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Prodrugs of 5-fluorouracil. VIII. Improved rectal and oral delivery of 5-fluorouracil via various prodrugs. Structure–rectal absorption relationships

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Summary

Various 3-acyl, 1-alkoxycarbonyl and 3-acyloxymethyl prodrug derivatives of 5-fluorouracil were evaluated as rectal and oral delivery forms of the parent drug. The rectal absorption characteristics of 13 derivatives and of 5-fluorouracil were assessed in rabbits by giving the compounds in aqueous enemas. Whereas 5-fluorouracil was not absorbed rectally the various prodrug derivatives showed a bioavailability of 5-fluorouracil ranging from 0 to 100%. Relationships between physicochemical properties and extent of absorption were derived and it was found that in order to achieve an extent of absorption of more than 50% the prodrugs should possess a partition coefficient between octanol and aqueous buffer (pH 7.4) greater than 0.5 and a solubility in water at pH 7.4 greater than 0.05 M. 3-Propionyl-5-fluorouracil and 1-butyloxycarbonyl-5-fluorouracil were identified as the most promising prodrugs showing a rectal bioavailability greater than 90%. When given orally to rabbits the latter derivative showed an absolute bioavailability of 5-fluorouracil of 58% as compared with 10% absorption following administration of 5-fluorouracil itself. The results obtained suggest the potential utility of these prodrug derivatives to enhance the rectal and/or oral delivery of the parent drug.

Introduction

5-Fluorouracil (substance no. 1) is a widely used antitumor agent. However, its clinical use is largely restricted to parenteral administration. Following oral administration it shows an incomplete and highly variable bioavailability, largely due to a marked first-pass metabolism (Cohen et al. 1974; Christophidis et al., 1978; Finch et al., 1979; Fraile et al., 1980; Phillips et al., 1980; Almersjö et al., 1980) which makes oral administration an unsuitable and unreliable mode of therapy. The rectal route of administration is of even less value than the oral one in that no absorption of 5-fluorouracil was observed after giving the drug to humans in the form of a rectal enema (Christophidis et al., 1978).

Studies were undertaken in this laboratory attempting to solve these delivery problems by the prodrug approach. It was thought that by bioreversible derivatization it may be feasible to diminish first-pass metabolism and to obtain prodrugs possessing a higher lipophilicity than the parent drug. The partition coefficient of 5-fluorouracil between octanol and water is only 0.15 (Buur and Bundgaard, 1984a) and this low lipophilicity may be a predominant factor for the poor

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biomembrane permeability of the drug. In previous studies various *N*-acyl (Buur and Bundgaard, 1984a and b), 3-alkoxycarbonyl (Buur and Bundgaard, 1984b), 1-alkoxycarbonyl (Buur and Bundgaard, 1986a), 1-carbamoyl (Buur and Bundgaard, 1985), *N*-acyloxymethyl (Buur et al., 1985) and *N*-alkoxycarbonyloxymethyl (Buur et al., 1986) derivatives of 5-fluorouracil were assessed as possible prodrugs. The water solubility, octanol–water partitioning behavior and the kinetics of conversion of the derivatives to 5-fluorouracil were determined and some promising prodrug derivatives were identified on this basis.

In the present work, the bioavailability of a number of these 5-fluorouracil prodrugs has now been assessed in rabbits following rectal and, in one case, oral administration with the purpose of obtaining information on their absorption characteristics and potential usefulness as prodrugs. The derivatives studied include nine 1-alkoxycarbonyl derivatives (nos. 2–10), three 3-acyl derivatives (11–13) and one 1-acyloxymethyl derivative (14). The physicochemical properties and hydrolytic stability of these compounds are summarized in Tables 1 and 2. The formulae are shown in Fig. 1. The data are taken from the previous studies cited. By including compounds with vastly different lipophilicities and aqueous solubilities it was a further aim of the present work to examine relationships between these physicochemical properties and extent of rectal absorption. In contrast to oral absorption only sparse information is available on the water and lipid solubilities required to ensure optimal rectal absorption of drug substances (Bundgaard et al., 1985)

TABLE 2

Half-lives of hydrolysis of various 5-fluorouracil prodrugs at 37°C

Compound	80% human plasma, pH 7.4 (min)	Buffer, pH 7.4 (min)	Buffer, pH 4.0 (h)
2	2	190	7.2
3	2	550	19.3
4	3	975	42
5	3	550	26.3
6	3	550	20.6
7	2	550	–
8	5	910	45
9	< 0.5	18	18 min
10	0.8	150	4.4
11	20	50	9.6
12	110	2880	130
13	15	220	6.1
14	140	8400	> 200

