Medical FAQs

ACTH Stimulation Test

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Introduction

The ACTH stimulation test (ACTH stim) remains the gold standard diagnostic test for diagnosing hypoadrenocorticism (Addison's disease) in both dogs and cats. It is also the only test that can diagnose iatrogenic hyperadrenocorticism (HAC; Cushing's Disease). The ACTH stim is an acceptable screening test for hyperadrenocorticism in dogs, but its reduced sensitivity (in comparison to the low-dose dexamethasone suppression test [LDDST]) produces more false negative results. The LDDST, not the ACTH stim, is the preferred screening test in cats for hyperadrenocorticism. Current literature suggests lower doses of ACTH, used in the ACTH stim, are acceptable for monitoring canine patients on mitotane and trilostane and for screening dogs for hypoadrenocorticism. This FAQ will focus on current recommendations for obtaining optimum results when performing ACTH stimulation testing in dogs and cats, what factors may affect serum cortisol concentrations when performing an ACTH stim, and how to maximize the supply of ACTH from a single product vial, thereby reducing costs.

References **Related Info** **Feedback: VINFAQ@vin.com**

Clinical Use Information

What are the different forms of ACTH and where do I get it?

There are various sources of ACTH. Currently, VIN endocrinology consultants recommend using ONLY commercially available ACTH – either Cortrosyn or Synacthen.

1. **Cortrosyn**: This product is available in U.S. through Henry Schein, 1-800-V-SCHEIN (800-872-4346) http://www.henryschein.com/ It is sold as an individual vial or a box of 10; 0.25 mg vial.
2. **Synacthen** (Alliance Pharmaceuticals): This product is available in Canada and Europe.
3. **Sandoz Cosyntropin**: This product is available in the U.S. but no studies have investigated its effects on serum cortisol concentrations in dogs with hyperadrenocorticism. One paper revealed it was effective in stimulating serum cortisol concentrations in normal dogs (Cohen *et al* 2012) when a full vial is used (250ug). So we assume it also does so in dogs with Cushing's disease at

the same dose, but we do not know for sure. So, unlike the former two products where we can use a lower dose to diagnose hyperadrenocorticism (5ug/kg), it is recommended to use the entire vial (0.25mg/250ug) per dog. There is no evidence at this time to support that this product is still effective after freezing.

4. **Cosacthen**: this is a veterinary licensed injectable tetracosactide that will be distributed by Dechra in the UK. It is assumed that this product will be used similarly to Synacthen where available.

Although compounded sources of ACTH exist, these products may vary and may not yield consistent results. Kemppainen *et al* evaluated 4 compounded ACTH formulations in healthy dogs (Kemppainen *et al*, 2005) and found that all 4 forms of compounded ACTH increased serum cortisol concentrations to a similar degree as a maximally stimulating dose of cosyntropin, when values were compared at 60 minutes following injection. Because of variability in duration of response, it was recommended that for best result interpretation, samples should be taken before and at both 1 and 2 hours post-ACTH. **Note that these studies were done in normal dogs**. Ideally, compounded forms should be tested in patients with hyperadrenocorticism before it can be said with confidence that they work just as well for diagnosis. Also note that there are other available sources of compounded ACTH available that were not tested and results could vary with the batch. Thus, even though the ACTH used in the study was active and produced a response, other batches from the same compounder might not.

How do I correctly perform and interpret an ACTH stimulation test in dogs and cats when screening for HYPERadrenocorticism (Cushing's disease)?

