearate) which is bound to LDL and VLDL in amounts 10-50 times those of other mammals. Normally, free circulating retinyl esters are a sign of hyper-vitaminosis A. The only exception to this are dogs and cats. Their use of the retinyl ester as a carrier molecule may explain the increased resistance of dogs and cats to hypervitaminosis A. (9)

Although it is commonly thought of as quite toxic, in fact, dogs and cats are very tolerant of vitamin A in general. (3) Vitamin A requirements increase with pregnancy and lactation, but because of its potential as a teratogen due to its effect on growth and differentiation, supplementation with dietary supplements containing large amounts of vitamin A is contraindicated. Due to the storage capacity of the liver for vitamin A and its wide availability in many foods and diets, vitamin A deficiency during pregnancy is rare.

The National Research Council has published the safe upper limits for vitamin A in dogs and cats. These values are expressed as a function of the metabolic body weight, which is different for dogs ($kg^{0.75}$) than for cats ($kg^{0.67)}$. For adult dogs, the safe upper limit is 6997 IU/ $kg^{0.75}$/day. For adult cats that value is 8230 IU/$kg^{0.67}$/day. (27)

Table of Safe Upper Limits (Expressed in IU) for Daily Vitamin A Supplementation (NRC 2008)

Body Weight in Kilograms	DOGS		CATS
1.0	2099		2469
2.25	4723		5555
5.0	10,495		12,345
10	20,990		24,690
15	31,485		
20	41.980		
25	52,475		
30	62,970		
35	73,465		
40	83,960		
50	104,950		

Clinical Veterinary Advisor – Etienne Côté (2007) states "Vitamin A requirement for cats is 10,000 IU/kg of diet fed, with levels ups to 100,000 IU/kg of diet tolerated. For dogs, the requirement is 3333 IU/kg of diet fed, with up to 33,330 IU/kg of diet tolerated."(48)

Reptiles

The lack of preformed vitamin A in the diet of many reptiles may predispose them to respiratory infections and squamous metaplasia. Not uncommonly squamous metaplasia can manifest with aural abscesses and/or ocular disease. Overdoses of vitamin A in reptiles you will see skin sloughing and liver problems can occur. A parenteral dose of 1000-2000 IU/kg IM can help to reverse signs of vitamin A deficiency. Oral dosing does not work as quickly but can also be clinically effective.

MONITORING PATIENTS for SAFE SUPPLEMENTATION with VITAMIN A

The chronic use of doses of 1000 IU/kg BID do not routinely cause adverse side-effects in most veterinary patients. However it is recommended to monitor tear film with routine Schirmer Tear Tests (STT) and blood tests for liver and kidney function. (42) These tests, paired with physical examinations at reasonable intervals to assess the patient using vitamin A enterally or parenterally is the medically-responsible approach to the relatively low potential for toxicity in dogs and cats. Performing an initial SST at the time of dispensing of the oral vitamin A supplement, and then testing at 30 days and then at 4-6 month intervals with help to reduce the potential for hypervitaminosis A.

It is conceivable that clients may accidentally administer the oral medication at home in excess of recommended dosages, or may give greater doses with the thought that "if a little is good, a lot is better." Accidental ingestion of a single 15 ml bottle of VBS Direct Liquid A Drops (1,050,000 IU retinyl palmitate) may result in acute intoxication, and if ingestion is observed, inducing emesis as soon as possible may avert a toxic crisis. Vitamin E has been found anecdotally to help reduce the toxic side effects of vitamin A toxicosis.

Administration of parenteral or enteral vitamin E may be of assistance in the event of acute or chronic vitamin A intoxication. Symptoms of acute ingestion of toxic amounts will resolve within 2 -12 months after cessation of supplementation. The length of time to complete recovery (if there aren't irreversible changes to the cornea or skeleton) is dependent upon the duration of the hypervitaminosis A and the biochemical uniqueness of the patient. (35)

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