Pharmacokinetics of acitretin and its 13-cis metabolite in patients on haemodialysis

A. E. STUCK¹, C. J. BRINDLEY², A. BUSSLINGER² & F. J. FREY¹

¹Medizinische Universitätspoliklinik, Bern, and ²F. Hoffmann-La Roche & Cie AG, Basel, Switzerland

- 1 Plasma concentrations of acitretin and its metabolite (13-cis acitretin) were measured in six patients on haemodialysis and six subjects without renal failure following a single oral dose of 50 mg of acitretin.
- 2 The mean areas under the plasma concentration vs time curves of acitretin and its metabolite were about 50% lower in patients on haemodialysis.
- 3 No retinoids were detectable in the dialysate.

Keywords acitretin pharmacokinetics haemodialysis renal failure 13-cis acitretin

Introduction

Acitretin (Ro 10-1670) is the active metabolite of etretinate (Tigason®-Roche). Acitretin and etretinate are equally effective against a similar spectrum of keratinising disorders (Geiger & Czarnetzki, 1988). However, acitretin differs from etretinate in that it is eliminated much more rapidly (Massarella *et al.*, 1985; Paravicini *et al.*, 1985).

Some patients with normal renal function are dialyzed for psoriasis (Nissenson *et al.*, 1979; Strenger-Klasen *et al.*, 1980) and in addition, patients with end-stage renal failure on dialysis may suffer from psoriasis (Kramer *et al.*, 1982). Both groups of patients may require retinoids for the treatment of their skin disease. Therefore, for rational therapy, the pharmacokinetics of these agents in patients with renal failure and the influence of haemodialysis on their plasma drug concentrations should be investigated. Etretinate kinetics have been studied in two patients on haemodialysis and two patients with chronic renal failure not on dialysis (Vahlquist, 1987). These authors measured plasma concentrations of etretinate and its metabolites acitretin and 13-cis acitretin in plasma samples obtained during the initial 24 h after dosing. Because of the short duration of blood collection and the small number of subjects investigated no definite conclusion can be drawn from this study. In the present

investigation the kinetics of acitretin and its isomeric metabolite, 13-cis acitretin (Paravicini *et al.*, 1981), were studied in patients with chronic renal failure on haemodialysis after oral dosing of acitretin.

Methods

Observations were made on six male patients with chronic end-stage renal disease on maintenance haemodialysis and in six healthy, male, aged-matched controls. All subjects gave informed consent to participate in the study. The study was approved by the Ethics Committee of our Institution.

The characteristics of the subjects are shown in Table 1. All were free of dermatological disease. No subject had anamnestic or laboratory evidence of liver disease. The patients were on maintenance drug therapy as usually prescribed for patients with end-stage renal failure (aluminium hydroxide, antihypertensives, antithrombotic drugs). The aetiology of the renal failure was nephrosclerosis, interstitial nephritis and reflux nephropathy.

Acitretin (50 mg) in two capsules was ingested with a glass of water after overnight fasting. Patients had breakfast at 30 min and controls

Table 1 Clinical data of subjects investigated

	Patients	Controls	P value
Number of subjects	6	6	—
Age (years)	50.8 ± 17.1	52.7 ± 18.7	NS
Weight (kg)	62.8 ± 6.4	77.1 ± 8.9	< 0.001
Creatinine clearance (ml min ⁻¹)	1.5 ± 2.0	103.4 ± 30.7	< 0.001
Albumin (g l ⁻¹)	30.2 ± 6.6	43.1 ± 1.9	< 0.001

immediately after dosing. Blood samples were drawn before and at various times during 96 h after dosing as shown in Figure 1. Note that in the patient shown in Figure 1, acitretin and 13-cis acitretin were not measurable at 72 and 96 h after dosing. Haemodialysis was started 4 h after dosing. This was performed using Centry II dialyzer units with single-pass dialysate flow and hollow-fiber cuprophane membrane artificial kidneys (Gambro Inc., Lund, Sweden). The surface area of the filters varied from 1–1.9 m². The median (range) duration of dialysis was 4 (2.5–4.5) h. Blood flow rate through the dialyzer ranged from 200 to 300 ml min⁻¹. Dialysate flow rate was 500 ml min⁻¹ in all patients. At four different times during haemodialysis blood samples were taken simultaneously from the afferent line to and the efferent line from the dialyzer. Dialysate samples were taken before and simultaneously with blood samples during haemodialysis.

