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Tissue distribution of [^{18}F]-5-fluorouracil in mice: effects of route of administration, strain, tumour and dose

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Summary. In a study investigating the usefulness of 5-fluorouracil labelled with fluorine 18 ([^{18}F]-5-FU) in cancer chemotherapy, the tissue distribution of the radiolabel was determined in mice at 2, 4 and 6 h after administration by varying several parameters such as the mode of administration, the strain of mouse, the presence of a tumour and the total dose of 5-FU. The tissue distribution of fluorine 18 after i.p. injection pointed to an altered behaviour of the drug and/or its metabolites when compared with values obtained after i.v. injection, but no difference was found in the accumulation of radiolabel in the tumour. A comparison of non-tumour-bearing BALB/c and C57Bl/6 mice revealed that the latter showed a higher radiolabel accumulation of the drug and its metabolites in the liver, kidney, intestines and coecum ($P < 0.05$ at 2 and 4 h). In tumour-bearing mice, especially at 2 h, the tissue accumulation of radiolabel was found to be significantly higher than in non-tumour-bearing controls (in BALB/c mice bearing colon 26 carcinoma, $P < 0.05$ for all tissues; in C57Bl/6 mice bearing colon 38 carcinoma, $P < 0.05$ for the blood, lung, liver, kidney, large intestines, coecum and muscle). Finally, a comparison of injections of a tracer dose of [^{18}F]-5-FU (2.5 mg/kg) vs a therapeutic dose (100 mg/kg) revealed only small differences in the accumulation of fluorine 18 in the liver and kidney.

The anticancer agent 5-fluorouracil (5-FU) is believed to exert its cytotoxic effect by inhibiting DNA synthesis through the formation of a ternary complex of 5-FdUMP with folate cofactor and thymidylate synthase and/or by incorporation of 5-FUTP into RNA [28, 35]. The dose-limiting toxicity of 5-FU is manifested as either myelosuppression or mucositis, depending on the scheduling of its administration [6, 23], although there are indications that its toxicity and antitumour activity are affected by circadian timing [4, 25].

5-FU remains the only drug that shows activity against human colorectal cancer, although the total response rate does not exceed 20%, even when it is given in combination with other drugs [9, 14]. However, it has recently been reported that a combination of 5-FU with leucovorin increases the response rate in colorectal cancer up to 40%, although gastrointestinal toxicity might also be more severe [8, 11, 27]. In addition, it has been reported that uridine can rescue mice and patients from toxicity induced by 5-FU [19, 22, 26, 36], whereas 5-FU combined with thymidine leads to increased toxicity [13, 29].

Although the plasma pharmacokinetics of 5-FU in humans on various administration schedules have been studied extensively [10, 12, 37], studies on tissue accumulation of 5-FU given either alone or in combination with other (cytostatic) agents are scarce. Lack of sensitivity, selectivity or the labour intensity of sensitive methods hampered the study on tissue distribution. In principle, [^{19}F]-NMR (nuclear magnetic resonance) spectroscopy can be used to distinguish 5-FU from its degradation products and to observe non-invasively the formation of 5-fluorounucleotides [2, 32]. However, 5-FdUMP or the ternary complex of 5-FdUMP with folate cofactor and thymidylate synthase are formed at cytotoxic concentrations that are below the sensitivity of [^{19}F]-NMR spectroscopy. 5-FUTP may reach concentrations up to 50 times those of 5-FdUMP and therefore may be made visible with [^{19}F]-NMR [5], but the question as to whether there is a relationship between the 5-FU nucleotide peak integral and its cytotoxicity [15, 17, 18, 32] should be investigated. Also, the amount of catabolic product in patients is not related to clinical success, i.e. to 5-FU cytotoxicity [18, 39].