TABLE 1

Physicochemical properties of 5-fluorouracil and various 5-fluorouracil prodrugs

Compound	pK_a (at 37°C)	log *P*		*S* (mg/ml)		S at pH 7.4 (M)
		pH 4.0	pH 7.4	pH 4.0	pH 7.4	
5-Fluorouracil (5-FU) (1)	8.0	−0.83	−0.96	11.1	13.9	0.11
1-Methoxycarbonyl-5-FU (2)	6.8	−0.68	−1.38	23.3	116.5	0.62
1-Ethyloxycarbonyl-5-FU (3)	6.9	−0.17	−0.79	6.9	28.8	0.14
1-Isopropyloxycarbonyl-5-FU (4)	6.8	0.20	−0.50	4.7	23.5	0.11
1-Butyloxycarbonyl-5-FU (5)	6.8	0.89	0.19	5.9	29.5	0.13
1-Isobutyloxycarbonyl-5-FU (6)	6.9	0.87	0.25	3.0	12.5	0.054
1-Hexyloxycarbonyl-5-FU (7)	6.8	2.04	1.34	1.5	7.5	0.029
1-Cyclohexyloxycarbonyl-5-FU (8)	6.8	1.42	0.72	0.92	4.6	0.012
1-Phenyloxycarbonyl-5-FU (9)	~ 6.8	0.64	−0.06	~ 0.9	~ 4.5	0.018
1-Benzyloxycarbonyl-5-FU (10)	~ 6.8	1.18	0.48	~ 0.08	~ 0.4	0.0015
3-Propionyl-5-FU (11)	7.2	0.19	−0.21	35.3	90.5	0.48
3-Benzoyl-5-FU (12)	6.9	0.80	0.16	1.3	5.4	0.023
3-Nicotinoyl-5-FU (13)	1.6; 6.4	−0.06	−1.10	2.7	29.7	0.13
1-Butyryloxymethyl-5-FU (14)	7.2	0.47	0.06	9.6	24.6	0.11

P is the partition coefficient between octanol and aqueous buffer at 22°C. *S* is the solubility in aqueous buffer at 22°C.

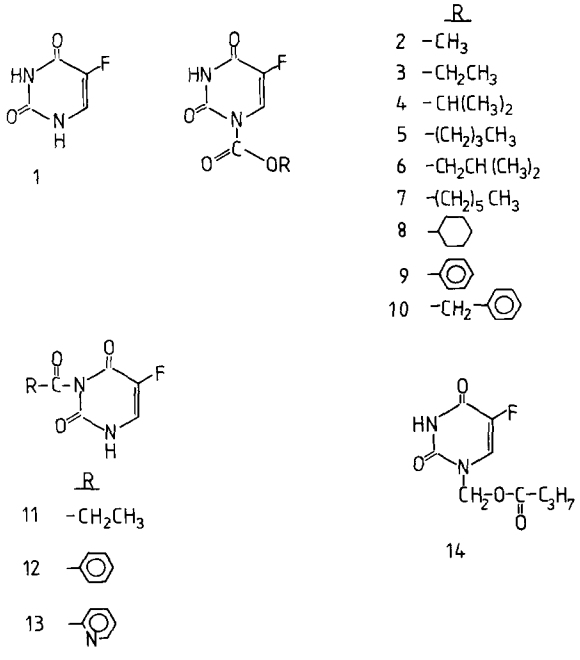

Fig. 1. 5-Fluorouracil and prodrugs.

Materials and Methods

Materials

5-Fluorouracil was purchased from Fluka AG, Switzerland and was used as received. The preparation of the 5-fluorouracil prodrugs studied has been described previously (Buur and Bundgaard, 1984a, 1986a and b; Johansen et al., 1983) except for the 1-alkoxycarbonyl derivatives 4 and 7. These compounds were synthesized by reacting 5-fluorouracil with isopropyl and *n*-hexyl chloroformate, respectively, in a mixture of acetonitrile and pyridine as described before (British Patent 1,542,053), m.p. 180–181°C (compound 4), reported m.p. 182°C; m.p. 68–69°C (compound 7), reported m.p. 70°C. The derivatives 4 and 7 had spectroscopic (UV and NMR) properties in agreement with their structures, cf. Buur and Bundgaard (1986a). Methylcellulose (Ph.Nord. 63 grade) was obtained from Nordisk Droge A/S, Copenhagen. For intravenous administration of 5-fluorouracil a commercial injection preparation (Fluoro-uracil (50 mg/ml), Roche AG, Basel, Switzerland) was used. All other chemicals and solvents used were of reagent grade.

