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International Journal of Pharmaceutics 231 (2002) 43–49

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

Topical delivery of 5-fluorouracil (5-FU) by 1,3-bisalkylcarbonyl-5-FU prodrugs

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Received 18 May 2001; received in revised form 20 August 2001; accepted 20 August 2001

Abstract

The solubilities in isopropyl myristate (S_{IPM}) and pH 4.0 buffer (S_{AQ}) and the partition coefficients between IPM and pH 4.0 buffer ($K_{IPM:AQ}$) have been measured for a series of 1,3-bisalkylcarbonyl-5-fluorouracil prodrugs (1,3-AC-5-FU). The 1,3-AC-5-FU prodrugs were each over 500 times more soluble in IPM, but all members of the series, whose solubilities could be estimated, were much less soluble in pH 4.0 buffer than 5-FU. The abilities of the 1,3-AC-5-FU prodrugs to deliver total 5-FU species through hairless mouse skin from IPM suspensions (J_i) were also measured. The 1,3-diacetyl derivative **2**, which exhibited the highest S_{AQ} in the series, gave the highest J_i value. Although the series of 1,3-AC-5-FU prodrugs was generally effective at increasing J_i (three to ten times), the best 1,3-AC-5-FU prodrug was not as effective as the best 1- or 3-alkylcarbonyl-5-FU prodrug (1- or 3-AC-5-FU) at increasing J_i and their ability to increase the concentration of total 5-FU species in the skin was generally less than that of the 1-AC-5-FU prodrugs, but greater than that of the 3-AC-5-FU prodrugs. Thus, the 1-AC-5-FU prodrugs remain the best prodrugs with which to enhance the topical delivery of 5-FU.

Keywords: 1,3-Bisalkylcarbonyl-5-fluorouracil; S_{AQ}; S_{IPM}; $K_{IPM:AQ}$; Solubility parameters; Diffusion cell experiments

1. Introduction

Previous attempts to improve the topical delivery of 5-fluorouracil (5-FU, **1**) with different series of prodrugs have focused on series where only one of the N–H groups in 5-FU was masked (Sloan et al., 1993; Beall et al., 1994; Beall and Sloan, 1996; Taylor and Sloan, 1998; Beall and Sloan, 2001). In most of those series, one or more members of the series were not only more lipid soluble than 5-FU, based on their solubilities in isopropyl myristate (S_{IPM}), but were more water soluble (S_{AQ}), based on estimates from their partition coefficients between IPM and pH 4.0 buffer (Beall et al., 1993a). Increases in the delivery of total 5-FU species (J_i) of up to 40 times were achieved in the 1-alkylcarbonyl-5-FU (1-AC-5-FU) series. The one report on the topical delivery of 5-FU,

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0378-5173/02/$ - see front matter
PII: S0378-5173(01)00869-9

with a series where both N–H groups were transiently masked, used a dialkylaminomethyl type (Mannich base) promoiety (Sloan et al., 1988). Although members of this type of prodrug were 500–1300 times more lipophilic than 5-FU, the best prodrug was the least lipid soluble member and it only improved J_i by five times. Aqueous solubilities were not measurable because of the very rapid estimated hydrolysis of that type of promoiety ($t_{1/2} \approx 1.3 \times 10^{-5}$ min) (Sloan et al., 1984).

