Biochemical Pharmacology, 1966, Vol. 15, pp. 435–446. Pergamon Press Ltd., Printed in Great Britain.

THE METABOLISM OF 5-FLUOROCYTOSINE-2^{14}C AND OF CYTOSINE-^{14}C IN THE RAT AND THE DISPOSITION OF 5-FLUOROCYTOSINE-2^{14}C IN MAN

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(*Received* 18 *September* 1965; *accepted* 1 *November* 1965)

Abstract—5-Fluorocytosine (5-FC), an antimetabolite of cytosine with specific fungistatic properties, was labeled in the 2-position with carbon-14.

On parenteral administration in rats, 5-FC-2^{14}C was not metabolized and was recovered quantitatively and rapidly, mostly in the urine. On oral administration, partial deamination to 5-fluorouracil (5-FU) occurred by action of the intestinal flora, resulting in the excretion of the known metabolites of 5-FU, α-fluoro-β-ureido-propionic acid, urea, and CO_2.

In man, after oral doses, no metabolic degradation of 5-FC-2^{14}C occurred. Apparent fungistatic concentrations of 10–40 μg/ml persisted in the blood for 6–10 hr after a single 2-g dose. The half-life of 5-FC in man was 4–8 hr.

The metabolic fate of cytosine-2^{14}C in the rat paralleled that of its antimetabolite in that significant degradation followed only its administration by the oral route.

5-FLUOROCYTOSINE (5-FC) was first synthesized by Duschinsky *et al.*[1] Unlike other compounds of this series, including 5-fluorouracil (5-FU), its riboside and deoxyriboside,[2] as well as the riboside and deoxyriboside of 5-FC,[3] 5-FC itself was found to lack significant cytostatic activity and toxicity in mammals. In contrast also to the other fluorinated pyrimidines, 5-FC exhibited practically no bacteriostatic activity *in vitro* but marked and rather selective antifungal activity against *Candida albicans*, *in vitro*[4] and *in vivo*.[4, 5] These properties suggested the clinical usefulness of 5-FC as a drug against systemic candidiasis.

As expected from its structure and demonstrated by the reversal of the inhibitory effects observed *in vitro* by cytosine, 5-FC can be considered an antagonist of cytosine, with which it will compete metabolically.[4] Such a direct function of 5-FC as an antimetabolite may be distinguished from a more indirect effect due to release of 5-FU from systems possessing the necessary deaminase.

Preliminary experiments in which ^{14}C-labeled 5-FC was incubated with *C. albicans* *in vitro* at fungistatic concentrations demonstrated incorporation into RNA as fluorouracil riboside. The mechanism by which this is effected remains to be investigated.

The low toxicity of 5-FC in mammals appeared to be consistent with the previously reported findings by Bendich *et al.*[6] that in rats, dietary cytosine was not a precursor of nucleic acid pyrimidines and was excreted mostly in unmetabolized form. A similar metabolic inertness of the fluorinated analogue was suggested by high recoveries of the intact compound in the urine after its oral administration to dogs.[7] However, the

semiquantitative nature of these metabolic data, together with the observation of toxic manifestations similar to those caused by 5-FU following the oral chronic administration at high doses of 5-FC to rats and dogs,[8] induced us to re-examine these metabolic relationships by means of more quantitative techniques.

In this paper we report the disposition of 5-FC labeled in the 2-position with ^{14}C and of similarly labeled cytosine in rats, after oral and parenteral administration. In addition, the results of a human study are presented in which 5-FC-2^{14}C was administered orally, and blood levels and the metabolic disposition of the compound were determined.

EXPERIMENTAL

Synthesis of 5-fluorocytosine-2^{14}C

The previously reported procedure[1] involved hydrolysis of 2-ethylmercapto-4-amino-5-fluoropyrimidine by refluxing with concentrated hydrobromic acid, a step leading to partial loss of the 4-amino group and to a product contaminated with 5-fluorouracil. Therefore a new method[9] starting from 5-FU (I) was elaborated and used for this preparation of 5-FC-2^{14}C (see Fig. 1).

