Unresponsiveness to Etretinate during Anticonvulsant Therapy

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Etretinate is a second-generation retinoic acid derivative which is found useful for the treatment of several disorders of keratinization. Anticonvulsants such as carbamazepine (CBZ) and phenytoin are potent hepatic microsomal enzyme inducers which increase the elimination, reduce the serum level and alter the bio-availability of certain drugs which undergo a similar metabolic pathway. We report the case of a young female with long-standing pityriasis rubra pilaris and well-controlled grand mal epilepsy, who did not respond to the recommended dose of etretinate while on anticonvulsants but improved dramatically on withdrawal.

This 15-year-old Malay girl of 34 kg presented in May 1991 with features of erythroderma. She had previously been seen at the Skin Clinic in 1981 with papular lesions over the knees, elbows, dorsal aspects of the hands and scaly, erythematous rashes over the palms and soles. A skin biopsy was consistent with the clinical diagnosis of pityriasis rubra pilaris, and the patient was treated with emollients. In 1987, she had a seizure and an electroencephalogram showed features of grand mal epilepsy. She was stabilized by the attending physician with CBZ 200 mg and valproic acid (VPA) 100 mg daily. As the pityriasis rubra pilaris progressed, the face was involved, the 'islands' of normal skin were replaced by advancing erythema, the whole body exfoliated and became erythrodermic. The girl was depressed and avoided school. Relevant investigations such as complete haemogram, liver function tests, serum lipids and blood urea were normal. We started her on etretinate 30 mg/day concurrently with the anticonvulsants.

During 2 months of etretinate therapy there was no clinical improvement, and cutaneous side effects such as cheilitis or dry mouth were absent.

Drug interaction was suspected, and we decided to withdraw CBZ with the help of the neurologist. The serum CBZ and VPA concentrations were low but inapplicable since a baseline value was not available for comparison. The serum lipid level was unchanged. VPA was increased to 350 mg in divided doses, and CBZ was gradually tapered and withdrawn. She was then restarted with etretinate 30 mg daily. Within 3 weeks there was a dramatic improvement of her skin. The lips and the mouth became dry with fissures. The girl became very cheerful, her weight increased by 2 kg in 6 weeks and she was able to continue her studies. The serum triglyceride concentration was slightly raised, but the liver enzymes were normal. Such were the effects of etretinate when administered with VPA but not with CBZ. Fortunately, she remains fit free.

Drug interactions involving etretinate are rare, and inhibition of its activity by CBZ, to the best of our knowledge, has not been reported. Etretinate therapy failed in our patient when it was given concurrently with CBZ and VPA, but significant clinical improvement was observed with etretinate and VPA only. This phenomenon is suggestive of interaction between etretinate and

CBZ, perhaps not involving VPA. We could not prove this interaction by pharmacokinetic studies since we were unable to measure the concentrations of etretinate and its metabolite at different stages. CBZ which is related to tricyclic antidepressants induces the metabolism of other drugs such as doxycycline, oral contraceptives and phenytoin [1]. The enzyme induction of VPA is not signif-

icant. One report suggests that the decreased effect of isotretinoin and another retinoid by ethanol was probably due to enzyme induction [2]. Our patient and her mother were well motivated, etretinate administration was properly supervised throughout and the compliance was good. We postulate that the therapeutic failure may be due to low etretinate bio-availability, resulting from the interference of absorption in the gut where it undergoes first-pass, presystemic hydrolysis [3], or due to enzyme induction. The other possibility may be the lack of transformation from etretinate into acitretin, the active metabolite. However, further studies involving the serum retinoid measurement are required to prove the mechanism of the interaction between etretinate and CBZ.

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References

Reynolds JEF: Antiepileptics; in Reynolds JEF (ed): Martindale. the Extra Pharmacopoeia. London. Pharmaceutical Press. 1989, pp 400-415.

Soria C, Alleque F, Galíana J, Ledo A: Decreased isotretinoin efficacy during acute alcohol intake. *Dermatologica* 1991;182:203.

Lucek RW, Colburn WA: Clinical pharmaco-kinetics of the retinoids. *Clin Pharmacokinet* 1985;10:38-62.