On the other hand, reports on the use of prodrugs to improve the topical delivery of 6-mercaptopurine (6-MP) found that when both N–H (S–H) groups were masked using an acyl type promoiety (alkylcarbonyloxymethyl; Waranis and Sloan, 1987) not only did members of the series exhibit from 235 to 8000 times greater S_{IPM} values than 6-MP, but the first two members also exhibited greater S_{AQ} values (2.6 and 1.5 times, respectively) and greater J_i values for the delivery of 6-MP from IPM ($\approx$60 times each). Compared to the best analogous series, where only one N–H (S–H) group was masked (Waranis and Sloan, 1988), the comparable bis derivative exhibited greater S_{IPM} and S_{AQ} values (comparing the 6,9-bisacetyloxymethyl-6-MP to 6-butyryloxymethyl-6-MP, where each have the same number of carbons in the acyl chain), was equally effective at enhancing the topical delivery of 6-MP and equally ineffective at enhancing the ratio of dermal to transdermal delivery achieved by 6-MP (Sloan, 1992). Hence, it is a logical progression in the evaluation of prodrugs of 5-FU to examine the effect on the topical delivery of 5-FU of masking both N–H groups in 5-FU with an acyl type promoiety. The 1,3-bisalkylcarbonyloxymethyl-5-FU series is not available for a direct comparison with the performance of the 6,9-bisalkylcarbonyloxymethyl-6-MP series, but members of the 1,3-bisalkylcarbonyl-5-FU (1,3-AC-5-FU) series had been synthesized as intermediates in the synthesis of the 3-alkylcarbonyl-5-FU (3-AC-5-FU) series (Beall et al., 1997; Beall and Sloan, 2001) and were readily available. Thus, the 1,3-AC-5-FU series were evaluated first to determine the effect of using two acyl type promoieties in a prodrug on its ability to enhance the topical delivery of 5-FU.

In this paper the solubilities in lipid – isopropyl myristate (S_{IPM}) – and in pH 4.0 buffer (S_{AQ}) of a series of 1,3-AC-5-FU prodrugs and their abilities to deliver 5-FU into and through hairless mouse skin are reported and compared with the performance of the 1- and 3-AC-5-FU series.

2. Methods and materials

Melting points were determined with a Meltemp capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were obtained at 90 MHz on a Varian EM-390 spectrometer. Ultraviolet (UV) spectra were obtained on a Shimadzu UV-265 spectrophotometer. The diffusion cells were from Crown Glass, Somerville, NJ (surface area 4.9 cm^2, 20 ml receptor phase volume). The diffusion cells were maintained at 32 °C with a Fisher circulating water bath model 25. TLC analyses were run on Brinkman Polygram Sil G/UV 254 plates. Isopropyl myristate (IPM) was obtained from Givaudan, Clifton, NJ. Theophylline (Th) and 5-fluorouracil (5-FU, **1**) were purchased from Sigma Chemical Co.; acid chlorides and all other reagent chemicals were from Aldrich Chemical Co.; all other solvents were from Fisher. The female hairless mice (25–30 g, 12–16 weeks old SKH-hr-1) were from Temple University, Skin and Cancer Hospital. The 1,3-bisalkylcarbonyl-5-FU prodrugs (1,3-AC-5-FU, **2–5**) were synthesized as previously described (Beall et al., 1997) and were identical with the literature prodrugs by ^{1}H NMR, TLC and mp.

2.1. Solubilities and partition coefficients

Lipid solubilities for **2–5** and partition coefficients for **2** and **3** (S_{IPM} and $K_{IPM:AQ}$, respectively) were determined according to a previously described procedure (Beall et al., 1993a; Beall and Sloan, 2001). For compound **2**, the volume ratios (IPM:AQ) varied from 1:0.5 to 1:6, while for compound **3** they varied from 1:2 to 1:10 for measurements of $K_{IPM:AQ}$; the reported K values are averages of K values obtained using different volume ratios.

Estimated aqueous solubilities (S_{AQ}) were calculated from S_{IPM} and $K_{IPM:AQ}$ values: $S_{AQ} = S_{IPM}/K_{IPM:AQ}$.

2.2. Diffusion cell experiments

The diffusion cell experiments were run according to previously described procedures (Sloan et al., 1986; Beall and Sloan, 2001) and were essentially identical to the latter with the following exception. Total concentrations of the IPM suspensions of **2–5** that were applied ranged from 0.5 to 2.0 M, which ensured that enough excess solid was present to maintain saturation for the duration of the application period.

