Re: Inclusion of Cyclosporine A in the FEI Equine Prohibited Substance List 2013.

On behalf of the International Equine Ophthalmology Consortium (IEOC) (http://www.equineophtho.org), we are writing to you in your role as Veterinary Director of FEI to express our concerns over the inclusion of Cyclosporine A (CsA) in the FEI Equine Prohibited Substance List (EPSL) 2013, which will remain extant during 2014. The FEI List Group of advisors on drug misuse has designated CsA a ‘Controlled Substance’, classifying CsA as a therapeutic agent which ‘has the potential to enhance performance at certain levels’ and which ‘might be used routinely to treat a specific clinical problem out of competition but which is not allowed during competition’ (http://www.fei.org/content/anti-doping-rules).

Our concerns relate specifically to the ophthalmic use of the drug. CsA is a potent immunosuppressing agent, acting via inhibition of calcineurin within effector T-cells to block transcription of IL-2, and at present the therapeutic use of CsA to manage potentially blinding eye disease represents the only routine use of this drug in equine clinical medicine. The drug is delivered exclusively by local administration, either applied topically in ointment or suspension form or surgically implanted suprachoroidally or episclerally in the form of a sustained release device. CsA is an important primary therapy in both immune mediated corneal disease and autoimmune uveitis, in particular Equine Recurrent Uveitis (ERU). In both instances long term and continuous medication is required to control the immunoinflammatory pathology (Gilger et al, 2005; Matthews and Gilger, 2010, Gilger et al, 2010). CsA is very poorly absorbed following topical ocular administration, and although the drug is reservoired in corneal stroma it does not reach therapeutic levels within the intraocular compartments, and this route is ineffective in the management of uveitis. It is for this reason that ocular implantation techniques were developed, and ocular implantation of CsA is now the therapy of choice for the management of ERU throughout the world (Lowe 2010, Spiess 2010). Importantly, it should be noted that bioavailability studies of suprachoroidally placed CsA sustained release devices, using currently applicable clinical protocols, have shown no systemically detectable levels of the drug for up to 9 weeks after implantation (Gilger et al, 2006). This strongly indicates very poor, if any, systemic absorption of the implanted drug.

ERU is an acutely painful, episodic ocular disease of equidae, and is the most common cause of blindness in horses throughout the world, reaching morbidity levels of up to 10% in some geographic areas (Dwyer,
1998). This represents a major welfare issue. In instances where CsA implants are used to control and treat the disease, affected horses are expected to return to normal athletic function and have a significantly reduced likelihood of suffering further episodes of the disease and of consequent blindness.

We are aware that, via its calcineurin binding action, CsA has been shown in laboratory animals to have an inhibitory effect at a molecular level on the hypertrophic responses of cardiac myocytes to stress, and may have some cardioprotective effects in human patients with ischaemic heart disease (Hausenloy et al, 2012). The therapeutic levels of systemically administered CsA currently being used in clinical trials on cardiac patients is 2.5-5 mg/kg. Extrapolated to a 500kg horse, this is some 2x10^5 times greater than the total ocular dose of CsA given to horses when the drug is administered topically or by ocular implants. We are firmly of the opinion that, even in the event of systemic absorption of ocularly administered CsA, the level of systemic exposure would be so low as to make any inotropic effect on cardiac function highly unlikely. Further, there being no evidence of neuroexcitatory or musculoskeletal effects of CsA in any species, the only reasonable conclusion is that ocular CsA is not, in any way or at any level, performance enhancing in the equine athlete.

It is the consensus opinion among IEOC members that this decision of the FEI List Group to designate CsA a ‘Controlled Substance’ has no basis in veterinary science or in clinical practice, and that the ruling prohibiting horses treated with this drug, specifically for immune mediated ocular disease, is retrogressive and unnecessary. Further, the ruling may have the unintended consequence of precipitating a significant welfare problem, in that since implanted drug cannot be withdrawn prior to competition, owners may elect to forego CsA treatment, opting for alternative and less effective therapies and placing some horses at much greater risk of long term painful ocular disease and blindness.

On behalf of the IEOC, we respectfully invite the members of the FEI List Group to review their current ruling on CsA, specifically where the drug is used locally in the treatment of immune mediated ocular disease.

Yours sincerely,

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References:


