5-Fluorouracil Concentrations in Human Plasma following R,S-1-(Tetrahydro-2-furanyl)-5-fluorouracil (Ftorafur) Administration

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Abstract

Following administration of i.v. doses of R,S-1-(tetrahydro-2-furanyl)-5-fluorouracil in cancer patients, discrepant results have been obtained by several investigators when assaying for 5-fluorouracil (FUra) plasma concentrations, ranging from 0.1 to 5 μg/ml at peak concentrations. The newly isolated R,S-1-(tetrahydro-2-furanyl)-5-fluorouracil metabolites with altered tetrahydrofuran moiety convert to FUra in vitro and may contribute to the high FUra plasma concentrations reported previously. We have observed FUra plasma concentrations considerably below those resulting from therapeutic slow FUra infusions (generally <0.1 μg/ml). Exceedingly low FUra concentrations after therapeutic doses of the prodrug R,S-1-(tetrahydro-2-furanyl)-5-fluorouracil suggest that metabolically generated FUras is further metabolized before redistribution to the systemic circulation.

The pyrimidine antimetabolites FT and FUra have similar antitumor activities but different selective tissue toxicities (12). FT is considered to be a slow metabolic release form of FUra which has been detected in low concentrations in human plasma after FT administration. However, there are large discrepancies between the reported peak FUra plasma concentrations resulting from FT administration, ranging from ≤5 μg/ml (2) to ≥1 μg/ml (7) and even below 100 ng/ml (1). Significant amounts of FUra metabolites have been isolated in rats (3), dogs, monkeys (5), and cancer patients (2) following [2-14C]FT administration. This supports the hypothesis that FT is metabolized to FUra to a large extent. Moreover, the myelotoxicity observed with FT clinically is comparable to that of FUra when FT is administered by slow i.v. infusion (12). One would, therefore, expect FUra plasma concentrations after FT doses to be similar to those found after equivalent doses of FUra given by slow i.v. infusion. However, this prediction is based on the assumption that metabolically generated FUra's freely distributes into the systemic circulation. It is also conceivable that the intracellularly formed FT may be rapidly metabolized to further products without reaching the circulation. The result would be relatively low FUra serum concentrations, in spite of significant FT conversion to FUra. We report here that FUra plasma concentrations in cancer patients after FT administration are considerably below those observed after an equivalent FUra infusion. High FUra concentrations after FT administration measured by other groups may represent an artifact arising mainly from a labile circulating FT metabolite, which we have recently isolated in our laboratory (1, 10).

Benvenuto et al. (2) reported FUra plasma concentrations of 1.7 μg/ml maintained over the observation period of 96 hr in cancer patients given a single FT dose of 4 to 5 g/sq m (total dose, 7 to 8 g). The theoretical FUra dose needed to achieve the plasma concentrations reported by Benvenuto et al. (2) in a 70-kg adult is approximately 24 g over 96 hr (37 g FT), assuming a plasma clearance of 2.1 liters/kg/hr for FUra (4). Furthermore, subsequent therapeutic FUra plasma concentrations during a 5-day infusion of FUra at the maximally tolerated dose of 30 mg/kg/day range only between 100 and 400 ng/ml (8), and concentrations above 1 μg/ml are normally expected to cause severe toxicities (11).

Spurious FUra determination as a metabolite of FT can arise from several sources. (a) The FT dose is usually contaminated with a small amount (0.15%) of FUra (1) which causes relatively high FUra plasma concentrations in the first 30 min after the FT infusion. In our recent study of FT disposition in cancer patients (1), we have observed initial FUra plasma concentrations of 200 ng/ml which rapidly declined with a half-life of about 10 min. Moreover, Benvenuto et al. reported FUra concentrations declined exponentially up to 2 hr after FT administration, when FT plasma concentrations were the highest. These observations speak against inhibition of FUra metabolism by FT as a possible cause of unusually high FUra plasma concentrations. (b) FUra may be formed from FT in vitro during storage and analytical work-up. Even a minor decomposition of FT to FUra may result in serious errors due to the large FT: FUra ratio in plasma (100 to 1000:1) (1, 7). (c) FT metabolites may convert to FUra in vitro. We have recently identified 2 hydroxylated FT metabolites, i.e., 3′-OH-FT and 4′-OH-FT, in rats, rabbits, and cancer patients (1, 10, 13). The 4′-OH-FT isolated from rabbit and human urine was partially converted to FUra by thymidine phosphorylase in vitro (1, 10, 13). This enzyme has been identified in human serum and plasma, and cancer patients were found to have higher enzyme activity than did normal subjects (9). Benvenuto et al. (2) subsequently found that a mixture of these 2 hydroxylated FT metabolites were partially converted to FUra when incubated with plasma and, to a lesser extent, with aqueous buffer. Furthermore, we have isolated a lipophilic metabolite of FT with an unsaturated

Received March 5, 1979; accepted July 10, 1979.
C=C bond in the tetrahydrofuran portion (dehydro-FT) as suggested by mass spectral evidence (1, 10). Dehydro-FT is chemically more labile than FT and releases FUra upon storage or when exposed to base and acid (1, 10).

Using storage and high-pressure liquid chromatographic assay conditions which minimize in vitro conversion of FT and its metabolites to FUra, we have measured plasma concentrations of FT, FUra, 4'-OH-FT, 3'-OH-FT, and dehydro-FT in 5 patients receiving FT intravenous (2 g/sq m i.v.) infused over 30 min (1). Results were similar in all patients. The plasma concentration-time curves of FT and its metabolites obtained from one patient with primary hepatoma and pleural effusions are given in Chart 1. FUra plasma concentrations are corrected for the FT dose contamination by FUra (0.15%) and for a 0.03% FT metabolism of the labile dehydro-FT metabolite. The plasma concentration ratios of FUra to FT were below 0.2%, which is lower than the 1% observed by Hills et al. (7), but in marked contrast to the initial 5%, steadily increasing with time recorded by Benvenuto et al. (2). Plasma concentrations of the labile dehydro-FT were the highest of all FT metabolites, reaching a plateau at 700 ng/ml after 4 hr and declining at a slower rate than did FT during the observation period of 24 hr. This kinetic behavior is similar to that of the FUra concentrations observed by Benvenuto et al. (2). Our data, therefore, suggest that previously reported high FUra plasma concentrations after FT administration were caused by partial or complete in vitro decomposition of the newly isolated, relatively labile dehydro-FT metabolite.

Previous reports of extensive conversion of FT to FUra metabolites and the similar antitumor activity of FT and FUra suggest that FT is activated to and metabolized via FUra. The findings in our studies of exceedingly low FUra plasma concentrations after a slow release FUra produrg, i.e., FT, support the hypothesis that intracellularly formed FUra is further metabolized without being redistributed via the systemic circulation. It is, therefore, important to elucidate the mechanism of intracellular activation, including the enzymes responsible for such activation. FT may be activated via hydroxylation followed by specific pyrimidine phosphorylase or by metabolism to dehydro-FT followed by nonenzymatic conversion to FUra. However, on the basis of kinetic consideration, one must assume that there are further, potentially more important, activation mechanisms which await further studies.

The alternate hypothesis that FT is activated to and metabolized via other metabolites independent of FUra cannot be ruled out at present.

References


Chart 1. Plasma concentration-time curves of FT and its metabolites, i.e., FUra, 4'-OH-FT, 3'-OH-FT, and dehydro-FT, in a patient given FT (2 g/sq m i.v.) infused over 30 min. Zero time refers to the end of infusion.
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