Apparatus

High-performance liquid chromatography (HPLC) was performed with a Spectra-Physics Model 3500B apparatus equipped with a variable-wavelength UV detector (8-μl 1-cm flow cells) and a 10-μl loop injection valve. The column used, 250 × 4 mm, was packed with Li-Chrosorb RP-18 (5-μm particles) (E. Merck, Darmstadt, F.R.G.). Readings of pH were carried out on a Radiometer Type PHM26 meter. Melting points were taken on a capillary melting-point apparatus and are corrected.

Test preparations

The enemas were prepared by dissolving or slurrying the compounds in water containing 0.5% w/v methylcellulose, and adjusting the pH to 7.4 with phosphate buffer, the total buffer concentrations being 0.005 M. The enema contained 10 mg 5-fluorouracil per ml or the equivalent amount (on a molar basis) of prodrug. The solutions used for oral administration were identical to the enema.

Bioavailability studies in rabbits

Male albino rabbits weighing 1.8–2.4 kg were fasted for 24 h prior to drug administration, but they had free access to water. The enemas (about 2 ml) were administered about 5 cm within the rectum using a rectal polyethylene tube. During the experiments the rabbits were kept in restraining boxes and it was controlled that there was no leakage from the anus. After administration, blood samples of about 0.5 ml were taken from the marginal ear vein at appropriate times in heparinized test tubes. The plasma samples obtained after centrifugation for 10 min at 5300 rpm were immediately analyzed for 5-fluorouracil by HPLC. An interval of at least 7 days was allowed prior to the next experiment with the same rabbit. Each rabbit was not used more than two times.

For oral administration aqueous solutions of 5-fluorouracil and 1-butyloxycarbonyl-5-fluorouracil (5) (10 mg 5-fluorouracil equivalents per ml) were given.

For i.v. administration Fluoro-uracil corresponding to 9 mg per kg of 5-fluorouracil was given in the marginal ear vein not used for blood sampling.

Analysis of plasma samples

The plasma samples were analyzed for 5-fluorouracil using a reversed-phase HPLC procedure. Samples of 100 μl were mixed with 100 μl of an aqueous 0.1 M $ZnSO_4$ solution followed by centrifugation for 2 min at 10,000 rpm. A 10-μl aliquot of the clear supernatant was injected into the chromatograph. The reversed-phase column was eluted with a 0.02 M sodium acetate buffer of pH 5.0 at a flow rate of 1.2 ml/min. The column effluent was monitored at 266 nm. 5-Fluorouracil was quantified by measuring the peak height in relation to those of standard solutions (prepared in rabbit plasma) chromatographed under the same conditions. The retention time for 5-fluorouracil was 4.2 min and the detection limit was 0.1 μg/ml plasma.

Determination of stability, solubility and partition coefficients of compounds 4 and 7

This was performed essentially as described previously for other 1-alkoxycarbonyl derivatives (Buur and Bundgaard, 1986a).

Results and Discussion

Pharmacokinetics of 5-fluorouracil following intravenous administration

The pharmacokinetics of 5-fluorouracil in rabbits has apparently not been reported previously. To obtain information on this, 4 rabbits were given 5-fluorouracil (9 mg/kg) by a fast i.v. bolus injection. Fig. 2 shows a typical plasma 5-fluorouracil concentration–time curve. It can be seen that there is a rapid α-distribution phase. This was observed for all 4 rabbits. The plasma concentration–time curves were well described mathematically by assuming a two-compartment open pharmacokinetic model as expressed by the following biexponential equation:

$$C_{pl} = A\,e^{-\alpha t} + Be^{-\beta t} \qquad (1)$$

where C_{pl} is the plasma concentration of 5-fluorouracil, α is the distribution phase rate constant, β is the elimination rate constant and t is the time after administration of the drug. The pharmacokinetic parameters shown in Table 3 were determined by curve-fitting using a least-squares method.