2.3. Analysis

The ^{1}H NMR spectra of the donor phases from the applications of **2–5** were run in DMSO-d_6. The C^6-**H** for 5-FU appeared at δ7.73, for the 3-AC prodrugs it appeared at δ7.90, and for the 1,3-AC prodrugs it appeared at δ8.40 in DMSO-d_6. Since this area of each spectrum was free from interference by IPM absorbances, the three signals were easily quantified by integration. The HPLC system used was previously described (Beall et al., 1993b; Beall and Sloan, 2001).

Since authentic samples of the proposed 1- and 3-alkylcarbonyloxymethyl-5-FU (1- and 3-ACOM-5-FU) prodrugs from the hydrolysis of the 1,3-bisalkylcarbonyl-5-FU (1,3-AC-5-FU) prodrugs in the receptor phase containing formaldehyde (Beall et al., 1993b, 1997) were not available (except 1- and 3-acetyloxymethyl-5-FU), each of the 1,3-AC-5-FU prodrugs ($1.12–1.24 \times 10^{-4}$ M) was allowed to hydrolyze completely in pH 7.1 phosphate receptor phase buffer containing 0.11% formaldehyde as control experiments. Values of molar absorptivities (ε) for these hydrolysate mixtures were obtained and compared to the value of ε for 5-FU under the same conditions.

2.4. Solubility parameters

The calculated solubility parameters (δ_i) were obtained using the method of Fedors (1974) as illustrated by Martin et al. (1985) and Sloan et al. (1986).

3. Results and discussion

3.1. Solubilities and partition coefficients

The lipid solubilities (S_{IPM}) of 1,3-bisacetyl-(**2**), 1,3-bispropionyl-(**3**), 1,3-bisbutyryl-(**4**) and 1,3-bisvaleryl-5-FU (**5**), the partition coefficients between IPM and pH 4.0 acetate buffer ($K_{IPM:AQ}$) and the estimated solubilities of **2** and **3** in pH 4.0 acetate buffer (S_{AQ}) are given in Table 1. The S_{IPM} values for **2** through **5** are generally greater than the S_{IPM} values for the 1- and 3-AC-5-FU

Table 1
Solubilities in IPM (S_{IPM}), partition coefficients between IPM and pH 4.0 buffer ($K_{IPM:AQ}$), solubilities in pH 4.0 buffer (S_{AQ}) estimated from (S_{IPM})/($K_{IPM:AQ}$) and calculated solubility parameters (δ_i)

Compound 1,3-[R(C = O)]$_2$-5-FU	S_{IPM}[a,b] (mM)	$K_{IPM:AQ}$ ($\pm$ S.D.)	S_{AQ}[c] (mM)	δ_i (cal cm^{-3})$^{1/2}$
1 5-FU	0.049		96	14.99
2 R = CH_3	26 (17.4)	2.11 (0.14)	12.4 (6.5)	12.21
3 R = C_2H_5	72 (113)	22.7 (3.6)	3.2 (2.9)	11.65
4 R = C_3H_7	625 (111)	ND[d]	ND[d]	11.24
5 R = C_4H_9	1180 (59)	ND[d]	ND[d]	10.93

[a] Less than $\pm$4% variation in measured S_{IPM}.
[b] S_{IPM} values in parentheses are for 1-butyryl-, 1-hexanoyl-, 1-octanoyl- and 1-decanoyl-5-FU, respectively (Beall and Sloan, 1996; Patrick et al., 1997).
[c] S_{AQ} values in parentheses are for 1-butyryl- and 1-hexanoyl-5-FU, respectively.
[d] Not performed because they were too poorly water soluble and unstable to be measured and estimated.

