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Ciclosporin A therapy is associated with disturbances in glucose metabolism in dogs with atopic dermatitis

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Abstract

The effect of ciclosporin A (CsA) on glucose homeostasis was investigated in 16 dogs with atopic dermatitis by determining plasma glucose, serum fructosamine and insulin concentrations, and serial insulin and glucose concentrations following a glucagon stimulation test, before and 6 weeks after CsA therapy at 5 mg/kg once daily. All dogs completed the study. Following CsA treatment, the median serum fructosamine concentrations were significantly higher (pretreatment 227.5 μmol/L; post-treatment 246.5 μmol/L; *P* = 0.001; reference range 162–310 μmol/L). Based on analyses of the areas under concentration-time curves (AUC) pre- and post-CsA treatment, plasma glucose concentrations were significantly higher (AUC without baseline correction 31.0 mmol/L/min greater; *P* = 0.021) and serum insulin concentrations were significantly lower (AUC without baseline correction 217.1 μIU/mL/min lower; *P* = 0.044) following CsA treatment. Peak glucose concentrations after glucagon stimulation test were significantly higher following CsA treatment (10.75 versus 12.05 mmol/L; *P* = 0.021), but there was no significant difference in peak serum insulin (52.0 versus 35.0 μIU/mL; *P* = 0.052). There was a negative correlation between baseline uncorrected insulin AUC and trough serum log CsA concentrations (*r* = −0.70, *P* = 0.005). The administration of CsA to dogs with atopic dermatitis leads to disturbances in glucose homeostasis. The clinical significance of this is unclear, but it should be taken into account when considering CsA treatment in dogs that already have such impairments.

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Introduction

Ciclosporin A (CsA) is a calcineurin inhibitor that inhibits T-cell activation and prevents synthesis of several cytokines, notably interleukin-2 (IL-2).[1,2] Without IL-2 stimulation, further T-cell proliferation is inhibited and T-cell cytotoxic activity is reduced. The marked ability to impair T-cell activation and proliferation has led to the use of CsA in a wide range of clinical scenarios in human and veterinary medicine.[2] Ciclosporin A shows variable efficacy in the treatment of many canine dermatoses, including atopic dermatitis (cAD),[3,4] anal furunculosis,[5,6] sebaceous adenitis,[7] pemphigus foliaceus[8] and sterile nodular panniculitis.[9] A recent meta-analysis of 10 studies containing 799 dogs found that CsA was highly effective for the treatment of cAD and adverse effects were minimal.[10] Ciclosporin A has also been used to treat a number of other canine conditions, including granulomatous meningioencephalitis[11] and myasthenia gravis.[12]

Early work indicated that CsA had a positive, protective effect on pancreatic β-cell function in experimental models of type 1, insulin-dependent diabetes mellitus.[13] Ciclosporin A treatment was found to prevent the development of diabetes mellitus in nonobese diabetic mice, presumably by inhibiting T-cell activation, which prevented the T-cell-mediated destruction of insulin-producing pancreatic β-cells.[13] Ciclosporin A has also been used in attempts to halt the progression of immune-mediated pancreatic islet cell destruction in people with recent-onset type 1 diabetes mellitus.[14] Subsequent studies evaluating the effects of CsA administration in humans with or at risk of developing type 1 diabetes showed that CsA administration caused modest improvements in glycaemic control, albeit not as dramatically as in the nonobese diabetic mouse.[15,16]

In contrast to the improvement in glycaemic control observed in experimental models of type 1 diabetes through modulation of autopathogenic, islet-reactive T cells, studies in transplantation medicine revealed that CsA can negatively disturb glycaemic control. For example, β-cell function was reported to be diminished in CsA-treated human recipients of pancreas and kidney allografts, and in dogs with autotransplants of segmental pancreatic tissue.[17–19] A deterioration in glucose homeostasis has frequently been observed in human transplant recipients treated with CsA.[17] The disturbance in glucose