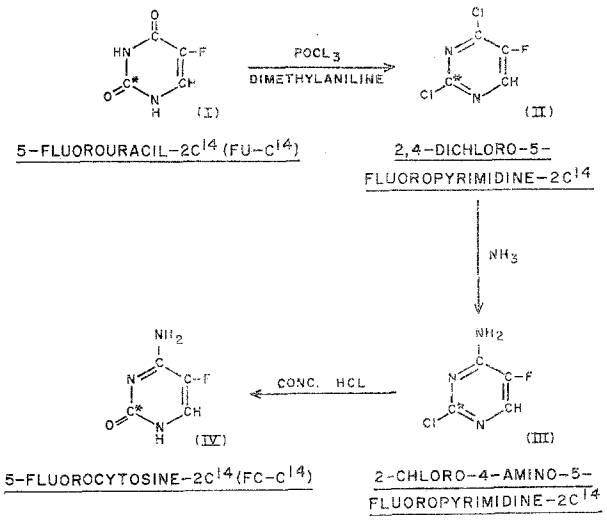

FIG. 1. Synthesis of 5-fluorocytosine-2^{14}C.

One hundred and thirteen mg (0·81 mmole) of 5-fluorouracil-2^{14}C (obtained from Calbiochem, Los Angeles, Calif.), specific activity 230 μc/mmole, in 1·619 g (10·56 mmoles) of freshly distilled phosphorus oxychloride and 185 mg (1·51 mmoles) of freshly distilled dimethylaniline, was refluxed for 2 hr. The reaction mixture was partitioned between ether and ice water. The latter, containing all the unreacted 5-FU-2^{14}C, was re-extracted twice more with ether. The residue of the combined ether extracts was sublimed at 16 mm and 50°, yielding 117 mg (0·70 mmole) of 2,4-dichloro-5-fluoropyrimidine-2-^{14}C (II). This product was dissolved in 2 ml ethanol and reacted with 0·50 ml concentrated aqueous ammonia at +5° for 18 hr. In contrast to the unfluorinated 2,4-dichloro-pyrimidine, which is converted with ammonia to about

equal amounts of 2-chloro-4-amino and 2-amino-4-chloro isomers, compound II gave mainly the former product (III).[10] Paper chromatography in the system isopropanol:HCl:H_2O (170:41:39) revealed a single radioactive peak of the characteristic R_f of 0·75. The reaction mixture was then taken to dryness and partitioned three times between water and ethyl acetate, whereby the NH_4Cl was removed with the aqueous phase. The combined solvent extracts were dried and evaporated to yield 85 mg (0·50 mmole) of (III) as a crystalline product, melting at 196–197°. Its solution in 0·1 N HCl showed the characteristic u.v. maxima at 235 mμ and 269 mμ.* This product (III) was suspended in 3·5 ml of concentrated HCl and heated to 93–95°. The ratio of the u.v. extinction at 270 mμ and at 300 mμ was measured periodically on a dilution of a small aliquot in 0·1 N HCl. After 2 hr this ratio had reached a value of 0·86, indicative of a completed hydrolysis to 5-FC (IV), and the reaction was stopped. The reaction mixture was taken to dryness and freed of excess HCl by repeated addition and re-evaporation of water. To the solution of the residue in 1·0 ml of water, 0·5 ml of concentrated NH_3 was added, whereby (IV) crystallized slowly. It was filtered and washed with ethanol and ether. A total of 50 mg (0·39 mmole) of (IV) of a specific activity of 232 μc/mmole was obtained, representing an overall yield of 45%.

On paper chromatography in the system ethyl acetate:formic acid:water (12:1:7) this product showed a single radioactive peak of $R_f = 0{\cdot}09$.

Cytosine-2^{14}C was obtained as the hemisulfate, from Calbiochem, Los Angeles, Calif., and its specific activity was diluted to the desired value.

Rat experiments

Sprague-Dawley rats weighing 200–300 g were used. Doses of 10–15 mg/kg and 4·8 to 6·1 $\times$ 10^6 cpm per rat of either compound were administered as aqueous solutions, either orally by stomach tube or by intraperitoneal injection.

The rats were housed in closed glass metabolism cages providing for separate collection of urines and feces. CO_2-free air was passed through the cage by suction, and the respiratory CO_2 was collected by drawing the effluent air stream through a sealed-in fitted glass disk into a column (2 in. $\times$ 12 in.) containing 200 ml of NaOH solution. The concentration of NaOH was 0·5 N for a 2 to 4-hr collection interval and 2·5 N for intervals of 4 to 12 hr. The CO_2 content of a 20-ml aliquot of a 0·5 N NaOH solution was precipitated and collected quantitatively as $BaCO_3$. A 100-mg aliquot thereof was suspended in 1 ml of water, admixed to 20 ml of 4% thixotropic gel (Cab-O-Sil) suspension in the dioxane phosphor solution, and was counted in the Packard TriCarb scintillation counter. The specific activity and the total radioactivity per fraction of collected $^{14}CO_2$ were calculated. Urines, aqueous homogenates of tissues, and ethanolic homogenates of feces were plated on stainless steel planchets, counted at intermediate thickness by means of a D-47 flow gas counter (Nuclear Chicago Corp.), and corrected for self-absorption.