Plasma was separated by centrifugation. Plasma and dialysate were stored at -20° C. Because of the light sensitivity of acitretin all manipulations of the samples were carried out under conditions of diffuse light.

Unchanged acitretin and its 13-cis isomeric metabolite were measured using a modification of the h.p.l.c. method described by Paravicini & Busslinger (1983). In order to achieve better separation of the isomeric compounds, the mobile phase was changed to n-hexane-methyl-salicylate-ethylacetate/propionic acid: 83/12.5/4/0.5 v/v. In addition, Ro 11-4768 was employed as the internal standard. All concentration data are reported as the mean of two determinations made on separate days. Calibration curves were obtained by least squares regression analysis, with weighting by 1/y of peak height ratio against concentration. Calibrations were linear between 4 and 500 ng ml⁻¹ ($r > 0.998$). The lower assay limit for both retinoids was between 4–6 ng ml⁻¹; the inter- and intra-assay variation was less than 6% ($n = 10$, range 20–500 ng ml⁻¹).

The area under the plasma concentrations vs time curve (AUC) was calculated for acitretin and 13-cis acitretin by the linear trapezoidal rule from time 0 to 24 h (AUC(0,24)). No attempt

was made to calculate the AUC beyond 24 h after dosing because the plasma concentrations observed were below or close to the assay limit. Similarly, the half-life was derived only from the initial decline (Figure 1). Time to peak ($t_{\max}$) and peak concentration ($C_{\max}$) were determined directly from the data. The body weight of the volunteers was higher than that of the patients on haemodialysis (Table 1). Therefore AUC(0,24) and $C_{\max}$ values were normalized to a 70 kg body weight.

For comparison of means the unpaired *t*-test was used. All data are reported as mean ± s.d.

Results

Figure 1 shows the plasma concentration vs time profiles of acitretin and 13-cis acitretin in a patient on haemodialysis and in a control subject. The mean $C_{\max}$ of acitretin was lower in the patients than in the control subjects (248 ± 105 vs 418 ± 185 µg l⁻¹, $P < 0.05$). The $t_{\max}$ of unchanged drug was slightly shorter in the patients than in the healthy volunteers (1.8 ± 0.4 vs 3.3 ± 1.5 h, $P < 0.05$). The $t_{1/2}$ of the initial decline in plasma concentrations of acitretin was similar in patients and control subjects (2.3 ± 0.5 vs 2.6 ± 1.1 h) (Figure 1). The elimination half-life could not be calculated because the plasma concentrations after 24 h were below or close to the assay limit. The mean AUC(0,24) of acitretin was lower in patients than in control subjects (1342 ± 381 vs 2430 ± 738 µg l⁻¹ h, $P < 0.005$) (Figure 2).

The $C_{\max}$ of the metabolite 13-cis acitretin was similar in subjects with and without renal failure (50.1 ± 66.5 vs 51.8 ± 35.7 µg l⁻¹, NS). The $t_{\max}$ of 13-cis acitretin was not significantly different between patients and control subjects (7.3 ± 11.2 vs 4.0 ± 1.1 h, NS). The variability of $C_{\max}$ and $t_{\max}$ was greater in patients than in controls. The mean (± s.d.) AUC(0,24) of 13-cis acitretin was 435 ± 313 in patients and 597 ± 186 µg l⁻¹ h in control subjects (Figure 2). The much higher coefficient of variation of the AUC(0,24) in patients than in control subjects was due to a very high value in one patient. When this patient was excluded from the statistical analysis, the

Figure 1 Plasma concentration vs time curves of acitretin (●) and 13-cis-acitretin (○) in a patient with renal failure (a) and in a control subject (b).

