Effect of Various Alcohols on Intestinal Net Water Flux and Theophylline Absorption in Rats

J. B. HOUSTON and GERHARD LEVY ˣ

Abstract □ Previous studies in this laboratory demonstrated that the rate of intestinal absorption of theophylline in rats is increased significantly by ethanol in low concentrations and that this absorption enhancing effect is associated with an increased net water flux from the intestine. It is now shown that other alcohols, namely methanol, *n*-propanol, *n*-butanol, glycerin, propylene glycol, and, to a lesser extent, mannitol and sorbitol, can also increase net water flux from the small intestine of anesthetized rats. Polyethylene glycol 200 and 400 had no such effect, suggesting that these compounds do not penetrate to a site of action that elicits the increased net water flux. At initial concentrations of 0.1 and 1.0 *M*, glycerin and propylene glycol increase significantly the intestinal absorption rate of theophylline from the small intestine of anesthetized rats. The results show that the theophylline absorption enhancing effect of ethanol is not limited to that particular alcohol.

Keyphrases □ Intestinal net water flux—effect of various alcohols, glycerin and propylene glycol effect on theophylline absorption in the rat □ Theophylline absorption—effect of glycerin and propylene glycol, rats, related to effect of various alcohols on intestinal net water flux □ Alcohols—effect on intestinal net water flux and theophylline absorption in rats

Koysooko and Levy (1) recently showed that the rate of intestinal absorption of theophylline in rats is increased significantly by ethanol in low concentrations and that there is a positive rank-order correlation between the theophylline absorption rate and the net water flux from the intestine. These observations led to three important questions: Can other alcohols also enhance theophylline absorption? Does ethanol enhance the absorption of other drugs? What is the mechanism of the absorption enhancing effect?

Reported here are results of an investigation concerned with the first of these questions. To proceed expeditiously, the effect of various concentrations of a number of alcohols on net water flux was determined first. Then, having established that most of these alcohols, in a certain concentration range, increase net water flux, the effect of two with particularly promising characteristics, glycerin and propylene glycol, on the intestinal absorption of theophylline was determined.

Table I—Effect of Polyethylene Glycol 200 and 400 on Net Water Flux from Small Intestine of Rats

Additive	Number of Animals	Rate of Net Water Flux[a], ml/cm/min × 10^4	Statistical Difference from Control
None	7	6.5 ± 0.5[b]	—
0.63% polyethylene glycol 200	4	6.6 ± 0.4	NS[c]
6.3% polyethylene glycol 200	4	7.1 ± 0.7	NS
0.63% polyethylene glycol 400	4	5.8 ± 0.8	NS
6.3% polyethylene glycol 400	4	6.0 ± 0.7	NS

[a] At steady state. [b] Mean ± *SD*. [c] NS = not significant.

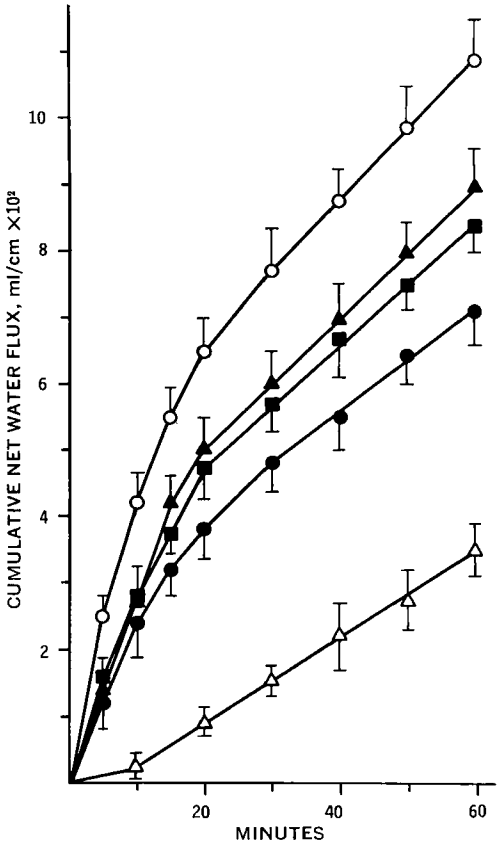

Figure 1—*Effect of alcohols in equimolar concentration on the cumulative net flux of water from the small intestine of the rat. Key:* △, *control* (n = 5); ●, n-*butanol* (n = 4); ■, *methanol* (n = 4); ▲, *ethanol* (n = 4); *and* ○, n-*propanol* (n = 4). *Vertical bars indicate 1* SD *in each direction. All alcohol concentrations were 0.25 mole/liter.*