The urinary excretion products of 5-FC-2^{14}C were characterized by paper chromatography on Whatman 1 paper developed with the solvent mixture isopropanol: conc. HCl:H_2O (170:41:39). The distribution of the radioactivity was determined by means of an Actigraph II paper scanner (Nuclear Chicago Corp.). This system separated intact 5-FC ($R_f = 0{\cdot}4$) from the faster-moving combined metabolites, which included 5-FU and/or its further degradation products α-fluoro-β-ureido-propionic

* The extinction ratio 300 mμ/270 mμ of (III) is less than 0·1.

acid (FUPA) and urea.[11, 12] They could be separated from 5-FC and from each other by one- and two-dimensional thin-layer chromatography with the solvent systems: I, ethyl acetate:formic acid:water (60:5:35); II, isopropanol:ammonia (20:1); and III, methanol:water (85:15). Typical two-dimensional thin-layer chromatograms and their evaluation by means of standards are shown in Fig. 2.

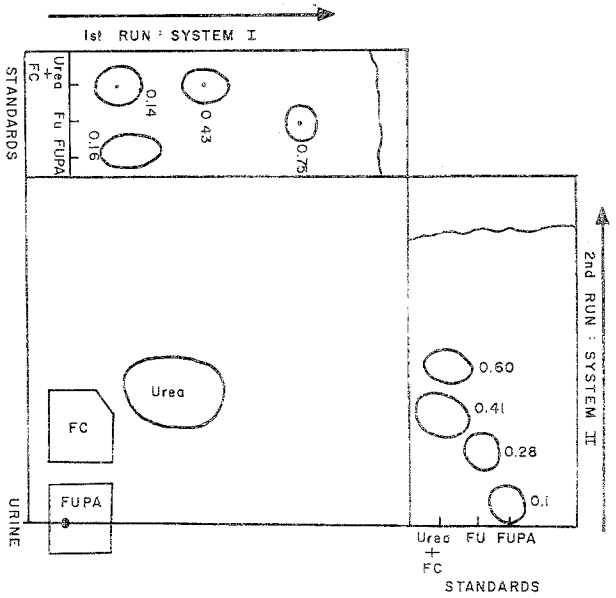

FIG. 2. Two-dimensional thin-layer chromatogram of the labeled urinary excretion products after oral doses of 5-fluorocytosine-2^{14}C in rat. The urine extract was chromatographed in system I, followed by system II. On both sides are shown the patterns of the standards, as run in both systems on separate plates, after one-dimensional development with the corresponding systems. See Methods for procedures of spotting and counting, and explanation of symbols (DHFU = dihydrofluorouracil is converted to 2-FUPA under the weakly alkaline experimental conditions).

5-FC and 5-FU were detected by examination under u.v. light, FUPA, and urea by spraying with dimethylaminobenzaldehyde, which yielded a yellow spot.[13] The distribution of the radioactivity on the plates was measured by scraping off the silica gel at a given area, and by scintillometrically counting the removed powder as a suspension in thixotropic gel dioxane phosphor solution, as described above for the counting of Ba$^{14}CO_3$.

Cytosine and uracil were separated by chromatography on Whatman 1 paper developed with tert-butanol:2·6 N HCl (7:3). The respective R_f values were 0·36 and 0·7.

Human experiments

Each of two human subjects received a single oral dose of 2 g 5-FC-2^{14}C and 50 μc (specific activity 3·2 μc/mmole) in form of the crystalline powder contained in five gelatin capsules of 400 mg each.

The experiments were conducted at Newark Beth Israel Hospital. The first patient (J.M.) was a female, age 57, weight 145 pounds, with the diagnosis of hypertension. The second patient (L.L.) was a female, age 57, unreported weight, with a diagnosis of diabetes and arterosclerosis.