Positron emission tomography (PET) also possesses the capacity for non-invasive study of metabolic processes. A strong advantage is its high sensitivity, although this technique lacks selectivity [34]. However, tissue distribution studies with [^{18}F]-5-FU using PET might give interesting complementary information. It is generally assumed

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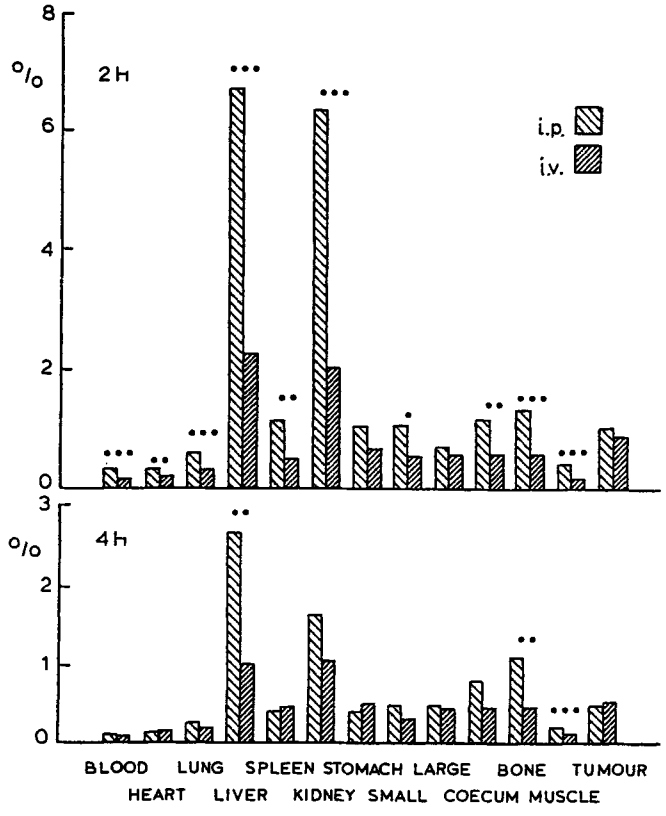

Fig. 1. Distribution of [^{18}F]-5-FU in nude mice bearing colon 38 carcinoma after i.p. and i.v. injection; values are expressed as the percentage of injected dose per gram of tissue and represent the means for 4 mice; the SD is comparable with those shown in Tables 1 and 2. • P <0.05; •• P <0.01; •1 P <0.001

that the level and persistence of bound 5-FU (complexed as 5-FdUMP or incorporated as 5-FUTP) in the cell is related to cytotoxicity. With [^{18}F]-5-FU the active metabolites carry the ^{18}F isotope, which implies that measurement of the level and persistence of this radiolabel during a certain period of time might reflect the efflux and persistence of the drug and its active metabolites in the several tissues. As such, biodistribution studies of fluorine 18 using PET might lead to working parameters for 5-FU in the evaluation of its antitumour activity and toxicity when it is given either alone or in combination with other agents.

5-FU produces gastrointestinal and hematologic toxic effects in rodents that are comparable with those seen in man [21]. As such, [^{18}F]-5-FU has been investigated as a tumour-localizing agent in rats and mice [1, 30]; also, some plasma kinetics over a period of 0–70 min have been reported [31]. In addition, for a variety of antitumour drugs it has been observed that rodent strain differences in drug clearance exist and that the distribution of the drug and its metabolites may be altered by the mode of administration or the presence of a tumour. Therefore, to test whether [^{18}F]-5-FU is an interesting additional tool for in vivo disposition studies of 5-FU, we decided to investigate whether a variation of parameters such as the mode of administration (i.p. or i.v.), the murine strain or the presence of a tumour is reflected in the tissue distribution pattern and tissue efflux of fluorine 18, even after relatively long periods (in this case, after 2–6 h).