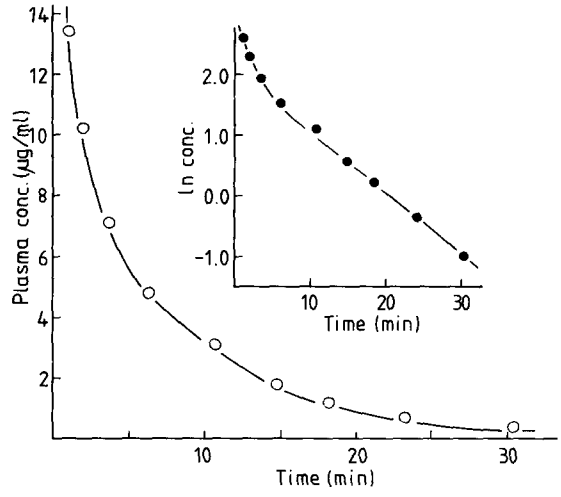

Fig. 2. Plasma concentration–time curve for 5-fluorouracil after i.v. administration of 5-fluorouracil (9.0 mg/kg) in a rabbit. The points are experimental and the curve constructed on the basis of Eqn. 1. The inset is a semilogarithmic plot of the data.

Several studies on the pharmacokinetics of 5-fluorouracil in humans have been performed (e.g. MacMillan et al., 1978; Christophidis et al., 1978; Finch et al., 1979; Phillips et al., 1980; Collins et al., 1980) and both one-compartment and two-compartment models have been proposed. The use

TABLE 3

Pharmacokinetic parameters for 5-fluorouracil following i.v. administration (9 mg/kg) in 4 rabbits (means ± S.D.)

A	(μg/ml)	9.64 ± 2.21
B	(μg/ml)	6.30 ± 1.5
α	(min^{-1})	0.47 ± 0.22
β	(min^{-1})	0.098 ± 0.003
V_1	(= dose/(A + B)) (l)	0.59 ± 0.11
V_{dAUC}	(l/kg)	0.49 ± 0.07
V_2	(l)	0.48 ± 0.13
AUC_0^∞	(μg·min/ml)	84.3 ± 10.1
Cl_B	(l/min)	0.104 ± 0.018

AUC_0^∞ is calculated from $(A/\alpha + B/\beta)$. When determined by the trapezoidal rule a value of 86.9 ± 15.5 μg·min/ml was obtained for AUC_0^∞.

of the different models seems, however, to be a result of differences in the frequency of plasma sampling at early times after drug administration. Due to the very rapid distribution phase this phase may easily be overlooked. In the human studies cited above elimination half-lives ($t_{1/2}(\beta)$) of 9–19 min, apparent distribution volumes (V_{dAUC}) of 0.20–0.35 l/kg and plasma clearances (Cl_B) of 0.8–1.7 l/min have been reported.

Rectal absorption

The major objective of the present work was to identify 5-fluorouracil prodrugs showing good bioavailability of the parent drug following rectal administration. Therefore, to sort out the most promising derivatives, the absorption characteristics of several prodrugs was assessed in rabbits. All compounds were given in the form of aqueous enemas, these being solutions or suspensions depending on the water solubility of the particular derivative. The amount of prodrug given was equivalent to 9.0 mg of 5-fluorouracil per kg. The absorption was characterized by the 5-fluorouracil plasma concentration–time curves. The area under these curves (AUC_0^∞) were determined by the trapezoidal rule and the systemic or absolute bioavailability ($F\%$) of the rectal preparations was determined according to:

$$F\% = \frac{AUC_{(\text{rectal})}}{AUC_{(\text{5-fluorouracil i.v.})}} \times 100 \qquad (2)$$

The doses given rectally and of 5-fluorouracil i.v. were identical on a molar basis. As described above the AUC value for 5-fluorouracil i.v. was determined in 4 rabbits.

The results of the rectal absorption studies are shown in Table 4 and Fig. 3. As seen from Fig. 3 the peak plasma concentration times occur very early, indicating a very high rate of prodrug absorption and a fast conversion of prodrug to drug in vivo. Analysis of the curves showed that the elimination rate constant (β) for 5-fluorouracil delivered rectally via the prodrug derivatives was essentially identical (within ± 10%) to the value observed following i.v. administration of 5-fluorouracil. Except for 3-benzoyl-5-fluorouracil (12) no intact prodrug was detected in any plasma samples in accordance with the rapid prodrug–drug conversion (Table 2). As seen from Table 2 compound 12 is only slowly hydrolyzed in plasma in vitro. It is noteworthy that although compound 14 is rather slowly hydrolyzed in human plasma in vitro no intact prodrug was observed. The findings demonstrate that the derivatives (except compound 12) possess the ability to be rapidly converted back to the parent drug in vivo.