1. The patient does not necessarily have to be fasted overnight when trying to make an initial diagnosis, but having a non-lipemic sample is usually preferred by laboratories. It is always best to check with the lab that you use and follow their testing policies. Fasting is **CONTRAINDICATED** when performing ACTH stimulation testing for monitoring dogs and cats receiving **TRILOSTANE**. More details here.
2. Collect a baseline serum sample for measuring the (pre-stimulation or basal) cortisol concentration.
3. Administer ACTH.
    a. **If using Cortrosyn or short-acting aqueous Synacthen/tetracosactide:** For ***dogs***, the dose is 5 mcg/kg IV or IM (Behrend, *et al* 2006) with a maximum dose of 250 mcg. Post-cortisol serum concentration samples are obtained 60 minutes later for dogs. For ***cats***, the dose is 125 mcg IV or IM. Collect post-stimulation samples at 30 minutes and 1 hour. The IV route is preferred.
    b. **If administering a compounded ACTH gel** (*not preferred*), inject 2.2 IU/kg IM (the quadriceps or semimembranous/semitendonosis muscles are usually used). Collect post-stimulation samples at 1 hour and 2 hours (Kemppainen, *et al* 2005).
    c. The VIN endocrinology consultants advise **AGAINST** using Synacthen depot formulation for diagnosing dogs with hyperadrenocorticism as there is not enough evidence in the current literature to make solid recommendations. Currently, no data exist about the best time to collect post-stimulation samples following Synacthen depot injection in dogs for diagnosing hyperadrenocorticism. If no other ACTH product is available, the consultants' "best guess" is to administer 5 mcg/kg IM and collect samples 2 and 3 hours later (and 4 hours later if possible, depending on cost) to increase the chance of measuring the cortisol concentration at peak stimulation. ***Note that the depot formulation is not administered IV, only IM.*** There are no studies available to make recommendations for using the depot formulation in cats.
4. Submit all cortisol samples to a reference laboratory you trust to obtain reliable results for cortisol concentrations.
5. Approximately 80-85% of dogs with pituitary-dependent hyperadrenocorticism (PDH) display an exaggerated response following ACTH stimulation. Approximately 60% of dogs with adrenal tumors (AT) display an exaggerated response following ACTH stimulation.

6. Unfortunately, the sensitivity of the ACTH stim for diagnosing hyperadrenocorticism in cats is not known.

How do I correctly perform and interpret an ACTH stimulation test in dogs and cats when screening for HYPOadrenocorticism?

Due to the unreliability of some compounded ACTH products, VIN endocrinology consultants advise **AGAINST** using these compounded products when screening dogs and cats for hypoadrenocorticism as they can increase the risk of false positive results. This would result in unnecessary long term medical therapy, and possibly hinder resolution of clinical signs by delaying the diagnosis of an alternative etiology. As such, using a reliable, manufactured ACTH product whenever possible is preferred. If compounded ACTH is the only available product, then the protocol outlined in the previous section for HYPERadrenocorticism is appropriate.

Dogs

1. Collect a baseline serum sample for a basal (pre-stimulation) cortisol concentration.
2. Administer ACTH.
    a. **If using Cortrosyn or short-acting aqueous Synacthen/tetracosactide**, administer 1 mcg/kg IV and collect a post-stimulation cortisol serum sample 1 hour later (Botsford *et al*, 2018). It is acceptable (but more expensive) to administer 5 mcg/kg Cortrosyn or short-acting aqueous Synacthen/tetracosactide IV or IM and collect a post-stimulation cortisol sample 1 hour later.
    b. In dogs, Synacthen depot can be administered at a dose of 5 mcg/kg IM with post-cortisol serum samples collected 1 hour later (Sieber-Ruckstuhl *et al*, 2015).
3. Submit all cortisol samples to a reference laboratory you trust to obtain reliable results for cortisol concentrations.
4. In most dogs with hypoadrenocorticism, cortisol is extremely low pre- and post-ACTH, i.e., non-detectable. Both levels are typically <55 nmol/L (2 mcg/dL).
5. See below for information on what can affect ACTH stimulation test results.
6. Although an in-house cortisol assay is available, there is some evidence to suggest that disagreement is possible between the in-house cortisol assay and reference laboratory results in about 25% of cases (Lane *et al*, 2017).

