Differential Hepatotoxicity of Two Oral Retinoids (Etretinate and Isotretinoin) in a Patient with Palmoplantar Psoriasis

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A 64-year-old woman developed biopsy-proven hepatitis during oral treatment of severe pustular psoriasis of palms and soles with an aromatic retinoid, etretinate. The elevations in hepatic enzyme levels reappeared when etretinate was reinstated 18 months later. Analysis of serum and subcutis showed normal therapeutic concentrations of the drug. Isotretinoin therapy, although apparently devoid of hepatotoxicity, was clinically only marginally effective. Evidence compiled from the literature suggests that etretinate-hepatitis is a drug-specific reaction. (Received October 27, 1984.)

Hepatotoxicity is an established adverse effect of hypervitaminosis A, a condition in which the liver accumulates massive amounts of vitamin A (1). Although synthetic derivatives of retinoic acid (retinoids) do not have this affinity for the liver (2) they may produce hepatitis in therapeutic doses. The aromatic retinoid, etretinate (Tigason®) has been incriminated in several cases (3-5).

Etretinate has been found to be particularly useful in the treatment of pustular psoriasis. Isotretinoin (Roaccutane®), the other commercially available oral retinoid, is usually less effective for this condition (6). The former drug is stored in fat tissues and is only slowly released (7). Fatty degeneration of the liver will presumably promote storage of etretinate (8) but, normally, the liver concentration is only 2-5 times that of e.g. kidney, spleen and skin (9).

In this communication, we describe a patient with palmar plantar pustular psoriasis (PPPP) who on treatments with etretinate twice showed hepatotoxicity which did not reappear during treatment with isotretinoin.

REPORT OF A CASE

A 64-year-old woman was admitted to hospital in 1979 with a 15-year history of pustular eruptions on the palms and soles. She also had nummular lesions on the trunk and PPPP was thus diagnosed. Treatment with oral methotrexate, tetracyclines, PUVA, topical steroids and low-voltage X-rays was unsuccessful. The disease was recalcitrant and interfered severely with the patient’s daily activity. She was hospitalized in August 1981, and, except for a slight leucocytosis, laboratory data were normal when Tigason® (0.85 mg/kg/day) was instituted on October 12, 1981. The patient’s condition improved markedly within the next few weeks (Fig. 1). There was a complete cessation of pustulation within 1 week and marked improvement of erythema and scaling within the next 2 weeks. The only side effect noted when the patient was discharged from the hospital on November 23, 1981, was a moderate cheilitis. Her fasting serum concentration of etretinate, analysed by high-pressure liquid chromatography, was 435 ng/ml; this value falls within the normal therapeutic range (200-600 ng/ml) (7). On January 8, 1982, a routine check-up revealed elevated serum aminotransferases. She did not complain of any symptoms referable to liver disease. A serum analysis, one week later, revealed a further deterioration and the patient complained of fatigue. She was immediately hospitalized and the etretinate treatment withdrawn. The liver function tests continued to deteriorate for another two weeks (patient’s max. values and ref. values: ASAT (GOT) 11.4 µkat/l (<0.6); ALAT (GPT) 15.9 µkat/l (<0.6); y-glutamine transferase (y-GT) 2.7 µkat/l (<0.4), alkaline phosphatase 6.7 µkat/l (<4.8)
and bilirubin 11.7 µmol/l (<20)). At this time, a percutaneous needle biopsy of the liver showed a marked inflammatory reaction with liver cell necrosis consistent with hepatitis (Fig. 2). The lobular architecture was well preserved and no steatosis or fibrosis was found in the specimen. Serology for autoantibodies, hepatitis A and B viruses, cytomegalovirus and toxoplasmosis was negative. The serum concentration of etretinate was 150 ng/ml, and the concentration in subcutaneous fat varied from 5.3 to 7.2 µg/g. The values are in the ranges usually observed 2 weeks after withdrawal of the

![Fig. 1. Serum aminotransferase (ALAT) activity and clinical performance during retinoid treatment of palmar plantar pustular psoriasis.](image)

![Fig. 2. Biopsy specimen from the liver (Feb. 10, 1982). Hepatocellular injury, resembling acute viral hepatitis. Inflammatory cells, acidophilic bodies and ballooning of liver cells (H&E, x265).](image)
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Drug (7). The liver function tests improved spontaneously after the withdrawal of etretinate therapy (Fig. 1). However, a few weeks later the hepatic symptoms reappeared, necessitating a 6 months prednisolone therapy. Within one month, the liver function tests were normalized, except for a continued increase of $\gamma$-GT (2.5 µkat/l).

