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Case report

Hepatic reactions to cyclofenil

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SUMMARY Thirty patients with hepatic reactions to cyclofenil, a non-steroidal drug with a stimulating effect on ovulation, are reviewed. The liver damage was probably related to metabolic idiosyncrasy, and was reversible in all patients.

Cyclofenil is a non-steroidal drug with a stimulating effect on ovulation. It is also used for treatment of scleroderma. Although changes of liver tests have been known to the manufacturer, published observations of increased serum aminotransferases in patients on cyclofenil have appeared only recently.[1] A recently experienced case of marked liver reaction to cyclofenil initiated a study of the 30 cases with abnormal liver tests during treatment with this drug reported between 1969–1980 to the Swedish Adverse Drug Reactions Advisory Committee under the Swedish Board of Health and Welfare.

PRESENT CASE

A 44-year-old woman, complaining of cold fingers since the middle of the 1960s, was seen in 1975 after deterioration, when a diagnosis of scleroderma was made. Liver tests were normal in June 1980. She was started on cyclofenil, 100 mg three times a day in August 1980. After one month the dosage was increased to 200 mg three times a day. Markedly increased serum aminotransferases were observed for the first time after 10 weeks of treatment (Table). The patient felt tired and experienced some pruritis, but was otherwise well and afebrile. There was no skin rash or lymphadenopathy, hepatomegaly, or splenomegaly.

A liver biosy, performed 10 days after discontinuation of cyclofenil showed a preserved lobular architecture, but some portal fibrosis and round cell infiltration. The limiting plate was destroyed, but there were no piecemeal necroses. Numerous acidophilic bodies were observed as well as ballooning and, around the central veins, hepatocytes with pyknosis and abundance of lipofuscin. Lymphocytes and histiocytes were seen in the vicinity of degenerated hepatocytes. Some Kupffer cell proliferation was also observed. There was no cholestasis or steatosis, and no granulomas.

A differential white cell count displayed a slight monocytosis (14%) but otherwise, haematological data were normal, as well as serum electrolytes and creatinine. Anti-HAV, HB_sAg, anti-HB_c, and anti-HB_s were negative, and repeated tests for viral infection gave no support for infection with Epstein-Barr virus, herpes simplex virus, or cytomegalovirus. A test for antimitochondrial antibodies was negative, whereas a weekly positive reaction for smooth muscle and antinuclear antibodies was obtained. (In 1979 the patient already had a weakly positive antinuclear antibody test.) She made a slow but complete recovery (Table).

REVIEW OF ALL REPORTED CASES

All the reported cases were previously reviewed by the Swedish Adverse Reactions Advisory Committee and judged as having a probable, or at least possible, causal relationship between the drug and the signs of liver injury.

The total series comprised 30 women patients aged 22–44 years (mean 29 years). The reason for prescribing cyclofenil was infertility or amenorrhoea in 28 patients and Raynaud's symptoms associated with scleroderma and mixed connective tissue disease in two.

The daily dosage was not reported in three patients. It was 100 mg in three patients, 200 mg in 21, 300 mg in one, 400 mg in one, and 600 mg in one patient.

The duration of treatment before the appearance of symptoms of liver disease was less than one

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Table *Liver tests before, during and after cyclofenil treatment*

	16/6	*29/8*	*26/9*	*6/11*	*10/11*	*18/11*	*21/11*	*24/11*	*26/11*	*1/12*	*9/12*	*27/1*
S-ASAT μkat/l (<0·7)	0·67	0·75	0·75	23	30	41	31	31	23	14	3·1	0·65
S-ALAT μkat/l (<0·7)	0·16	0·19	0·34	22	28	29	22	22	18	7·3	2·1	0·30
S-ALP μkat/l (<5·0)	2·2			5·6		6·4	5·7	4·9		3·5	2·7	2·0
S-bilirubin μmol/l (<21)	4·1			12		42	46	32	26	18	8·0	7·0

Cyclofenil was started on 8 August and stopped on 12 November.
ASAT = aspartate aminotransferase. ALAT = alanine aminotransferase. ALP = alkaline phosphatase.

month in four, one to two months in 13, two to four months in 11, and more than four months in two patients.

Other drugs were used by four women: vaginal sulphonamide in one, oral sulphonamide in one, thioridazine intermittently for several years in one, and tablets containing acetylsalicylic acid, barbiturates, phenprobamate, and dextropropoxiphen in one. None of the patients was challenged with any of these drugs, or with cyclofenil.

A low grade fever was reported in four patients, pruritis in 10, nausea or vomiting in 20, diarrhoea in three, abdominal pain in three, and arthropathy in two. None of the women had skin rash or lymphadenopathy. A positive test for antinuclear antibodies was shown already before administration of cyclofenil in the patients with scleroderma and mixed connective tissue disease. The titres did not change during the course of their liver disease. The test was performed in only four of the other patients and was weakly positive (1:10) in two. One of these patients showed LE-cells in all of four tests. She had taken cyclofenil for nine months during the last year and complained of arthralgias as her only symptoms. HB_sAg was negative in all 19 patients where this test was performed. Eight patients had a normal leucocyte differential count, three had a very slight eosinophilia, one had a very slight lymphocytosis, and one a monocytosis. The patient with positive LE-cell phenomenon had leukopenia.