Cats

1. Collect a baseline serum sample for a basal (pre-stimulation) cortisol concentration.
2. Administer ACTH. **If using Cortrosyn or short-acting aqueous Synacthen/tetracosactide,** administer 125 mcg IV or IM per cat and collect post-stimulation cortisol samples at 30 minutes and 1 hour. There are no studies investigating the use of Synacthen depot in cats for diagnosing hypoadrenocorticism. There is a single study showing that Cortrosyn administered at 5 ug/kg IV resulted in peak cortisol concentrations at 60-75 minutes post injection in healthy cats (DeClue *et al*, 2011). It is assumed this protocol could be appropriate for diagnosing cats with HYPOadrenocorticism.
3. Submit all cortisol samples to a reference laboratory you trust to obtain reliable results for cortisol concentrations.
4. In most cats with hypoadrenocorticism, cortisol is extremely low pre- and post-ACTH, i.e., non-detectable. Both levels are typically <55 nmol/L (2 mcg/dL).
5. See below for information on what can affect ACTH stimulation test results.

How do I correctly perform an ACTH stimulation test when monitoring dogs and cats receiving trilostane or mitotane?

1. ***Compounded ACTH products are not recommended*** as some batches may be inactive and fail to stimulate the patients adrenal reserve making it hard to interpret a result when a pet is receiving mitotane or trilostane. As such, a reliable, manufactured product such as Cortrosyn or Synacthen/tetracosactide is preferred whenever possible under these circumstances. If it is the only available product, then follow the guidelines as written for HYPERadrenocorticism screening.
2. ***Synacthen depot*** **has not been rigorously evaluated** through any peer-reviewed literature with respect to monitoring dogs or cats receiving mitotane or trilostane, so there are currently no recommendations.
3. The following guidelines below on monitoring dogs and cats are for *veterinarians practicing primarily in the United States* where the ACTH stimulation test is still considered an acceptable test to monitor patients on trilostane for Cushing's disease. In some parts of the world (Europe/UK), the ACTH stimulation test is not used to monitor patients on trilostane for Cushing's disease. In those areas it is performed when an animal on trilostane becomes ill and a screening test for HYPOadrenocorticism is desired.

Dogs

1. For dogs receiving mitotane or trilostane as treatment for hyperadrenocorticism, a dose of 1 mcg/kg IV can be used as described in the preceding section when using Cortrosyn (cosyntropin) or aqueous short-acting Synacthen/tetracosactide (Aldridge *et al,* 2016). A dose of 5 mcg/kg IV or IM is an acceptable alternative. But if finances are a concern, a lower dose is deemed appropriate.
2. The timing of the ACTH stimulation test in relation to pill administration is not important in dogs receiving mitotane. It is recommended during the induction period using Mitotane to call the owner every day, beginning on day 3, to discuss the dog's clinical signs. The most reliable sign signaling the end of induction is a subtle decrease in the appetite. At that point, stop the mitotane and run an ACTH stimulation test to confirm whether the end of induction has been reached. If there has been no change in the dog's clinical signs by 7-10 days on the drug, run an ACTH stimulation test at that point, as some dogs never show a change in their clinical symptoms of Cushing's, even when the endpoint of induction has been reached. Stop administration of mitotane immediately if the dog is sick until a stimulation test can be performed.
3. The ACTH stimulation test has never been validated as the monitoring test of choice for dogs receiving trilostane. According to Dechra, the manufacturer of the trilostane product Vetoryl, the ACTH stimulation test should be performed 2-6 hours after trilostane is administered to the dog with a **FULL MEAL**. The exact hour post-pill (2, 3, 4, 5, or 6) that the test is started is not critical. But for consistency in interpretation of results and subsequent post-pill cortisol concentrations, the SAME post-pill time should be repeated each time an ACTH-stimulation test is performed. As an example, if the first post-pill ACTH stimulation test is started 4 hours after the pill is given with food, then all others ideally should be started at 4 hours post-pill. For more information on ACTH stimulation testing and result interpretation with trilostane, see this Trilostane FAQ.

