Alternate day corticosteroid causes alternate day hyperglycaemia

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Summary: Patients taking alternate day corticosteroid treatment have greater impairment of glucose tolerance on the corticosteroid day than on the alternate day. Allowance for this must be made in the detection and management of diabetes mellitus in these patients.

Introduction

The efficacy of corticosteroids in the treatment of many immunological and inflammatory diseases is proven but side effects often limit dosage. Synthetic analogues of cortisone such as prednisolone have reduced the unwanted mineralocorticoid effects but still impair the response to infections, suppress the pituitary-adrenal axis, induce Cushing's syndrome and provoke diabetes mellitus. Alternate day steroid treatment was introduced on the hypothesis that the therapeutic effect lasted longer than the metabolic and endocrine disturbances with reduced toxicity and adrenal suppression on the rest day.¹ This has been confirmed² but the diabetogenic potential of this approach has been less well studied.³

A diabetic patient taking alternate day prednisolone noticed that his glycosuria was worse on the treatment day. We confirmed this in him and a further diabetic patient and then examined blood glucose levels in normal subjects and non-diabetic patients taking prednisolone in varying doses.

Case reports

Case 1

A 55 year old Caucasian male with steroid responsive nephrotic syndrome due to proliferative glomerulonephritis was controlled by 20 mg enteric-coated prednisolone on alternate days. Three years after starting treatment he developed symptomatic diabetes which was treated by a 160 g carbohydrate diet and glibenclamide. In 1985 he noted that glycosuria was more marked on the prednisolone day (Figure 1); Blood glucose levels taken at 17.00 hours on treatment

($n = 4$) and rest days ($n = 4$) confirmed hyperglycaemia on the prednisolone day only. The mean blood glucose was 11.2 mmol/l on the prednisolone day and 6.1 mmol/l on the rest day. Mean difference was 5.1 ± 1.6 mmol/l ($P < 0.01$);

Case 2

A 78 year old Caucasian diabetic woman with presumed interstitial nephritis was treated with daily prednisolone then switched to prednisolone 20 mg alternate days. Enteric-coated prednisolone was taken at 08.00 hours and blood glucose estimated at 15.00 hours. Blood glucose levels taken over a 2 week period at 15.00 hours showed that hyperglycaemia was more marked on prednisolone days ($n = 6$) than on rest days ($n = 6$). Mean blood glucose was 21.8 mmol/l on the prednisolone day and 13.0 mmol/l on the rest day. Mean difference was 8.8 ± 4.4 mmol/l ($P < 0.01$).

Patients and methods

Blood glucose concentrations were studied in normals given a single dose of prednisolone and in patients taking alternate day prednisolone for at least one month. All patients had presented with nephrotic syndrome, rapidly progressive idiopathic glomerulonephritis, systemic vasculitis or lupus nephritis but at the time of study all except one in group B and one in group C had a serum creatinine concentration below $200 \mu\text{mol/l}$.

Groups B and D were studied while taking their usual alternate morning dose of prednisolone coated with cellulose acetate phthallate (Deltacortril enteric: Pfizer) but uncoated prednisolone was substituted when the response to glucose loading was studied (groups A and C). Estimations were carried out in the

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Figure 1 Relative frequencies of degrees of glycosuria measured at 18.00 hours on prednisolone ($n = 99$) and no treatment days ($n = 79$) in a subject on longterm alternate day treatment. There is a clear increase in the frequency of significant glycosuria ($\frac{1}{4}$ % or more) on prednisolone days ($\chi^2 = 9.3$, $P < 0.01$). □, Prednisolone; ▤, no treatment day.

afternoon for convenience but inpatients and normals were also studied in the morning. The response to both high dose (groups A and B) and low dose prednisolone (groups C and D) were studied.

Group A (High dose prednisolone with glucose loading)

Five normal subjects of mean age 32 (range 23–47) years took either uncoated prednisolone 0.7 mg/kg or placebo tablets at 08.00 hours on two successive days. Blood glucose was measured at 09.00 hours while fasting, 12.00 hours and 15.30 hours. The subject then took 75 g glucose by mouth and further samples were taken at 16.00 hours, 16.30 hours, 17.00 hours and 17.30 hours. Three subjects took prednisolone on the first day.

