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Decreased Disappearance Rate of 1-(2-Tetrahydrofuryl)-5-Fluorouracil (FT-207) from the Blood and its Unresponsiveness to Tocopheryl Nicotinate and Indomethacin in Patients with Primary Hepatocellular Carcinoma

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Abstract

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DECREASED DISAPPEARANCE RATE OF 1-(2-TETRAHYDROFURYL)-5-FLUOROURACIL (FT-207) FROM THE BLOOD AND ITS UNRESPONSIVENESS TO TOCOPHERYL NICOTINATE AND INDOMETHACIN IN PATIENTS WITH PRIMARY HEPATOCELLULAR CARCINOMA

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Abstract. The disappearance rates(K) of FT-207 from the blood in patients with primary hepatoma and advanced cirrhosis of the liver were significantly lower than those in control patients with cancer but normal liver function. Pretreatment with tocopheryl nicotinate and indomethacin increased the K values in the control subjects, but was without effect on the K values in patients with primary hepatoma.

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The antitumor agent, 1-(2-tetrahydrofuryl)-5-fluorouracil (FT-207) is a derivative of 5-fluorouracil (5-FU), which has been widely used in cancer patients (1). We have recently developed a technique for determining FT-207 in the blood using high pressure liquid chromatography (HPLC) (2). Impaired formation of 5-FU following FT-207 administration to carbon tetrachloride-injured mice has been reported (3). Ohira (4) demonstrated that inhibitors of lipid peroxide formation and inducers of drug-metabolizing enzymes in liver microsomes produced marked acceleration of FT-207 metabolism *in vivo*. These results led us to investigate the pharmacokinetics of FT-207 in patients with primary hepatoma by measuring its disappearance rate (K) from the circulating blood using our new technique. FT-207 has to be metabolized by the liver to become fully active (4) and markedly decreased levels of drug-metabolizing enzymes in injured liver have already been reported (5). Metabolism of this drug may be altered in patients with primary hepatoma and cirrhosis of the liver. Our previous report confirmed a direct correlation between the activities of hepatic microsomal drug-metabolizing enzymes and the clearance rates of FT-207 from the circulating blood in liver-injured rats (7). This report describes a marked decrease of FT-207 clearance and its unresponsiveness to toco-

pheryl nicotinate and indomethacin in patients with hepatoma and advanced cirrhosis of the liver.

MATERIALS AND METHODS

Eight patients with cancer and normal liver function or primary hepatoma each received a single intravenous dose of 16 mg FT-207/kg body weight. The patients studied include four cases of primary hepatoma and one case each of gastric, lung, ovarian and uterine cancers. The latter four cases had normal liver function and were used as the control. All hepatoma patients had advanced cirrhosis of the liver. The diagnosis of hepatoma was made from liver scintigrams and serum α_1-fetoprotein levels. Blood was taken at 1, 3, 5, 12 and 24 h after FT-207 injection. Patients with hepatoma or lung cancer were pretreated for 3 days with tocoheryl nicotinate and indomethacin at a daily dose of 600 mg and 75 mg, respectively. The concentrations of FT-207 in the blood were assayed by HPLC as described previously (2). Since the disappearance of FT-207 from the circulating blood followed first-order kinetics, the half-life ($t_{1/2}$) was obtained by plotting logarithmic concentration against time in hours, and the disappearance rate K was calculated by the equation: $K=0.693/t_{1/2}$.

RESULTS

The K values of FT-207 after a single intravenous injection to a patient with lung cancer were compared with those of a patient with primary hepatoma.

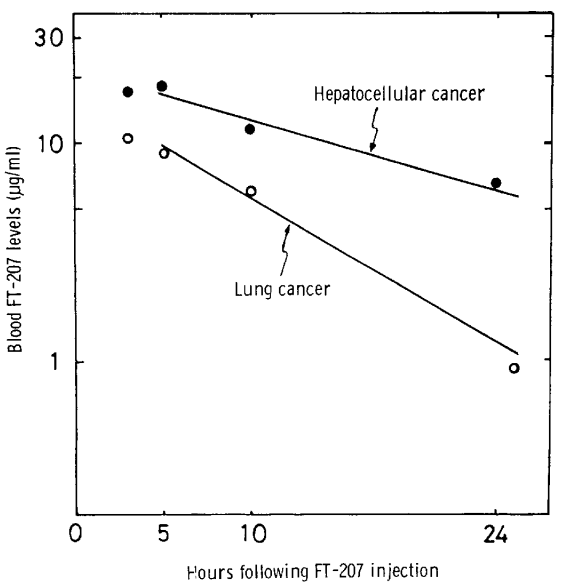

Fig. 1. Time courses of blood levels of FT-207 following intravenous injection to patients with primary hepatoma or lung cancer.

Slower clearance of FT-207 and higher blood concentrations occurred in hepatoma patients with advanced cirrhosis (Fig. 1). The disappearance rates in four patients with primary hepatoma were significantly less ($P<0.05$) than those in four control patients with normal liver function (Table 1). Increases in K values of FT-207 were observed after pretreatment of a control patient with tocopheryl nicotinate. The administration of indomethacin, however, produced a slower clearance of FT-207 compared with the no pretreatment control. (Fig.