Cats

1. At this time, the best method of monitoring trilostane therapy in cats remains undetermined. The accepted approach is to monitor treatment with ACTH-stimulation tests, with similar post-pill timing/administration as is used in dogs with hyperadrenocorticism. See the Trilostane FAQ.
2. In the rare instance a cat is treated with mitotane versus trilostane for hyperadrenocorticism, the same protocols as outlined in the HYPER and HYPOadrenocorticism sections can be followed. Mitotane does not seem to work as well in cats for Cushing's disease as does trilostane.

What should I do when ACTH stimulation results are normal in a suspected HAC case?

There are several things that you should do if the ACTH stimulation test results don't agree with your suspicions.

1. Review the list of variables that might have affected the test.
2. Remember that a normal ACTH stimulation test result does not rule out HAC, especially if appropriate signs and laboratory findings support the diagnosis. Approximately 15-20% of dogs with pituitary-dependent hyperadrenocorticism and 40% of dogs with a functional adrenal tumor will have a normal ACTH stimulation test. Therefore, if clinical suspicion of hyperadrenocorticism is high in a dog with a normal ACTH stimulation test, perform a LDDST (a test with higher sensitivity). Make sure the dog is not systemically sick and no glucocorticoids of any form are being administered before performing the LDDST. The dexamethasone suppression test is the preferred screening test for Cushing's disease in cats. REMEMBER, the dose used in cats is **0.1mg/kg** dexamethasone IV which can be confusing as this dose is for the high dose dexamethasone suppression test in dogs.
3. Examine other blood test results and evaluate clinical signs to support the diagnosis of HAC. Most dogs with HAC have proteinuria and hypertension, so the absence of both of these, coupled with an inconclusive ACTH stimulation test makes HAC less likely. The accuracy of the UCCR is highly questionable currently given more recent publications; the UCCR is not as sensitive as we once believed. An elevated UCCR can occur in dogs that are stressed by hospital visits; therefore, it is best if the owner collects a urine sample at home and brings it to the clinic. While these tests and signs, taken in total, may suggest that HAC is unlikely, none can definitively rule out the disease. Despite this, the UCCR is not a SPECIFIC test for Cushing's disease. While we expect most dogs with Cushing's disease to have a positive UCCR, a positive UCCR does NOT mean a dog has Cushing's disease. Any disease or environmental factor causing stress to a dog or cat can result in an elevated UCCR. It is also important to understand that a dog can have Cushing's disease and still have a NORMAL UCCR.
4. Two things you should NOT do in such cases to try to diagnose HAC:
    a. Endogenous ACTH (eACTH) testing: This test is not used to diagnose HAC, but rather to differentiate between PDH and AT if the ACTH test or the LDDS test is indicative of HAC. Do not measure eACTH when the ACTH or LDDS tests are inconclusive, because results will not confirm HAC.
    b. Abdominal ultrasound: This test is not used to diagnose HAC, but rather to differentiate between PDH and AT if the ACTH test or the LDDS test is indicative of HAC. The test requires that both adrenal glands are visualized and that the ultrasongrapher is experienced. However, if an ultrasound is performed to look for other causes of the clinical signs and both adrenal glands are of normal size and shape, HAC can be deemed unlikely.
5. An exaggerated response to an ACTH stimulation test in a dog with suspected hypoadrenocorticism (Addison's disease) rules out hypoadrenocorticism. However, HAC is extremely unlikely if the dog does not have the common signs of HAC and is showing clinical signs of hypoadrenocorticism.

What could it mean when I perform an ACTH stimulation test in a suspect HAC case and the results suggest HYPOadrenocorticism?

In general, there are a few things to consider:

1. The clinical signs are due to administration of exogenous glucocorticoids.
2. A compounded form of ACTH was used and the peak response was missed.
3. The test was performed incorrectly.
4. The patient has received therapy with ketoconazole, mitotane, trilostane, or a progestin, all of which can suppress cortisol production.
5. The patient has a tumor producing a progestin or a cortisol intermediate.

