



CYP17 INHIBITOR ABIRATERONE ACETATE AS A PROMISING FUTURE TREATMENT FOR CANINE CUSHING'S SYNDROME: IN VITRO INVESTIGATIONS

Introduction: Cushing's syndrome or hypercortisolism is one of the most frequently diagnosed endocrine disorders in dogs. At present, medical management of canine hypercortisolism consists of treatment with trilostane or mitotane. Both treatments have disadvantages associated with the induction of undesired hypoadrenocorticism. Therefore, a more specific inhibition of glucocorticoids is desirable. Our recent studies indicate that the steroidogenic enzyme cytochrome P-450c17 (CYP17) could be an interesting target for selective inhibition of cortisol production without impeding

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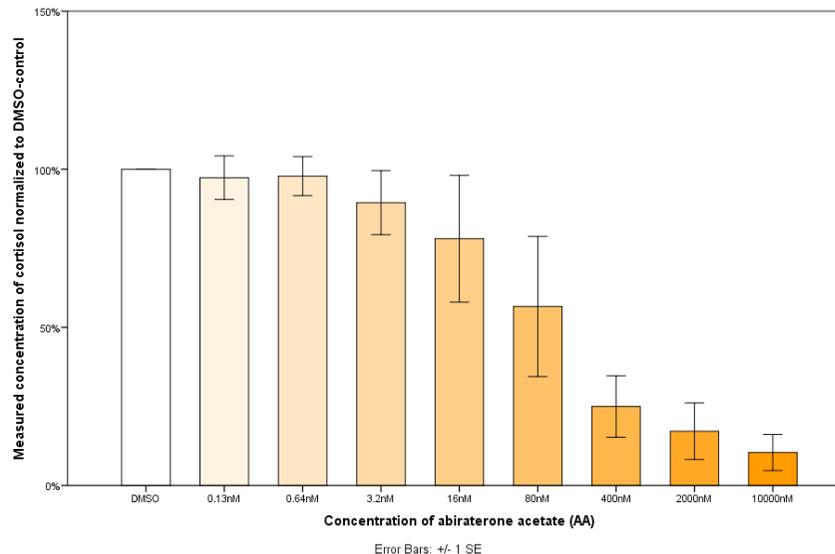


Figure 1: Effect of abiraterone acetate (AA) on cortisol synthesis in normal adrenocortical cells

the synthesis of aldosterone. Abiraterone acetate (AA), a highly selective irreversible CYP17-inhibitor, is already successfully used in the treatment of castration-resistant prostate cancer in humans. As side effects of AA are mostly related to hypocortisolism, this approach seems interesting as a novel medical treatment option for canine hypercortisolism.

Aim of the study: To determine the effects of AA on cortisol and aldosterone synthesis in canine primary adrenocortical cell culture.

Material and methods: Canine primary adrenocortical cell cultures from six normal adrenal glands were incubated with various concentrations of AA. ACTH-dependent hypercortisolism was mimicked by co-incubation with synthetic ACTH (Synacthen®). After 72 hours, culture medium was removed for hormone measurements.

Results: The CYP17-inhibitor AA dose-dependently decreased cortisol concentration in ACTH-stimulated adrenocortical cells with an IC50 value of 356 nM ($P < 0,0001$) (Figure 1). At the highest AA concentration of 2µM, cortisol concentration was suppressed to 90%, while aldosterone concentration did not decrease.

Conclusions: We conclude that AA is effective in reducing cortisol synthesis without impeding aldosterone production in vitro. AA is therefore a promising future treatment option in the medical management of canine hypercortisolism.