Monitoring Trilostane in Treating Hyperadrenocorticism

Trilostane, a competitive inhibitor of an essential enzyme in the production pathways of cortisol, corticosterone, aldosterone, and androstenedione, has been the approved drug of choice for treating dogs with hyperadrenocorticism in England for the past few years, and it has recently been approved by the FDA for use in the U.S. However, trilostane therapy can be challenging to monitor. Adrenocorticotropic hormone (ACTH) stimulation testing is the gold standard, but exogenous ACTH may override the action of trilostane as a competitive enzyme inhibitor, thereby confounding the results. Identifying a therapeutic serum concentration of trilostane may provide a valuable new metric for monitoring the response to treatment in patients with pituitary-dependent hyperadrenocorticism. An ex vivo study was conducted to determine the 50% effective concentration (EC50) of trilostane and its most active metabolite, ketotrilostane, for inhibiting adrenal gland secretion of cortisol, corticosterone, and aldosterone. Canine adrenal gland tissues were sliced, placed in tissue culture, and stimulated with ACTH alone or with 5 concentrations of trilostane or ketotrilostane. At 0, 1, 2, 3, 5, and 7 hours, media and tissue slices were assayed for cortisol, corticosterone, aldosterone, and potassium concentrations. The EC50 of trilostane for cortisol and corticosterone secretion was 480 and 95.0 ng/mL, respectively. The EC50 of ketotrilostane for cortisol and corticosterone secretion was 98.4 and 39.6 ng/mL, respectively. Ketotrilostane was more potent than trilostane with respect to inhibition of cortisol and corticosterone secretion. This model provided useful ex vivo pharmacodynamic data for trilostane and ketotrilostane in the dog. Future in vivo studies are needed to validate the use of these assays in dogs with hyperadrenocorticism.

Commentary: At present, there is no consensus regarding the ideal method to monitor adrenal function of dogs receiving trilostane. The ACTH stimulation test, the standard for adrenal function assessment during mitotane therapy, is not as helpful for monitoring trilostane therapy. Although trilostane effectively inhibits cortisol secretion in dogs, supraphysiologic ACTH doses may overcome the inhibitory effect, producing inaccurate results that do not reflect actual adrenal function in trilostane-treated dogs. Thus, a new test to monitor adrenal function during trilostane treatment is needed. The results from this ex vivo study do not translate directly to clinical use, but they may facilitate future development of clinical drug monitoring tools for accurate assessment of adrenal function in dogs undergoing trilostane treatment.—*Thomas Schermerhorn, VMD, Diplomate ACVIM*

Determination of the concentrations of trilostane and ketotrilostane that inhibit ex vivo canine adrenal gland synthesis of cortisol, corticosterone, and aldosterone. McGraw AL, Whitley EM, Lee HP, et al. ***AM J VET RES*** 72:661-665, 2011.

Avoiding Thermal Injury with Electrocautery

A 2-year-old Labrador retriever underwent surgery to correct a ruptured cranial cruciate injury and died because of complications involving the electrocautery unit. Anesthetic monitoring included an esophageal ECG probe placed above the base of the heart. A monopolar electrosurgery unit (ESU) was used during surgery to control bleeding. Surgery was uneventful and the dog received routine postoperative care. The day after surgery, the dog was dehydrated and had an elevated heart rate (150 beats/min). The dog initially responded to fluid administration, but respiratory distress later developed and the dog continued to deteriorate. Imaging revealed bilateral pleural effusion; thoracentesis revealed a septic exudate. A contrast esophagram revealed an esophageal perforation, but the dog died before surgery could correct the defect. Among the necropsy findings were two linear transmural perforations of the esophagus just dorsal to the heart. Histologic examination of tissue from this area was consistent with a full-thickness thermal injury. An alternative current pathway injury from the ESU to the esophageal ECG monitor probe was suspected as the cause of the esophageal necrosis and perforation and subsequent death. An investigation of the ESU, ECG monitoring device, surgical procedures, grounding pads, coupling gels, and ground plates for the ESU and ECG monitoring devices revealed several possible contributing factors to the incident. Corrective measures included avoiding the use of rectal or esophageal probes when using electrosurgery, moving the ESU from beneath the surgical table to eliminate fluid contact with the unit and prevent further corrosion, and replacing the ESU handpieces with ones that could detect alternative pathway currents.

Commentary: The authors describe an unusual case of esophageal burns in a Labrador retriever secondary to use of an esophageal ECG probe and monopolar ESU. An alternative current pathway between the esophageal ECG probe and the monopolar ESU caused full-thickness burns to the esophagus and resulted in the dog's death. The authors describe a method for handling such incidents and detail how to avoid such a situation.—*Lindsey Snyder, DVM, MS, Diplomate ACVA*

An alternative pathway electrosurgical unit injury in a dog. Burgess RCF, Freeman LJ, Jennings RN, Lenz SD. ***VET SURG*** 40:509-514, 2011.