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Effect of Complex Formation on Drug Absorption XV: Structural Requirements for Enhancement of Intestinal Absorption of Steroids by *N,N*-Di-*n*-propylpropionamide

Keyphrases ☐ Drug absorption, prednisone, prednisolone—structural requirements for enhancement by *N,N*-di-*n*-propylpropionamide complex formation ☐ Steroid–dialkylpropionamide complexes—structural requirements for formation ☐ Complex formation, prednisone/prednisolone–*N,N*-di-*n*-propylpropionamide—structural requirements ☐ Intestinal absorption, prednisone, prednisolone—structural requirements for enhancement by dialkyl propionamide complex formation

Sir:

N,N-Di-*n*-propylpropionamide (propyl-amide) and certain other substituted propionamides form complexes with prednisone and prednisolone in a lipoid solvent and enhance the transfer of these steroids across intestinal and synthetic lipoid barriers (1–3). The absorption-enhancing effect of propyl-amide appears to involve the formation of a steroid–propyl-amide complex in the barriers. The absorption-enhancing effect is relatively specific, since propyl-amide does not affect the intestinal absorption of several nonsteroid drugs with which it interacts in an organic solvent (4). To explore further the specificity of this effect, the influence of propyl-amide on the absorption of several struc-

Table I—Effect of *N,N*-Di-*n*-propylpropionamide on the Intestinal Absorption and Solubility of Selected Steroids

Steroid	Experimental Conditions	Percent Absorbed[a] 40 min.	Ratio[b]	80 min.	Ratio[b]	S/S_0[c]	Structural Difference from Prednisolone
Prednisolone (I)	Control	22.4 (2.00)	1.56	37.6 (1.90)	1.47	2.4	—
	0.4% propyl-amide	35.0 (1.52)[d]		55.2 (1.30)[d]			
Hydrocortisone (III)	Control	31.5 (1.58)	1.30	52.5 (1.44)	1.20	1.6	Lacks 1,2-double bond
	0.4% propyl-amide	41.0 (1.14)[d]		62.9 (1.32)[d]			
Corticosterone (IV)	Control	44.3 (2.97)	1.05	59.4 (2.19)	1.06	1.6	Lacks 1,2-double bond and 17-OH
	0.4% propyl-amide	46.6 (1.00)		63.0 (1.04)			
Desoxycorticosterone (V)	Control	62.8 (1.32)	0.93	80.2 (0.89)	0.96	1.1	Lacks 1,2-double bond, 17-OH, and 11-OH
	0.4% propyl-amide	58.5 (1.48)		76.8 (0.90)			

[a] Mean of four rats; standard error in parentheses. [b] Ratio of the mean percent absorbed in the presence of propyl-amide to the mean percent absorbed without the amide. [c] Ratio of the apparent solubility of the steroid in isopropyl myristate containing 2% propyl-amide to its solubility in isopropyl myristate, at 25°. [d] Statistically significantly different from the control value ($p < 0.01$).

turally related steroids from the rat intestine was investigated.

Male Sprague-Dawley rats were prepared as described previously (3) for determining the rate of drug absorption in the presence of a constant concentration of complexing agent. An aqueous solution of tritium-labeled steroid containing 0.9% NaCl, 1 m*M* ^{14}C-butanol, and 0.4% propyl-amide (when present) was circulated through a segment of the small intestine. The concentration of propyl-amide was maintained constant by infusing it into the perfusion solution at a rate equal to the absorption rate of the amide. Samples of the intestinal solution were removed periodically and the concentrations of steroid, butanol, and propyl-amide (when present) were determined as described previously (3). The method used to determine steroid solubility in isopropyl myristate was also described (1). Butanol was used as an "internal standard" to reduce rat-to-rat variability in absorption kinetics (3). Since the absorption of some of the steroids was not monoexponential, apparent first-order absorption rate constants were determined from each consecutive pair of steroid concentrations in the intestinal solution of each rat. This constant was multiplied by the average butanol absorption rate constant for all of the animals and divided by the butanol absorption rate constant for that particular animal. The normalized absorption rate constant thus obtained was used to normalize the absorption data listed in Table I. This adjustment was relatively small; most of the absorption data were changed by only about 5% from the uncorrected values. It was shown previously that the absorption of butanol is not affected by propyl-amide (3).

The results of the steroid absorption and solubility experiments are summarized in Table I. It was shown in a previous report that the effect of propyl-amide on the intestinal absorption and apparent lipoid solubility of prednisone (II) is similar to the effect of the amide on the absorption and apparent solubility of prednisolone (I) (1, 2). Steroid molecules with a 1,2-double bond (I and II) interact more strongly with propyl-amide than compounds saturated in this position (III, IV, and V). The loss of the 17-hydroxyl group does not affect the interaction with amide (compare the solubility ratios of III and IV), while removal of the 11-hydroxyl group makes the interaction negligible (compare the solubility ratios of IV and V). The replacement of the 11-hydroxyl group with a carbonyl group has no apparent effect (1). The intestinal absorption data for I and III suggest that a decrease in the steroid–propyl-amide association constant results in a reduced absorption-enhancing effect of the amide, as would be expected (1). More significantly, the absorption data indicate that the steroid absorption-enhancing effect of propyl-amide is related either to the presence of the 17-hydroxyl group or to the presence of at least two hydroxyl groups (or one hydroxyl and one carbonyl group) on the steroid nucleus, since the amide enhances appreciably the absorption of I, II (2), and III but has no effect on the absorption of IV and V.