Dogs with hyperadrenocorticism caused by **excessive production of a progestin or a cortisol intermediate such as corticosterone** from an adrenocortical tumor can have low or blunted cortisol concentrations despite clinical signs suggesting cortisol excess (Syme *et al*, 2001). Excess production of a progestin can potentially be proven by performance of the Tennessee sex hormone panel. There are no commercially available diagnostic assays for cortisol intermediates. If a patient has clinical signs of HAC, no history of exogenous glucocorticoid or progestin administration, an adrenal tumor on imaging, suppressed cortisol, progesterone and 17-hydroxy-progesterone concentrations on an ACTH stimulation test, and suppressed endogenous ACTH concentrations, a presumptive diagnosis can be made of an adrenal tumor secreting a cortisol intermediate.

Should I be performing the Tennessee sex hormone panel to screen my patients for Cushing's disease?

The VIN endocrinology consultants **do NOT recommend** routinely running this sex hormone panel for suspected Cushing's cases. It is reasonable to run this expanded panel when a dog or cat has clinical signs that strongly suggest Cushing's disease but both the ACTH stimulation test and low-dose dexamethasone suppression test are normal and an adrenal tumor is documented on advanced imaging such as abdominal ultrasound or CT scan.

The reasons why this test is recommended only in select situations are:

1. The ***specificity*** of sex hormone panel testing must be considered. In one study, 6 dogs with either non-functional adrenal tumors or pheochromocytoma had serum elevations of several sex hormones (Hill *et al*, 2005). In another study, serum cortisol, 17-hydroxy-progesterone, and corticosterone concentrations after ACTH stimulation were significantly correlated both in dogs with neoplasia and in dogs suspected to have HAC, suggesting that as adrenal function is increased either by adrenal disease or nonspecifically by non-adrenal illness, production of all hormones increases proportionately (Behrend *et al*, 2005). The specificity of 17-hydroxy-progesterone measurements in another single study was 55% (Monroe *et al*, 2012).
2. Most dogs in which this test is run seem to have elevations in one or more of these sex hormone bringing into question their significance in these cases.
3. Only elevations in post-ACTH concentrations of cortisol, progesterone and 17-hydroxy-progesterone are relevant, as these hormones can produce glucocorticoid effects and clinical signs of hyperadrenocorticism. Basal concentrations of any of the hormones are not helpful; we do not diagnose hyperadrenocorticism based on basal cortisol, so elevated basal concentrations of sex hormones also should not be used.

What things might affect the ACTH stimulation test and produce inconclusive or erroneous results?

The ACTH stimulation test is considered a simple and safe test. It is a relatively reliable screening test for diagnosis of hyperadrenocorticism (HAC; Cushing's disease) and is the gold standard for diagnosis of hypoadrenocorticism (Addison's disease). However, the test can be affected by several variables, which should be taken into consideration when interpreting results.

1. **Human or laboratory error** in administration of the ACTH or in processing of the sample is always possible; any test can produce a spurious result. Laboratories can, on rare occasion, report results from another patient as your patient's results. In some instances, the veterinarian or technician simply forgets to administer the ACTH prior to obtaining the post-stimulation cortisol serum sample. Obtaining the post-ACTH sample at an inappropriate time can also influence results, especially if using a compounded ACTH product or using the lower 1 ug/kg dose of Cortrosyn. Most compounded ACTH products come with recommendations to draw a post-

stimulation serum sample 2 hours following injection. Some dogs can peak earlier (e.g., 1 hour post injection). Therefore, if samples are not taken at both 1 and 2 hours post-ACTH, a peak cortisol concentration could be missed in some dogs. When using the lower dose of Cortrosyn, cortisol concentrations can start to decrease quickly after the peak at 1 hour post-ACTH. When using a dose of 5 ug/kg, cortisol stays high longer, so being a little late on drawing the post sample has less effect.

