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Metabolism of 1-(2-tetrahydrofuryl)-5-fluorouracil to 5-fluorouracil in partially hepatectomized rats

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Changes in the metabolism of 1-(2-tetrahydrofuryl)-5-fluorouracil (tegafur) to 5-fluorouracil (5-FU) were examined in the plasma, lung, liver, stomach, small intestine, spleen and kidney in two-thirds partially hepatectomized rats. Concentrations of tegafur and 5-FU in plasma and tissues were determined 30 min after injecting 100 mg/kg of tegafur via the tail vein. The 5-FU concentration in the plasma remained unchanged for the first 7 days after hepatectomy. The tissue level of 5-FU was higher in the liver and kidney than in other organs examined, but there were no changes in levels of 5-FU in each organ examined. Our observations support the peroposal that the conversion of tegafur to 5-FU is maintained in partially hepatectomized rats.

Key words: 5-Fluorouracil, partial hepatectomy, rat, 1-(2-tetrahydrofuryl)-5-fluorouracil.

Introduction

The β-nicotinamide adenine dinucleotide phosphate reduced form (NADPH)-dependent mixed-function oxidase system located in the endoplasmic reticulum of the liver plays a major role in the metabolism of various anticancer drugs.[1] Changes in this activity can affect the rate of metabolism of such drugs and, conceivably, alter the duration of action and toxicity. 1-(2-Tetrahydrofuryl)-5-fluorouracil (tegafur) and UFT (a combination of tegafur and uracil in a molar ratio of 1:4) are clinically prescribed for gastrointestinal cancers, including primary and metastatic liver tumors.[2,3] Tegafur is transformed to 5-fluorouracil (5-FU) primarily by hepatic drug-metabolizing enzymes which exhibit antineoplastic effects.[4] Iversen *et al.*[1] reported changes in these enzymes in the regenerating liver after partial resection. We examined the influence of partial hepatectomy on the conversion from tegafur to 5-FU. 5-FU concentrations in plasma and various organs were assayed following the i.v. administration of 100 mg of tegafur to two-thirds hepatectomized rats.

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Materials and methods

Drugs

Tegafur was obtained from Taiho Pharmaceutical Co. (Japan) and 5-FU was from Kyowa Hakko Co. (Japan).

Animals

Non-fasted male Wistar rats weighing between 150 and 200 g were kept under conditions of controlled temperature and humidity, and alternating 12 h light and dark cycles. Water and a conventional diet were given *ad libitum* throughout the experiment. Two-thirds hepatectomy was performed according to Higgins and Anderson.[5] Tegafur (100 mg/kg) was injected via the tail vein in a bolus, daily for 7 days following surgery. The rats were killed and plasma and organ tissues were immediately placed in liquid nitrogen. Five rats were used for each day: pre-hepatectomy and post-hepatectomy days 1, 2, 3, 5 and 7.

Assay of drug concentration

The concentrations of tegafur and 5-FU in plasma and organ tissues were determined using the gas chromatographic–mass fragmentographic method.[6,7] The tissues were homogenized with 2 volumes of saline and centrifuged at 1670 *g* for 10 min. Plasma and tissue homogenate volumes of 1 ml were adjusted to pH 2.0 with 5N HCl, chloroform was added and the preparation was shaken vigorously. The aqueous layer was used to determine the level of 5-FU and the chloroform layer was used to determine the level of tegafur.

Statistical analysis

The data were analyzed using the paired *t*-test; $p < 0.05$ was considered to be statistically significant.

Results

The plasma and organ tissue levels of tegafur and 5-FU were determined for 7 days following two-thirds hepatectomy (Figure 1). Drug concentrations in the plasma were maintained for 7 days at 180 μg/ml for tegafur and 0.075 μg/ml for 5-FU (Figure 1a). Following the i.v. administration of tegafur there was an equal distribution of the drug in each organ, both in intact and in the partially hepatectomized rats. The tissue level of tegafur in each organ remained unchanged. The level of 5-FU was higher in the liver and kidney than in the lung, stomach, small intestine and spleen. There were no changes in levels of 5-FU in each organ during the first 7 days after hepatectomy. Thus, partial hepatectomy in rats did not alter the conversion from tegafur to 5-FU.

Discussion

After tumor resection, including primary and metastatic liver tumors, the remaining tumor foci should be exposed to anticancer drugs during the early postoperative period because the doubling time of tumor cells in a small focus is often shorter than in a larger one.[8,9] Tegafur and UFT (a combined oral preparation of tegafur and uracil in a molar ratio of 1:4), both fluorinated pyrimidines, have been prescribed for primary and metastatic liver tumors.[2,3] As the *in vitro* metabolism of tegafur to 5-FU was noted in microsomal fractions of the liver in the presence of HADPH, tegafur is primarily converted to 5-FU in the liver.[4] It was reported that these enzymes decrease in the regenerating liver, in particular the level is lowest on post-operative day 3, after partial resection.[8] The possibility that the efficacy of tegafur and UFT decreases in the regenerating stage of the liver remains to be examined. We determined the influence of two-thirds partial hepatectomy on the conversion from tegafur to 5-FU in rats. When administered i.v., tegafur is transferred to each organ and is metabolized to 5-FU; thus, 5-FU levels in the plasma and the organs should reflect the metabolic activity *in vivo*. The 5-FU level did not change between the intact and regenerating livers, at 30 min after injecting tegafur, and even at 15 and 60 min after injection there was no change (data not shown). Our findings show that a decrease in drug-metabolizing enzymes of the liver does not alter the conversion from tegafur to 5-FU. The 5-FU level in the kidney was much the same as that in the liver; therefore, in the former, tegafur probably converts to 5-FU *in vivo*. Thus, in rats, two-thirds hepatectomy does not alter the pharmacokinetics of tegafur.