Table 2
Experimental rates of delivery of total 5-FU species by the prodrugs from IPM through hairless mouse skin (J_i), concentrations of total 5-FU species retained in the skin (C_S), dermal/transdermal (D/T) delivery ratios, the rates of delivery of theophylline from PG (J_j) after removal of the prodrugs and log permeability coefficients (log P_i) obtained from the log of J_i/S_{IPM}

Compound 1,3-[R(C = O)]$_2$-5-FU	J_i[a,b] (± S.D.)	C_S (μmole)	D/T[c]	J_j[a]	Log P_i (cm h^{-1})
1 5-FU	0.24	3.7	0.131	1.2	0.69
2 R = CH_3	2.2 (0.5) [1.3]	10.0	0.039	1.6	−1.07
3 R = C_2H_5	0.69 (0.06) [1.1]	4.5	0.055	1.6	−2.02
4 R = C_3H_7	0.98 (0.06) [0.60]	12.0	0.104	1.1	−2.80
5 R = C_4H_9	0.95 (0.05) [0.13]	8.8	0.079	0.87	−3.09

[a] Units of μmole cm^{-2} h^{-1}.
[b] J_i values in brackets are for 1-butyryl-, 1-hexanoyl-, 1-octanoyl- and 1-decanoyl-5-FU, respectively (Beall and Sloan, 1996; Patrick et al., 1997).
[c] Calculated from $\{C_S/[(4.9\ cm^2)(24\ h)]\}/J_i$ to give a dimensionless ratio.

prodrugs containing the same number of carbons in the acyl chain. For reference, the S_{IPM} values for the 1-butyryl-, 1-hexanoyl-, 1-octanoyl- and 1-decanoyl-5-FU derivatives are given in Table 1 for comparison with **2** through **5**, respectively; only the S_{IPM} value for 3-butyryl-5-FU (22.0 mM) is available from the 3-AC-5-FU series. The difference in S_{IPM} values is accentuated for the longer alkyl chain members of the 1-AC-5-FU series, where the alkyl chains are sufficiently long that intermolecular interactions of the alkyl chains lead to higher melting points and lower lipid solubilities (Beall and Sloan, 1996). Regardless of the fact that the 1,3-AC-5-FU derivatives contain the same number of carbon atoms in their combined acyl chains, the individual alkyl chains are not sufficiently long for intermolecular interactions to dominate their physical properties.

Partition coefficients ($K_{IPM:AQ}$) values could only be determined accurately for the first two members of the series. This is due to the very high S_{IPM} values for **4** and **5**. In order to observe measurable changes in the UV absorbances of the prodrug/IPM phases after partitioning, it was necessary to use much larger than 1:10 (IPM:AQ) phase volume ratios. This led to erratic solute transfer from IPM to AQ in the short time available for partitioning of derivatives exhibiting very short $t_{1/2}$ values in water (Beall et al., 1997). The methylene π value for the difference between log $K_{IPM:AQ}$ for **2** and **3** is only 0.51, which is much lower than the mean methylene π value calculated from the difference in log $K_{IPM:AQ}$ for other homologous series of prodrugs of 5-FU (0.60 ± 0.05, Beall and Sloan, 1996). This result suggests that the solubilities of the 1,3-AC-5-FU series, similar to the 3-AC-5-FU series, are not well-behaved. Again, the reason for the poor behavior may be due to the fact that each contain the 3-acyl group which is perpendicular to the plane of the 5-FU ring (Beall et al., 1993b). This could cause non-uniform packing in the crystal lattices of adjacent members of the series. Since $K_{IPM:AQ}$ values were only measurable for **2** and **3**, S_{AQ} could also be estimated only for **2** and **3**. The S_{AQ} values for **2** and **3** are greater than the S_{AQ} values for the members of the 1-AC-5-FU series containing the same number of carbon atoms in the acyl chain (Table 1), but the S_{AQ} value for **2** is less than that estimated for 3-butyryl-5-FU (23 mM). The S_{AQ} values for 1-butyryl- and 1-hexanoyl-5-FU are also included in Table 1 for comparison with **2** and **3**.