TABLE 1. DISAPPEARANCE RATES(K) FOR FT-207 IN PATIENTS WITH PRIMARY HEPATOMA AND OTHER CANCERS

Disease	K	Mean ± S. E.
Hepatocellular carcinoma	0. 079	0. 064 ± 0. 007
Hepatocellular carcinoma	0. 053	
Hepatocellular carcinoma	0. 075	
Hepatocellular carcinoma	0. 050	
Gastric cancer	0. 103	0. 115 ± 0. 009 ($P<0.05$)
Ovarian cancer	0. 103	
Lung cancer	0. 113	
Uterine cancer	0. 139	

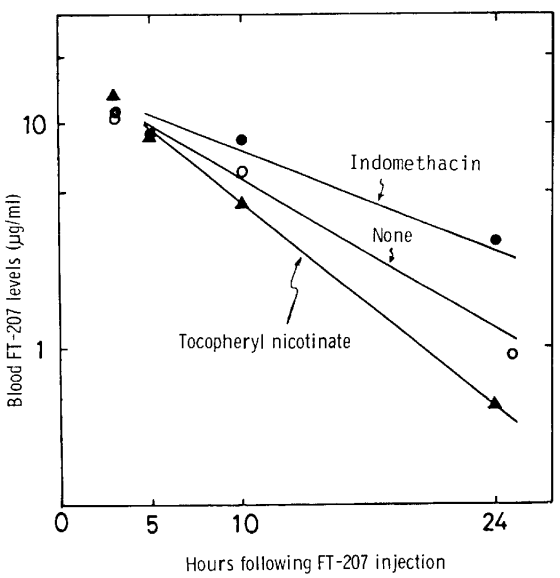

Fig. 2. Changes in the disappearance rates of FT-207 due to pretreatment of a patient with lung cancer with indomethacin and tocopheryl nicotinate. Pretreatment as described in Materials and Methods. K values: no pretreatment=0.113, indomethacin=0.072 and tocopheryl nicotinate=0.151.

2). On the other hand, in a patient with hepatocellular carcinoma, the K values were not affected by pretreatment with tocopheryl nicotinate or indomethacin (Fig. 3).

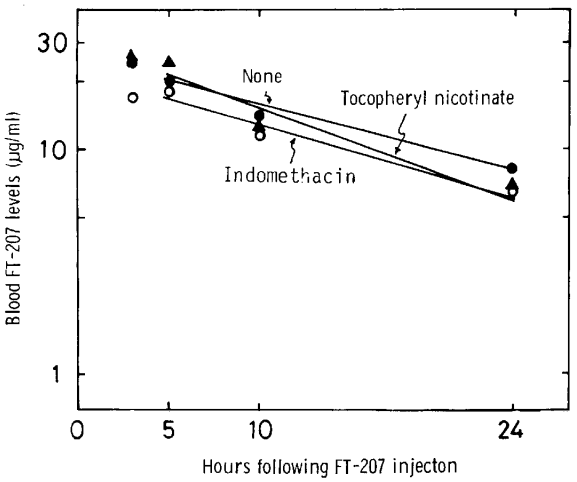

Fig. 3. Disappearance rate of FT-207 from the blood after pretreatment of a patient with primary hepatoma with indomethacin and tocopheryl nicotinate. K values: no pretreatment=0.053, indomethacin=0.047 and tocopheryl nicotinate=0.067.

DISCUSSION

Markedly decreased levels of hepatic microsomal enzymes and slower clearances of many drugs from the circulating blood have been reported under various conditions such as advanced cirrhosis of the liver and primary hepatoma (7). Since the cleavage of 5-FU derivative to 5-FU has been reported to be mainly enzymatic (8), the disappearance rates of FT-207 ought to be much slower in hepatoma patients with advanced cirrhosis than in patients with cancer but normal liver function. The present experiment confirmed higher blood levels of FT-207 after injection and slower clearance in liver-injured patients. The blood levels of FT-207 increased daily after continuous oral administration of FT-207 at 600 mg per day and reached plateau levels of 10–20 μg/ml in hepatoma patients, which were much higher than those in control patients (5–13 μg/ml) (9). Microsomal P-450 content and K values of FT-207 clearance were determined at the same time by pretreating rats with phenobarbital, indomethacin, diclofenac sodium and CCl_4 (known to affect microsomal enzyme activities) (10–12). The results suggest that K values are the most effective parameter of FT-207 metabolism in liver.

The livers of experimental animals bearing transplatable tumors also showed lower contents of cytochrome P-450 (4). Therefore the clinical efficacy

of FT-207 may be increased by inducing microsomal drug-metabolizing enzymes. The accelerated clearance of FT-207 in cancer patients with normal liver function was obtained by pretreating with tocopheryl nicotinate, which supplied NADPH to the microsomal drug-metabolizing system by inhibiting lipid peroxidation in liver (4). However, K values were unresponsive to this pretreatment in primary hepatoma. This poses problems to the use of FT-207 in patients with primary hepatoma. Pretreatment of hepatoma patients with phenobarbital or tocopheryl nicotinate to increase the efficacy of antitumor agents should be reconsidered in view of our findings. Our previous data also indicate that FT-207 was much more effective for adenocarcinoma of the gastrointestinal tract than for primary hepatoma (9). A direct correlation between increased FT-207 clearance and inhibition of hepatic RNA synthesis is now in progress in our laboratory.

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