EXPERIMENTAL

Male Sprague–Dawley rats, 280–350 g, were fasted overnight but had free access to water at all times. They were anesthetized with urethan, 1.5 g/kg ip. Net water flux from the intestine and theophylline absorption were determined as previously described (1). Briefly, a portion of small intestine was cannulated *in situ* and 7 ml of an alcohol solution was introduced into the intestinal lumen (2, 3). This solution was aspirated periodically for determination of net water flux. The solution consisted of various concentrations of methanol[1], ethanol[2], *n*-propanol[1], *n*-butanol[3], propylene glycol[1], glycerin[1], mannitol[4], sorbitol[4], polyethylene glycol 200[3], and poly-

[1] Fisher Scientific Co., Fair Lawn, N.J.
[2] Commercial Solvents Corp., Terre Haute, Ind.
[3] Baker Chemical Co., Phillipsburg, N.J.
[4] Nutritional Biochemical Corp., Cleveland, Ohio.

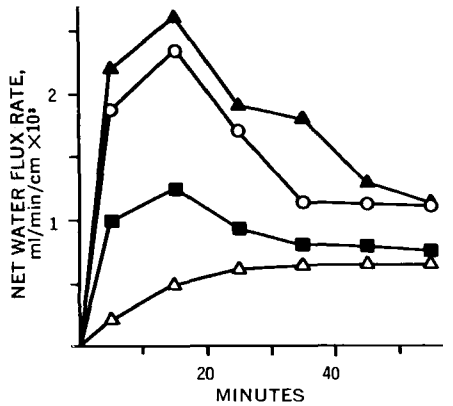

Figure 2—*Effect of various concentrations of propylene glycol on the rate of net water flux from the small intestine of the rat; mean of three experiments for propylene glycol and five experiments for control. Key:* △, *control;* ■, *0.01* M; ○, *0.1* M; *and* ▲, *1* M.

ethylene glycol 400[5] dissolved in Sørensen's phosphate buffer solution, pH 6.4. Sodium chloride was added as required to make the hypotonic solutions isotonic.

For the absorption studies, theophylline[4] was added in a concentration of 50 mg/100 ml and 0.2-ml portions were removed from the intestinal lumen periodically for determination of theophylline concentrations. The volume of drug solution in the intestine was maintained constant by addition of 0.9% sodium chloride solution from a 5-ml syringe before the removal of each sample. The difference between the total volume of saline solution added over a defined period and the volume of solution removed for assay served as a measure of net water flux. No samples were removed from solutions that did not contain theophylline. Positive and negative fluxes indicate net water flow out of and into the intestinal lumen, respectively. Theophylline concentrations were determined spectrophotometrically by the method of Schack and Waxler (4).

RESULTS AND DISCUSSION

Figure 1 shows the effect of methanol, ethanol, *n*-propanol, and

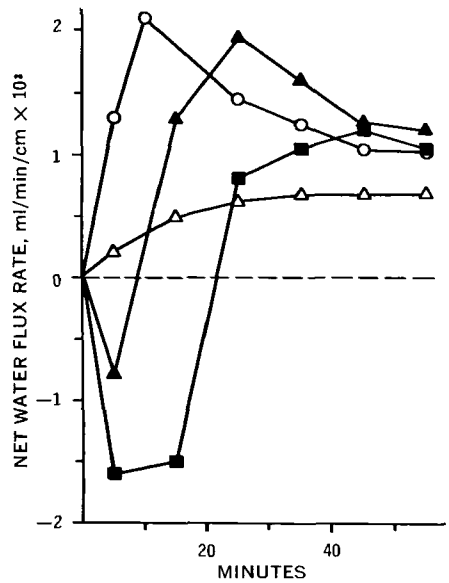

Figure 3—*Effect of various concentrations of glycerin on the rate of net water flux from the small intestine of the rat; mean of three experiments for glycerin and five experiments for control. Key:* △, *control;* ○, *0.1* M; ▲, *1* M; *and* ■, *2.5* M.

[5] Union Carbide Co., New York, N.Y.