3.2. Diffusion cell experiments

The results from the diffusion cell experiments ($n = 3$) are given in Table 2. It was necessary to use IPM, a nonprotic solvent, as the vehicle for the delivery of 5-FU by the 1,3-AC-5-FU prodrugs because they are very unstable in protic solvents (Beall et al., 1997). It was also necessary so that these J_i values could be compared with J_i values for the 1- and 3-AC-5-FU series and with

J_i values from prodrugs of 6-MP and theophylline where IPM was used as well. Using IPM as the vehicle, only the intact 1,3-AC-5-FU prodrugs were observed in the donor phases when the residues from the donor phases were analyzed by ^{1}H NMR spectroscopy.

Quantitation of total 5-FU species in the receptor phase delivered by the 1,3-AC-5-FU prodrugs presented the same difficulties as encountered during quantitation of total 5-FU species delivered by the 3-AC-5-FU prodrugs (Beall and Sloan, 2001). Since it was necessary to use 0.11% formaldehyde in the receptor phases of the diffusion cells to prevent deterioration of the mouse skins (Sloan et al., 1991), and the 3-AC-5-FU intermediates formed from the hydrolysis of the 1,3-AC-5-FU in the skin and receptor phase subsequently underwent partial trapping by formaldehyde and rearrangement to 1- and 3-alkylcarbonyloxymethyl-5-FU derivatives (1- and 3-ACOM-5-FU), the receptor phases initially contained a complex mixture of 5-FU, 3-AC-5-FU, 1- and 3-ACOM-5-FU. Furthermore, since the only authentic samples of 1- and 3-ACOM-5-FU derivatives were of 1- and 3-acetyloxymethyl-5-FU, it was not possible to quantitate each component of the mixture in the receptor phases. Instead, samples of the 1,3-AC-5-FU prodrugs were hydrolyzed at pH 7.1 in the presence of 0.11% formaldehyde for 72 h. Initially, the corresponding 3-AC-5-FU derivatives were formed in a very rapid and complete reaction, but after 72 h the same mixtures of 5-FU and 1- and 3-ACOM-5-FU derivatives were formed that had been obtained after the hydrolysis of the 3-AC-5-FU derivatives under the same conditions. The measured molar absorptivities (ε) of these hydrolysates (λ_{max} at 266 nm) from **2**, **3**, **4** and **5** were 3.0, 1.4, 1.9 and 2.9%, respectively, less than the molar absorptivity of 5-FU measured under the same conditions. Therefore, the value of ε for 5-FU itself was used to calculate the concentration of total 5-FU species in the receptor phases. This approximation leads to a $< 5\%$ underestimation of total 5-FU in the receptor phase.

All of the 1,3-AC-5-FU prodrugs were more effective than 5-FU at delivering total 5-FU species through hairless mouse skin from IPM suspensions. As observed for similar previously studied series (Sloan, 1992), there was no direct relationship between the lipid solubilities (S_{IPM}) of the prodrugs and their abilities to deliver total 5-FU species through skin (J_i). On the other hand, there was a direct relationship between the pH 4.0 aqueous buffer solubilities (S_{AQ}) and J_i for **2** and **3** which had also been observed for previously studied series. The most water soluble member of the series was **2** and it gave the highest flux, however it gave only one-fourth the flux of the best 1-AC-5-FU derivative (1-acetyl-5-FU) and one-half the flux of the best 3-AC-5-FU derivative (3-propionyl-5-FU). However, when the performance of **2** was compared with that of 1- and 3-butyryl-5-FU (derivatives containing the same number of carbons in the acyl chain), the J_i value for **2** was the same as that of 3-butyryl-5-FU and nearly twice that of 1-butyryl-5-FU. For reference, the J_i values for 1-butyryl-, 1-hexanoyl-, 1-octanoyl- and 1-decanoyl-5-FU are included in Table 2 for comparison with **2** through **5**, respectively; the J_i value for 3-butyryl-5-FU is 2.2 μmole cm^{-2} h^{-1}.

