

CHANGES IN PREDNISOLONE PHARMACOKINETICS AND PROTEIN BINDING DURING TREATMENT WITH RIFAMPICIN

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Summary

Prednisolone pharmacokinetics and protein binding were studied after i.v. injection before and after three weeks of rifampicin therapy. The elimination half-time for prednisolone fell by $44.8\% \pm 8.1\%$ ($p < 0.01$) and the area under the time-concentration curve by $47.5\% \pm 7.3\%$ ($p < 0.01$). The reduction in area under the time concentration curve of free, non-protein bound prednisolone was $56.5\% \pm 9.8\%$ ($p < 0.01$). The reduction in AUC was greater ($p < 0.05$) for free prednisolone than for total prednisolone because of non-linear protein binding of prednisolone.

The total body clearance of prednisolone increased from 73.5 ± 14.6 ml/min to 142.7 ± 35.8 ml/min ($p < 0.01$). There was no change in the volume of distribution of prednisolone. Because of the marked reduction in the extent of bioavailability of total, and especially free, prednisolone, dosage adjustments should be made accordingly if prednisolone and rifampicin are prescribed concomitantly.

Introduction

Rifampicin, widely used in the treatment of tuberculosis, is a potent inducer of drug metabolising enzymes [1, 2]. Rifampicin and glucocorticoids are sometimes prescribed concomitantly, and a clinically important decrease in glucocorticoid effect during rifampicin treatment has been reported in Addison's disease [3, 4], nephrotic syndrome [5], and pericarditis [6].

Prednisone and prednisolone are the most commonly prescribed glucocorticoids for systemic therapy [7]. The effect of rifampicin treatment on the elimination half-time of prednisolone has been reported in one subject only [5].

In the present study we report the changes in prednisolone pharmacokinetics and serum protein binding in seven patients studied before and after three weeks of rifampicin treatment.

Material and methods

Seven patients (mean age 59 years, range 44–78, three female) gave their informed consent to participate in the study. All were to start rifampicin treatment because of suspected or verified tuberculosis. All had normal renal and hepatic function tests, except AW who was uraemic. Serum protein concentrations were normal in all subjects. None of the patients had been using drugs known to induce liver enzymes before starting rifampicin therapy. Each subject was studied before and after three weeks of rifampicin treatment (300–450mg/day). No other enzyme inducing medication was used concomitantly.

On the morning of investigation, 27mg prednisolone sodium phosphate (Hydeltrasol, MSD, USA), corresponding to 20mg prednisolone, was injected intravenously in a forearm vein over one minute (20mg in the uraemic patient). Blood samples were drawn from an indwelling venous cannula in the opposite arm at 0, 0.25, 0.5, 1, 1.5, 2, 4, 6, 7, 9 and 11 hours after the injection. Serum was stored at -20°C until analysis. Serum concentrations of prednisolone were measured by a specific radioimmunoassay [8] and the serum protein binding of prednisolone by equilibrium dialysis at 37°C [9]. The concentrations of free, unbound prednisolone were calculated using a modification of the method of Behm and Wagner [9, 10].

Pharmacokinetics

The elimination half-time ($t_{1/2}$) was expressed by $0.693/\beta$, β being the apparent first-order elimination rate constant calculated by linear least squares regression analysis of the logarithms of the terminal 8 data points. The areas under the time-concentration curve of total (AUC_{tot}) and free (AUC_{free}) prednisolone were measured by the trapezoid rule, the calculated values of free prednisolone concentrations being used to calculate the AUC_{free} [9]. The AUCs from the last measurement to infinity were measured by C_t/β , C_t being the prednisolone concentration (total and free) at time t . The volume of distribution (VD) was calculated by $\frac{\text{i.v. dose}}{\text{AUC}_{\text{tot}} \times \beta}$ and the total body clearance (Cl_t) by $\frac{\text{i.v. dose}}{\text{AUC}_{\text{tot}}}$.

Results are presented as means \pm 1 standard deviation (SD). Statistical analysis was performed using the Wilcoxon test.