2. **Using outdated or compounded ACTH products** can yield false results. Most specialists recommend against use of compounded ACTH products because of their questionable reliability. Cortrosyn (cosyntropin) or Synacthen (available in Europe and Canada) are preferred short acting preparations.
3. **Oral or injectable prednisone, prednisolone, methylprednisolone, or hydrocortisone** administered 12-24 hours before the ACTH test is conducted will result in erroneous test results because these drugs cross-react in the cortisol assay and falsely elevate the apparent cortisol concentration. Thus, prednisone, prednisolone, methylprednisolone, and hydrocortisone should be discontinued at least 12 hours before the ACTH stimulation test is performed. If a suspect Addisonian patient is given dexamethasone, the ACTH stimulation can be performed at any time, because dexamethasone does not cross-react on the cortisol assay and one dose would not cause complete suppression of the cortisol concentrations, i.e., does not cause the type of results we see in Addisonians. Although dexamethasone does not cross react with the cortisol assay, it will, as with any steroid, eventually SUPPRESS the pituitary-adrenal axis if administered for an extended period of time. So the ACTH stimulation test needs to be performed quickly even when administering glucocorticoids that do not cross-react with the cortisol assay.
4. **Long term use of any glucocorticoid**, even topical preparations for the eyes, ears, or skin, may suppress the pituitary-adrenal axis resulting in a blunted ACTH stimulation response (a less-than-normal rise in the cortisol response). The length of time that is required for the pituitary to recover from exogenous suppression depends on the form, route, dose, and duration of glucocorticoid administration and will vary with each patient. For example, if one injection of Depo-medrol was given, an ACTH stimulation should not be performed for at least 4 to 6 weeks. Even a single injection of dexamethasone can suppress serum cortisol concentrations by up to 33% for 5 to 7 days.
5. **Chronic stress** caused by concurrent illness can result in activation of the hypothalamic-pituitary-adrenal axis and can result in adrenocortical hyperplasia. As a result, some sick dogs have higher cortisol concentrations than normal dogs; about 50% of sick dogs will have a false positive low-dose dexamethasone suppression test (LDDST) and about 20-30% will have a false positive ACTH stimulation suggestive of hypercortisolemia (Kaplan *et al*, 1995). Ideally, dogs with serious illness should be treated for these conditions first, before attempting diagnosis of HAC. The effect of chronic illness can cause a dog being tested for hypoadrenocorticism to have an exaggerated response to ACTH, i.e., a result consistent with hyperadrenocorticism. But if a dog truly has Addison's disease, it will not matter if the dog is stressed or ill at the time of testing provided no long-term glucocorticoid preparations have been administered as mentioned above in #4. That dog with true hypoadrenocorticism will still have minimal to NO response to ACTH stimulation testing.
6. **Anti-convulsive medications** (such as phenobarbital, primidone, or phenytoin) can cause clinical signs and laboratory findings mimicking those of HAC. Some evidence suggests that the LDDST can be affected by phenobarbital administration in dogs, so the ACTH stimulation test is recommended if a dog is receiving phenobarbital. (Dyer *et al* 1994).
7. **In-house cortisol assays** have become more popular and available. Disagreement can exist in cortisol concentrations between results obtained in-house and in a reference lab (Lane *et al* 2017). This is a greater concern when trying to diagnose a patient with hypoadrenocorticism, as excluding the diagnosis incorrectly could result in devastating consequences, even death, for the patient. Alternatively, a false positive result in a patient may result in long-term unnecessary treatment. The VIN database has multiple cases where the in-house cortisol results excluded a diagnosis of hypoadrenocorticism, but when the same sample was evaluated at a reference laboratory, the diagnosis was confirmed. Therefore, if in-house cortisol results do not agree with

clinical suspicion, submitting samples to a reference lab for a second measurement is strongly recommended.

