ASSESSMENT OF THE TOLERANCE OF A HYDROCORTISONE ACEPONATE CONTAINING EAR SPRAY SOLUTION ON HEALTHY ADULT DOG'S AUDITION & HYPOTHALAMO-PITUITARY-ADRENAL AXIS FUNCTION

Paul Schreiber[1], Magali Dolon[1], Peter Pan[2], Alice Bidaud[1], Philippe Briantais[1], Pierre Jasmin[1], Jean-Baptiste Rascle[1]
[1]Virbac SA, Carros, France; [2]Virbac Taïwan, Tapei, Taïwan; *pierre.jasmin@virbac.com

Introduction

A hydrocortisone aceponate glucocorticoid diester (HCA)-containing ear spray solution demonstrated similar efficacy compared to an approved otic formulation containing a prednisolone-miconazole-polymyxin combination in the treatment of erythemato-ceruminous otitis externa (ECOE) in dogs, in which bacteria and yeast overgrowths were detected on cytology[1].
Objective was to assess the tolerance of the ear spray containing only hydrocortisone aceponate glucocorticoid diester (HCA group) compared to a placebo of NaCl solution (CTRL group), in healthy adult dogs.

Methods

On sixteen healthy adult dogs included, 8 received 0.44ml/ear once a day the HCA ear spray solution (HCA group) and 8 an NaCl control solution (CTRL group), for 14 consecutive days. Dogs were followed at D-7, D0, D14, and D35 for clinical examinations, video-endoscopic ear observations (*Figure 1*), body weight, food consumption, hypothalamo-pituitary-adrenal (HPA) axis function via ACTH stimulation test, and audition *via* the Auditory Brain Response (ABR) test, previously validated in dogs[2,3] (*Figure 2*). ABR test results, food consumption, body weight and ACTH test results underwent a statistical analysis.

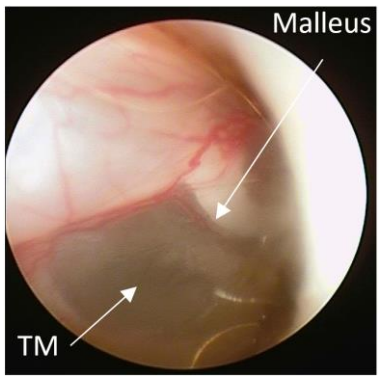

Figure 1: Video-endo-otoscopic ear observation of the tympanic membrane.

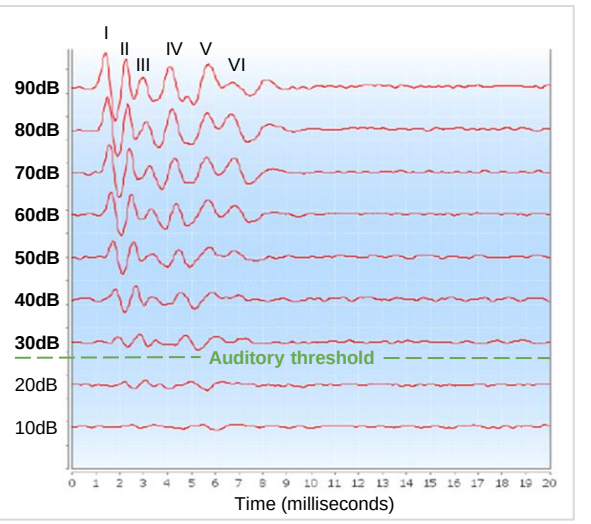

Figure 2: Representative ABR measures and waveforms (I to VI).