Although all of the 1,3-AC-5-FU prodrugs were more effective that 5-FU at causing accumulation of total 5-FU species in the skin based on the C_S values in Table 2, they were not nearly as effective as 5-FU itself based on the D/T delivery ratios that are also listed in Table 2. The C_S values reflect how much of total 5-FU species were in the skin when the donor phases were removed, while the D/T delivery ratios normalize the C_S values for J_i. D/T delivery ratios less than that of 5-FU itself indicate that the prodrugs were not effective in preferentially increasing dermal delivery compared to 5-FU. Thus, the 1,3-AC-5-FU prodrugs increased C_S, but not as much as J_i was increased. For instance, **2** increased J_i by ten times, but only increased C_S by 2.5 times. By comparison, three members of the 1-AC-5-FU series of prodrugs gave D/T delivery ratios comparable to that of 5-FU. On the other hand, the best 3-AC-5-FU prodrug gave a D/T ratio that was less than half that given by 5-FU. The reason for this difference between the 1- and 3-AC-5-FU prodrugs has been discussed elsewhere in detail (Beall and Sloan, 1996). The 1,3-AC-5-FU pro-

drugs are intermediate in their ability to enhance dermal compared to transdermal delivery.

The differences in delivery of total 5-FU species by the members of the 1,3-AC-5-FU series of prodrugs does not appear to be due to significant differences in damage to the skin caused by their application in IPM. Application of a standard solute/vehicle (theophylline/PG) after removal of the prodrug/IPM donor phase and a 24-h leaching period, gave the J_j values listed in Table 2. Thus, using J_j values as one measure of damage, the damage caused by **2** through **5**/IPM was comparable to the damage caused by 5-FU/IPM. Normalization of J_j values by dividing by the respective J_i values (data not shown) did not lead to any changes in the rank order of performance by the 1,3-AC-5-FU prodrugs.

When the log permeability coefficients (log P_i) from Table 2 were plotted against the respective calculated solubility parameters (δ_i) for the 1,3-AC-5-FU prodrugs from Table 1, a straight line (plot not shown) was obtained with a slope (0.61, $r = 0.995$) which is similar to that obtained for the 1-AC-5-FU prodrugs (0.89, $r = 0.99$) and the 3-AC-5-FU prodrugs (0.80, $r = 0.996$). Thus, the 1,3-AC-5-FU series behaves in a manner that is similar to the 1- and 3-AC-5-FU series. As the members of the series become more lipophilic based on decreasing δ_i values, they become less efficient at delivering the parent drug from a lipoidal vehicle (decreasing P_i value).

4. Conclusions

Although the 1,3-AC-5-FU prodrugs were about twice as effective at enhancing the topical delivery of total 5-FU species as the previously reported 1,3-bis derivatives (1,3-bisdialkylaminomethy-5-FU prodrugs), masking both NH groups as a 1,3-bis derivative was not as effective as masking only one NH group when the promoiety was an acyl group. The 1,3-AC-5-FU prodrugs were less effective than the 1- or 3-AC-5-FU prodrugs (unless members containing the same number of carbons in their acyl chains were compared) because of their relatively poor aqueous solubility. At least one member of the two mono series was more water soluble than 5-FU, but in the bis series the best aqueous solubility exhibited by any member was only 0.12 times that of 5-FU. The fact that the first few members of the 1,3-AC-FU series were much more lipid soluble than the first few members of the two different mono series, which were the best performers in those series, did not compensate for the lack of aqueous solubility of the 1,3-AC-5-FU series. Also, the fact that the highly lipophilic 1,3-AC-5-FU prodrugs hydrolyzed rapidly to much more water soluble 3-AC-5-FU prodrugs did not offer any advantage over the 3-AC-5-FU prodrugs themselves suggests that the opposite approach should be evaluated: a more water soluble bis prodrug which hydrolyzes rapidly to a more lipid soluble mono prodrug.

Acknowledgements

The authors acknowledge the interest and support of Dr Noel Meltzer and the partial support by a grant from Hoffmann-LaRoche.

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