Materials and methods

C57Bl/6, BALB/c and NMRI (nu/nu) mice (females) were obtained at 6–8 weeks of age from Harlan Cpb. (Zeist, The Netherlands). All animals were kept in an area with a standardized light-dark cycle (with the nude mice maintained under aseptic conditions [3]) for at least 10–14 days prior to the beginning of an experiment. Mice had access to food and water ad libitum. Colon 26 and 38 are murine colon carcinomas; colon 26 was maintained in BALB/c mice and colon 38, in C57Bl/6 and nude mice. The sources and growth characteristics of these tumours have previously been described [26, 38]. When mice were between 2 and 3 months of age, tumours were transplanted s.c. as 1- to 5-mm^3 fragments in both flanks of the animals. At the time of the experiments, C57Bl/6 and BALB/c mice weighed 18–25 g, nude mice weighed 28–30 g and the tumour mass was 80–200 (colon 26) and 200–500 mg (colon 38); colon 26 carcinoma was implanted 14 days prior to the investigations and colon 38, 30 days before the experiments.

The mice were killed by cervical dislocation at 2, 4 and 6 h after i.v. or i.p. injection of 400 µCi [^{18}F]-5-FU in 100 µl saline (specific activity, 1 Ci/mmol at the moment of injection), which corresponds to approximately 2.5 mg/kg 5-FU. [^{18}F]-5-FU was prepared as previously described elsewhere [38]. To avoid a possible variance due to circadian timing, all animals were injected at around 2 p.m. Tissues were removed, weighed and assessed for radioactivity in an LKB Compugamma counter. P values were calculated using Student's t-test.

Results and discussion

Route of administration

Recently we reported the biodynamics of [^{18}F]-5-FU in tumour-bearing and non-tumour-bearing nude mice after i.v. administration [38]. In animal chemotherapy and other 5-FU studies the drug is often given by i.p. injection. Because in nude mice no difference in tissue distribution was observed between control and tumour-bearing animals [38], we used colon 38 carcinoma-bearing nude mice to investigate a possible difference in tumour and tissue distribution after i.p. vs i.v. administration of [^{18}F]-5-FU (Fig. 1). After 2 h, the relative accumulation of radiolabel in the blood, lung, liver, spleen, kidney, muscle and bone was about 2–3 times higher for the i.p. injection than for i.v. administration (P <0.01). At 4 h, the difference had decreased but was still substantial (P <0.01) for liver, muscle and bone. Thus, the fact that one introduces a different kind of absorption process by i.p. injection (different from that occurring after a direct i.v. injection) was clearly reflected in the data for tissue distribution of radiolabel. Interestingly, in the tumour the amount of label was comparable for both modes of administration. Therefore, when we regard the relative bone accumulation as a rough measure of myeloid toxicity and the relative tumour accumulation as a measure of antitumour activity, these data indicate that i.p. injection might lead to more toxic side effects than i.v. injection.

Murine strain

In experimental chemotherapy studies, different strains of mice are often used. Because strain differences in drug clearance have been observed with other drugs, we studied the tissue distribution of [^{18}F]-5-FU at 2, 4 and 6 h in

non-tumour-bearing BALB/c and C57Bl/6 mice, strains that have been used in 5-FU chemotherapy studies [24, 26]. It is noteworthy that these and all of the following experiments dealt with i.p. injection because, as mentioned above. all chemotherapeutic studies of optimal drug dose, dose regimen, circadian timing and uridine rescue have used i.p. injection. The results are compiled in Table 1. At 2 h in both strains, the relative accumulation of label was highest in the liver and kidney, intermediate in the gastrointestinal tract and spleen and lowest in the blood, lung, muscle and heart. The high accumulation at 2 h in the liver and kidney, the organs responsible for 5-FU degradation, is in agreement with that found in 5-FU studies in other strains of mice [7, 21, 30, 32], as well as with that of prodrugs of 5-FU such as 5'-deoxy-5-fluorouridine [33] or encapsulated 5-FU [20]. Besides this general trend, subtle differences between the BALB/c and C57Bl/6 mice were found. In the blood, liver, kidney, intestines and coecum, the accumulation of label at 2 and 4 h was higher in C57Bl/6 mice ($P < 0.05$); in the liver, intestines and coecum. this tendency was still present at 6 h.

