Effects of 5-Fluorouracil Prodrugs on the Central Nervous System in Mice and Rats

Katsuo Toide¹, Norio Unemi¹ and Tomio Segawa²

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Abstract: The effects of the central nervous system (CNS) of mice and rats were determined for the 5-fluorouracil prodrugs, 1-(2-tetrahydrofuran)-5-fluorouracil (FT), a combination of FT and uracil in a molar ratio of 1:4 (UFT), and 1-hexylcarbamoyl-5-fluorouracil (HCFU). Both FT and UFT failed to produce a significant prolongation of hexobarbital sleeping time in mice, while HCFU, at the same dose levels, caused a significant (P < 0.01) prolongation of hexobarbital sleep. FT, UFT, and HCFU produced a slight suppression of coordinating ability in mice, but the effect of HCFU was more pronounced than that of FT and UFT. There were no significant changes in 5-hydroxytryptamine contents in the cerebral cortex and only small insignificant changes of dopamine contents in the corpus striatum by any of the drugs examined. Furthermore, HCFU was more potent than FT and UFT in potentiating the actions of ethanol. These results suggest that HCFU is more toxic to the CNS than are FT and UFT.

5-Fluorouracil (5-FU) has been widely used for the treatment of cancer. In addition to its antitumor activity, however, 5-FU possesses various side effects such as gastrointestinal (GI) and hematological toxicity (1).

1-(2-Tetrahydrofuran)-5-fluorouracil (FT) (Fig. 1) was synthesized as a derivative of 5-FU by Hiller et al. (2) and is now commonly used as an oral antitumor agent in Japan. Because FT is slowly converted to 5-FU (3), its toxicities in bone marrow and GI tracts are lower than those of 5-FU (4). However, FT passes easily through the blood brain barrier and produces occasionally side effects in the central nervous system (CNS), including lethargy, ataxia, confusion, dizziness, and hallucination (5, 6). 5-FU occasionally also causes reversible cerebellar ataxia (7).

It was found that coadministration of uracil with FT increased 5-FU level in tumor and blood, possibly because uracil inhibits the degradation of 5-FU formed from FT in the liver (8). There-

Fig. 1 Chemical structures of FT, UFT and HCFU.

References

fore, UFT (Fig. 1), a new type of anti tumor agent consisting of FT and uracil in a molar ratio of 1:4, has been developed for the purpose of increasing the antitumor activity of FT without producing the severe toxicity as 5-FU (9), and there are no reports concerning the CNS side effects of UFT so far (10).

Recently, 1-hexylcarbamoyl-5-fluorouracil (HCFU) (Fig. 1) has been developed as a derivative of 5-FU. Because of its lipophilicity, this compound is easily taken up into tumor tissues, and it is converted non-enzymatically to the active substance 5-FU (11), whereas FT is mainly converted enzymatically to 5-FU in the liver. HCFU was shown to be an effective anti-tumor agent in clinical trials (12). However, the characteristic subjective symptoms such as heat sensation and pollakiasuria were reported at high doses in clinical trials with HCFU (12). Moreover, patients treated with HCFU experienced consciousness disturbances following the ingestion of alcoholic beverages (13, 14).

In the present study it was attempted to investigate the CNS side effects of 5-fluorouracil produgs and to examine the interaction of these antitumor agents and ethanol.

Materials and Methods

**Animals.** Male ddY strain mice weighing 20 to 25 g and male Wistar strain rats weighing 150 to 180 g were used. They were housed at 22 ± 1°C and 55 ± 5% relative humidity under controlled lighting conditions.

**Chemicals.** The following agents were used: FT (Takbo Pharmaceutical Co., Ltd.), uracil (Wako Pure Chemicals, Ltd.), HCFU (Mitsui Pharmaceutical Co., Ltd.), hexobarbital sodium (Sigma), ethanol (Wako Pure Chemicals, Ltd.), dopamine (Nakarai Chemicals, Ltd.), 5-hydroxytryptamine creatinine sulfate complex (Sigma) and chlorpromazine hydrochloride (Shionogi Pharmaceutical Co., Ltd.).

**Sample preparation and drug treatment.** FT, UFT and HCFU were suspended in 5% gum arabic solution and given per os (p.o.) at a volume of 1 ml/100 g body weight. Ethanol (25% v/v solution) was given p.o. at a volume of 0.1 to 0.2 ml/10 g body weight.

Chlorpromazine was given intraperitoneally (i.p.). Before drug administration, the animals were starved for 16 h but given water *ad libitum.*

**Analytical and pharmacological methods**

1. **Effect on hexobarbital-induced sleeping time in mice.**

At 1 h after test drugs administration (p.o.), all mice were injected i.p. with 70.0 mg/kg hexobarbital, and the duration of sleep, measured as the time from loss to restoration of righting reflex, was recorded. The mean sleeping time of each group was calculated and compared with that of the control group treated with 5% gum arabic.

2. **Effect of hypnosis induced by ethanol in mice.**

Mice were treated orally with test drugs 60 min prior to administration of ethanol (4000 mg/kg, p.o.), and the effect of drug was regarded as positive when a mouse showed a loss of righting reflex over 20 min.

3. **Effect on coordinating ability in mice.**

Mice capable of staying on a rotation rubber rod (3.0 cm diameter, 15 rpm) for longer than 1 min were selected and were trained for three more days. Groups of 8 mice were tested each time after drug administration (p.o.). When a mouse slipped off the rod within 1 min, the test was considered positive.

4. **Effect on brain monoamines in rats – determination of 5-hydroxytryptamine (5-HT) and dopamine (DA).**

For the determination of 5-HT and DA, animals were killed by microwave irradiation (4.5 kW, 1.0 sec.). The brain was rapidly removed, and cerebral cortex and corpus striatum were separated by the method of Glowinski and Iversen (15). 5-HT in the cerebral cortex was measured spectrofluorimetrically by the method of Curzon and Green (16). DA in the corpus striatum was extracted by the method of Anton and Sayre (17) and measured spectrofluorimetrically by the method of Chang (18).

**Statistical analysis**

Differences between control and experimental values were analyzed by Student's t-test.

**Results**

**Effect on hexobarbital-induced sleep**

Both FT (90.0 and 270.0 mg/kg, p.o.) and UFT (291.6 and 874.8 mg/kg, p.o.) did not produce a significant prolongation of hexobarbital sleeping time. In contrast, HCFU (90.0 and 270.0 mg/kg, p.o.) caused a significant (P < 0.01 and P < 0.05) prolongation of hexobarbital sleeping time (Fig. 2). Chlorpromazine also produced a significant prolongation of hexobarbital sleeping time (P < 0.001).

**Effect on coordination ability**

Within 1 h after administration, FT (90.0 and 270.0 mg/kg, p.o.) and UFT (291.6 and 874.8 mg/kg, p.o.) did not...