Results

After three weeks of rifampicin therapy, the prednisolone $t_{1/2}$ had fallen by $44.8\% \pm 8.0\%$ and the AUC_{tot} by $47.5\% \pm 7.4\%$ (Figure 1). The AUC_{free} was reduced by $56.5\% \pm 9.8\%$. The differences are highly significant ($p < 0.01$).

The Cl_t increased from $73.5 \pm 14.6\text{ml/min}$ to $142.7 \pm 35.8\text{ml/min}$ ($p < 0.01$). The VD did not change significantly ($23.5\text{L} \pm 3.6\text{L}$ versus $25.4\text{L} \pm 4.6\text{L}$, $p > 0.05$). The reduction in AUC_{free} was significantly greater than the reduction in AUC_{tot} ($56.5\% \pm 4.6\%$ versus $47.5\% \pm 7.3\%$, $p < 0.05$) (Table I).

TABLE I. Prednisolone pharmacokinetics before and after three weeks' rifampicin treatment

Patient	Elim. t _{1/2} hrs		AUC _{tot} ng/ml/hr		VD (L)		Cl ml/min		AUC _{free} ng/ml/hr		Reduction in AUC in %	
	Before	After	Before	After	Before	After	Before	After	Before	After	AUC _{tot}	AUC _{free}
GS	4.18	1.65	4407	1842	27.4	25.9	76	181	711	272	58.2	61.7
AP	3.60	2.13	4940	3088	21.1	19.9	67	108	1035	535	37.5	48.3
JK	3.67	2.13	4948	2639	21.4	25.6	67	126	1274	556	46.7	56.4
SS	3.22	1.97	3272	1731	28.4	32.8	102	193	760	319	47.1	58.0
EH	3.51	2.19	5152	2959	19.6	21.3	65	113	1139	647	42.6	43.2
AS	4.13	2.28	5194	2462	23.0	26.8	64	135	982	284	52.6	71.1
AW	4.47	2.26	2709	1559	35.7	31.4	92	160	NA	NA		
Mean	3.72	2.11	4652	2453	23.5	25.4	73.5	142.7	983	435	47.5	56.5
± 1SD	0.37	0.23	732	563	3.6	4.6	14.6	35.8	217	162	7.3	9.8
P	< 0.01		< 0.01		NS		< 0.01		< 0.01		< 0.05	

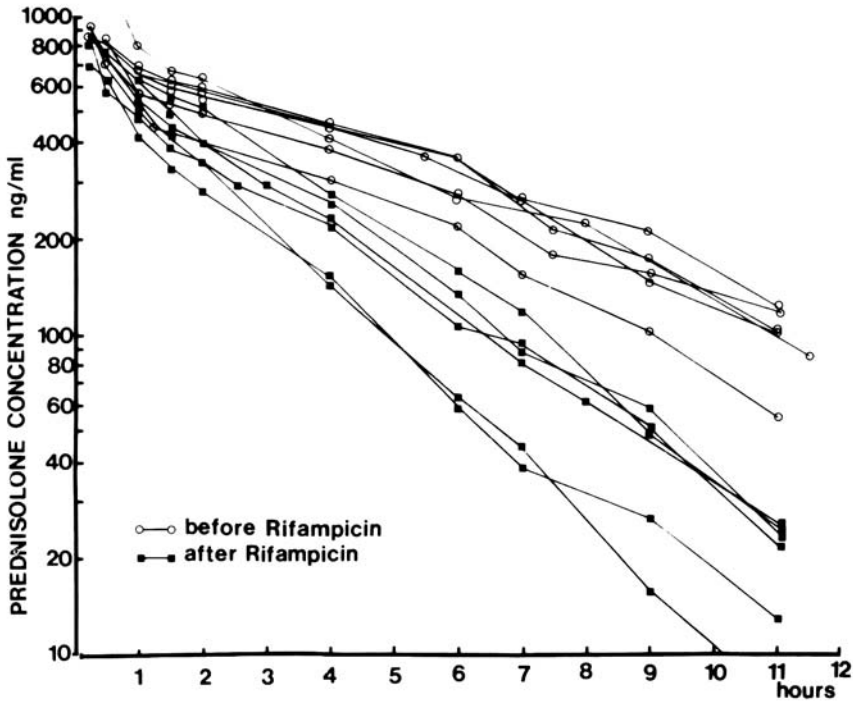


Figure 1. Serum prednisolone concentrations after i.v. injection of 20mg prednisolone in six patients before and after three weeks of rifampicin treatment