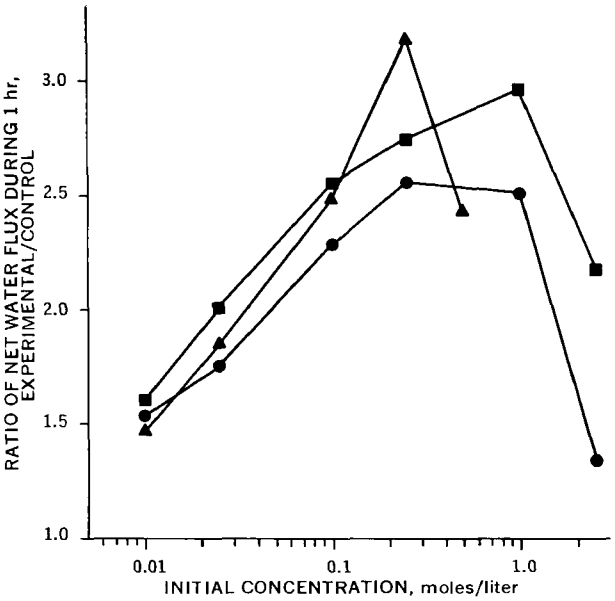

Figure 4—*Net water flux–concentration profile for ethanol* (●), *propylene glycol* (■), *and* n-*propanol* (▲) *expressed as a ratio relative to the control; mean of three experiments each. The water flux is that determined at 60 min.*

n-butanol, at an initial concentration of 0.25 *M*, on the net water flux from the rat small intestine. Following an initial apparent lag period, the net water flux from buffer solution without alcohol proceeded at an essentially constant rate of 6.5×10^{-4} ml/cm/min (Fig. 1). All four alcohols had a statistically significant net water flux enhancing effect ($p < 0.001$ for the 10- and 60-min data). The order of effectiveness was *n*-butanol < methanol ≃ ethanol < *n*-propanol. It should be recognized that the shape of the cumulative net water flux *versus* time curves is affected by the decrease of alcohol concentration with time due to absorption. Similarly, the relative order of effectiveness of the alcohols reflects not only their intrinsic activity but also their relative rate of absorption from the GI tract.

The effect on the net water flux of propylene glycol and glycerin, two compounds of particular pharmaceutical interest, was studied over a wide concentration range (from 0.01 to 2.5 *M* initial concentration). Figure 2 shows the time course of the net water flux from the intestine after instillation of 0.01, 0.1, and 1.0 *M* solutions of propylene glycol. The rate of the net water flux first increased and then slowly decreased with time.

Figure 3 represents the time course of the net water flux rates following instillation of 0.1, 1.0, and 2.5 *M* glycerin solution. The 1.0 and 2.5 *M* solutions initially caused a negative net water flux which eventually became positive and exceeded the control value. An initially negative net water flux was also produced by 2.5 *M*

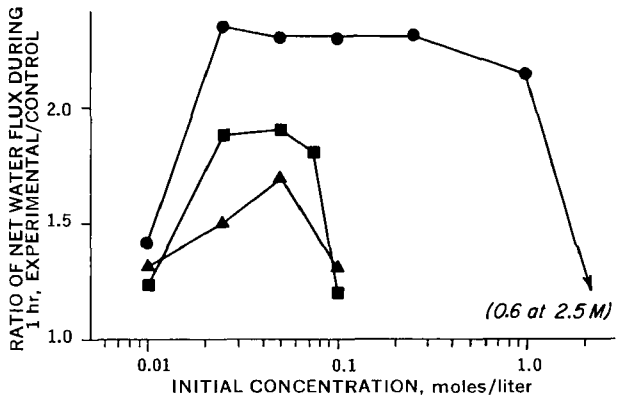

Figure 5—*Net water flux–concentration profiles for glycerin* (●), *mannitol* (■), *and sorbitol* (▲). *Details are given in previous figure.*

Table II—Effect of Propylene Glycol and Glycerin on Theophylline Absorption and Net Water Flux from Small Intestine of Rats[a]

Additive[b]	Number of Animals	Weight of Animals, g	Length of Cannulated Segment of Intestine, cm	Net Water Flux, ml/cm/25 min × 10^2	Statistical Difference from Control	Theophylline Absorption, % Unabsorbed at 25 min	Statistical Difference from Control
None	5	297 ± 34	101 ± 6	1.2 ± 0.15	—	25.3 ± 3.1	—
0.1 *M* propylene glycol	4	317 ± 17	99 ± 5	5.15 ± 0.32	$p < 0.001$	13.8 ± 3.2	$p < 0.005$
1.0 *M* propylene glycol	4	290 ± 29	102 ± 4	5.7 ± 0.72	$p < 0.001$	10.9 ± 1.5	$p < 0.005$
0.1 *M* glycerin	4	319 ± 25	102 ± 7	4.25 ± 0.33	$p < 0.001$	17.2 ± 1.9	$p < 0.01$
1.0 *M* glycerin	4	300 ± 13	101 ± 4	3.0 ± 0.40	$p < 0.001$	15.0 ± 3.7	$p < 0.005$

[a] Results are listed as mean ± *SD*. [b] All solutions contained theophylline, 50 mg/100 ml.

propylene glycol. This result was probably due to the high osmotic pressure gradient caused by these more concentrated solutions, an effect that decreases with time as the alcohol concentration is lowered by absorption.