Group B (High dose prednisolone without glucose loading)

Six in-patients of mean age 68 (range 48–82) years with active renal disease were studied while taking enteric-coated prednisolone mean dose 1.06 (range 0.58–1.42) mg/kg at 08.00 hours on alternate days. Blood glucose was measured at 09.00 hours and 11.00 hours, 15.00 hours and 18.00 hours on both treatment and rest days.

Group C (Low dose prednisolone with glucose load)

Eight out-patients of mean age 50 (range 33–62) years with stable renal disease normally taking alternate day enteric-coated prednisolone mean dose 0.23 (range 0.16–0.35) mg/kg substituted uncoated prednisolone 20 mg (mean dose 0.27 mg/kg) at 08.00 hours on the treatment day. A 75 g glucose load was taken at 17.00 hours and blood glucose was measured at 18.00 hours on consecutive treatment and rest days.

Group D (Low dose prednisolone without glucose load)

Fifteen patients of mean age 50 ± 12.4 years with stable renal disease taking alternate day enteric-coated prednisolone mean dose 0.21 ± 0.09 mg/kg attending an afternoon clinic returned for a further blood glucose estimation at the same time on the following day. The mean time between taking the prednisolone and blood glucose estimation was 7.0 ± 1.3 hours.

Diet and activity were similar in all groups on the prednisolone day and the rest day. Allocation to prednisolone or rest day was random. Blood glucose was measured in venous whole blood by an enzymatic method. Statistical analysis was by Student's paired t -test unless otherwise stated.

Table I Mean blood glucose in 5 normal subjects given prednisolone or placebo before and after glucose loading

Time of day	Mean blood glucose $\pm$ standard deviation (mmol/l)		Mean difference (mmol/l)
	Prednisolone day	Placebo day	
09.00 hours	4.0 $\pm$ 0.7	3.6 $\pm$ 0.4	0.4 $\pm$ 0.3
12.00 hours	4.9 $\pm$ 0.8	3.4 $\pm$ 0.3	1.5 $\pm$ 0.8**
15.30 hours	5.8 $\pm$ 1.1	3.9 $\pm$ 0.6	1.9 $\pm$ 0.8***
16.00 hours	7.7 $\pm$ 0.6	5.9 $\pm$ 1.2	1.8 $\pm$ 1.3
16.30 hours	8.8 $\pm$ 2.4	5.2 $\pm$ 1.7	3.6 $\pm$ 1.3***
17.30 hours	7.0 $\pm$ 2.2	3.4 $\pm$ 0.7	3.6 $\pm$ 2.5*

Prednisolone or placebo was taken at 08.00 hours and glucose at 15.30 hours; * $P < 0.05$, ** $P < 0.02$, *** $P < 0.01$.

Results

Group A – High dose prednisolone – normal subjects with glucose loading

In all subjects mean blood glucose concentration was higher on the prednisolone day than the rest day at all times before and after glucose loading except for the fasting sample one hour after uncoated prednisolone (Table I).

Group B – High dose prednisolone in in-patients without glucose loading

In six in-patients taking high dose enteric-coated prednisolone blood glucose was significantly higher 7 and 10 hours after prednisolone than on the rest day (Table II).

Group C – Low dose prednisolone in out-patients with glucose loading

One hour after a glucose load mean blood glucose was 9.2 mmol/l on the prednisolone day and 6.4 mmol/l on the rest day. The mean difference was 2.8 ± 1.0 mmol/l ($P < 0.01$). Blood glucose concentration was higher on the prednisolone day in all but one subject.

trations on the prednisolone day ($\chi^2 = 4.8$, $P < 0.05$). Mean blood glucose was 4.9 on the prednisolone day and 4.3 on the rest day, mean difference 0.6 ± 1.0 mmol/l ($P < 0.05$).