Heparinized blood specimens (10 ml) were drawn at 1, 2, 5, 8, 12, 24, 48, and 72 hr. Pulmonary CO_2 was sampled at 0, 1, 2, 4, 6, 8, 12, 24, 36, 48, and 72 hr by having the patients exhale during a 5-min period through a trap containing 25 ml of 4 N NaOH. Urines were collected for the periods of 0–2, 2–4, 4–6, 6–12, and 12–14 hours, and then in daily portions for 6 more days. Feces were collected in daily portions for 7 days.

Urines or dilutions thereof in 1 ml of water were counted scintillometrically after admixture to the standard dioxane phosphor solution. Feces and CO_2 were counted as described above. Blood extracts were obtained by admixing 12 ml anhydrous ethanol to 2 ml blood. After shaking for 15 min and centrifugation, 5-ml aliquots of the supernatant fluid were evaporated. The residues, dissolved in 1 ml water, were admixed to the standard dioxane phosphor solution and counted scintillometrically. Recoveries of added 5-FC-2^{14}C from blood by this procedure of extraction exceeded 95%. The urinary excretion products were characterized by two-dimensional thin-layer chromatography as described for the rat urines. For the separation of specific impurities encountered in some of the human urines, the two-dimensional system n-butanol:water (86:14) followed by system I proved advantageous. In this system the respective R_f values were: for 5-FC, 0·27 and 0·13; for 5-FU, 0·44 and 0·55; for FUPA, 0·0 and 0·28; for urea, 0·27 and 0·28.

RESULTS

Disposition of 5-FC-2^{14}C in rats

Intraperitoneal administration. Three rats were given 5-FC-2^{14}C by the intraperitoneal route. The first experiment was terminated 12 hr after a dose of 14·5 mg/kg ($6{\cdot}1 \times 10^6$ cpm/rat). In the urines, 60·2% of the radioactivity was recovered; the feces contained 1·5%, and the respiratory CO_2 fraction 0·4%.* The tissue radioactivity appeared not to be concentrated in any specific organ, and amounted to less than 1% of the dose. In a second rat, sacrificed 48 hr after a dose of 10·5 mg/kg ($4{\cdot}28 \times 10^6$ cpm/animal), the total urinary radioactivity accounted for 96·7%, the feces for 0·6%, and the CO_2 for a negligible portion of the dose. The urinary excretion rates are plotted semilogarithmically against time in Fig. 3. These rates are seen to reach a peak after 2 to 4 hr and to decline rapidly thereafter, with a half-life of less than 2 hr. In both experiments all the urinary radioactivity was identified as intact 5-FC.

A third rat was treated with daily doses of 12 mg unlabeled 5-FC/kg for 3–4 weeks (a total of 21 doses injected), prior to a final dose of the labeled compound (12 mg/kg) This experiment attempted to establish a possible stimulation or induction of 5-FC-metabolizing enzymes by repeated exposure to this compound, since it was suspected that conversion into a nucleoside or into 5-FU might account for toxic manifestations observed[8] after chronic administration of 5-FC. The obtained excretion pattern indicated no such changes: 28 hr after the last labeled dose, 89·5% of the ^{14}C was present in the urines, again exclusively in the form of the intact 5-FC, whereas the feces and the CO_2 fractions accounted for no more than 0·2% and 0·4% respectively.

Oral administration. Three rats received 5-FC-2^{14}C by the oral route. In a first experiment a dose of 12 mg/kg was administered. By the end of a 30-hr period, 66·1% of this dose had been recovered in the urines. The rate curve is seen in Fig. 3. Of this urinary portion, 76% was excreted during the first 13 hr, entirely in the form

* The low recovery of the radioactivity in this experiment has to be ascribed to an inaccurate or incomplete urinary figure.

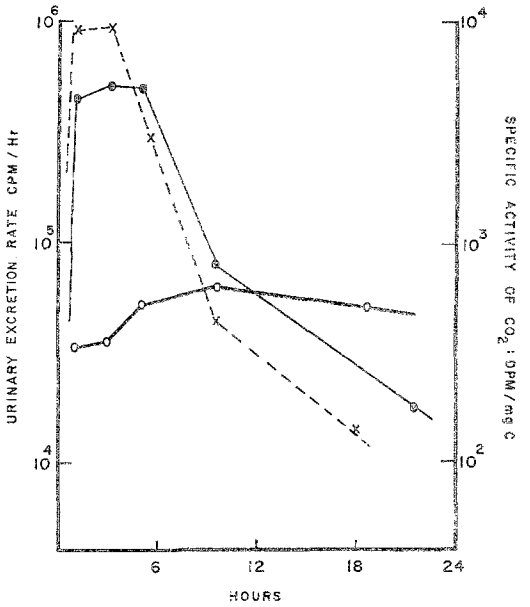

FIG. 3. Excretion rates of radioactivity after administration of cytosine-2^{14}C (10–15 mg/kg) in rats. Urinary excretion after i.p. dose, ×——×; urinary excretion after oral dose, ●——●; specific activity of respiratory $^{14}CO_2$ after oral dose, ⊙——⊙.

