

# Diabetogenic effect of cyclosporin

J J BENDING, C S OGG, G C VIBERTI

## Abstract

A young woman given a renal allograft for polycystic kidney disease developed insulin dependent diabetes mellitus 25 days after transplantation. There was no family history of diabetes, plasma glucose concentrations had been normal at presentation and on five subsequent occasions, and at no time were islet cell antibodies detectable. Plasma C peptide concentrations, however, were greatly suppressed after transplantation and remained so for up to six months.

The immunosuppressive regimen had included cyclosporin A, which had been difficult to regulate and caused definite signs of toxicity in the patient. By virtue of its reported toxicity for  $\beta$  cells and the reversal of the diabetes several months after the dose was reduced cyclosporin was incriminated as the probable causative agent.

Dose related  $\beta$  cell toxicity of cyclosporin A may be a risk in recipients of this drug and warrants careful monitoring of drug and glucose concentrations.

## Introduction

Cyclosporin A is a fungal metabolite with unique T lymphocyte suppressive effects which can prevent transplant rejection. It has recently been used to treat newly diagnosed insulin dependent diabetes mellitus—a disease known to be associated with an autoimmune process—in an attempt to improve the rate and duration of remission.<sup>1</sup> Recent work suggests, however, that cyclosporin may be toxic to  $\beta$  cells,<sup>2</sup> though this remains controversial.<sup>3</sup>

We report the case of a young woman who developed insulin dependent diabetes after renal transplantation for non-diabetic renal disease. Cyclosporin toxicity may have been implicated.

## Case report

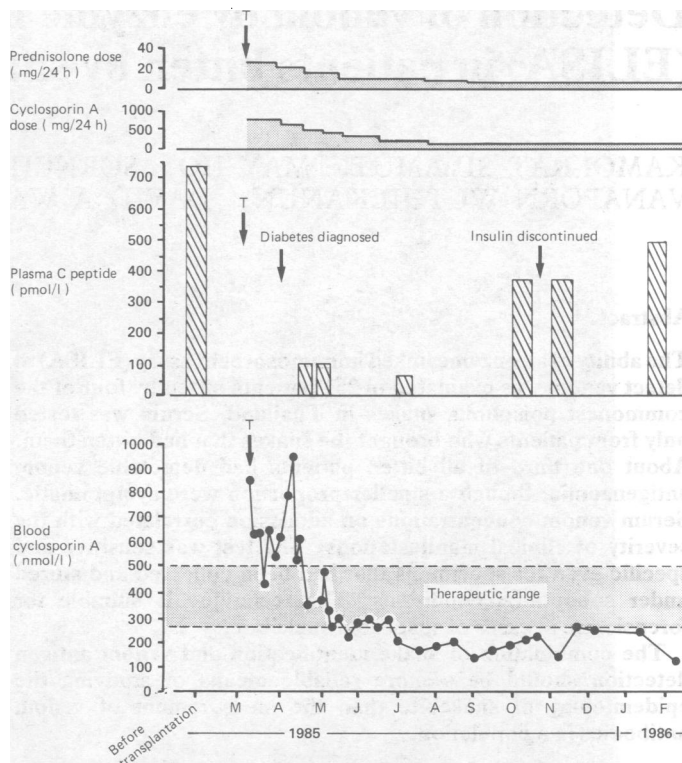
An 18 year old woman presented in 1984 with a history of renal failure due to polycystic kidney disease but no past or family history of diabetes mellitus. Plasma glucose concentration (YS1, Yellow Springs, United States) at presentation was 5.5 mmol/l, and five subsequent estimations ranged from 4.6 to 6.3 mmol/l.

Cadaveric renal allograft transplantation was performed in March 1985. Cyclosporin A (initially 670 mg daily, equivalent to 11.7 mg/kg body weight) and prednisolone (initially 25 mg daily) were given as immunosuppressive treatment. Whole blood cyclosporin concentrations (18 hours after dosing) were initially considerably higher than the required therapeutic range and the dose was therefore reduced (figure). Despite sequential adjustments of the dose the patient developed signs of cyclosporin toxicity with hirsutism,

tremor, and non-specific interstitial changes in the graft biopsy specimen at five weeks. Prednisolone was reduced to 22.5 mg daily three weeks after transplantation with stepwise reductions to a maintenance dose of 10 mg daily by six months (figure).

Twenty five days after transplantation the patient was unwell and dehydrated and gave a five day history of polyuria and polydipsia. A plasma glucose concentration of 44 mmol/l confirmed a diagnosis of diabetes, and insulin (50 U daily) was started. Three months later improved diabetic control allowed gradual reduction of insulin, and six months after onset of the diabetes insulin was withdrawn. Twelve months later glucose tolerance remained normal with a plasma glucose concentration of 6.7 mmol/l two hours after a 75 g load.

