the early stages and increased their viability in the last stages of cultivation. This effect was manifested more clearly in the experimental cultures of embryonic liver from CBA mice, whose survival rate under normal conditions was lower than that of C57BL. Other workers have observed the same effect in organ cultures of embryonic liver and kidney tissues [3, 4, 7] during the transplacental action of various carcinogens, whereas the transplacental exposure to pyrene, the noncarcinogenic analogue of benzo(a)pyrene did not increase the survival rate of organ cultures of the lungs [2].

LITERATURE CITED

1. V. I. Gel'shtein, Vopr. Onkol., No. 10, 58 (1961).
2. T. S. Kolesnichenko, Vopr. Onkol., No. 5,68 (1976).
3. T. S. Kolesnichenko, Vopr. Onkol., No. 10, 48 (1972).
4. T. S. Kolesnichenko, Byull. Éksp. Biol. Med., No. 5, 71 (1973).
5. T. S. Kolesnichenko and N. V. Popova, Byull. Éksp. Biol. Med., No. 9, 1116 (1976).
6. E. A. Luria, Hematopoietic and Lymphoid Tissue in Culture [in Russian], Moscow (1972).
7. L. M. Shabad, T. S. Kolesnichenko, and Yu. D. Sorokina, Transplacental Carcinogenesis and Organ Cultures [in Russian], Moscow (1975).
8. B. I. Fuks and G. B. Fridman, in: Problems in Oncology [in Russian], No. 6, Moscow (1953), pp. 79-84.

PHARMACOKINETICS OF FTORAFUR-2-^{14}C IN RATS WITH WALKER'S CARCINOSARCOMA

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The pharmacokinetics of ftorafur-2-^{14}C (FF) after intravenous injection was investigated in experiments on rats with Walker's carcinosarcoma. The level of FF and its metabolites in the blood plasma was shown to fall in the manner of a three-phase process. The concentration of the compound in the tissues falls in the order: kidneys, small intestine, tumor, stomach, muscles, heart, liver, lungs, spleen, brain, and fat. The presence of FF-2-^{14}C and its metabolite, endogenous 5-fluorouracil, was observed in the tumor. Excretion of the compound continued for 48 h, 52.2% being excreted through the kidneys, 38% through the lungs, and 0.8% of the injected dose with the feces.

KEY WORDS: ftorafur; 5-fluorouracil; permeability; metabolism; Walker's carcinosarcoma.

The ability of ftorafur-2-^{14}C (FF) and its metabolite 5-fluorouracil-2-^{14}C (5-FU) to penetrate into tumor tissue was investigated and the length of stay of the compound in the body of animals with tumors was estimated.

EXPERIMENTAL METHOD

Noninbred male albino rats weighing 170-200 g were used. Ftorafur-2-^{14}C had a specific radioactivity of 2.8 μCi/mg. The compound was given intravenously as a single dose of 150 mg/kg (11 μCi/kg). The animals were killed 0.25, 0.5, 1, 2, 3, 6, 10, and 24 h after injection of the compound and the radioactivity was determined in the blood and various organs with the SL-30 (Intertechnique) scintillation counter with correction of the

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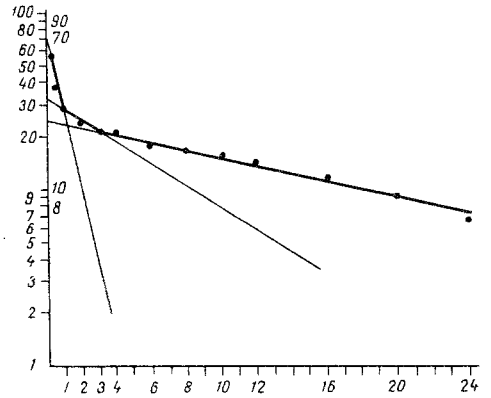

Fig. 1. Level of radioactivity in blood plasma of rats with Walker's carcinosarcoma after intravenous injection of labeled FF. Abscissa, time (in h); ordinate, radioactivity of blood plasma (in cpm/ml · 10^3).

TABLE 1. Level of Radioactive Products in Tissues of Rats with Walker's Carcinosarcoma after Intravenous Injection of FF-2-^{14}C

Tissue	Substance identified	Radioactivity at various times after injection of FF-2-^{14}C			
		1 h	3 h	6 h	10 h
Liver	FF	9 900	20 100	13 920	8 400
	5-FU	1 160	3 120	2 300	2 530
Brain	FF	7 440	17 400	13 500	8 550
	5-FU	560	1 300	1 200	950
Tumor	FF	10 800	24 200	16 100	9 630
	5-FU	840	2 100	1 620	1 370

TABLE 2. Values of Total, Renal, and Pulmonary Clearances for Three Phases of Kinetics of FF-2-^{14}C in Rats with Walker's Carcinosarcoma

Clearance, ml/h	Phase of pharmacokinetics		
	I	II	III
Total	56,2	20,5	15,2
Renal	4,5	6,7	7,8
Pulmonary	3,4	6,2	6,2

results for 100% efficiency. Samples were prepared for analysis of radioactivity in the tissues and biological fluids by Mahin's method [11] and for analysis of radioactivity excreted with the expired air by Jeffay's method [10]. To identify the compound and its metabolites thin-layer chromatography in a chloroform–methanol (9:1) solvent system was used [9]. To determine the coefficient of distribution (P) of FF in an octanol–water system the method of Hansch [8] was used. To equalize the experimental data during changes in the concentration of the compound in the blood the method of least squares was used [5]. The method of calculating the pharmacokinetic parameters was taken from the paper by Kivman et al. [2].

