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# HOW TO SELECT THE BEST TREATMENT OPTION FOR A DOG WITH CUSHING'S SYNDROME

The goal of treatment of hypercortisolism is to eliminate the cause. Depending on the etiology, this may be achieved by transsphenoidal hypophysectomy, adrenalectomy, radiotherapy, or medical treatment with trilostane or o,p'-DDD (mitotane).

**Pituitary-dependent hypercortisolism**

**Surgical treatment**

Ideally, the treatment of canine PDH should be removal of the ACTH-producing adenoma [1]. Otherwise, the tumor may continue to grow and eventually lead to neurological signs associated with an intracranial mass. However, hypophysectomy requires the joint efforts of a neurosurgeon, an endocrinologist, a radiologist, and an intensivist and it is therefore not available in most cases [2]. A CT scan of the pituitary is a surgical prerequisite for localization of the gland in relation to the anatomical landmarks and for assessment of pituitary size [3]. In the hands of a skilled neurosurgeon, microsurgical transsphenoidal hypophysectomy has proved to be a safe and effective treatment for Cushing's disease in dogs.

Following hypophysectomy, hormone replacement therapy consists of lifelong administration of cortisone acetate and thyroxine. Desmopressin, a synthetic vasopressin analogue, is needed temporarily because in dogs removal of the pituitary adenoma by hypophysectomy also removes the pars nervosa, via which the antidiuretic hormone arginine vasopressin, secreted by the hypothalamic paraventricular and supraoptic nuclei, reaches the systemic circulation [4, 5].

The major complications of hypophysectomy are postoperative mortality, hypernatremia due to acute vasopressin deficiency, prolonged central diabetes insipidus, keratoconjunctivitis sicca (KCS), and residual or recurrent hypercortisolism [2,5]. Postoperative mortality and severe hypernatremia have been reduced over the years as a result of better intensive care facilities and the learning curve of the critical care specialist. Patient selection has also contributed to the decrease in postoperative mortality. In dogs with larger pituitary tumors and tumor extension rostrally or caudally over the dorsum sellae, transsphenoidal debulking surgery may be only palliative and radiotherapy might be preferred.

**Medical treatment**

Selective or nonselective destruction of the adrenal cortex with **o,p'-DDD (mitotane)** has long been the medical treatment of choice for PDH in dogs, however since a decade it has been largely replaced by **trilostane**, a competitive inhibitor of 3β hydroxysteroid dehydrogenase (HSD3B) [1].

Trilostane is absorbed rapidly from the gastrointestinal tract. Administration with food significantly increases the rate and extent of absorption. There is marked variation in the optimal dose and to avoid adverse effects due to overdosage, treatment is started at a relatively low oral dose of 1 mg/kg body weight twice daily [6].

The effectiveness of trilostane therapy is judged by 1) resolution of the clinical signs associated with glucocorticoid excess and 2) the results of an ACTH stimulation test. Within about a week on an appropriate dose of trilostane, there is a clear reduction in polydipsia, polyuria, and polyphagia, although notable improvement in the skin and coat, reduction of central obesity, and increased physical activity requires 3 to 6 months of adequate doses. The purpose of performing an ACTH stimulation test in a dog on trilostane therapy is to determine whether there is sufficient adrenocortical reserve at the time of maximal effect of trilostane, which is about 2-3 hours after administration. Despite its widespread use, the ACTH stimulation test has never been validated for use during trilostane therapy. Nowadays, an alternative monitoring of trilostane therapy is a matter of intense investigations.

Trilostane is generally well tolerated at the recommended dose and with appropriate monitoring. Overdosage results in cortisol deficiency and sometimes even mineralocorticoid deficiency [1]. The most common clinical signs are inappetence, weakness, diarrhea, weight loss, and abdominal pain. If they appear, trilostane must be stopped immediately. Recovery is usually rapid but trilostane will still be required

to control the clinical signs of hypercortisolism. Hence the dose is reduced by 50% and monitoring is continued.