Because there is an inverse relationship between the absorption rate of Steroids I–V and the absorption-enhancing effect of propyl-amide on these steroids, it may be speculated that the absorption of the more rapidly absorbed Steroids IV and V is rate limited by their diffusion to the mucosal surface. This could then account for the lack of effect of the amide on the absorption of these two compounds. However, propyl-amide does not affect the absorption of IV and V even in the 60–120-min. time period, when the apparent absorption rate constants of IV and V have decreased to about the same value as that of III.

There is evidence that hydroxyl groups on the steroid molecule cause increased interaction of the steroid with the biologic barrier (5). Complexation with propyl-amide may interfere with this interaction and thereby overcome its absorption-retarding effect. Further studies with other steroids and related molecules may yield additional information on the nature of the interaction of these substances with the intestinal barrier.

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Comments on the Apparent Shape of Micelles

Keyphrases ☐ Micelles—spherical shape ☐ Surfactants—formation of spherical micelles

Sir:

In a recent communication (1), it was argued that micelles of common single-chain surfactants are probably not spherical. The argument centers on the calculation of the maximum radius, R, for the core of a spherical micelle from the length of a fully extended alkyl chain and the fact that such values are not large enough to account for spherical micelles of the sizes reported in the literature.

It was shown by geometric consideration that for a spherical micelle:

$$R = 1.772\left(\frac{zn}{d}\right)^{1/3} \qquad \text{(Eq. 1)}$$

where z is the aggregation number of the micelle, n is the number of carbon atoms in the linear alkyl moiety, and d is the core density of the micelle. It was assumed that the length of the fully extended hydrocarbon chain is equal to $1.27n$ and, therefore:

$$1.772\left(\frac{zn}{d}\right)^{1/3} \leq 1.27n \qquad \text{(Eq. 2)}$$

From this:

$$z \leq 0.368dn^2 \qquad \text{(Eq. 3)}$$

The value of 1.27 in Eq. 2 is the average bond distance in angstroms between two carbon atoms in the extended alkyl chain. There are actually $n - 1$ such bonds, plus the bond between the α-carbon and the hetero atom of the polar group. This latter bond will have a length that varies with the groups involved, usually greater than 1.27 Å. In a similar series of calculations, Tartar (2) arbitrarily chose a fraction of this bond length to include in his estimation of R, *e.g.*, 1.42 Å/2 for the C—S bond in an alkyl sulfate molecule. Actually, using $1.27n$ is no less arbitrary than this approach, while offering the possibility of calculating approximate maximum core radii without regard to molecular structure.

Table I—Calculated Values of Maximum Radius (Å)

n[a]	$1.27n$	$1.27(n-1) + 2.71$	$1.27n + 2$
10	29	40	45
12	42	55	61
14	58	73	78
16	77	94	101
18	98	118	126

[a] n is the number of carbons in the alkyl chain.

In *Reference 1*, no consideration was given to the length of the terminal C—H bond or to the van der Waals radii of the terminal hydrogens. These two factors combine to add a value[1] of about 2 Å to the length of the chain (2, 3). If this factor is taken into account, Eqs. 1 and 2 become:

$$R \leq 1.27n + 2 \qquad \text{(Eq. 4)}$$

and:

$$z \leq \frac{1.27}{1.772}n^{2/3}d^{1/3} + \frac{2}{1.772}\frac{d^{1/3}}{n^{1/3}} \qquad \text{(Eq. 5)}$$

respectively.

Since the micelle size is dependent upon the cube of the radius, the small 2 Å error in R produces a large error in aggregation number. Table I shows the results of solving Eqs. 2 and 5 for several common chain lengths.

Included also in Table I are values taken from the calculations of Tartar (2). Since his calculations depend on the specific surfactant used, these values are for a series of alkyl sulfates. For all common surfactants, Tartar's values are greater than those obtained by Schott (1) but less than those calculated according to Eq. 5.

Figure 1 is taken directly from *Reference 1*, but it also includes values calculated by the two methods just described. It is clear that a greater proportion of the aggregation numbers from the literature lie close to or below the theoretical lines when the calculation is altered. This is particularly true for the ionic surfactants. In this regard, it is interesting to note that Tartar carried out his calculations assuming the micelle to be an oblate spheroid and, in most cases, ionic surfactants in the absence of salt had ratios of the major-to-minor axes equal to or nearly unity, indicating spherical or near spherical shape.

It is further argued in *Reference 1* that spherical micelles would have to have an area of 67–70 Å^2 per head group. Since this is over twice the limiting area per

[1] The value of 2 Å is probably a minimum value. The large group volume of a terminal methyl group with respect to the volume of a methylene group is very likely associated with an increase in length along the axis of the hydrocarbon chain. The radius of a hemisphere having a volume of 32.6 Å^3 (the volume of a terminal methyl group) is 2.5 Å.