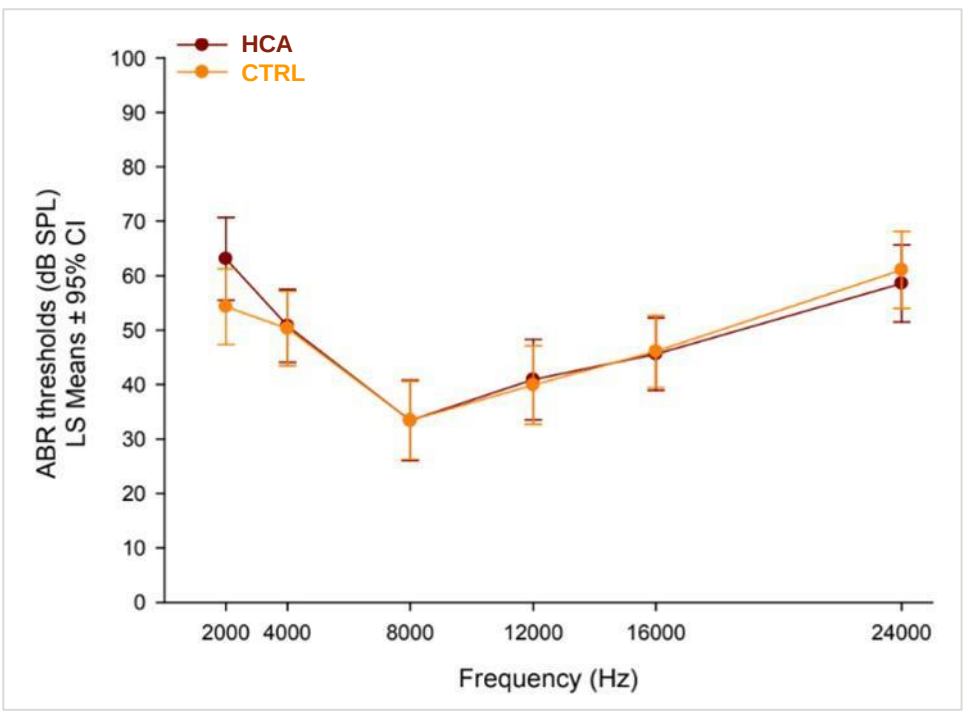

Figure 3: Mean LS Mean ABR thresholds at various frequencies from both ears in Control and HCA-treated groups, 14-days post-treatment.

Results

Clinical observations

No relevant clinical observations or treatment-related effects were reported during the whole in-life phase. And there were no statistical differences on body weight or food consumption between groups (HCA or CTRL).

Video-endo-otoscopic ear observations

At any time point, all animals exhibited healthy and non-perforated tympanic membranes, except for the observation of some white opaque areas on D14 on the tympanic membrane of two animals of the HCA group. Since the tympanic membrane of one animal was not visible before treatment, a link to the treatment cannot be confirmed or excluded regarding this finding. In the second dog this observation was only seen unilaterally, and can be considered as a rare finding. In both dogs, the observations were spontaneously fully reversible on D35. To conclude, with the exception of one unilateral and transient white opaque area in one treated dog, the otoscopic observations did not reveal specific observation after HCA treatment (*Figure 1*).

ABR auditory tests

The ABR thresholds were similar before (D-7) and after dosing (D14 and D35) in the CTRL and HCA groups. No statistically significant differences were observed at any frequency, and for each time point. In conclusion, there was no effect of the HCA ear spray solution on the dog's audition (*Figures 2 and 3*).

ACTH stimulation tests

At each timepoint (Baseline i.e. D-7, D15 and D36) there were no statistically and biologically significant differences on plasmatic cortisol levels before the ACTH Test between the two treatment groups, cortisol levels were within biological ranges excluding an hypoadrenocorticism syndrome in the 8 dogs treated with HCA ear solution. All post-ACTH stimulation cortisol levels were within biological ranges in the treatment (HCA) group and the NaCl control (CTRL) group, with no biological significant variation over-time or differences between groups. In conclusion, two consecutive weeks of the HCA ear spray solution treatment, with 0.44ml per ear, two ears treated per animal, had no effect on the adrenal function and the HPA axis.

Conclusion

After 14 consecutive days of treatment at the maximal recommended therapeutic dose, the HCA ear spray solution did not induce any adverse effects. There was no effect on body weight or food consumption parameters and no ototoxic effects nor hearing impairment were observed. There was no effect on the HPA axis evaluations, with the observation of a normal and active adrenergic function, and no induction of iatrogenic hypoadrenocorticism.
The daily topical application of the HCA diester glucocorticoid-containing ear spray solution for up to 14 days in adult dog ears was very well tolerated.

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