THE PHARMACOKINETICS OF 5-FLUOROURACIL-2-C^{14}

A. P. Gilev, D. V. Meirena,
Kh. B. Khagi, M. N. Koptelova,
and É. A. Shafro

UDC 615.277.3:547.854.]4.015.4

The dynamics of the concentration of radioactivity in the blood serum, organs, and urine was investigated after intravenous injection of 5-fluorouracil-2-C^{14} into rats. The preparation is rapidly absorbed from the blood into the tissues in which it accumulates rapidly in high concentrations and it is excreted quickly from the body. The half-elimination period of 5-fluorouracil in the blood is 15 min. It is excreted chiefly by extrarenal routes.

KEY WORDS: fluorouracil; pharmacokinetics; radiometry.

The action of the antitumor compound 5-fluorouracil (5-FU) is accompanied by serious toxic side-effects [1, 4]. In recent years a search has therefore been made for analogs of 5-FU with a less toxic action [2]. Progress in this search is dependent on the discovery of the causes of the toxic properties of 5-FU, and to some extent these could be attributable to its pharmacokinetic characteristics [7-14].

The distribution of this compound in the tissues and the rate of its elimination from the body were investigated.

EXPERIMENTAL

Noninbred male albino rats weighing 170-230 g were given an intravenous injection of 5-fluorouracil-2-C^{14} (5-FU-2-C^{14}) in a dose of 60 μCi/kg. The radioactivity of the organs and biological fluids was determined. Four rats were used at each time of the investigation. Urine was collected for 24 h during water loading (50 ml/kg). To determine the radioactivity, 20% aqueous homogenates of the tissues were prepared. The samples were applied to disks of FN-3 chromatography paper, and the radioactivity was determined by the USS-1 liquid scintillation counter (counting efficiency 36% for C^{14}). The radioactivity of the blood serum and urine was determined without any preliminary treatment. The results were expressed in pulses/min/g tissue or in pulses/min/ml biological fluid.

The degree of binding of the compound with the blood serum proteins was investigated by equilibrium dialysis with rabbits [3]. The 5-FU was estimated spectrophotometrically (λ_{max} = 267 nm).

The clearance of 5-FU was calculated by the method described by Rudzit [6].

The empirical curves reflecting the accumulation of the compound in the urine were matched by the method of regression analysis [5].

RESULTS AND DISCUSSION

The radioactivity of the blood serum was determined 15 and 30 min and 1, 2, 3, 6, 10, and 24 h after the injection of 5-FU-2-C^{14}. As Fig. 1 shows, during the first 60 min the serum level of the compound fell sharply.

The writers have shown that 5-FU is not bound by the blood serum proteins; this is evidently one factor responsible for the rapid clearance of this compound from the serum.

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga. (Presented by Academician of the Academy of Medical Sciences of the USSR V. V. Zakusov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 78, No. 12, pp. 39-41, December, 1974. Original article submitted March 1, 1974.

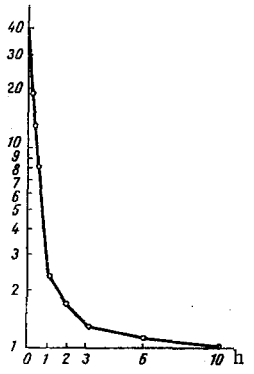

Fig. 1

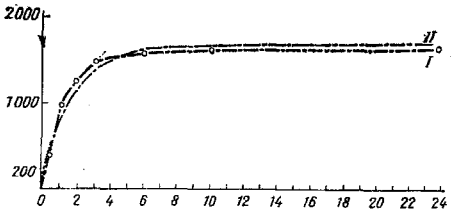

Fig. 2

Fig. 1. Radioactivity of blood serum of rats after intravenous injection of 5-fluorouracil-2-C^{14}. Abscissa, time (in h); ordinate, radioactivity of serum (in pulses/min/ml · 10^3).

Fig. 2. Radioactivity in urine of rats after intravenous injection of 5-fluorouracil-2-C^{14}: I) experimental curve; II) theoretical curve. Remainder of legend as in Fig. 1.

TABLE 1. Radioactivity (in pulses/min/g) in Tissues of Various Rat Organs after Intravenous Injection of 5-Fluorouracil-2-C^{14}

Time after injection (in h)	Brain	Thymus	Heart	Lungs	Liver	Kidneys	Spleen	Skeletal muscles	Stomach	Small intestine	Large intestine
1	33 600	400	0	9200	32 600	9400	12 400	23 600	3400	11 600	21 200
6	0	0	5600	0	0	400	5 200	10 000	0	4 400	4 000
10	0	0	0	0	0	0	0	0	0	0	0

During the first hour until equilibrium was established between the blood serum and tissues, the logarithm of the 5-FU concentration in the blood serum changed as a linear function of time. The decrease in the concentration of 5-FU in the blood serum in the first phase could therefore be described by a linear equation by means of which the half-elimination period of 5-FU was calculated: its value was 15 min.

In the second phase of the concentration dynamics, 1 h after injection of the compound, its serum level fell very slowly. This phase mainly reflects the clearance of the compound from the blood serum was a result of its metabolism and excretion. It is not described by an experimental function and was not subjected to mathematical analysis.

The radioactivity of the tissues was determined 1, 6, and 10 h after the injection of 5-FU-2-C^{14}. The character of the distribution of radioactivity with time did not depend on the organ studied. The highest radioactivity was observed during the first hour, when it was particularly high in the brain, liver, large intestine, and skeletal muscles (Table 1). In most organs the radioactivity was negligible after 6 h.

The excretion of radioactive substances in the urine was determined 30 min and 1, 2, 3, 6, 10, and 24 h after injection of the compound. The kinetics of the excretion of 5-FU with the urine was found to be a linear function.

It will be clear from Fig. 2 that during the first 2 h, 5-FU-2-C^{14} and its metabolic products were excreted very rapidly with the urine, after which the rates of excretion of the radioactive substances fell sharply.

Calculation showed that in 24 h only 15% of the 5-FU was excreted through the kidneys. The great importance of extrarenal factors in the excretion of 5-FU was also reflected in the extrarenal clearance, calculated for the first phase of the concentration dynamics (Table 2).

Two general conclusions can be drawn from the data on the pharmacokinetics of 5-FU. First, the high rate of absorption of 5-FU accompanied by the rapid accumulation of the compound in some organs and tis-

TABLE 2. Clearance of 5-FU-2-C^{14} in Rats

Index	Value of Index
Level of radioactivity at time of injection (in pulses/min/ml)	30,000
Apparent distribution volume of 5-FU in the body (% of body weight)	175
Plasma constant (in min^{-1})	0.045
Half-elimination period in plasma (in min)	15
Clearance (in ml/min):	
total	16.5 (100%)
renal	5.9 (35.7%)
extrarenal	10.6 (64.1%)

sues. The high concentrations of 5-FU built up in the tissues during the first few minutes after its injection may be responsible for its acute toxic effects. Second, the high rate of elimination of 5-FU from the tissues is another detrimental feature of the compound, for the effectiveness of chemotherapeutic agents is known to be determined not only by their concentration but also by the duration of their stay in the tissues.

In the attempt to obtain effective analogs of 5-FU the object must therefore be to achieve a steady accumulation of the compound and its maintenance in the tissues for a longer time.

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