**Introduction**

Cyclosporin (CsA) is a parenteral (oral or intravenous) or topical active antiinflammatory/immunosuppressing agent. It is a polypeptid, cyclic, lipophilic metabolite of the fungus Tolypocladium inflatum.

It has been used for the treatment of various inflammatory cutaneous diseases such as atopic dermatitis and psoriasis in human patients for many years. But its main use has been as immunosuppressant in patients with organ transplants. It has been used in canine patients systemically since 2002, mainly for the control of canine atopic dermatitis but also in other inflammatory and immune-mediated skin disorders.

**Mechanism of action**

CsA acts binding to cytosolic proteins of the family of cyclophilin. The CsA-cyclophilin complex has a high affinity to calcineurin, a fundamental enzyme in the activation of T-lymphocytes. When this CsA complex blocks the capacity of action of calcineurin, the CsA is actually impeding the coding of the genes responsible for the synthesis of cytokines such as IL-2 or IL-4 and its receptors. As a consequence, both the cellular and the humoral response are affected.

CsA inhibits selectively the activation of cells involved in the inflammatory process (mast cells, eosinophils, lymphocytes, Langerhans cells, keratinocytes) 4. CsA induces inhibition of degranulation of mast cells and the production of several cytokynes. A large part of the functions of the eosinophils and lymphocytes will be inhibited and the number of Langerhans cells in the epidermis will be reduced. As a consequence of the latter, there will be a higher risk of infections and developement of neoplasia in individuals treated with CsA (observed in human patients) 5.

**Pharmacokynetics, dose and bioavailability.**

There is a wide variation in the capacity of absorption of CsA between different patients, and even within one individual depending on several metabolic factors. The levels in blood usually peak at 1.5-4 hours post oral administration. CsA is metabolised into more than 30 different metabolites through the hepatic cytochromic enzyme P4503A4. The subunits of ciclosporin are fairly resistant to degradation and it is believed that many of them will retain biological activity and could contribute to effects of immune-suppression and toxicity.

The bioavailability of the ingested drug is usually around 25-35% in humans and 23-45% in dogs. The presence of food in the gastrointestinal tract can reduce the bioavailability in 20%.

This drug is available commercially in various formats, including oral solution, capsules and injectable.
form. Of all of them, the microemulsion is the one with best absorption. The veterinary product (Atopica™) is a microemulsion similar to Neoral™.

CsA, once absorbed, is accumulated in the body fatty tissues and in the blood cells (in humans, in 50-60% of erythrocytes and 10-20% in leukocytes), probably due to their high content of cyclophilin. Therefore, the measurement of levels of CsA in blood will be much more precise than in plasma. CsA does not reach the CNS in significant quantities.

The recommended dose in veterinary medicine is of not more than 5mg/kg/day in dogs and 5-8 mg/kg/day in cats. The therapeutic dose has to be maintained for 2-3 weeks, until the clinical signs are under control, then the dose is gradually reduced in frequency of administration (every 48 hours, every 72 hours and so on).

**Interactions, drugs affecting the metabolism of CsA.**

The main metabolic mechanism of CsA takes place in the liver through the enzyme complex P4503A4. Therefore all the substances competing for the same enzyme will cause an increase of the levels of CsA. The drugs with inducing P4503A4 will accelerate the metabolism of CsA and the reduction of the levels in blood. Subsequently, the activity of CsA can be increased or decreased by administering concomitantly substances affecting the activity of the enzyme responsible for the metabolism of CsA (table 1). An example would be the use of grapefruit juice containing bioflavonoids which can inhibit the metabolism of CsA affecting the cytochrome P4503A, increasing the bioavailability of CsA. The same happens with ketoconazole, as it reduces the amount required of CsA to maintain therapeutic levels in blood.

**Adverse side effects**

In human patients there is an accumulation of experience and information for over twenty years of use of CsA which is summarised below. For this reason, even if it does not fully fulfill the aim of this talk, it can be of use for the clinician to have a summary of the information known regarding unwanted side effects in human and canine patients.

**In human patients**

**Renal toxicity**

SUCH EFFECTS HAVE NOT BEEN REPORTED IN DOGS. In humans, three levels of nephrotoxic side effects have been described:

- **With immediate effect**, on transplanted kidneys, already affected by ischaemia.
  - **Effects after 3-6 weeks** of the start of dermatological treatment with CsA: hypertension, reduce glomerular filtration rate and tubular dysfunction (tubular acidosis, hyperkalaemia, hyperuricaemia, decreased fractional excretion of sodium). All these effects are reversible once the dose and frequency of treatment are reduced or discontinued.

- **Chronic renal toxicity**, as a consequence of accumulative subclinical toxicity. This situation will arise without previous evidence of abnormal blood levels of urea or creatinine or abnormal blood pressure values. This is the most frequent form of nephrotoxicity seen in long term dermatological therapy in humans. In these cases, the values of creatinine are usually elevated and should be monitored to identify nephrotoxicity as soon as possible. It is believed that this phenomenon is a consequence of the failure in regulation of intrarenal vasoconstriction and
reduction on the levels of prostaglandins regulating vasodilation8,10.