EXPERIMENTAL RESULTS

As will be seen in Fig. 1, the total radioactivity of the blood plasma fell in the manner of a three-phase exponential process. The half-elimination period of the compound and of its metabolic products in each of the three successive phases was 0.75, 4.95, and 13.57 h, respectively. The compound and its metabolites, by

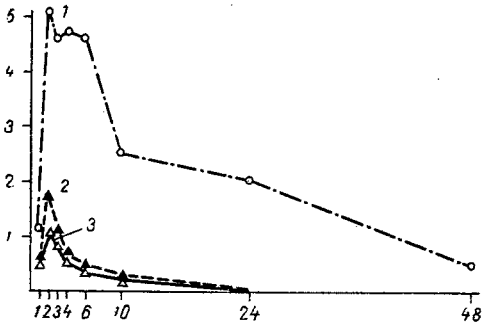

Fig. 2. Level of FF-2-^{14}C and its metabolites in urine of rats with Walker's carcinosarcoma: 1) FF-2-^{14}C; 2) 5-FU-2-^{14}C; 3) FUDR-2-^{14}C. Abscissa, time (in h); ordinate, radioactivity (in cpm/ml · 10^3).

gradually penetrating into the tissue, ultimately filled the whole "volume" of the body. This is shown by the value of the apparent distribution volume, which was 34% for the first phase, 81.3% for the second, and 97.3% for the third.

The high value of the apparent distribution volume was evidently the result of the ease with which passive diffusion of labeled FF takes place through cell membranes. This feature of the action of FF can be explained by its physicochemical properties. Substances dissociated only a little at physiological pH values, with log P within the range between 1 and −1, have optimal conditions for passive diffusion through biological membranes [7]. With $pK_a = 7.8$ and log P = 1.02, FF belongs to this class of compounds.

The level of radioactivity of the tissues reached a maximum of 3 h after injection of the compound and then fell gradually. After 24 h the radioactivity in the tissues was about 10% of its maximum. The concentration of the preparation in the organs fell in the order: kidneys, small intestine, tumor, stomach, muscles, heart, liver, lungs, spleen, brain, and fat.

Ftorafur is known to be broken down in the rat with the formation of endogenous 5-FU [1, 6]. Data on the relative distribution of this metabolite and also of FF in the liver, tumor, and brain of the experimental animals are given in Table 1. The highest concentration of 5-FU in the liver points to the basic role of this tissue and, in particular, of its microsomal fraction [6], in the metabolism of FF to endogenous 5-FU. The presence of endogenous 5-FU in the tumor is a very important finding, for this metabolite of FF has high cytostatic activity. Appreciable quantities of labeled 5-FU also were present in the tissues of the brain. Since no foreign compounds are metabolized in the brain [4], the endogenous 5-FU was evidently brought by the blood stream.

The study of the excretion of radioactivity after intravenous injection of FF-2-^{14}C showed that excretion of the compound and of its metabolites continued until 48 h: 52.2% of the label was excreted by the kidneys, 38% by the lungs, and 0.8% with the feces, making a total of 91% of the injected dose. The kidneys thus play the main role in the excretion of FF. This is shown not only by the data on the balance of excretion, but also by the values of the renal clearance (Table 2). The excretion of labeled FF with the urine was accompanied by excretion of its metabolites, of which 5-FU-2-^{14}C and 5-fluoro-2-deoxyuridine-2-^{14}C (FUDR-2-^{14}C) were identified (Fig. 2).

Thus FF penetrates readily into tumor tissue. The appearance of 5-FU in the tumor tissue after injection of FF must be regarded as an important factor in the mechanism of the antitumor action of FF. While FF itself has no primary antitumor activity [3], it ensures the prolonged circulation of endogenous 5-FU, to which the chemotherapeutic effect of the compound is evidently due, in the body of the tumor carrier.

LITERATURE CITED

1. S. A. Giller, D. V. Meiren, Kh. B. Khagi, et al., Vopr. Onkol., No. 9, 84 (1975).
2. G. Ya. Kivman, É. A. Rudzit, and V. P. Yakovlev, in: Methods of Experimental Chemotherapy [in Russian], Moscow (1971), p. 479.
3. D. V. Meiren and A. K. Belousova, Vopr. Med. Khim. No. 3, 288 (1972).

4. D. Park, The Biochemistry of Foreign Compounds [Russian translation], Moscow (1973), p. 288.
5. N. A. Plokhinskii, Biometrics [in Russian], Moscow (1970).
6. É. L. Urbanovich, D. V. Meiren, and A. P. Gilev, in: Abstracts of Scientific Proceedings of the Third All-Union Biochemical Congress [in Russian], Vol. 1, Riga (1974), p. 264.
7. M. Hakala, in: Handbuch der Experimentellen Pharmakologie (ed. by A. Heffter), Vol. 38/1, Berlin (1974), p. 240.
8. C. Hansch, P. Maloney, T. Fujita, et al., Nature, 194, 178 (1962).
9. J. P. Horowisz, J. J. McCormick, K. D. Philips, et al., Cancer Res., 35, 1301 (1975).
10. H. Jeffay and J. Alvarez, Anal. Biochem., 33, 612 (1961).
11. D. T. Mahin and R. T. Lofberg, Anal. Biochem., 16, 500 (1966).