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Pharmacokinetics of Acitretin

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Acitretin, the metabolite of etretinate, is eliminated far more rapidly from the human body than is etretinate. It has therefore been suggested that only a short period of contraception would be required following the completion of long-term therapy. However, recent studies have demonstrated the presence of etretinate in the plasma of acitretin-treated patients. In this paper, we review the results of studies at our centre in view of the recently discovered metabolic pathways for acitretin. Re-esterification of acitretin to etretinate, however, results in a loss of the metabolic advantages of acitretin. Because of this new knowledge, the recommended contraception period after acitretin therapy has been lengthened to 2 years.

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Etretinate and acitretin have similar antipsoriatic activity (1). However, since both compounds are teratogenic a contraception period following completion of treatment with these molecules is obligatory (2). Because of its high lipophilic properties, etretinate is stored in the adipose tissue and, after discontinuation of a treatment, the drug is released very slowly from this compartment, necessitating the mandatory contraception during the ensuing 2 years (3, 4).

Acitretin, the main metabolite of etretinate, does not accumulate in any particular tissue and is eliminated far more rapidly than etretinate. Consequently, a period of contraception lasting only 2 months is deemed sufficient after acitretin treatment (5, 6). In consequence, large numbers of patients previously treated with etretinate have been placed on acitretin therapy (7). Results of the analysis of blood samples from these patients indicated that acitretin did not drastically prolong the elimination of the etretinate that was stored in the adipose tissue. The very slow elimination of etretinate in one of the subjects was attributed to his obesity.

However, some years later and contrary to all expectations, a peak co-eluting with etretinate was detected in high performance liquid chromatographic traces of plasma samples from acitretin-treated patients.

Additional spectroscopic analysis (UV, MS) unequivocally identified this peak as etretinate. Based on results of animal studies at Hoffmann-La Roche (Basle, Switzerland and Nutley, NJ, USA), it is now known that alcohol can play an important role in the synthesis of etretinate from acitretin (8, 9).

At our centre, 20 patients (17 males, 3 females; age range 20–65 years) were treated for at least 12 weeks with acitretin (30 mg/day, orally). Blood samples were taken on starting the therapy, during the treatment, and also after completion of the therapy. The samples were analysed by high performance liquid chromatography for acitretin, 13-*cis*-acitretin, as well as for etretinate (10). The method consists of purification of the injected extract on a precolumn followed by column-switching and gradient elution of a reversed phase column. A representative chromatogram is shown in Fig. 1. In none of the patients was etretinate present in the plasma when starting the acitretin therapy. However, in 10 of the 20 patients the extra etretinate peak was found after only a few days of therapy with acitretin. Moreover, in the same patients, acitretin and 13-*cis*-acitretin persisted in the plasma much longer than expected after the discontinuation of acitretin treatment. In 6 of the etretinate-positive patients, the levels of etretinate were ≤5 ng/ml. Two patients had levels around 10 ng/ml, while in the remaining 2 patients, levels up to 60 or even 100 ng/ml were found. The samples positive for etretinate on the column-switching HPLC system (10) were reanalysed on an adsorption system based on the isocratic elution of a 15 × 0.46 cm I.D. Chromspher Silica column with *n*-hexane-methylsalicylate-acetic acid (200:18:0.3, by vol) at a flow rate of 0.85 ml/min. The effluent was monitored at 360 nm. The results obtained on both HPLC systems were in close mutual correlation and again positively identified 'the peak' as etretinate, as in both systems it co-chromatographed with an etretinate standard.

In a more recent study the pharmacokinetic behaviour and the distribution of acitretin were evaluated in its target tissue itself, i.e. the epidermis, in healthy volunteers. 13-*Cis*- and *trans*-

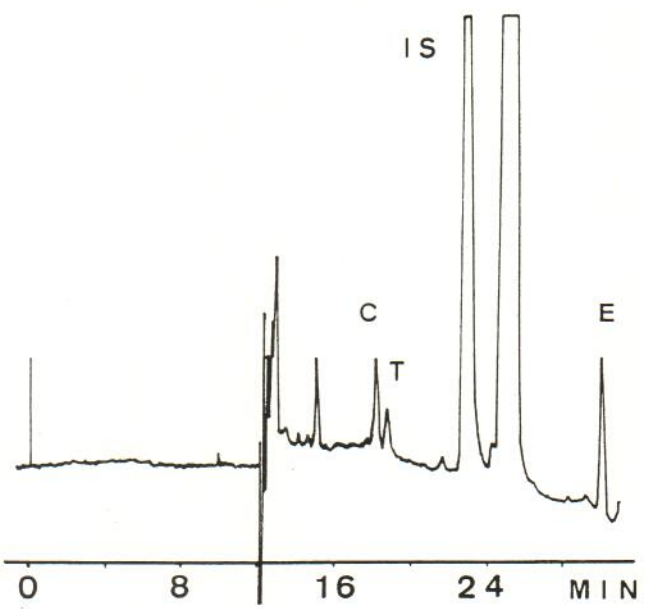

Fig. 1. Representative HPLC chromatogram on the column-switching system. Peak identification, C: 13-*cis*-acitretin; T: acitretin; IS: internal standard (13-*cis*-retinoic acid); E: etretinate. Levels were 8.1, 4.6 and 12.9 ng/ml for 13-*cis*-acitretin, acitretin, and etretinate, respectively.

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acitretin were measured by HPLC in plasma, blister fluid and epidermal samples. After multiple dosing (50 mg orally for 13 days) no accumulation of *trans*-acitretin was found in plasma or blister fluid. However, AUC values for *trans*-acitretin in the blister roof tended to be higher after multiple dosing (11). In an extension of this study to 12 psoriatic patients and to longer periods of treatment with acitretin (2 months to 3.5 years, 25 mg acitretin/day) plasma, skin biopsy material and subcutaneous fat were analysed. Trough levels of acitretin were consistently at the limit of quantification in both adipose tissue and skin, while the peak level was reached within 5 h of the intake of acitretin, suggesting a rapid penetration of the drug into skin and adipose tissue and indicating that neither skin nor adipose tissue functions as a storage compartment for acitretin. Here too, etretinate formation was demonstrated in the plasma of 2 patients who later admitted to being regular beer drinkers. In the same 2 patients, the etretinate concentrations in adipose tissue exceeded 1 μg/g wet weight, thus confirming the storage of etretinate in this tissue and illustrating again this unusual metabolic pathway of acitretin (12).

These results, together with data from other centres, have serious implications for acitretin management of patients. The recommended 2-year contraception period following etretinate therapy has now been extended to acitretin and leads to the loss of many of the earlier-described advantages of acitretin, compared with etretinate.

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