of the intact 5-FC-2^{14}C. The remaining 24%, excreted more gradually thereafter, consisted of a mixture of 5-FC and metabolites. The two-dimensional thin-layer chromatograms of the 13–24 hr urine, developed in system I followed by system II (see Fig. 2), showed 84% of the ^{14}C to reside in 5-FC, 6% in FUPA, 10% in urea, but none in the location 5-FU. In the 24–28 hr urines the distribution was similar, namely 82% in 5-FC, 12·3% in FUPA, 5–7% in urea, and again none in 5-FU.

By means of a second two-dimensional thin-layer experiment, in which system III was followed by system II, it was possible to exclude the presence of any metabolites other than FUPA and urea. Design and line of evidence of this experiment are explained in Fig. 4. These results suggested that deamination to 5-FU was the only primary step of 5-FC degradation. The labeled urinary metabolites, accounting for 3·4% of the ingested dose, represented only a small fraction of the 5-FC which had undergone metabolic degradation. The larger fraction, accounting for 20·6% of the dose, was recovered as pulmonary $^{14}CO_2$, which is the end product of 5FU metabolism.[11]

The specific activity of the pulmonary $^{14}CO_2$, which reflects the rate of $^{14}CO_2$ excretion, indirectly indicates the rate at which 5-FU is degraded. The rate curve shown in Fig. 3 is characterized by a slow rise reaching a maximum after 12 hr, followed by a gradual decline. This pattern differs distinctly from those reported by Chaudhuri *et al.*[11] for 5-FU. After administration of 5-FU-2^{14}C to mice, these authors observed a rapid rate of metabolism to pulmonary $^{14}CO_2$ for the first 4 hr, which dropped to low values thereafter. The same pattern was also found after 5-FU-2^{14}C in human subjects. From this comparison it could be inferred that the rate-limiting step of the formation of $^{14}CO_2$ after administration of 5-FC-2^{14}C is its deamination

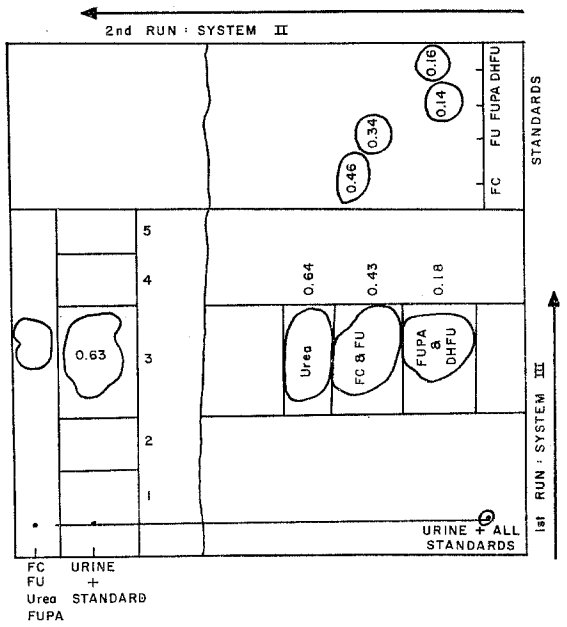

FIG. 4. Two-dimensional thin-layer chromatograms of radioactive metabolites in rat urine after oral 5-FC-2^{14}C, demonstrating exclusive presence of the metabolites identified in Fig. 2. First, by a one-dimensional chromatogram in system III followed by counting segments covering the entire length of the strip, all the counts were shown to reside with the expected metabolites at $R_f = 0{\cdot}63$. Then, a two-dimensional chromatogram with system III followed by system II was run, and the entire length of the lane corresponding to the $R_f = 0{\cdot}63$ of the first dimension was counted. All the counts were shown to reside exclusively in the positions of the expected metabolites. 5-FU would coincide with 5-FC in this system but can be discounted on the basis of the results shown in Fig. 2, which established its absence. DHFU, the direct precursor of FUPA, is not stable in this system and is separated in form of the latter.

to 5-FU-2^{14}C. Of the 4% of the counts excreted in the feces, 70% could be identified chromatographically as intact 5-FC, 6% as 2-FUPA, and 16·2% as 5-FU.