Oral administration of a drug solution with an alcohol additive results in a gradual decrease of the alcohol concentration due to dilution with GI fluids and absorption. Therefore, it is important to determine the relationship between alcohol concentration and effect on the net water flux. Figure 4 represents such concentration–effect profiles for ethanol, *n*-propanol, and propylene glycol. The latter is more effective than ethanol and both increase the net water flux over a wide concentration range. The decrease in the effect on the net water flux at higher concentrations of the alcohols is probably due to the high osmotic pressure of the solutions which causes water flow into the intestinal lumen. In the case of *n*-propanol, this abrupt decrease in the effect on the net water flux may be due in part to the toxic effect of this alcohol. Animals that received 1 *M* solutions of *n*-propanol expired after about 30 min.

Figure 5 shows the concentration–effect profiles for glycerin, mannitol, and sorbitol. Unlike the latter two, glycerin is effective over a wide concentration range and its effect on the net water flux is almost independent of concentration over an approximately 100-fold range. Its maximum effect is, however, somewhat less than that of propylene glycol. The much less pronounced effectiveness of mannitol and sorbitol may be due to a decreased accessibility of these very polar and larger molecules to the site of action that elicits the increased net water flux. Consistent with this speculation is the lack of any effect on the net water flux of polyethylene glycol 200 and 400 (Table I). The net water flux values reported for these compounds are the steady-state values, *i.e.*, the slope of a plot of cumulative net water flux *versus* time following the initial lag phase as shown in Fig. 1 for the control (no alcohol) solution.

Propylene glycol and glycerin, in concentrations of 0.1 and 1.0 *M*, significantly increased the rate of absorption of theophylline from the rat small intestine (Figs. 6 and 7 and Table II). Thus, as previously found with ethanol (1), there is an association between enhanced absorption of theophylline and net water flux. As stated previously (1), this does not necessarily indicate a causative rela-

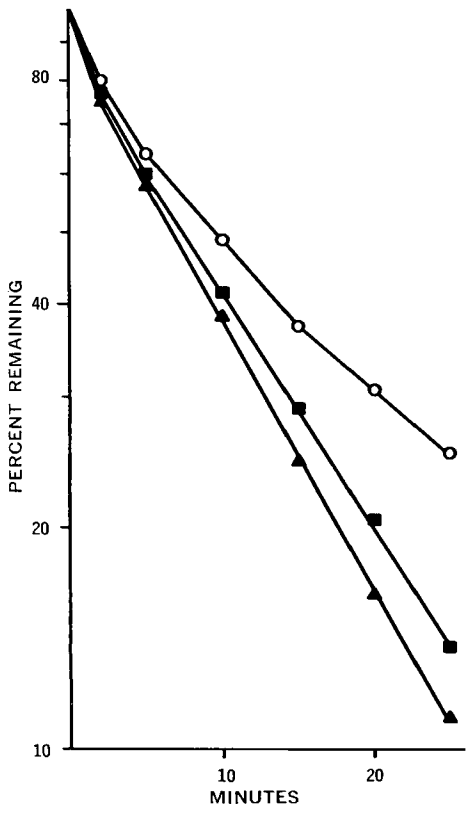

Figure 6—*Effect of propylene glycol on the time course of theophylline absorption from a 50-mg/100 ml solution instilled into a cannulated segment of small intestine of anesthetized rats. Key:* ○, *control* (n = 5); ■, *0.1* M *propylene glycol* (n = 4); *and* ▲, *1* M *propylene glycol* (n = 4).

