Potassium clorazepate (Tranxene)-induced jaundice

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Summary
A first report of jaundice and hepatic necrosis probably due to potassium clorazepate is described. The histology is discussed and it is suggested that the drug should not be given in the presence of suspected hepatic dysfunction.

Introduction
Potassium clorazepate is a tranquilliser of the benzodiazepine group which has had no serious toxic effects reported to date. A case of jaundice and hepatic necrosis, probably due to this drug, is now described.

Case report
A 27-year-old man presented to his general practitioner in August 1976 with symptoms of depression. There was no previous history of mental or physical illness and no history of any alcohol ingestion. He was married with 3 children and smoked 30 cigarettes/day. Treatment was commenced with clorazepate 15 mg once daily in October with little improvement in his symptoms, and the dose was increased to 30 mg daily in November. No other medication was given.

In December 1976, 2 months after starting treatment, jaundice and fever were noted with pruritus, dark urine and pale stools. There was anorexia and weight loss of 9.5 kg in 2 months. He complained of tiredness and listlessness and had been off work for 2 months. He worked as a burner in the shipyards but there were no symptoms or signs of lead poisoning.

Clorazepate was continued until February 1977 and he was seen at a medical out-patients clinic a few weeks later. At this time there was general wellbeing but icterus and a large 4-fingerbreadth, firm liver were still present.

In-patient investigation showed his bilirubin was 130 µmol/l (normal 3-22 mmol/l); alkaline phosphatase 29 KAu. (3-13 KAu.), SGOT 620 u./l (12-42 u./l); SGPT 880 u./l (8-55 u./l) and γ-GTP 104 u./l (<45 u./l). There was no anaemia, blood film was normal and the ESR was 15 mm in the first hour. Serological examination for anti-smooth muscle and anti-mitochondrial antibodies was negative. Liver biopsy was carried out on 3 occasions over the following 5 months and the histology is reported below.

Over this period the jaundice disappeared, the liver became impalpable and enzyme and bilirubin levels returned to normal.

Admission was arranged to the assessment ward of

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Fig. 1. First biopsy of liver. Low power view: note the widening of the portal areas with an intense triaditis, and the parenchymal inflammation with focal liver cell necrosis (HE, x 110).
a psychiatric hospital for 3 months and a course of
electroconvulsive therapy was given followed by
treatment with L-tryptophan and phenelzine.

Histology of liver biopsies

1. February 1977 (Fig. 1). This showed mild
centrilobular cholestasis. In addition, there was
focal liver cell necrosis, single cell eosinophilic
necrosis and reactive Kupffer cell hyperplasia. The
most striking changes involved the portal tracts
which were markedly swollen and oedematous with
extension of their young fibrous tissue septa, pro-
ducing portal-portal bridging. Within the portal
tracts and fibrous septa there was a marked, mainly

![Image 1](http://pmj.bmj.com/)

**Fig. 2** Second biopsy of liver. (a) Low power to show the well marked
portal-portal fibrous linkage producing a monolobular fibrotic pattern
(Gordon and Sweet's reticulin, × 72). (b) Portal area and fibrous septum,
in which there is a persisting chronic inflammatory reaction and some mild
ductal proliferation (HE, × 232).
mononuclear cell infiltrate. This was predominantly lymphocytes, but small numbers of plasma cells, pigment-laden macrophages and a few eosinophils were also noted. At the fibrous/parenchymal interface there was conspicuous ductal proliferation with spillover of inflammatory cells into the adjacent parenchyma.

2. May 1977 (Fig. 2). Apart from some prominence of ceroid-containing Kupffer cells the parenchyma was unremarkable. The portal inflammation was considerably less than in the first biopsy. There was, however, well marked fine fibrous septa formation producing portal-portal linkage and a monolobular fibrotic pattern. Parenchymal ductal proliferation persisted especially within some portal areas.

3. July 1977 (Fig. 3). There was a moderate degree of centrilobular macrovesicular steatosis. Thin fibrous septa persisted with well defined portal-portal bridging. There was a mild residual chronic inflammatory cell infiltrate in the portal tract, focally intense in some, but with no evidence of spillover into the parenchyma and with now no evident ductular proliferation.

Discussion

The temporal relationship between ingestion of clorazepate and development of liver dysfunction suggests a cause-and-effect relationship. The manufacturers have no reports of liver damage due to clorazepate but the Committee on Safety of Medicines have 2 recorded instances of jaundice (personal communication, 1977). Those patients, of course, may have been receiving more than one drug at the time.

The clorazepate was continued for 6 weeks after the appearance of the jaundice, and it is disturbing that there is persistence of the residual monolobular pattern of fibrosis 6 months after stopping the drug. Whether the patient will go on to develop a true cirrhosis is uncertain.

It is suggested that this drug should not be given to patients with any evidence of hepatic dysfunction, and should be discontinued as soon as jaundice is observed.

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