In a second experiment, the distribution of the radioactivity was measured in a rat killed 6 hr after an oral dose of 12 mg/kg. As shown in Table 1, 7·7% was present in the tissues. The concentrations of the ^{14}C in the individual organs were of the same order of magnitude. As in the previous 30-hr experiment, about two thirds of the dose had been absorbed and again excreted unchanged in the urine within this 6 hr period, while 20–30% had remained unabsorbed and had reached the colon. This amount is seen to correspond to the fraction which in the 30-hr experiment had been recovered in form of the 5-FU degradation products, urinary FUPA and urea, and pulmonary CO_2.

Since our parenteral experiments had demonstrated that 5-FC was not metabolized by tissue enzymes, the results of the two oral experiments clearly pointed to a degradation of 5-FC to 5-FU in the colon by action of its bacterial flora, followed by a gradual absorption of 5-FU, and then by its metabolism in the tissues along the known pathways.

A third rat received daily oral doses of 10 mg unlabeled 5-FC/kg for a period of

TABLE 1. DISTRIBUTION OF RADIOACTIVITY AFTER ORAL ADMINISTRATION OF 5-FC-2^{14}C IN THE RAT

	cpm × 10^3		Concentration ratio	Percent of
	per total	per gram	tissue/blood	dose
Tissue				
Blood		1·67	1·00	
Liver	25·40	2·11	1·21	
Kidney	8·66	3·45	2·07	
Spleen	2·65	1·89	1·13	
Heart	1·70	1·54	0·93	
Lung	2·44	1·64	0·97	
Brain	1·18	0·84	0·51	
Fat	3·37	2·81	1·79	
Muscle	9·10	2·02	1·21	
Carcass	349·60	1·45	0·87	
Total tissue	404·10			7·7
Stomach	25·0			0·5
Small intest.	233·0			4·3
Large intest.	1080·0			20·3
Urine	3580·0			67·0
CO_2	69·0			1·3
Recovery	5391·0			101·1

Dose: 5·35 × 10^6 cpm (10 mg/kg).

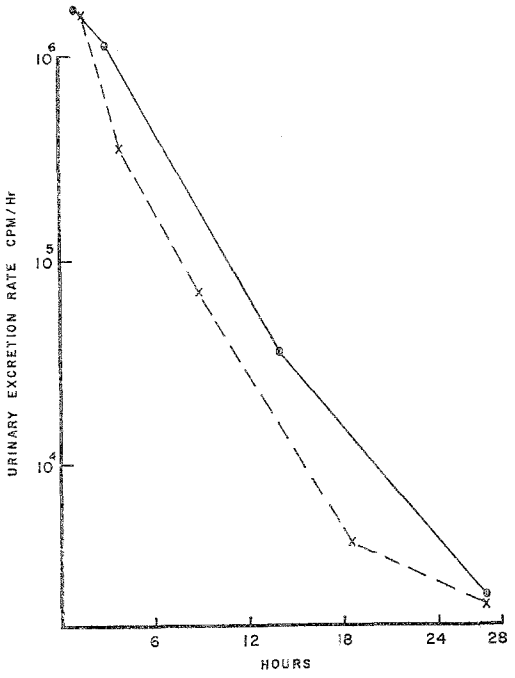

FIG. 5. Excretion rates of radioactivity in urines of two rats after i.p. doses of cytosine-2^{14}C (10–15 mg/kg).

3 weeks, followed by the same dose of the labeled compound. Under these conditions 79% of the dose was recovered in the urine, mostly as intact 5-FC, 0·2% in the feces, and only 5% in the pulmonary CO_2 fraction. In the light of our previous conclusions it may be assumed that this reduced metabolic degradation resulted from an effect of the 5-FC on the intestinal flora during the pretreatment period.

Disposition of cytosine-2^{14}C in rats

An intraperitoneal dose of cytosine-2^{14}C (10·2 mg/kg and $6{\cdot}25 \times 10^6$ cpm) was injected into two rats. Of these doses, 94·5% and 90·6%, respectively, were recovered in the urines within 30 hr. The excretion-rate curves, presented in Fig. 5, indicate a more rapid onset of the excretion than after 5-FC, but a similar half-life of the maximal excretion rates. Of the excreted radioactivity, 99% represented the intact compound. The respiratory $^{14}CO_2$ accounted for 1%, and the feces for 0·3–0·6% of the dose. The latter portion revealed, on chromatography, a small but definite component of uracil2-^{14}C.