TABLE 4

Bioavailability of 5-fluorouracil and various prodrugs following rectal administration to two rabbits

Compound	AUC_0^∞ (μg·min·ml^{-1})		Bioavailability (%) (Mean)
	Rabbit I	Rabbit II	
1	0.0	0.0	0
2	55.7	19.9	44
3	39.6	44.6	49
4	24.9	18.0	25
5	90.8	82.7	101
6	49.1	36.7	50
7	18.9	10.2	17
8	4.5	11.7	9
9	0.0	0.0	0
10	0.0	0.0	0
11	70.2	89.6	93
12	31.5	18.0	29
13	0.3	0.2	3
14	54.2	53.1	62

All compounds were given in aqueous enemas at a dose of 9 mg 5-fluorouracil equivalents/kg.

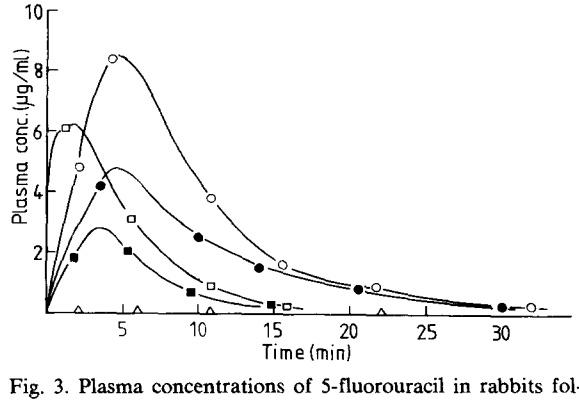

Fig. 3. Plasma concentrations of 5-fluorouracil in rabbits following rectal administration of 5-fluorouracil (△), compound 3 (□), compound 4 (■), compound 5 (○) and compound 14 (●) in amounts corresponding to 9 mg/kg of 5-fluorouracil.

No detectable absorption (i.e. < 2%) of 5-fluorouracil was observed which corresponds to previous findings in a rectal absorption study in man also using an aqueous enema preparation (Christophidis et al., 1978). This supports the suitability of the rabbit model for prediction of the rectal absorption characteristics of the compounds in man.

The results given in Table 4 show that the absorption behaviour of the various 5-fluorouracil derivatives varies widely. Thus, whereas the derivatives 5, 6, 11 and 14 are absorbed to an extent of 50–100% the compounds 8, 9, 10 and 13 as well as 5-fluorouracil itself show no or only a very slight absorption.

Drug absorption from the rectum is not essentially different from that in other parts of the gastrointestinal tract and passive diffusion is regarded as the main governing absorption mechanism (De Blaey and Polderman, 1980; De Boer et al., 1982). Therefore, the solubility and partitioning properties of the drug or prodrug substances are considered to be of paramount importance. However, only sparse information is available on the water and lipid solubilities required to ensure optimal rectal absorption of drug substances, even in qualitative terms, which contrasts with the much greater knowledge concerning the oral absorption (e.g. Ho et al., 1977; Yalkowsky and Morozowich, 1980; Dressman et al., 1985). Since only a little fluid is present in the rectum, a greater water-solubility is certainly required for a compound to be absorbed rectally as compared with oral absorption. For rabbits, Nishihata et al. (1984) have recently shown that the effective rectal fluid volume available to dissolve drugs is only about 0.1 ml. On the other hand, a certain lipophilicity, e.g. as expressed in terms of octanol–water partition coefficients, is required to allow a permeation through the rectal membrane. Thus, it has been shown that the extent of rectal absorption of some water-soluble penicillins in rabbits increases with increasing partition coefficients (Murakami et al., 1981). Since water-solubility and lipophilicity generally show a reverse relationship it is apparent that an optimal balance between these properties is required to achieve optimal absorption.

Analysis of the different absorption behaviour of the 5-fluorouracil derivatives revealed, in fact, that a proper balance between water-solubility and lipophilicity is essential to obtain good absorption. In Fig. 4 the observed bioavailability of the compounds has been plotted against log P, respectively log S. The pH value of the rectal fluid is in the range of 7.5–8 (Bitterman et al., 1967; De Blaey and Polderman, 1980) and therefore, the partition coefficients (P) and solubilities (S) used in the plots were those obtained at a physiological pH (7.4) rather than those representing the undissociated forms of the compounds (Table 1). As can be seen from Fig. 4 there is no direct relationship between bioavailability and lipophilicity or water-solubility.