Her skin disease relapsed a few weeks after the cessation of etretinate-therapy before prednisolone was initiated. Although pustulation was less disturbing in December 1982, the erythema and scaling were severe and prompted a second trial with retinoid. With her informed consent, isotretinoin (Roaccutane®) was instituted at a dose of 50 mg daily. At this time, the liver function tests were normal except for an increased $\gamma$-GT-level (2.5 µkat/l). A second liver biopsy before the start of isotretinoin treatment (indicated in Fig. 1) showed a moderate periportal inflammation and a slight steatosis and fibrosis. The histological architecture of the liver was well preserved. The etretinate concentration in subcutis was still high (4.2 µg/g).

Only minimal improvement was recorded after 6 months of isotretinoin treatment and the patient experienced in addition to cheilitis, an intolerable generalized pruritus. Otherwise, blood chemistry examinations were normal, except for a continued elevation of $\gamma$-GT (2.5 µkat/l). In June 1983, one month after stopping isotretinoin therapy, a subcutis biopsy showed that small amounts (0.5 µg/g) of etretinate remained in the fat tissue (a normal finding 18 months after treatment), whereas isotretinoin could not be at all detected. An increased pustulation, possibly related to the discontinuation of isotretinoin prompted a third trial with retinoid. Thus, after informed consent, a low dose of etretinate was given for a total of two weeks (Fig. 1). The treatment was terminated when it became evident that the liver function tests again showed a liver reaction with serum aminotransferase elevation (ASAT 2.01 µkat/l; ALAT 2.62 µkat/l; $\gamma$-GT 4.2 µkat/l). There were no generalized symptoms of hypersensitivity such as eosinophilia or skin rash. After cessation of etretinate therapy the liver function tests normalized within 6 weeks and up to February 19, 1984 blood chemistry has not revealed any abnormalities except for a continued, slight elevation of $\gamma$-GT. The patient had a normal $\gamma$-GT value from the beginning and she denies any intake of alcohol.

DISCUSSION
The finding in this patient that etretinate was superior to isotretinoin in the treatment of PPPP is in accordance with a recent double-blind crossover study (6).

Only 8 cases (our case included) of biopsy proven hepatitis in connection with etretinate treatment have been reported (3, 5, 10, 11). All patients were middle-aged or elderly women; a sex distribution which is unlikely to reflect the use of the drug. It is therefore plausible, that women are more prone to develop hepatitis as a result of etretinate treatment. The interval between onset of etretinate therapy and appearance of hepatitis has varied from 2 weeks to 6 months and the dose regimens have been normal.

In at least 4 cases (our case included), the laboratory data associated with hepatitis have shown a biphasic pattern, i.e. a second maximum occurred a few weeks after cessation of therapy (5, 11). In our opinion, this is an uncommon reaction pattern and is presumably related to specific mechanisms involved in the development of etretinate hepatitis.

Drug hepatotoxicity may be of two types (12): one type is unpredictable, usually rare, and causes liver damage through an idiosyncratic host response; the other, characteristic of intrinsic hepatotoxins, is a dose dependent, toxic reaction associated with a high incidence of injury in exposed individuals. Although slightly or intermittently raised transaminases have been recorded in etretinate-treated patients with a frequency of up to 30% (11, 13), prospective studies of liver function and structure have not as yet established that progressive and self-perpetuating liver damage may be initiated with etretinate treatment (14).

Four conclusions regarding retinoid hepatotoxicity can be drawn from our case: Firstly, the reproducible association between etretinate treatment and hepatic reactions, unequivocally identifies the drug as the causative agent. This seems to have been demonstrated in only three previous cases (4, 5); Secondly, there was no evidence of overdosing or abnormal accumulation of the drug as cause of the hepatitis. Thirdly, the fact that the functionally closely related compound isotretinoin produced no apparent hepatic reaction...
Gingival Hyperplasia by Nifedipine
Report of a Case

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We describe a case of gingival hyperplasia in a 36-year-old renal transplantation recipient treated with nifedipine for severe arterial hypertension. The appearance of the gingival disorder was probably related to nifedipine intake. Histologically, in addition to the findings of acanthosis, papillomatosis and connective tissue hyperplasia, there was also an important plasma cell inflammatory infiltrate. Key words: Ca antagonists; Drug-induced side effects. (Received November 6, 1984.)

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