After oral administration of cytosine-2^{14}C, 10·5 mg/kg, 59·3% of the ^{14}C appeared in the urine. The rate curve is shown in Fig. 6. Within the first 4 hr, 37% was recovered, entirely in form of intact cytosine, while subsequent portions contained the intact compound in combination with uracil and a number of chromatographically poorly resolved, unidentified degradation products. The fecal radioactivity, containing 10·3% of the dose, was evenly distributed between cytosine and uracil. The pulmonary CO_2 fraction accounted for 19·1% of the ^{14}C. This percentage corresponded

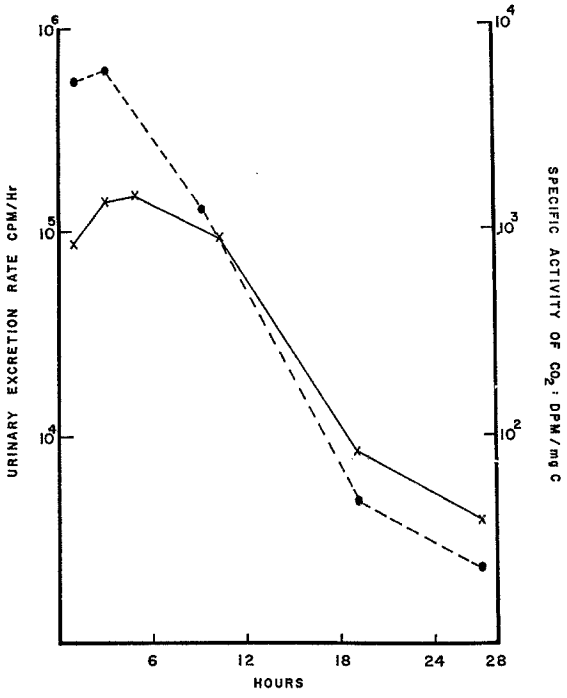

FIG. 6. Excretion rates of radioactivity in a rat after an oral dose of cytosine-2^{14}C (10–15 mg/kg), in urine, ●——● (left ordinate); and pulmonary CO_2 rate as specific activity (right ordinate), ×——×.

closely to the value obtained under the same condition with 5-FC-2^{14}C. However, the rate curve, shown in Fig. 6, differed from that seen after 5-FC-2^{14}C. The specific activity reached an earlier maximum and fell off more rapidly, at a rate paralleling the decline of the urinary excretion.

These results established a close analogy of the disposition of cytosine and of 5-fluorocytosine, and substantiated the previously postulated[7] inertness of cytosine to the mammalian tissue enzymes. Both pyrimidines are metabolized only by intestinal bacteria after oral ingestion. It is interesting to relate these findings to the recently reported lack of such an analogy between cytosine and its 5-iodo derivative.[14] The latter, quite toxic in mice, is found to be extensively metabolized, after parenteral administration, to iodo uracil and to iodinated acyclic degradation products.

Disposition of 5-FC-2^{14}C in humans

Two patients received a single oral dose of 2 g of 5-fluorocytosine-2^{14}C. In both cases an excretion of most of the radioactivity in the urines indicated a high absorption. In Patient J.M., 89% was recovered in the urine and 10·8% in the feces; in Patient L.L., 93% in the urine and 0·5% in the feces. The excretion curves, shown in Fig. 7, revealed different individual excretion rates, in that their half-lives were 3·5 hr in Patient J.M. and 8 hr in Patient L.L. According to two-dimensional thin-layer chromatography, all the counts of the urines and of the feces of both patients represented intact 5-FC-2^{14}C. Also, no radioactivity was detectable in the pulmonary CO_2 fraction which,