On the other hand, by taking both lipophilicity and water-solubility into account and considering only those compounds showing an extent of absorption greater than 3%, the following correlation can be derived:

$$F = 0.52\ (\pm 0.14)\ \log P + 0.80\ (\pm 0.16)\ \log S + 1.40\ (\pm 0.19) \quad (3)$$

$$(n = 9;\ r = 0.899)$$

where F is the absorption fraction. This equation is graphically illustrated in Fig. 5. As seen from the plot compound 7, however, shows a large deviation and the compound was therefore not included in the regression equation.

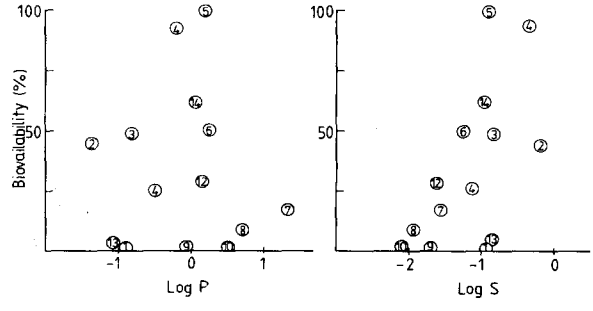

Fig. 4. The rectal bioavailability of 5-fluorouracil and various 5-fluorouracil prodrugs plotted against log P and log S for the compounds. The numbers refer to the compounds listed in Table 1. S refers to the molar solubility at pH 7.4 and P to the partition coefficient between octanol and pH 7.4 buffer.

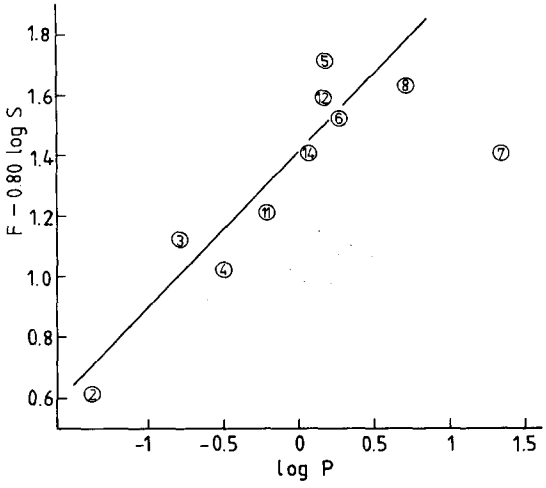

Fig. 5. Plot showing the relationship between rectal absorption fraction (F), log P and log S for various 5-fluorouracil derivatives according to Eqn. 3. Compound 7 was omitted in the construction of the regression line.

Another and possibly more informative way of delineating the properties of lipophilicity and water-solubility required to obtain optimal absorption is to consider the extent of absorption as a function of water-solubility for those compounds possessing a certain minimum lipophilicity and vice versa. Examination of the data in such a manner revealed, in fact, a good proportionality between bioavailability and aqueous solubility provided that a certain lipophilicity is possessed. This is demonstrated in Fig. 6 which encompasses those compounds with log $P > -0.3$.

From the plot shown in Fig. 6 the following

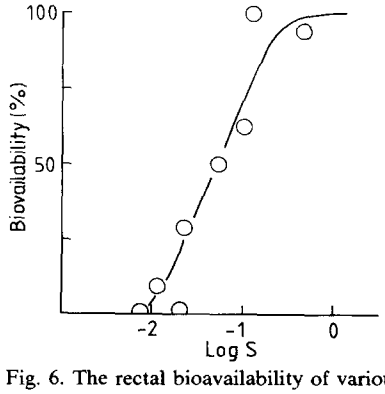

Fig. 6. The rectal bioavailability of various 5-fluorouracil prodrugs with a log $P > -0.3$ plotted against log S. S refers to the molar solubility at pH 7.4.

requirements to lipophilicity and aqueous solubility can apparently be defined: in order to provide a bioavailability of at least 50% following rectal administration in rabbits a 5-fluorouracil prodrug should possess (i) a partition coefficient between octanol and aqueous buffer (pH 7.4) greater than 0.5 ($\sim \log P > -0.3$) and (ii) a solubility in water at pH 7.4 greater than 0.5 M (at 20–25°C). Thus, by selecting 5-fluorouracil prodrug derivatives with such physicochemical characteristics it should be feasible to obtain an efficient absorption of 5-fluorouracil after rectal administration although the specific values given do not necessarily, of course, apply to absorption in man.

