Effect of Hepatic Insufficiency on 5-Fluorocytosine Concentrations in Serum

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Hepatic function failed to influence serum concentrations of the antifungal agent 5-fluorocytosine when the drug was given intravenously to rabbits with CCl_4 -induced hepatic insufficiency or orally to a patient with postnecrotic cirrhosis.

5-Fluorocytosine (5-FC) is a new oral antifungal agent that has been used in the treatment of candidiasis and cryptococcosis (5). Preliminary studies have indicated that a sizeable fraction of an oral dose of 5-FC is excreted unchanged in the urine in humans (2). Studies in this laboratory have demonstrated that 5-FC serum concentrations and half-life are markedly increased in the presence of renal insufficiency (1). Studies to assess the effect of hepatic insufficiency on serum concentration of 5-FC have not been previously reported. Such studies would be of clinical relevance for several reasons: (i) patients with systemic candidiasis often have underlying illnesses which may include hepatic insufficiency, (ii)

cryptococcosis has been reported (3) to cause severe hepatic insufficiency, and (iii) 5-FC itself can cause impaired hepatic function (1). In addition, metabolic degradation of 5-fluorouracil, a closely related pyrimidine analogue, occurs primarily in the liver.

Ten New Zealand White male rabbits weighing 2 to 3 kg were given 50 mg of 5-FC/kg intravenously as a single bolus. Blood samples were then drawn every 30 min for 2 hr, hourly for 4 hr, and then at 24 hr after the 5-FC dose. Seven days later, these same 10 rabbits were given a single dose of CCl_4 (0.1 ml/kg) by nasogastric tube. This has been reported to cause acute toxic hepatitis within 24 hr in the rabbit, which progresses to cirrhosis, hepatic insufficiency, and death within 2 weeks (4). At 48 hr after the dose of CCl_4 , the rabbits were re-challenged intravenously with 50 mg of 5-FC per kg. Serial blood samples were collected as before. All 10 rabbits had normal hepatic and renal function at the time of the first 5-FC

FIG. 1. 5-FC concentrations in the serum of 10 rabbits after a single intravenous dose of 5-FC before (solid line) and after (dashed line) carbon tetrachloride-induced hepatic insufficiency.

TABLE 1. 5-FC concentrations in the serum of a single patient with hepatic dysfunction compared with controls^a

Time after 5-FC dose (hr)	5-FC serum concn (µg/ml) ^b	
	Patient G. G.	Controls
1	44.3 ± 3.2	53.0 ± 5.2
2	52.0 ± 6.5	55.9 ± 3.4
6	46.0 ± 5.4	44.4 ± 4.1

^a Ten patients with cryptococcal disease with normal renal and hepatic function being treated with the same dose of 5-FC as G. G. (100 mg per kg per day, orally).

^b Mean ± SE.

challenge. By 48 hr after CCl_4 , serum glutamic pyruvic transaminase was $2,907 \pm 639$ international units (normal, 5 to 30 IU), alkaline phosphatase was 162.1 ± 18.3 IU (normal, 40 to 90 IU), and both bilirubin and serum creatinine remained normal.

5-FC concentrations in serum were measured by use of a previously described cylinder-plate bioassay (1) and are shown in Fig. 1. Although the serum concentrations were slightly lower in the hepatotoxic animals, the differences were not statistically significant. In all 10 rabbits, samples drawn immediately prior to each 5-FC dose and 24 hr after the 5-FC dose demonstrated no bioactivity. The reason for the slight rise in 5-FC concentration at 2 hr in both groups of animals is not known.

A single patient (G. G.) with biopsy-proven postnecrotic cirrhosis and cryptococcal meningitis being treated with 5-FC, 100 mg per kg per day given in equal divided doses at 6-hr intervals, was studied. Serum glutamic pyruvic and oxaloacetic transaminases ranged from 38 to 183 IU (normal, 5 to 35 IU), and alkaline phosphatase ranged from 148 to 560 IU (normal, 30 to 78 IU); serum bilirubin and creatinine remained normal. These abnormal liver functions antedated 5-FC therapy and were not exacerbated by this drug. 5-FC con-

centrations in serum were measured at 1, 2, and 6 hr after a dose and did not differ from concentrations determined simultaneously in 10 patients with cryptococcosis with normal renal and hepatic function being treated with the same dose of 5-FC (Table 1). Unlike renal insufficiency, mild to moderate hepatic insufficiency does not appear to have a significant influence on 5-FC concentrations in the serum of rabbits or humans.

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