Figure 2 AUC(0,24) values of acitretin and 13-cis-acitretin in patients with renal failure and in control subjects. The individual values for all subjects and the mean values (bars) are shown.

mean AUC(0,24) of 13-cis-acitretin was significantly lower in the patients than in the control subjects (310 ± 67 vs 597 ± 186 $\mu\text{g l}^{-1} \text{h}$, $P < 0.001$). At 96 h after dosing, 13-cis-acitretin was

Figure 3 A comparison of plasma concentrations of acitretin in samples collected simultaneously from the afferent and efferent lines of the dialyzer. Four blood samples were collected from each patient ($n = 6$). Each symbol represents data for one patient. The line is the line of identity.

detectable in five out of six samples obtained from control subjects, but only in one out of six plasma samples from the patients.

In order to assess the possible removal of acitretin and 13-cis-acitretin by haemodialysis blood concentrations in the afferent and efferent lines of the dialyzer and concentrations in the dialysate were measured concomitantly. Acitretin and 13-cis-acitretin were not detected in any of the 24 dialysate samples. The finding that the plasma concentrations of acitretin (Figure 3) and 13-cis-acitretin (results not shown) in the efferent line were not lower but slightly higher than those in the afferent line ($P < 0.001$) confirmed that significant loss of the retinoids did not take place into the dialysate.

Discussion

The mean AUC(0,24) value of acitretin in patients on haemodialysis was approximately 50% lower than in control subjects. This cannot be explained by unusually high AUC values in the controls, since the volunteers had AUC values comparable with those observed in psoriatic patients with normal renal function, as described by Larsen *et al.* (1987). It is conceivable that the difference in retinoid concentrations between controls and patients with renal failure was due to the 30 min difference in the time at which breakfast was consumed. In order to evaluate this hypothesis, the results obtained in patients with renal failure were compared with those in a group of patients

($n = 5$) suffering from psoriasis (Paravicini *et al.*, 1985) who ingested breakfast 1 h after drug administration. Patients with renal failure had lower AUC(0,24) values of acitretin than the psoriatic patients with normal renal function (1342 ± 381 vs $1923 \pm 355 \mu\text{g l}^{-1} \text{ h}$, $P = 0.01$) after an oral dose of 50 mg of acitretin, indicating that the reduced AUC in renal patients was not related to the delay in food intake.

On the basis of the present investigation we cannot establish the mechanism accounting for the lower drug concentrations in the patients with renal failure. Since patients on haemodialysis were taking oral aluminium hydroxide, a decreased systemic availability due to an impaired absorption of acitretin might account for lower plasma concentrations of total acitretin. Alternatively, the lower plasma concentrations might be due to an increased total body clearance of acitretin as a consequence of the comedication or due to an increased volume of distribution of acitretin in the patients on haemodialysis. Acitretin is mainly bound (99.9%) to albumin (data on file, Roche). Since patients on dialysis had lower albumin concentrations (Table 1), an increased volume of distribution due to a decreased binding to plasma proteins may contribute to their lower total concentrations of acitretin compared with those in controls.

Acitretin is converted into 13-cis acitretin and *vice-versa* (data on file, Roche). The lower acitretin concentrations in plasma of patients might be attributable to an increased conversion of acitretin into 13-cis acitretin or to a reduced conversion of 13-cis acitretin into acitretin. This is unlikely, however, in view of the finding that

the mean ratios of the AUCs of 13-cis acitretin to acitretin were similar in subjects with and without renal failure (0.32 ± 0.16 vs 0.29 ± 0.18 , NS). The lower concentrations of the biologically active metabolite 13-cis acitretin in patients with renal failure compared with those in controls may be due to the lower concentrations of its parent compound (acitretin) or to an increased catabolism of 13-cis acitretin to unidentified metabolites.

No acitretin or 13-cis acitretin was detected in the dialysates. However, it is conceivable that concentrations below the assay limit ($< 4 \text{ ng ml}^{-1}$) were present. Thus, during a 4 h dialysis period with a dialysate flow of 500 ml min^{-1} , less than 0.5 mg could have been lost, indicating that dialysis treatment cannot account for the lower AUCs of the retinoids in patients with renal failure compared with those in controls. The plasma concentrations of acitretin and 13-cis acitretin were slightly higher in plasma samples obtained from the efferent compared with the afferent line of the dialyzer. This difference was most likely due to haemoconcentration as a consequence of loss of plasma water into the dialysate.

In order to ascertain the practical relevance of the present findings, multiple doses of acitretin should be given and both the total and unbound concentrations of acitretin and its metabolite should be measured in patients with renal failure.

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