Among the derivatives studied the most promising prodrug candidates are compounds 5 and 11. These derivatives show an almost complete rectal absorption and are rapidly hydrolyzed in human plasma (cf. Table 2). In addition, upon bioconversion these derivatives release non-toxic promoieties (propionic acid (compound 11), butanol and carbon dioxide (compound 5)).

As seen from the stability data in Table 2 these compounds are not sufficiently stable to be formulated in a ready-to-use aqueous enema formulation even at an acidic pH value. However, when formulated in suppository preparations based on e.g. cocoa butter, the compounds may show an acceptable stability. Studies on the stability of the compounds in various suppository formulations are presently being carried out. Human absorption studies with the two derivatives are also in progress.

3-Alkoxycarbonyl derivatives of 5-fluorouracil are chemically much more stable than the corresponding 1-alkoxycarbonyl derivatives but also more resistant to undergo enzymatic hydrolysis (Buur and Bundgaard, 1984b, 1986a). Thus, when incubated in human plasma at 37°C for 4 h 3-ethyloxycarbonyl-5-fluorouracil (15) showed no detectable hydrolysis to 5-fluorouracil whereas a half-life of 5 h for the hydrolysis in a 30% rat liver homogenate was observed (Buur and Bundgaard, 1984b). When compound 15 was given rectally to two rabbits high plasma concentrations of intact substance were observed, indicating an efficient absorption. However, no detectable levels of 5-fluorouracil were seen which is in agreement with the

in vitro stability data. Thus, despite a favourable absorption characteristic compound 15 or related 3-alkoxycarbonyl derivatives may not be useful as prodrugs.

Peroral absorption

In order to get some indication on the peroral absorption behaviour of the 5-fluorouracil prodrugs showing good rectal absorption compound 5 and 5-fluorouracil were each given orally to two rabbits (cross-over design) in equivalent doses (9 mg 5-fluorouracil equivalents/kg). The plasma concentration vs time curves obtained are shown in Fig. 7. The extent of absorption, determined as described above in the rectal absorption study, was 10% (mean of 7 and 13%) for 5-fluorouracil and 58% (mean of 51 and 65%) for the 1-butyloxycarbonyl derivative (5). As was the case for rectal absorption no intact compound 5 was detected in the plasma samples. The results of the experiment clearly show that the 5-fluorouracil prodrug exhibits a greatly enhanced bioavailability as compared with 5-fluorouracil per se.

In conclusion, the results obtained suggest that it is readily feasible to improve the rectal and oral delivery of 5-fluorouracil by using the prodrug approach. As demonstrated above successful prodrugs for rectal absorption should possess a proper balance between water-solubility and lipophilicity. Compounds showing such characteristics combined with a facile conversion to 5-fluorouracil in vivo include 3-propionyl-5-fluorouracil and 1-butyloxycarbonyl-5-fluorouracil.

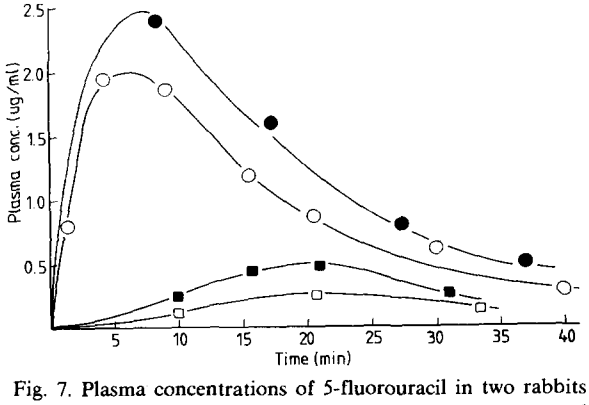

Fig. 7. Plasma concentrations of 5-fluorouracil in two rabbits following oral administration of 5-fluorouracil (squares) and compound 5 (circles) in amounts corresponding to 9 mg/kg of 5-fluorouracil. The filled symbols refer to rabbit A and the open symbols to rabbit B.

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