Tumour-bearing vs non-tumour-bearing mice

The distribution of a drug and/or its metabolites may be altered by the presence of a tumour. Therefore, we injected C57Bl/6 mice bearing colon 38 carcinoma and BALB/c mice bearing colon 26 carcinoma with [^{18}F]-5-FU and compared the distribution of label with that in non-tumour-bearing mice. For C57Bl/6 mice, the relative pattern of radiolabel distribution was comparable in tumour-bearing and non-tumour-bearing animals except in the liver and kidney. In these tissues at 2 h, the accumulation of label was 2–3 times higher in tumour-bearing mice than in controls ($P < 0.001$; Table 2). At 2 h the blood, lung, large intestine. coecum and muscle also showed small differences ($P < 0.05$); however, after 4 and 6 h the distribution of label was comparable. More pronounced differences were observed between tumour-bearing and non-tumour-bearing BALB/c mice. In the blood, liver and kidney at 2 h, the accumulation of label was >4 times higher in tumour-bearing mice ($P < 0.001$); in tissues from the gastrointestinal tract. spleen, lung, muscle and heart, the accumulation of label was about twice that found in non-tumour-bearing BALB/c mice ($P < 0.01$). At 4 h, significant differences ($P < 0.05$) were observed in the blood, intestines, coecum. bone and muscle.

Thus. our results not only confirm the possible effect of a tumour on the tissue distribution of 5-FU and/or its metabolites but also show that this effect may be dependent on the type of tumour: the effect of the presence of colon 38 carcinoma was less marked than that of colon 26. Besides this. the tumour efflux rate of radiolabel from the 5-FU-sensitive colon 38 carcinoma was slower than that of colon 26 (Fig. 3), which is less responsive to 5-FU [25]. This latter trend is in accordance with the hypothesis that we introduced earlier [38] on the basis of our experiments with nude mice; in this model we observed that the 5-FU sensitivity of colon 38 carcinoma was related not to the initial tumour uptake of radiolabel but rather to a slower tumour efflux of radiolabel, 5-FU and its anabolites.

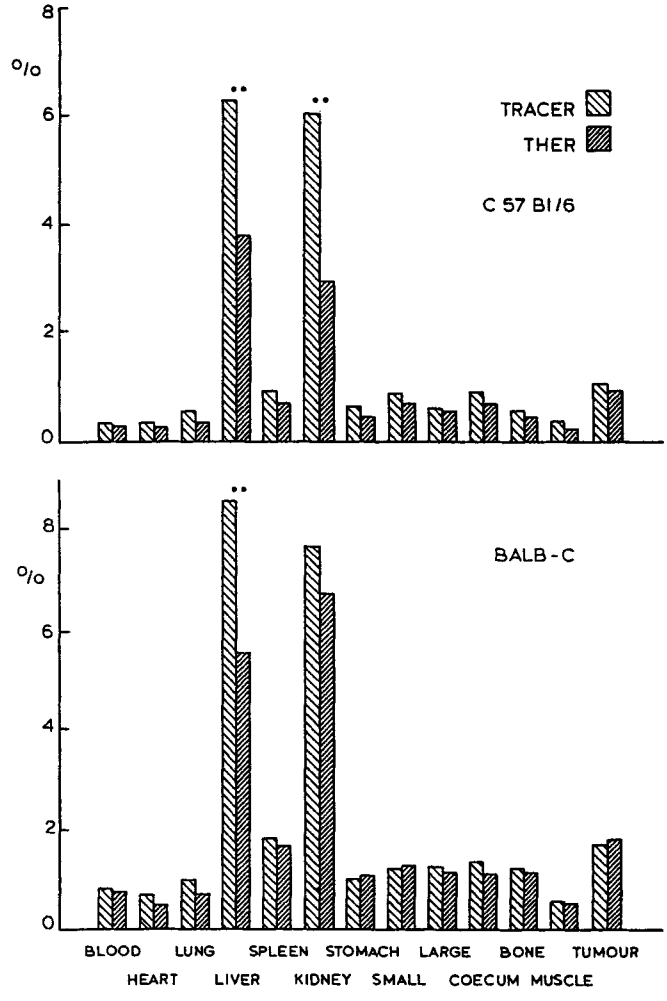

Fig. 2. Distribution of [^{18}F]-5-FU at the tracer dose (2.5 mg/kg) and therapeutic dose (100 mg/kg) in C57Bl/6 mice bearing colon 38 carcinoma and BALB/c mice bearing colon 26 carcinoma at 2 h after i.p. injection; values are expressed as the percentage of injected dose per gram of tissue and represent the means for 4 mice; the SD is comparable with those shown in Tables 1 and 2.●● $P < 0.01$