Random C peptide concentrations (measured by radioimmunoassay<sup>4</sup>), which had been normal immediately before transplantation, became greatly suppressed for up to six months after transplantation but had returned towards normal a year after transplantation. Results of immunofluorescence tests for serum islet cell antibodies were negative at diagnosis of diabetes and remained so throughout.



Plasma C peptide concentrations before and after renal transplantation (T) (normal value >500 pmol/l) and serial whole blood cyclosporin A concentrations.

## Discussion

There are several possible explanations for the diabetes in this patient. Diabetes may have occurred as a secondary effect of treatment with corticosteroids. Corticosteroids, however, induce a rise in circulating insulin and plasma C peptide concentrations in non-diabetics<sup>5</sup> and patients with Cushing's syndrome,<sup>6</sup> and it is difficult to accept the occurrence of "steroid induced" diabetes in the face of substantial suppression of circulating C peptide values.

Alternatively, diabetes may have occurred spontaneously, withdrawal of insulin coinciding with the remission ("honeymoon") period that occurs after treatment in some patients. It is uncommon, however, for young patients to become insulin independent with

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normal glucose tolerance for more than 18 months after the initial diagnosis and in the presence of continued prednisolone treatment. Moreover, the patient had no family history of diabetes and no detectable islet cell antibodies at the time of diagnosis.

We are left with the possibility that diabetes was induced by cyclosporin. Though cyclosporin has prevented the development of insulin dependent diabetes in spontaneously diabetic animal models, it inhibited  $\beta$  cell proinsulin biosynthesis and insulin release in cultured mouse and human pancreatic islets.<sup>7</sup> The association of C peptide depression with high blood cyclosporin concentrations in our patient may be relevant.

The suggestion that cyclosporin may be associated with the appearance of post-transplantation diabetes in renal allograft recipients<sup>2</sup> has not been confirmed by other workers, who found that this occurs regardless of the immunosuppressive regimen and whether or not cyclosporin is included.<sup>3</sup>

We suggest that dose related  $\beta$  cell toxicity of cyclosporin A may be a risk in recipients of the drug. This phenomenon appears to be reversible by reducing the dose and underlines the need for careful monitoring of drug and glucose concentrations.

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# Detection of venom by enzyme linked immunosorbent assay (ELISA) in patients bitten by snakes in Thailand

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## Abstract

The ability of an enzyme linked immunosorbent assay (ELISA) to detect venom was evaluated in 251 patients bitten by four of the commonest poisonous snakes in Thailand. Serum was tested only from patients who brought the snakes that had bitten them. About one third of all bitten patients had detectable venom antigenaemia, though a smaller proportion were symptomatic. Serum venom concentrations on admission correlated with the severity of clinical manifestations. The test was sensitive and specific even for specimens that had been collected and stored under suboptimal conditions. The technique is suitable for forensic use in cases of suspected snakebite.

The combination of snake identification and venom antigen detection should be a more reliable means of studying the epidemiology of snakebite than the measurement of venom antibodies in a population.

## Introduction

Snakebite is a common medical emergency in many tropical countries. Most patients do not provide conclusive evidence of the

species that bit them by bringing the dead snake with them to the hospital. In some instances, even when the snakes are brought, the medical staff are unable to identify them. Clinical diagnosis based on signs and symptoms may be very misleading. For example, in Thailand the Malayan pit viper (*Calloselasma rhodostoma*), green pit viper (*Trimeresurus albolabris*), and Russell's viper (*Vipera russelli*), all produce a similar syndrome of local swelling, spontaneous bleeding, and no blood clotting. In the absence of a dead snake or in a case of mistaken identification the wrong monospecific antivenom may be given to the patient. Identification of the snake that bit them is therefore of the utmost importance for the proper management of patients with snakebite.

The application of the enzyme linked immunosorbent assay (ELISA) to identifying the biting species in cases of snakebite was first described by Theakston *et al.*<sup>1</sup> Since then diagnostic kits based on the assay and prepared by the Commonwealth Serum Laboratory in Australia have been used with some success.<sup>2,3</sup> ELISA has also been used in snakebite studies in Malaysia, Burma, Thailand, the United States, and Ecuador.<sup>4-9</sup> Modifications of the original test have been found to be necessary to minimise the problems of non-specific reactivity and cross reactivity encountered commonly with serum specimens from rural populations in the tropics.<sup>10</sup>

The present study was undertaken to determine the incidence of systemic envenoming among snakebite victims and to validate the modified ELISA procedure<sup>11</sup> for the large scale testing of serum samples collected by paramedical staff in rural Thailand.

## Patients and methods

As part of a countrywide survey conducted in Thailand to determine the distribution of snake species causing morbidity and mortality the nursing staff in provincial hospitals were requested to record on standard forms the history and clinical signs of every patient who presented with snakebite. The signs sought were local swelling; bleeding from the site of the bite and gums

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