DIFFERENT PREDNISOLONE PHARMACOKINETICS IN CUSHINGOID AND NON-CUSHINGOID KIDNEY TRANSPLANT PATIENTS

H Bergrem, J Jervell, A Flatmark

Rikshospitalet University Hospital, Oslo, Norway

Summary

Prednisolone pharmacokinetics have been compared in 16 Cushingoid and 46 non-Cushingoid long term kidney transplant recipients. The Cushingoid patients had a significantly (p<0.05) higher peak concentration, a longer elimination half-time, a greater area under the time-concentration curve of total and free prednisolone, and a lower total body clearance of prednisolone. It is suggested that prednisolone pharmacodynamics may be influenced by pharmacokinetic differences, and that differences in renal function may be an important contributing factor.

Introduction

Prednisolone is used almost universally in kidney transplantation. Little is known about optimal dosages, and patients taking similar prednisolone doses may develop different degrees of side-effects. The purpose of the present study was to elucidate the possible connection between some Cushingoid side-effects and prednisolone pharmacokinetics.

Patients and methods

Sixty-two long-term (mean 62 months) kidney transplant recipients taking prednisolone 10mg/day gave their informed consent to participate in the study. Sixteen patients (mean age 56yr, 11 female) were classified as Cushingoid and 46 (mean age 44yr, 11 female) as non-Cushingoid by a combination of Cushingoid facial features and skin atrophy. There was no difference in liver function tests or serum protein concentration. Creatinine clearance was significantly (p<0.02) lower in the Cushingoid patients (90 ± 31 vs 67 ± 25ml/min).

After an overnight fast, each patient received two 5mg prednisolone tablets orally. Food was allowed after one and a half hours. Blood samples were drawn
at appropriate intervals of 14 hours. Serum prednisolone concentrations were measured by radioimmunoassay [1]. The apparent in vivo concentrations of free prednisolone were calculated by non-linear regression analysis of the free prednisolone concentrations obtained by equilibrium dialysis [2]. Pharmacokinetic parameters were calculated by model independent methods [2]. Statistical analysis was by the Wilcoxon test.

Results

The Cushingoid patients had a nine per cent higher (p<0.05) peak prednisolone concentration (C<sub>max</sub>), and 11 per cent longer (p<0.05) elimination half-time (t<sub>1/2</sub>), a 20 per cent larger (p<0.01) area under the time-concentration curve (AUC) of total prednisolone (AUC<sub>tot</sub>), a 15 per cent larger (p<0.05) AUC of unbound prednisolone (AUC<sub>free</sub>), and a 17 per cent lower (p<0.01) total body clearance (Cl<sub>t</sub>) of prednisolone than the non-Cushingoid patients. There was no statistically significant difference in time of peak concentration (T<sub>max</sub>), volume of distribution (VD), or proportion of free prednisolone (P<sub>free</sub>, AUC<sub>free</sub>/AUC<sub>tot</sub> × 100) (Figure 1).

![Figure 1. Prednisolone pharmacokinetics in transplant patients (prednisolone 10mg/orally). C<sub>max</sub> = peak prednisolone concentration. T<sub>1/2</sub> = prednisolone elimination half-time. AUC<sub>tot</sub> = area under the time-concentration curve of total (bound + free) prednisolone. AUC<sub>free</sub> = AUC of free prednisolone. Cl<sub>t</sub> = total body clearance of total prednisolone](image)

Discussion

These results suggest that differences in prednisolone pharmacokinetics may influence prednisolone pharmacodynamics. Two previous studies have compared prednisolone pharmacokinetics in Cushingoid and non-Cushingoid kidney transplant patients [3,4]. Gamertoglio et al [3] found a prolonged elimination
half-time in Cushingoid patients, and a significantly lower Clt. Frey et al [4], however, were not able to demonstrate such differences. In both studies, results may have been influenced by administration of different steroid doses, as prednisolone pharmacokinetics are dose dependent [5,6]. The present Cushingoid group contained more females and had a higher mean age than the non-Cushingoid group, factors which may have influenced the degree of Cushingoid appearance. However, the pharmacokinetic differences are unlikely to be due to these factors, but more likely to differences in renal function, which may influence both renal [7] and total body prednisolone clearance [8,9,10].

