# Effect of Complex Formation on Drug Absorption XIV: Effect of *N,N*-Di-*n*-propylpropionamide on Intestinal Absorption of Certain Nonsteroid Drugs in the Rat

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**Abstract** □ The effect of 0.5% *N,N*-di-*n*-propylpropionamide on the intestinal absorption of salicyluric acid, barbital, *p*-aminohippuric acid, *N*-acetyl-*p*-aminophenol, phenol red, riboflavin, and tetracycline was determined in rats. The amide has no significant effect on the absorption rate of any of the drugs, although complex formation between the amide and several of the drugs in an organic solvent and enhanced transfer through an artificial lipoid barrier could be demonstrated. These results indicate that the absorption-enhancing effect of the amide (previously noted with prednisone and prednisolone) is relatively specific, depending not only on the interaction between drug and complexing agent but also on the possible interaction of one or both of these substances with a structural or functional component of the intestinal wall.

**Keyphrases** □ *N,N*-Di-*n*-propylpropionamide—effect on intestinal drug absorption of seven compounds, rats □ Intestinal drug absorption, rats—role of *N,N*-di-*n*-propylpropionamide on rate of seven compounds □ Drug absorption—effect of *N,N*-di-*n*-propylpropionamide on seven compounds, rats

Previous investigations in this series showed that the intestinal absorption of prednisone and prednisolone and the transfer of these drugs through an artificial lipoid barrier are increased significantly by *N,N*-di-*n*-propylpropionamide (to be referred to as propyl-amide) due to complexation of the amide with the steroids in the barriers (1–3). These studies have now been extended to certain nonsteroid drugs, most of which are intrinsically poorly absorbed but form complexes with the amide in a lipoid solvent.

## EXPERIMENTAL

Drug absorption from the *in situ* rat intestine was determined in anesthetized male Sprague-Dawley rats weighing 260–310 g. as described previously (2). A solution of each drug in isotonic sodium phosphate buffer (and tromethamine buffer for barbital at pH 8.4) alone or with 0.5% propyl-amide was placed in the intestine, and samples were removed periodically for assay. The effect of 2% propyl-amide on the apparent solubility of each drug in isopropyl myristate and the effect of 2% propyl-amide on the isopropyl myristate/water apparent partition coefficient of each drug were determined by methods described previously (1). The effect of the amide on the rate of transfer of salicyluric acid from a pH 1 aqueous source solution across an artificial lipoid barrier to a pH 7 aqueous sink solution was also determined by a previously described method (1).

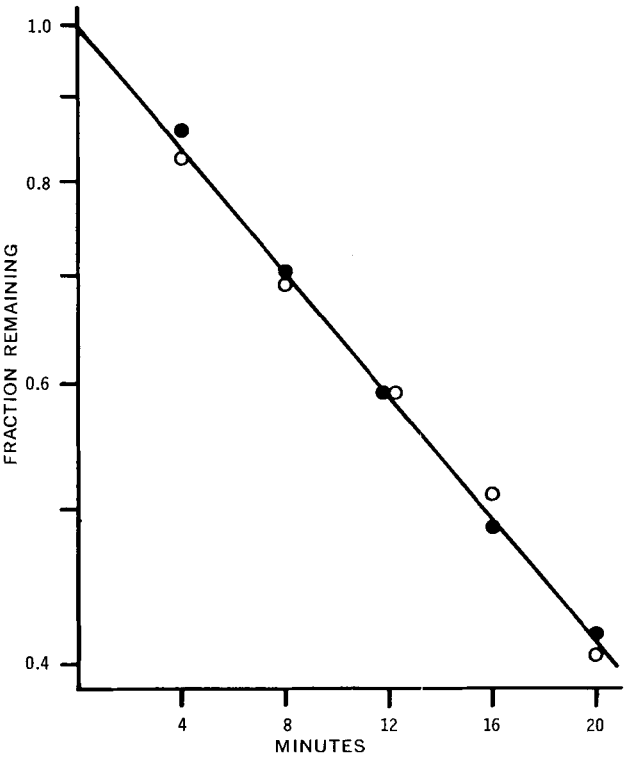


**Figure 1**—*Effect of* N,N-*di*-n-*propylpropionamide (initial concentration, 0.5%) on the absorption of* N-*acetyl*-p-*aminophenol from the* in situ *rat intestine; average of four animals each. Key:* ●, *control; and* ○, *with amide.*

**Table I**—Effect of *N,N*-Di-*n*-propylpropionamide on the Absorption of Certain Drugs from the Rat Intestine and on Their Apparent Solubility and Apparent Partition Coefficient

| Drug | Initial Concentration, mg./ml. | Initial pH | Percent Absorbed[a] Control | Percent Absorbed[a] With[b] Propyl-Amide | $S/S_0$[c] | $PC/PC_0$[d] |
|---|---|---|---|---|---|---|
| Salicyluric acid | 2.0 | 6.4 | 31, 34 | 26, 36 | 2.6 | 2.6 |
| Barbital | 0.40 | 6.0 | 88, 88 | 86, 84 | 1.5 | 1.5 |
| Barbital | 0.40 | 8.4 | 80, 79 | 80, 66 | | |
| *p*-Aminohippuric acid | 0.10 | 6.7 | 14, 12 | 11, 7 | 2.5 | —[e] |
| *N*-Acetyl-*p*-aminophenol | 2.0 | 6.4 | 74[f] | 74[f] | 2.2 | 2.3 |

[a] At 30 min.; data from two animals. [b] Initial concentration 0.5%. [c] Ratio of the apparent solubility of the drug in isopropyl myristate containing 2% propyl-amide to the solubility of the drug in isopropyl myristate. [d] Ratio of the apparent partition coefficient of the drug between isopropyl myristate containing 2% propyl-amide and 0.1 *N* HCl in water to its isopropyl myristate/0.1 *N* HCl partition coefficient. [e] Absolute values too low to determine. [f] Extrapolated from the data in Fig. 1.