Discussion

Glucocorticoids impair glucose tolerance by reducing glucose utilization in peripheral tissues and increasing hepatic glucose output inducing a state of insulin resistance.³ The effect occurs within hours but blood glucose is usually abnormally elevated only in response to a glucose load and after the first week of treatment glucose tolerance improves except in those with pre-existing impairment of glucose tolerance.^{3,4} Nevertheless frank diabetes does occur often within 6 months of starting treatment. It is usually non-ketotic type II diabetes with insulin resistance.⁵

There are a few studies that compare the diabetogenic potential of daily and alternate day steroid regimes. There was no obvious difference in the incidence of diabetes in patients with chronic liver disease treated with the two regimes⁶ but in a retrospective study of transplant patients switched from daily to alternate day steroids mean blood glucose fell by 20%,⁷ although details of the timing of blood

Table II Mean blood glucose in 6 in-patients taking high dose alternate day prednisolone

Time of day	Mean blood glucose $\pm$ standard deviation (mmol/l)		Mean difference (mmol/l)
	Prednisolone day	Rest day	
09.00 hours	5.9 $\pm$ 2.3	5.3 $\pm$ 2.0	0.6 $\pm$ 2.0
11.00 hours	7.3 $\pm$ 3.2	5.3 $\pm$ 1.2	2.0 $\pm$ 3.1
15.00 hours	7.7 $\pm$ 1.7	5.3 $\pm$ 1.0	2.4 $\pm$ 2.1*
18.00 hours	8.8 $\pm$ 1.9	5.8 $\pm$ 1.0	3.0 $\pm$ 1.6*

Prednisolone was taken at 08.00 hours; * $P < 0.05$.

Group D – Low dose prednisolone in out-patients without glucose loading

Eleven of fifteen subjects had higher glucose concen-

glucose estimations were not reported. In a mixed group of 9 patients mean fasting and post-prandial blood glucose levels were higher on a thrice daily than on an alternate day regime.² Because this study

reported mean values over a 6 day period, it was unable to demonstrate the sustained alternate day nature of the diabetogenic effect.

Impairment of glucose tolerance or exacerbation of diabetes specifically related to the prednisolone day with alternate day glucocorticoid treatment has not been reported previously although it is physiologically predictable.

However in one study of children taking alternate day prednisolone subjected to insulin tolerance tests blood glucose appeared to be higher both before and after insulin on the prednisolone day.⁸ Also neutrophil leucocytosis, lymphopenia, eosinopenia⁹ and mental disturbance¹⁰ may occur on the treatment day and proteinuria is reduced.¹¹ Therefore a cyclical response is seen in several tissues.

This study shows elevation of blood glucose levels on the prednisolone day in subjects taking high dose prednisolone with and without glucose loading. With low dose prednisolone it can be shown by glucose loading and also is seen without loading in two overtly diabetic subjects. The difference between blood glucose concentrations on the two days in non-diabetic subjects taking low dose prednisolone is small but statistically significant. Serial blood glucose estimations in these patients might show a more marked difference than was demonstrated by a single mid-afternoon estimation. As all patients had been treated for more than a month there is no evidence that the effect of glucocorticoids on carbohydrate metabolism

is lost with time as has been suggested.⁴

This study demonstrates elevation of blood glucose in all groups on the afternoon of the treatment day. By next morning differences have disappeared even in those taking high dose prednisolone and by the following afternoon glucose tolerance tests were normal in 3 healthy subjects. Elevation of blood glucose was first seen 4 hours after high dose uncoated prednisolone. It was not significant 3 hours after enteric-coated high dose prednisolone but the number of patients studied was small. The time of onset of elevation of blood glucose in subjects taking low dose prednisolone was not studied. Peak plasma concentration of uncoated prednisolone occurs at 2 hours and is delayed approximately one hour by enteric coating.¹² The bioavailability and half life of both preparations is similar, plasma levels being negligible within 24 hours.¹² The maximal metabolic effect on carbohydrate metabolism is delayed a few hours after the peak plasma glucocorticoid concentration.¹³

The effect of alternate morning treatment with prednisolone on carbohydrate metabolism occurring specifically on the treatment day should be taken into account in the detection and management of diabetes when this treatment is used. Urine and blood samples should be collected after midday and evening meals on the prednisolone day for early detection of diabetes. A 48 hour glucose profile is necessary to assess control in established diabetes.

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