**Gastrointestinal side effects.**

The most frequent side effects observed in humans are nausea, vomition, anorexia and diarrhoea. Also described are hyperbilirubinaemia and transitory elevation of liver enzymes. These signs will abate or disappear once the treatment is stopped or the dose reduced 25%. For this reason, the use of other concomitant hepatotoxic drugs has to be assessed with caution and be avoided in patients with liver disease.

**Neurological side effects.**

During the first week of treatment, the patient may develop tremors in the hands, hyperaesthesia and paraesthesia in the extremities. Also described are epileptic-type convulsions secondary to the administration of CsA. But in some of these cases, low levels of magnesium were also identified11, and in other cases the patient had received high doses of intravenous methylprednisolone12. Another type of neurological toxicity has been reported in humans receiving intravenous ciclosporin, characterised by lethargy, confusion, fits, cortical blindness and hemiplegia4.

**Haematological side effects.**

Coagulation dysfunction (hypercoagulability) has been described in patients with organ transplant receiving CsA. The cause can be attributed to altered platelet function and haemostasis. Fibrinolysis and endothelial damage have also been reported in patients treated with CsA.

**Mucocutaneous side effects.**

The most common complication is hypertrichosis, which seems to develop in almost all the patients treated. Gingival hypertrophy has been observed in 8-70% of the cases and tends to peak 6 months into the treatment.

Pileous keratosis has been observed in 21% of the cases, sebaceous hyperplasia in 15% of the cases and epidermal cysts in 28% of the patients (predominantly in the face and reducing in size and number as the treatment progresses). Other adverse side effects in the skin are acute pruritic very erythematous eczema, angioedema and urticaria. Also noted has been a high incidence of keratoacanthoma, sebaceous hyperplasia and viral verrucas.

**Skeletal side effects.**

Osteoporosis and myopathies have been observed with high doses of CsA.

**Side effects on the immune system.**

There is controversy regarding the cause of increased number of bacterial infections, whether they are consequence of the immunesuppression caused by CsA. But it has also been observed that the incidence of infections with CsA is lower than in treatments of azathioprine and prednisolone. It should be however closely monitored.

**Neoplastic side effects.**

Development of tumours has been observed in animals treated with CsA, but the incidence is not higher than with other immunesuppressant drugs. The relative risk of suffering lymphoma in human patients treated with CsA is 27.5%. The risk with other immunosuppressants increases to 33.8% and 58.6%. The majority involve B-cells, non-Hodgkin type.
An increase in carcinomata in penis, vulva and anus have been described, some of them evolving from preexisting verrucae.

Both in human and canine species, its use is not recommended in patients with hypersensitivity to any of the components or adjuvants, or in patients with previous history of malignant neoplasia. It should be used with caution in patients with renal or liver disease. It has been proved foetotoxic and embriototoxic in rats and rabbits at doses 2-5 times above the recommended dose, therefore the use during pregnancy should be carefully monitored or avoided altogether.

**In canine patients**

This drug has been used in dogs only since 2002. Therefore, with less than 10 years experience, the information regarding adverse side effects published in articles and personal communications is more limited and summarised below: 9,13,14 y15

- Digestive: vomition, anorexia, soft faeces, diarrhoea. These are the most frequent signs.
- Proliferative: Viral papillomatosis (particularly if used in higher doses), generalised lymphadenopathy.
- Muco-cutaneous: Gingival hyperplasia, hirsutism (thick hair and dense coat), cutaneous nodules and cysts.
- Development of infectious diseases: toxoplasma and leishmania.
- Metabolic: hypoalbunaemia/hyperproteinaemia.
- Neurological: convulsions, facial and neck tremors, peripheric neuropathy, lethargy, drowsiness.
- Behavioural: aggression, irritability, depression.
- Metabolic: Diabetes mellitus
- Musculo-skeletal: joint pathologies

**Applications in Canine Dermatology**

It has been used to treat a wide number of inflammatory and immune-mediated conditions of the skin:

- Granulomatous sebaceous adenitis.
- Atopic dermatitis
- Sterile pyogranulomatous dermatitis in the Pitt-Bull Terrier.
- Neutrophilic dermatosis
- Perianal fistulae
- Bacterial hypersensitivity
- Reactive histiocytosis
- Epitheliotrope lymphoma
- Discoid lupus erythematosus
- Vesicular cutaneous lupus erythematosus
- Terminal otitis
- Sterile nodular panniculitis
- Pemphigus foliaceus
- Interdigital pododermatitis
- Hypersensitivity reactions
- Implant rejection

In some cases we have enough clinical evidence to prove that the administration of CsA is efficacious for the treatment and control of some of these diseases. However, in the majority of these conditions, the published evidence available is insufficient to demonstrate its efficacy (it is mainly based on isolated or anecdotal cases).
References