Another but life-threatening side effect of trilostane is adrenocortical necrosis [7]. Its etiology is uncertain but thought to be related to increased basal ACTH concentration [8]. Trilostane therapy causes basal ACTH concentration to increase as a physiologic reaction to the lowering of the plasma cortisol concentration. Presumably, elevated ACTH levels in dogs with PDH could also lead eventually to adrenocortical necrosis. Dogs with suspected adrenocortical necrosis are presented as emergencies and deserve prompt corticosteroid substitution and supportive therapy with fluid, an antiemetic, and an analgesic. Usually, glucocorticoid supplementation must be continued after the dog is discharged.

ACTH concentration also increases in normal dogs treated with trilostane. This is associated with an increase in pituitary size (as assessed by MRI) and histological evidence of pituitary corticotroph hyperplasia and bilateral adrenocortical hyperplasia [1]. It seems reasonable to assume that trilostane could result in an increase in size of pituitary tumors, but no evidence for this has been reported. Nevertheless, at the author`s institution a control CT scan is obtained 12 months after initiation of therapy when trilostane is used in a dog with a pituitary microadenoma. This objective evaluation of the size of the pituitary tumor enables surgical intervention to be undertaken in time, if needed.

The median survival time for dogs with PDH treated with trilostane once daily was 662 days and twice daily 900 days [9, 10]. In these studies no attempt was made to relate the size of the pituitary tumor to the survival time.

**Pituitary irradiation therapy**

Radiation therapy is considered to be the treatment of choice for pituitary macrotumors with suprasellar extension [11]. Radiotherapy is effective in reducing the size of such pituitary tumors, but with a quite variable delay, from 1 to 16 months. The reduction in size is gradual in onset but can continue for a year or more after completion of the therapy. The improvement in clinical signs of hypercortisolism is associated with reduced pituitary ACTH secretion and may not be evident until a few months after therapy. Hence, treatment with trilostane is advocated until this occurs.

**Adrenal-dependent hypercortisolism**

**Surgery**

The treatment of choice for unilateral ACT is **adrenalectomy**, because successful removal eliminates both the tumor and the associated clinical signs of glucocorticoid excess, without the need for lifelong medication. Because of the atrophy of the cortex of the nontumorous contralateral adrenal gland, due to the longstanding glucocorticoid excess, glucocorticoid substitution is needed temporarily [1]. Substitution is started at the time of anesthesia and is continued for 6 to 8 weeks after surgery. The dose of glucocorticoid is decreased gradually to facilitate progressively increasing feedback stimulation of pituitary ACTH secretion.

In recent years, laparoscopic adrenalectomy has gained in popularity [12]. Its potential advantages over open techniques include reduced manipulation of other abdominal organs, an excellent view of abdominal structures, decreased surgical wound complications, and improved postoperative comfort. While ATs up to 5 cm in diameter do not pose a problem for laparoscopic removal, if ingrowth in the blood vessels is suspected, the open technique is preferred.
The median survival time after adrenalectomy is about 2 years, although some dogs survive more than 4 years [13].

**Medical treatment**

The adrenocorticolytic drug **mitotane** (o,p'-DDD) has been the mainstay of medical treatment for inoperable ACTs and/or metastases. While cortisol excess can be treated successfully by selective destruction of the adrenal cortex, the aim of mitotane therapy in cortisol-secreting ATs is complete destruction of the adrenocortical tumor tissue [1].

If there is metastasis of a functional AT or if neither adrenalectomy nor adrenocortical destruction with mitotane is an option, **trilostane** therapy can be used as a palliative treatment [6]. Although the manufacturer's recommended dose of trilostane does not

differentiate between treatment of pituitary and adrenal hypercortisolism, experience has shown that ATs are more sensitive to trilostane than are hyperplastic adrenal glands. At the author`s institution, the starting dose of trilostane used in dogs with AT is 0.5 mg/kg body weight twice daily. Monitoring of trilostane therapy consist of evaluation of clinical signs and the ACTH stimulation test, as in trilostane therapy for PHD.
The median survival time in dogs with ATs treated with mitotane were 10 and 15.6 months and in those treated with trilostane it was 14 months [14, 15]. In both studies mitotane was used in a protocol for selective destruction to resolve the clinical signs and not for complete destruction of the AT and metastases. It is thus not surprising that the survival times for mitotane and trilostane were similar. However, in both studies survival of animals with metastases was significantly shorter than in those without. This supports the use of the protocol to attempt complete destruction with mitotane and continuing weekly administration.

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