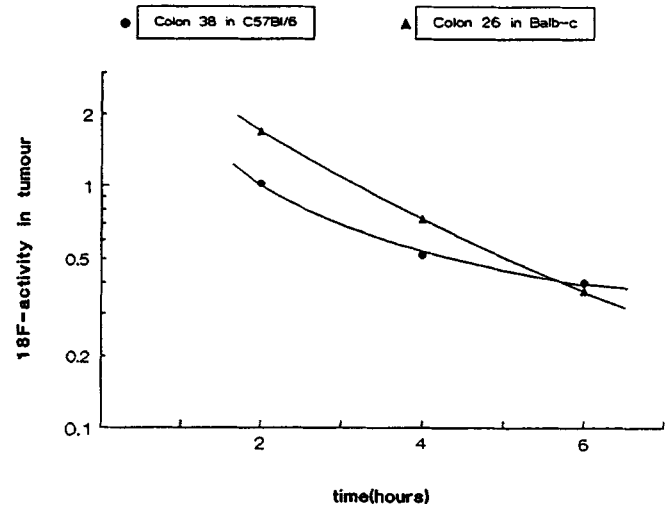

Fig. 3. Comparison of the efflux of radiolabel from colon 38 (5-FU-sensitive) and colon 26 (less responsive) carcinomas

Table 1. Distribution of [^{18}F]-5-FU in non-tumour-bearing C57Bl/6 and BALB/c mice after i.p. injection

	C57Bl/6 2 h	BALB/c 2 h	C57Bl/6 4 h	BALB/c 4 h	C57Bl/6 6 h	BALB/c 6 h
Blood	0.24±0.02	0.19±0.02*	0.08±0.02	0.05±0.01*	0.04±0.01	0.03±0.01
Heart	0.28±0.03	0.33±0.05	0.13±0.02	0.20±0.08	0.07±0.01	0.12±0.04
Lung	0.39±0.06	0.33±0.03	0.22±0.05	0.16±0.01	0.11±0.03	0.11±0.01
Liver	2.67±0.34	1.95±0.36*	1.02±0.44	0.40±0.01*	0.42±0.15	0.25±0.06
Spleen	0.97±0.13	0.92±0.12	0.64±0.09	0.93±0.10**	0.37±0.06	0.66±0.18*
Kidney	2.94±0.44	1.49±0.20***	1.18±0.31	0.51±0.03**	0.43±0.08	0.37±0.07
Stomach	0.66±0.16	0.41±0.05*	0.28±0.10	0.33±0.17	0.27±0.11	0.19±0.05
Intestines (small)	1.16±0.30	0.55±0.04**	0.71±0.18	0.35±0.02**	0.64±0.21	0.31±0.04*
Intestines (large)	0.79±0.06	0.62±0.09*	0.90±0.26	0.27±0.04**	0.56±0.20	0.35±0.07
Coecum	1.46±0.16	0.80±0.13***	1.06±0.22	0.47±0.07**	0.80±0.17	0.39±0.05**
Bone	0.98±0.14	0.77±0.05	1.04±0.32	0.72±0.11	0.82±0.39	1.01±0.26
Muscle	0.21±0.02	0.21±0.02	0.16±0.03	0.11±0.01	0.09±0.02	0.08±0.01

Values are expressed as the percentage of injected dose per gram of tissue and represent the means ± SD for 4 mice
*P <0.05; ** P <0.01; *** P <0.001