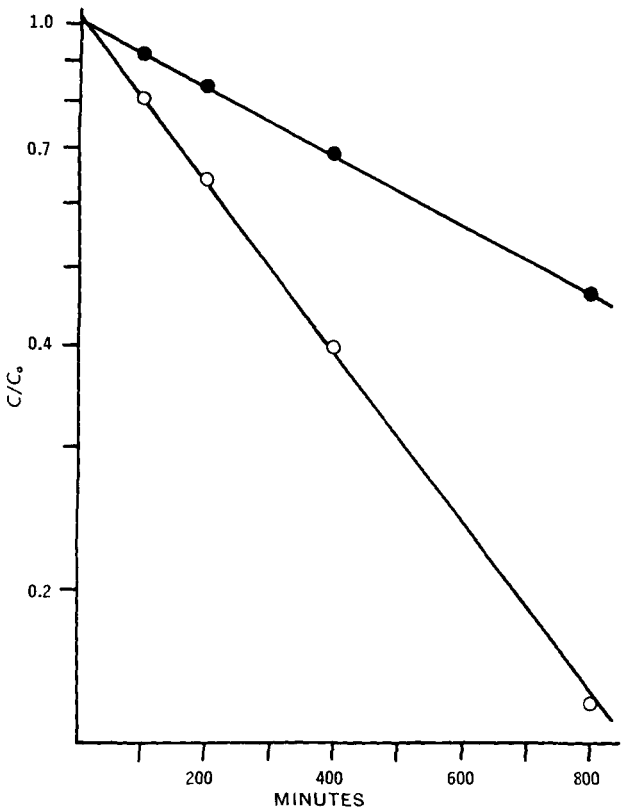


**Figure 2**—*Effect of* N,N-*di*-n-*propylpropionamide on the transfer of salicyluric acid from a well-stirred pH 1 source solution through an artificial lipoid barrier to a well-stirred pH 7 sink solution. Key:* ●, *control; and* ○, *2% amide in the barrier.*

Riboflavin concentrations were determined by fluorometry (4); barbital concentrations were determined spectrophotometrically (5); phenol red concentrations were determined spectrophotometrically at 560 nm. after the samples were diluted appropriately with 0.03 *N* NaOH; *p*-aminohippuric acid concentrations were determined by the colorimetric method of Bratton and Marshall (6); tetracycline concentrations were determined by the fluorometric method of Kohn (7); *N*-acetyl-*p*-aminophenol concentrations were determined by the colorimetric method described by Levy and Yamada (8) and by Levy and Regårdh (9); and salicyluric acid concentrations were determined colorimetrically (10, 11).

## RESULTS AND DISCUSSION

The absorption of salicyluric acid, barbital, *p*-aminohippuric acid, and *N*-acetyl-*p*-aminophenol is not affected by propyl-amide, even though the amide interacts with these drugs in an organic solvent (isopropyl myristate), increases their apparent partition coefficient between this solvent and water (Table I and Fig. 1), and enhances transfer through a synthetic lipoid barrier in the case of the one drug studied (Fig. 2). In addition, propyl-amide has no apparent effect on the intestinal absorption of phenol red, riboflavin, or tetracycline (Table II). Complex formation between these three substances and the amide is likely, since they all contain at least one electron-accepting group (12), but this could not be determined readily due to the low solubility of these compounds in isopropyl myristate.

The lack of effect of propyl-amide on the absorption of the nonsteroid drugs is in contrast to the pronounced influence of this amide on the intestinal absorption of prednisone and prednisolone (2, 3) and indicates that the enhancement of the intestinal absorption of the steroids by propyl-amide is a relatively specific effect. This specificity may be related to the fact that hydroxylated steroids interact appreciably with biologic membranes (13, 14). A study of the relative absorption rates of a series of steroids showed that the presence of hydroxyl groups on steroid molecules markedly slows their intestinal absorption (13). A similar observation was made with respect to their percutaneous absorption and could not be explained solely on the basis of a decreased barrier–aqueous phase partition coefficient (14).

The specificity of the absorption-enhancing effect of the amides may provide an unusual opportunity for determining the structural requirements for the interaction of drugs with biologic barriers. The ready availability of steroids with diverse substituent configurations permits a methodical assessment of the structural characteristics required of molecules whose absorption can be enhanced by propyl-amide and certain other amides (2, 3). Preliminary results of such a study will be reported in a subsequent article.

**Table II**—Effect of *N,N*-Di-*n*-propylpropionamide on the Intestinal Absorption of Phenol Red, Riboflavin, and Tetracycline in Rats

| Drug | Initial Concentration, mg./ml. | Initial pH | —Percent Absorbed[a]— Control | With Amide |
|---|---|---|---|---|
| Phenol red | 0.15 | 6.0 | 18, 13 | 20, 2 |
| Riboflavin | 0.008 | 6.4 | 17, 15 | 15, 10 |
| Tetracycline | 0.02 | 6.6 | 12, 11 | 16, 12 |

[a] At 30 min.; data from two animals.

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