The present results indicate that decreased prednisolone Clt may increase steroid side-effects, and suggest that the clinical use of prednisolone might be improved by monitoring serum concentrations, especially in patients with markedly reduced renal function.

Acknowledgment

This study was supported by grants from the Norwegian Council for Science and the Humanities and the Norwegian Medical Depot.

References

10 Bergrem H. Kidney Int 1983: in press

Open Discussion

DE VECCHI (Milan) At what time of the day do your patients usually take their steroid dose, in the morning, in the afternoon, or randomly?

BERGREM About 30 months after transplantation the patients take a single dose of 10mg prednisolone in the morning.

DE VECCHI At what time did you perform your experiments?

BERGREM Starting early in the morning at around 8.00 a.m.

HAYRY (Helsinki) I understand that your age and sex distribution was biased in these two groups. Have you run normal healthy controls with a corresponding age and sex distribution?
BERGREM No, the purpose of the study was to compare Cushingoid and non-Cushingoid patients and I agree that the two groups are different. We have done a lot of studies on prednisolone pharmacokinetics in normal controls and there is some variation in the pharmacokinetic parameters. We have also done studies in non-transplanted patients with impaired renal function and they have a prolonged elimination half-time and decreased clearance of prednisolone.

HÄYRY Do you really think that these extremely small differences would explain the very dramatic effects that you see in the patients?

BERGREM If you assume that the biological action is due to the free drug, and if you look at the amount of free prednisolone in a dosage interval there can be about a four-fold difference. Following a dose of 10mg one patient will have only one-fourth of the free drug compared to another patient and I think that, probably, this has an effect. I also think having a high concentration towards the end of the day when the body is geared to not having glucocorticoids probably increases this effect.

McGEOWN (Belfast) One of the difficulties about a study like this is the division of your patients into the Cushingoid and non-Cushingoid. I'd like more details as to how you decided who was Cushingoid and non-Cushingoid? For instance, obese patients may sometimes look fairly similar to Cushingoid patients if you don't take other factors into account. The reduced clearance in the patients with Cushingoid changes, who had impaired renal function, may be due to oedema as waterlogging can affect the clearance of prednisolone.

BERGREM Regarding the selection of the patients, this was done by two relatively experienced nephrologists who selected these patients on a subjective basis. We did not look at body weights, we decided to make it practicable and therefore we decided to get an impression of the degree of Cushingoid appearance and to look at the extremes of this population. We know that it is very difficult to make a fair selection but we did it that way and looked at the extremes. For your second question, one of these patients was oedematous.

KOPP (Munich) Have you any idea about salt balance or hypertension with relation to Cushingoid appearances in your patients?

BERGREM We have the data but we haven't looked at them.

BARNES (Chairman) One of the notable things about transplant patients is that they take an awful lot of tablets. Did you control the other tablets that these patients were taking or were they only taking prednisone and azathioprine?

BERGREM No, a lot of them used frusemide and hypotensive drugs, but I can say that there was no difference in blood pressure and certainly there was no difference in the distribution of these drugs between the two groups.
GABRIEL (London)  Your paper is stimulating and provocative but don’t you feel you should have done this study on these patients before they were transplanted to look at the kinetics before they were fouled up by varying doses of prednisolone and all the awful things that happen to transplant patients?

BERGREM  I think that would be very difficult because at that time they would be practically anephric and they would have a very very long elimination half-time which would not relate to the time after a successful transplant.

GABRIEL  It is still perfectly possible to produce AUCs and other pharmacokinetic data on single dose basis with or without renal function.

BERGREM  Well, we didn’t do that.

BAHIER (Chicago)  In the US most people use prednisone which requires particular metabolism to become prednisolone. Do you think this could be a factor in determining whether certain patients become Cushingoid?

BERGREM  Prednisone is a biologically inactive pro-drug of prednisolone and there have been some papers in the past in patients with markedly impaired hepatic function indicating that they have incomplete conversion to prednisolone. There is one study in kidney transplant patients from Gambertoglio* in San Francisco who finds no difference in prednisolone bioavailability from prednisone or prednisolone. I think practically speaking there is not much difference but certainly when you give prednisolone you know what you are giving and you don’t have to worry about the hepatic conversion.