Discussion

One of the most serious implications of enzyme induction reported is the decrease in kidney transplant survival in children taking anti-epileptic medication [11]. This finding was subsequently supported by a study in rats which showed that administration of phenobarbital almost abolished the effect of prednisolone treatment on heart as well as kidney allograft survival [12].

Although rifampicin is one of the most potent inducers of drug metabolising enzymes used in clinical practice, the present study is the first to quantify the changes in prednisolone pharmacokinetics during rifampicin treatment, and to describe the changes in the free, biologically active fraction of the drug. The marked changes in the prednisolone AUC_{tot} , $t_{1/2}$, and Cl_t in the present study are most likely due to enzyme induction by rifampicin alone, as prednisolone, given on two occasions some weeks apart, does not change these pharmacokinetic parameters [9]. Hepatic clearance of drugs may increase with an increase in the liver blood flow, as seen with phenobarbital treatment [13], but rifampicin does not alter the liver blood flow [14].

The protein binding of prednisolone is non-linear [9, 10], and the present study

shows that the proportional reduction in AUC_{free} was significantly greater than the reduction in AUC_{tot} (Table I). In one patient, AS, the reduction in AUC_{free} was 71 per cent, i.e. the assumed biological activity of an i.v. dose of 20mg prednisolone was reduced by more than two thirds. Although the dose-response relationship for prednisolone is largely unknown, cortisol doses in Addison's disease had to be increased three- to four-fold during rifampicin therapy [3]. The present results indicate that the dose of prednisolone during rifampicin therapy should at least be doubled to obtain the same AUC_{free} as without rifampicin. A shorter dosage interval may also be indicated.

In few clinical situations is the possible ill-effect of a markedly reduced extent of prednisolone bioavailability as serious as in kidney transplantation, where most patients are treated with high doses of prednisolone to prevent rejection. Low prednisolone levels have been associated with an increased graft loss, whether secondary to empirical reduction of the daily prednisolone dose [15, 16], or to enzyme induction due to treatment with anti-epileptic drugs [11].

If antituberculous therapy is indicated during glucocorticoid treatment, alternative drugs such as INH combined with myambutol may be used, as these have little or no enzyme inducing effect. If rifampicin must be prescribed, adjustments of the prednisolone dose should be undertaken as indicated.

Acknowledgments

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Open Discussion

GABRIEL (London) Pharmacokinetic data are to some extent laboratory variables not necessarily relevant to clinical events. Did the transplants of the patients who received rifampicin suffer because of apparent lack of prednisolone?

BERGREM These were not transplant patients. I have said nothing about the clinical aspects. This is a report of the pharmacokinetic changes in patients with normal renal function and one who was moderately uraemic.

RITZ (Heidelberg) The last two papers represent a concentrated effort to make steroid therapy more safe to the patient by tailoring dosage to the patient's pharmacokinetics. However, what we are really interested in is not absolute free prednisolone concentrations, interesting though they may be, but interaction with glucocorticosteroid receptors. Could you therefore briefly comment to what extent the changes of absolute free prednisolone concentrations translate into changes of glucocorticosteroid receptor occupancy?

BERGREM We really don't know what we are interested in. Some people say that it is that the vascular anti-inflammatory effects, more a prostaglandin-like effect, of steroids that are most important. We don't know whether it is the receptor media it effects. We have not yet done any receptor studies. I agree with you that the pharmacokinetic studies are only a basis on which to build on, and so I don't have an answer to your question.

MCGEOWN (Belfast) I would like to take issue with the statement that it is more important to treat the graft than the patient, which was the implication of the last comment. Surely we are more concerned with the patient's survival than the graft survival?

BERGREM Yes.