Table 2. Distribution of [^{18}F]-5-FU in C57Bl/6 mice bearing colon 38 carcinoma and BALB/c mice bearing colon 26 carcinoma after i.p. injection

	C57Bl/6:			BALB/c:		
	2 h	4 h	6 h	2 h	4 h	6 h
Blood	0.35±0.07*	0.09±0.03	0.04±0.01	0.79±0.19***	0.13±0.05*	0.05±0.01*
Heart	0.33±0.06	0.12±0.03	0.06±0.01	0.68±0.13**	0.18±0.08	0.15±0.04
Lung	0.56±0.04**	0.18±0.06	0.11±0.02	1.00±0.32**	0.25±0.12	0.15±0.05
Liver	6.33±0.55***	1.45±0.40	0.58±0.22	8.54±2.17***	0.81±0.36	0.36±0.09
Spleen	0.92±0.19	1.10±0.39	0.59±0.12	1.81±0.20***	1.03±0.06	0.73±0.31
Kidney	6.08±0.93***	1.28±0.48	0.57±0.16	7.64±1.82***	0.87±0.33	0.39±0.08
Stomach	0.64±0.14	0.47±0.20	0.35±0.12	0.99±0.28**	0.36±0.04	0.22±0.07
Intestines (small)	0.88±0.18	0.65±0.21	0.48±0.09	1.20±0.09***	0.51±0.10*	0.42±0.08*
Intestines (large)	0.61±0.13*	0.61±0.08	0.53±0.03	1.22±0.37*	0.74±0.32*	0.28±0.11
Coecum	0.92±0.18**	0.70±0.07*	0.59±0.16	1.35±0.12***	0.79±0.09**	0.54±0.12
Bone	0.88±0.11	0.93±0.28	1.34±0.10	1.21±0.14**	1.20±0.25*	1.09±0.12
Muscle	0.33±0.06**	0.15±0.02	0.11±0.03	0.53±0.09***	0.19±0.04**	0.12±0.04
Tumour (n = 8)	1.02±0.05	0.52±0.06	0.40±0.05	1.69±0.45	0.73±0.15	0.37±0.14

Values are expressed as the percentage of injected dose per gram of tissue and represent the means ± SD for 4 mice
Significance of differences between tumour-bearing and non-tumour-bearing (control) mice: * P <0.05; ** P <0.01; *** P <0.001

Tracer vs therapeutic doses

The above-mentioned experiments were conducted using a tracer dose of 5-FU equivalent to 2.5 mg/kg; however, the therapeutic dose of 5-FU is much higher. Since this might affect the distribution of label and, as such, limit the applicability of [^{18}F]-5-FU, we compared the i.p. injection of 2.5 mg/kg [^{18}F]-5-FU with that of a therapeutic dose of 100 mg/kg 5-FU supplemented with the same amount of label. Figure 2 shows the results at 2 h. It is noteworthy that in most of the tissues, including both colon 26 and 38 carcinomas, the amount of radiolabel was comparable for the tracer and therapeutic doses.

Interestingly, in both murine strains a lower amount of radiolabel was found in the liver and kidney when radiolabel had been given simultaneously with the therapeutic dose; this might be related to the saturation of metabolism in these tissues. The liver and kidney are the main organs responsible for the degradation of 5-FU into fluoro-dihydrouracil and, subsequently, into fluoroureidopropionate and fluoro-β-alanine [16]. As has been demonstrated in vivo with [^{19}F]-NMR [32], these breakdown products form the majority of fluorine-containing compounds in these organs and their formation is dependent on the dose.

Conclusions

Using [^{18}F]-5-FU, differences in the biodistribution of fluorine 18 were observed by the variation of parameters such as the mode of administration, the strain of mouse and the presence of a tumour. This observed parameter dependency indicates that [^{18}F]-5-FU might be an interesting, sensitive tool for in vivo disposition studies of 5-FU, such as investigations of the effects of its coadministration with other (cytostatic) agents or studies on the scheduling of its administration.

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