The highest serum bilirubin recorded in each patient ranged between normal in two patients and above 200 μmol/l (11·2 mg/ml) in four with a mean of 110 μmol/l (6·5 mg/ml) in the 28 patients where this test was performed. Serum alkaline phosphatases were normal in 5/21 and more than twice the upper limit of normal in five. All 28 patients with reported serum aminotransferases had raised levels, in 13 of the patients to values above 20 μkat/l (normal ≤0·7 μkat/l). In 22/28 there was a predominance of S-ALAT over S-ASAT. There was no relation between the maximum ALAT value and the dosage of cyclofenil or the duration of treatment. The time for normalisation of liver tests after stopping the administration of cyclofenil was reported in only 12 patients, and was about four weeks in six, two months in four, and five months in one, whereas in one patient a normalisation had not yet occurred after four months.

A fine needle aspiration biopsy for cytological investigation was available in one patient, showing a slight cholestasis without liver cell necroses or inflammatory cells. A needle biopsy was available in six patients. These all showed lesions resembling viral hepatitis, with lymphohistiocytic portal tract inflammatory reaction as well as lobular changes consisting of ballooning of hepatocytes, hepatocellular necrosis, infiltration by lymphocytes and histiocytes, and Kupffer cell proliferation (Fig. 1). In one patient, the liver biopsy also showed numerous small epithelioid cell granulomas with occasional giant cells and a few eosinophils. The granulomas were mostly seen near the portal tracts. Three biopsies displayed slight cholestasis with bile plugs in canaliculi. A striking observation was the increased amount of lipofuscin observed in five patients. The pigment occurred as fine granules in centrilobular hepatocytes (Fig. 2), interstitially, or in phagocytes in portal tracts and Kupffer cells. Some heavily pigmented hepatocytes showed degenerative changes with lysis (Fig. 3).

Discussion

In the present series of 30 patients, the long delay before signs of liver damage appeared, the lack of relation between maximum ALAT level and dosage of cyclofenil as well as the histological picture make a direct toxic effect improbable.

Eighty per cent of the liver reactions to cyclofenil occurred one to four months after initiation of therapy. Only four patients had a reaction within a month. This clearly does not suggest a hypersensitivity reaction, as this type of liver damage usually occurs during the first five weeks of treatment.[2] The lack of skin rash, lymphadenopathy, and prominent eosinophilia also argues against a hypersensitivity reaction. On the other hand, hepatic injury attributable to metabolic

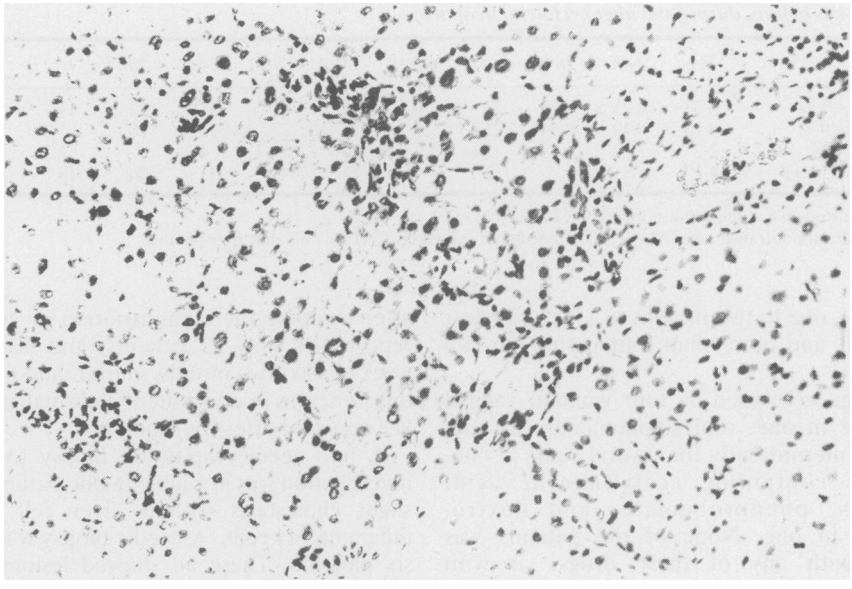

Fig. 1 *Liver parenchyma showing marked ballooning of hepatocytes, hepatocellular necrosis and inflammation. Haematoxylin and eosin, ×150 (original magnification).*

idiosyncrasy may appear after weeks or months of taking the drug and usually presents without the systemic features mentioned above.[2] The histological picture observed in our patients is compatible with such a reaction as well as with a hypersensitivity reaction. In contrast with the isoniazid-induced liver damage, however, which most likely is because of metabolic idiosyncrasy, the injury was not more serious even though the period of treatment before the recognition of the hepatic injury was longer.[3]