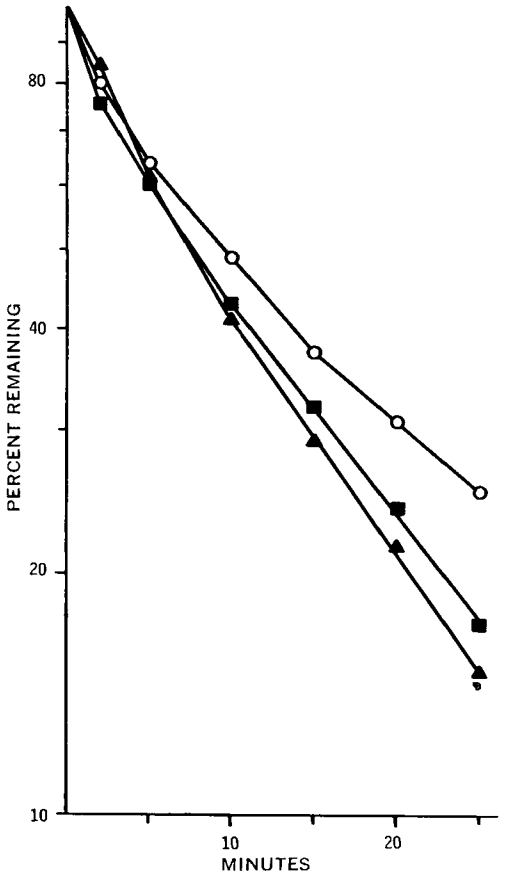

Figure 7—*Effect of glycerin on the time course of theophylline absorption from a 50-mg/100 ml solution instilled into a cannulated segment of small intestine of anesthetized rats. Key:* ○, *control;* ■, *0.1* M; *and* ▲, *1* M.

Table III—Effect of Theophylline on Net Water Flux from Small Intestine of Rats in Presence of Sørensen's Buffer, Propylene Glycol Solution, and Glycerin Solution

Additive	Net Water Flux, ml/cm/20 min × 10^2	
	Theophylline Present[a]	Theophylline Absent[b]
None	0.95 ± 0.15	0.90 ± 0.25
0.1 *M* propylene glycol	4.30 ± 0.35	4.45 ± 0.40
1 *M* propylene glycol	4.45 ± 0.70	4.55 ± 0.65
0.1 *M* glycerin	3.65 ± 0.30	3.50 ± 0.35
1 *M* glycerin	1.60 ± 0.45	1.80 ± 0.50

[a] Mean of four animals ± *SD*; initial theophylline concentration of 50 mg/100 ml. [b] Mean of three animals ± *SD*. None of these values differed significantly ($p > 0.6$) from those in the presence of theophylline.

tionship between these two effects. The mechanism of the absorption enhancing effect of the alcohols is still being investigated in this laboratory. The magnitude of the effect of propylene glycol and glycerin on the net water flux was not affected by the presence of theophylline, nor did theophylline affect the net water flux from alcohol-free solutions (Table III).

The results of the present study show that the absorption enhancing effect of ethanol on theophylline is not specific to that alcohol. It is shared by propylene glycol and glycerin and, most likely, by other alcohols that were found to increase the net water flux from the intestine. Some of the compounds studied are suitable (and are used widely) as components of pharmaceutical formulations. The fact that they act in very low concentration is particularly striking. Their potential for enhancing the absorption of certain drugs under clinical conditions remains to be explored.

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Convective Diffusion Model for a Transport-Controlled Dissolution Rate Process

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Abstract □ A mathematical model based on convective diffusion was developed to describe the rate of dissolution from the surface of a compressed compact. Experimental studies were carried out to test the model. The basic experimental apparatus consisted of a modified rotating-filter–stationary basket dissolution test apparatus. Dissolution rates from rectangular and circular surfaces of an homologous series of *p*-aminobenzoate esters permitted testing the theory with respect to solubility, geometry, and agitation conditions. The correlation between experimental results and theory was reasonably good considering that the test conditions were somewhat less than ideal.

Keyphrases □ Diffusion model, convective—transport-controlled dissolution rate process, *p*-aminobenzoates and modified rotating-filter–stationary basket apparatus □ Dissolution rate, transport controlled—convective mathematical diffusion model tested using *p*-aminobenzoates and modified rotating-filter–stationary basket apparatus □ Transport—as controlling factor in dissolution rate process, convective mathematical diffusion model proposed and tested

Reviews of the literature concerning dissolution rates of drugs (1–3) indicate that the most widely accepted theory for dissolution rates is that proposed by Noyes and Whitney in 1897 and subsequently modified to include the stagnant or unstirred diffusion layer concept of Nernst and Brünner[1]. In this form, the rate expression is:

$$\frac{dc}{dt} = \frac{AD}{hv}(c_0 - c) \qquad \text{(Eq. 1)}$$

(The notation is defined at the end of the text.)

It can be seen that the rate is directly proportional to the area exposed, the diffusivity, and the solubility and inversely proportional to the diffusion layer thickness. The first three variables enumerated can be determined by independent measurements, whereas the effective diffusion layer thickness, h, is a model-dependent parameter. As such, its significance and utility outside the confines of the model are necessarily limited.

Transport-controlled dissolution in a stirred liquid involves two fundamental processes: molecular diffusion and forced convection as a result of fluid flow. Although hydrodynamic factors have been discussed and considered to some extent, particularly in regard to the rotating-disk technique (4, 5), a rather general

[1] See review articles for appropriate references.