8. **Critically ill** human and animal patients can show marked heterogeneity in adrenocortical function. As mentioned above with regards to chronic stress and illness, many patients will display higher than normal cortisol concentrations. Drugs such as ketoconazole inhibit the 11-beta-hydroxylase enzyme in the steroid synthesis pathway causing lowered serum cortisol concentrations. P-glycoprotein appears to be an important component of the HPA axis in dogs. It restricts entry of cortisol into the brain, limiting cortisol's feedback inhibition of CRH and ACTH. ABCB1 (formerly MDR-1) mutant dogs don't have p-glycoprotein and thereby allow more cortisol to be present within the brain; this produces greater feedback inhibition of the HPA axis and cortisol synthesis. Plasma basal and ACTH-stimulated cortisol concentrations can be significantly lower in ABCB1 mutant dogs compared with ABCB1 wild-type dogs (Mealey *et al*, 2007).

How do I stretch my Cortrosyn supply?

Cortrosyn is expensive. Once reconstituted, it has a limited shelf-life. However, you can aliquot and store Cortrosyn after reconstitution for up to 6 months if done correctly (Frank & Oliver 1998).

Cortrosyn is supplied in vials of 250 mcg. If using the intravenous route, this amount is much more than is necessary to perform an ACTH stimulation test in small- to medium-sized dogs (see "How to Perform the ACTH Test" sections above). Residual portions of reconstituted Cortrosyn can be aliquoted and stored for subsequent use following these directions:

1. Once Cortrosyn is reconstituted, aspirate 50 mcg doses into 5 labeled insulin syringes (or 25 mcg doses into 10 insulin syringes). This will allow you to perform multiple ACTH tests. The syringes (or a container with the batch of pre-loaded syringes) should be labeled with the product, dose, and date.
2. Freeze each of the syringes at -20°C. Avoid storing these in a frost-free freezer when possible -- these periodically warm up to de-frost and can therefore ruin the aliquoted stock. Repeated freeze-thawing compromises the integrity of the Cortrosyn. Since many practitioners use frost-free freezers, it is also recommended to put these plastic syringe aliquots into a styrofoam box with ice-packs inside the box to prevent thawing during one of these warming cycles. Aliquots can be stored frozen for up to 6 months without loss of efficacy.
3. DO NOT store reconstituted Cortrosyn in glass containers or vials -- it needs to be stored in **PLASTIC** syringes.
4. We assume the same directions apply to the aqueous short-acting Synacthen product.
5. At this time, there is no evidence to support that the Sandoz® cosyntropin product can be frozen. Until further studies are performed, it is recommended to use the entire vial when using this product.
6. A recent abstract (the study has not appeared in the peer-reviewed literature) reported that Synacthen depot can be frozen and remain effective. Per the study, 50 unit aliquots can be stored in plastic syringes at -20°C and protected from light for up to six months as described for Cortrosyn above (Pinto *et al*, 2017).
7. Once a plastic syringe containing an aliquot of previously reconstituted Cortrosyn is thawed, it CANNOT be refrozen. The entire aliquot needs to be administered at that time. It does not matter if a dog or cat gets more ACTH than intended under most circumstances. To defrost a plastic syringe, gently hold it in your hand or under your arm for a few minutes and it will quickly become liquid which you can inject. It is not necessary to run the syringe under hot water to defrost the frozen product.

[Top]

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2. Hyperadrenocorticism, adrenal-dependent. VINcyclopedia, canine, chapter
3. Hyperadrenocorticism. VINcyclopedia, feline, chapter
4. Hypoadrenocorticism. VINcyclopedia, canine, chapter
5. Hypoadrenocorticism. VINcyclopedia, feline, chapter

Rounds and other Resources

1. Diagnosing hyperadrenocorticism. VIN Medical FAQ
2. Treating hypoadrenocorticism. VIN Medical FAQ

[Top]

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