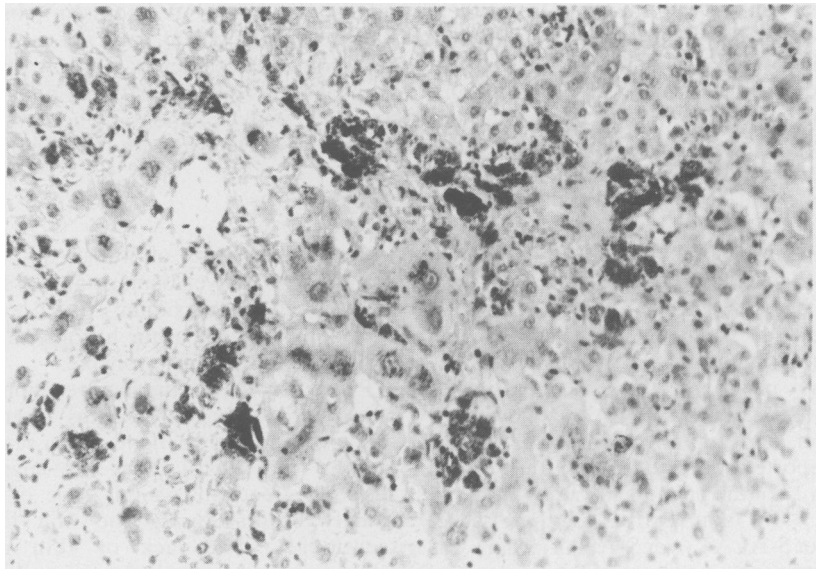

Fig. 2 *Liver parenchyma with numerous lipofuscin-filled hepatocytes and inflammation. Long Ziehl-Neelsen, ×180 (original magnification).*

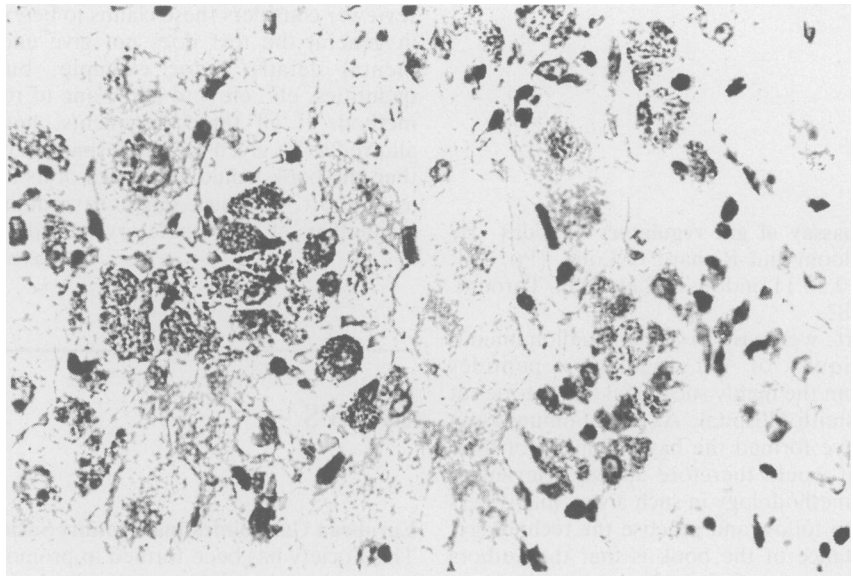

Fig. 3 *Numerous lipofuscin-containing liver cells, partly necrotising. Long Ziehl-Neelsen, ×720 (original magnification).*

A striking observation is the increased amount of lipofuscin in the liver. Large amounts of hepatocellular lipofuscin have been described in patients with renal damage after excessive intake of phenacetin and similar drugs.[4 5] Otherwise, as far as we know, such changes have not been described in association with drug-induced liver damage. For example, it is not mentioned in the guidelines for diagnosis of therapeutic drug-induced liver injury in liver biopsies, reviewed by an international group of distinguished hepatologists.[6] According to Popper and Schaffner,[7] lipofuscin accumulates when metabolic activities are decreased, but rapidly disappears in hepatic disorders. Its abundant appearance under the present conditions is, therefore, surprising.

Cyclofenil is used not only in Sweden, but also in England, France, Italy, Japan, and Germany. It is, therefore, surprising that there are no reports of liver damage from these countries in view of the rather high incidence of reactions in our country. Based on a registered total sale of about 3·3 millions of 100 mg tablets during 1971–80 and a presumed average treatment amounting to two tablets daily for 90 days, the incidence of reported liver reactions in Sweden during the period can be estimated at 1·3%. As mentioned in the introduction, increased aminotransferase values have recently also been reported in a Swedish study of cyclofenil treatment in progressive systemic sclerosis.[1] It may well be, therefore, that there is a geographic difference in susceptibility to the drug, such as has been observed for oestrogen-induced liver damage, which is more common in Scandinavia and Chile.[8]

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