When tegafur is converted to 5-FU, the latter is more rapidly phosphorylated to fluoro-nucleotides and becomes more cytotoxic against regenerating liver cells.[10] The activity of these enzymes greatly influences the effects of 5-FU.[11] Adjuvant chemotherapy with fluorinated pyrimidines following hepatic resection is initiated after activities of the enzymes involved in nucleotide metabolism revert to normal ranges.

Conclusion

The metabolism of tegafur to 5-FU was examined in partially hepatectomized rats. Tegafur 100 mg/kg was injected via the tail vein, then 30 min later the plasma and organ tissue levels of tegafur and 5-FU were determined. The tissue levels of these drugs remained unchanged in the plasma and in all organs examined for 7 days after surgery.

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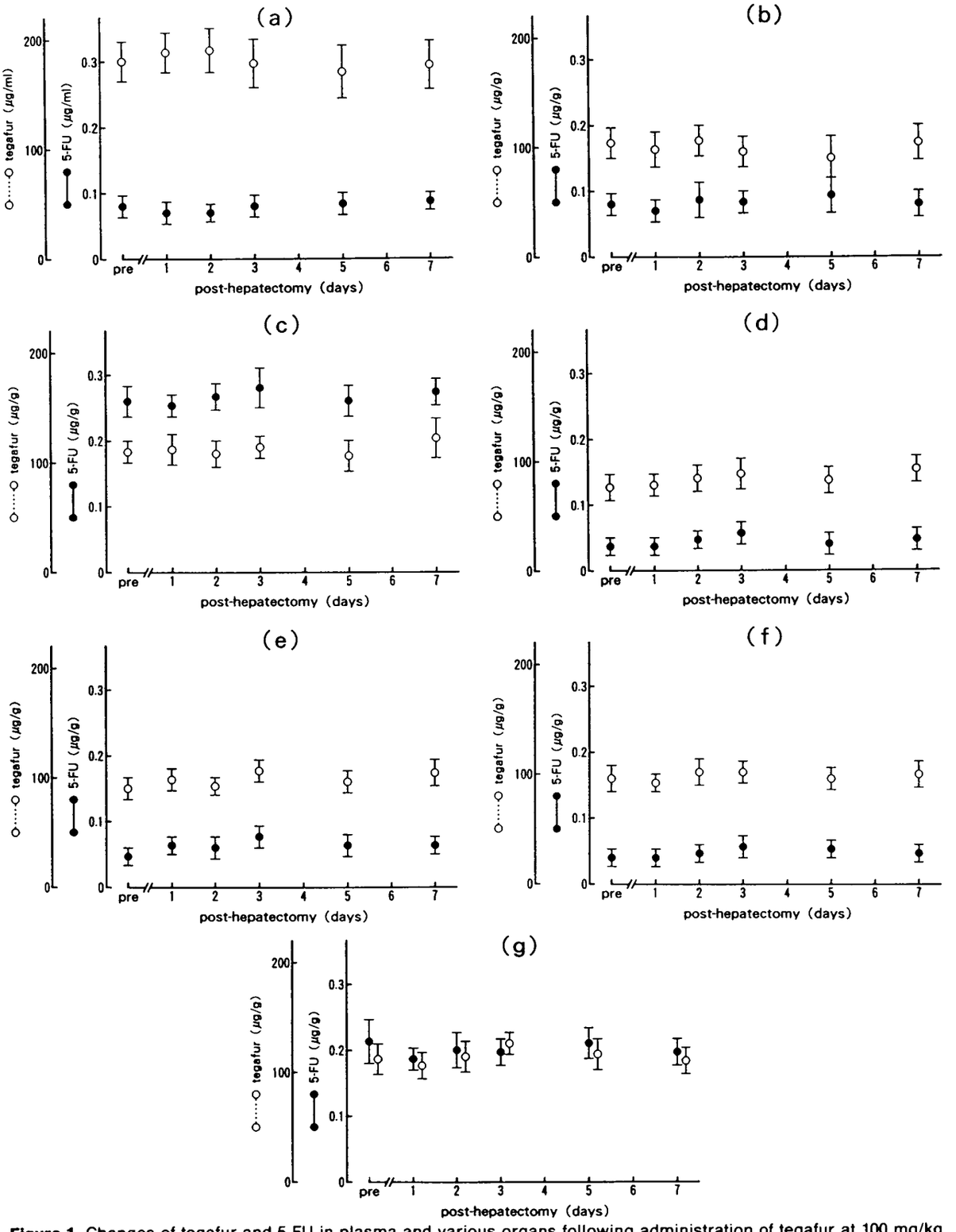

Figure 1. Changes of tegafur and 5-FU in plasma and various organs following administration of tegafur at 100 mg/kg to partially hepatectomized rats via the tail vein: (a) plasma, (b) lung, (c) liver, (d) stomach, (e) small intestine, (f) spleen and (g) kidney. Data obtained on each day are shown as mean ± SD.

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