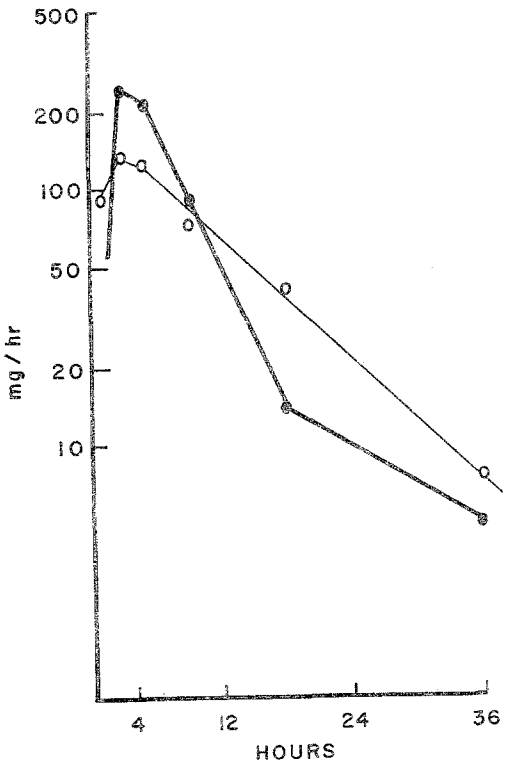

FIG. 7. Urinary excretion rates of 5-FC-2^{14}C in two patients after single oral doses of 2 g: Patient J.M., ●——●; Patient L.L., ○——○.

based on the counting sensitivity, was calculated to indicate degradation rates of less than 0·1 % of the dose per hour for the entire experimental period. Therefore no measurable metabolic conversion of 5-FC had occurred.

The blood level curves of the two subjects, seen in Fig. 8, showed a close similarity except that again in Patient J.M. the drug levels fell off more rapidly (half-life of 4·9 hr) compared with Patient L.L. (half-life of 8·2 hr). The closeness of these values to the corresponding half-lifes of the urinary excretion rates indicated a close interrelationship of blood levels and renal clearance.* From the urinary excretion per minute and the corresponding plasma levels taken between 3 and 5 hr after administration of the drug, a renal clearance of 55–56 ml plasma/min was calculated for Patient J.M. and of 36–39 ml/min for Patient L.L.

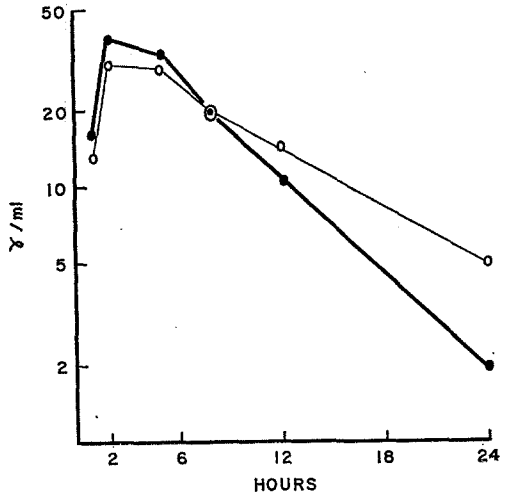

FIG. 8. Blood levels of 5-FC-2^{14}C in two patients after single oral doses of 2 g: Patient J.M., ●——●; Patient L.L., ○——○.

These half-lives in both patients are seen to be considerably longer than those of 5-FU which have been shown by Chaudhuri *et al.*[11, 12] to be nearer 1 hr. In both subjects, the 5-FC concentration in blood rose to 30–40 μg/ml within 2 hr, remained above 20 μg/ml between 2 and 8 hr, and above 10 μg/ml between 2 and 12 hours. Since *in vitro* as well as *in vivo*, a fungistatic effect could be achieved in mice within this concentration range,[5] the blood-level data suggest that chemotherapeutic levels are maintained in patients for a period of 6–10 hr after a single 2-g oral dose of 5-FC.

The blood-level data also permitted an estimate of the general tissue distribution of the compound. If the total amounts of unexcreted 5-FC present in the system at any given time are divided by the total body weight, average body concentrations are obtained which agree, within 10–20 %, with the 5-FC levels measured at that time in the blood. This suggests that the average 5-FC levels in the tissues and in the blood are of the same order of magnitude. Thus, 5-FC is distinguished from other chemotherapeutic agents such as the sulfonamides, which are known to achieve tissue levels far below their corresponding plasma levels.

* Taking into account, also, the unusual metabolic inertness and the low toxicity of this organic compound, 5-FC may be considered an ideal drug for studying renal excretion processes and renal function.

Acknowledgements—We wish to thank Dr. L. Levinson and Dr. Donald Rothfield of the Beth Israel Hospital, Newark, N.J., for their cooperation in supervising the administration of the labeled drugs and the collection of the samples in the human study.

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