method of Jackson and Hudson (11, 12). Titration over 5 hr showed that 2.1 moles of periodate was consumed and that 0.98 mole of formic acid had been produced by the oxidation, indicating a ribofuranose ring structure.

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Effect of Ethanol on Theophylline Absorption in Humans

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Abstract □ This study was carried out to determine if ethanol, which enhances theophylline absorption from the rat small intestine, has a similar effect when administered orally to human subjects. Seven normal adults received 200 mg of theophylline/m^2 of body surface area, in 50 ml of either aqueous solution or hydroalcoholic solution containing 20% ethanol. There was no significant difference in the average plasma concentrations of theophylline produced by these two solutions, but three subjects (all female) experienced nausea after taking the aqueous solution while none became nauseous after taking theophylline in the hydroalcoholic solution.

Keyphrases □ Theophylline—effect of ethanol on absorption, humans □ Ethanol—effect on absorption of theophylline, humans □ Absorption—theophylline, effect of ethanol, humans

Theophylline is an effective bronchodilator used widely for the treatment of asthma. It is desirable to have oral dosage forms available from which this drug is rapidly absorbed so that acute attacks of asthma can be treated and relieved promptly at home. There have been claims that the absorption of theophylline is enhanced if administered in hydroalcoholic solution, but the evidence is conflicting (1–4).

Recently, an initial concentration of 5% ethanol was found to increase significantly the absorption of theophylline from a ligated segment of small intestine of anesthetized rats, and a constant concentration of 2% ethanol (and even lower concentrations in unpublished studies) increased appreciably the absorption of theophylline from the perfused small intestine of anesthetized rats (5). This absorption-enhancing effect of ethanol was associated with an increase in the net flux of water from the intestinal lumen and may be due to solvent drag (5). The study described here was initiated to determine if the rate of absorption of theophylline can be increased in humans by administering the drug in hydroalcoholic rather than in aqueous solution.

EXPERIMENTAL

Seven healthy volunteers (four females and three males), 24–33 years old and capable by education and background (registered nurses and graduate students in pharmaceutics) to give informed consent, participated in the study. They were instructed to abstain from coffee, tea, chocolate, cola drinks, and alcoholic beverages for 24 hr before and during the study and to take no drugs (except oral contraceptives if these were used regularly) for 3 days before and during the study.

Theophylline, 200 mg/m^2 body surface area, dissolved either in 50 ml of water or in 50 ml of hydroalcoholic solution containing 20% (v/v) ethanol, was administered in the morning 1 hr after a light breakfast. The two preparations were given in crossover fashion, 1 week apart. Fifteen milliliters of blood was withdrawn through an indwelling venous catheter into a heparinized syringe immediately before drug administration, and 10-ml blood samples were obtained at 10, 30, 60, 120, 240, 360, and 480 min thereafter. Plasma was separated and stored in a freezer pending assay.

At the end of the experiment, each subject was given a card with the questions: "Did you notice any pharmacologic effects during the day? If so, what and when?" There was no additional questioning, elaboration, or discussion to prevent any biased suggestive influences on the response to the question.

Theophylline concentrations in plasma were determined by the spectrophotometric method of Schack and Waxler (6), modified for smaller sample volumes and greater sensitivity (7). Blank values and recovery of theophylline were determined for each subject by assaying the zero-time plasma as such and after adding theophylline to yield a concentration of 10 μg/ml. The blank values ranged from 1.48 to 3.47 μg apparent theophylline/ml, and the recovery of added drug ranged from 85.1 to 97.7%. The analytical re-

Table I—Theophylline Concentration in Plasma of Healthy Adults after Oral Administration of an Aqueous Solution of Theophylline[a]

Subject	Sex	Age, years	Body Weight, kg	Height, cm	Minutes 10	30	60	120	240	360	480
					Theophylline Concentration, μg/ml						
1	F	24	49.5	160	3.59	11.91	11.80	13.35	10.05	7.43	4.83
2	F	27	63.0	171	2.99	8.62	10.71	9.82	8.30	7.25	5.78
3	F	33	63.0	162	6.75	14.88	13.64	11.78	9.37	8.07	6.75
4	F	28	55.2	160	2.02	9.69	13.14	13.74	10.51	7.82	6.47
5	M	27	71.4	169	6.96	9.95	11.41	11.16	9.37	8.07	7.65
6	M	28	66.8	173	14.34	13.98	13.52	11.37	8.58	7.68	6.15
7	M	29	75.0	188	14.08	13.46	12.70	10.94	8.13	6.15	5.02
Mean					7.25	11.78	12.42	11.74	9.19	7.50	6.09
SD					5.10	2.42	1.13	1.38	0.90	0.67	0.99

[a] Two hundred milligrams of theophylline/m² of body surface area.

sults were corrected for each individual according to these values. Ethanol concentrations in plasma were determined by the GC method of Cooper (8) with certain modifications (5).

RESULTS

The plasma theophylline concentrations after oral administration of the drug in aqueous and hydroalcoholic solution are listed in Tables I and II, respectively, and the average data are shown in Fig. 1. There was no statistically significant difference (by paired *t* test) between the theophylline concentrations produced by these two solutions at any time, but peak concentrations in four of the seven subjects appeared earlier with the aqueous solution. Theophylline concentration peaks in the other three subjects occurred at the same time with both solutions.

The concentrations of ethanol in the plasma after administration of theophylline in hydroalcoholic solution are listed in Table III. Maximum concentrations were usually achieved at 30 min; the ethanol concentrations in plasma became negligible 2 hr after administration of the hydroalcoholic solution. The apparent biological half-life of theophylline, determined from the exponential portion of the individual plasma concentration curves, averaged slightly less than 7 hr (Table IV). Three of the seven subjects (all but one of the female subjects in the study) reported nausea after administration of the aqueous solution, while there were no reports of nausea after administration of the hydroalcoholic solution (Table V).

DISCUSSION

The minimum effective plasma concentration of theophylline is generally considered to be about 5 μg/ml, and the average therapeutic concentration is about 10 μg/ml (9). The results of this study show that the minimum effective concentration could be achieved in most subjects within 10 min and maintained in the subjects for 480 min after administration of 200 mg theophylline/m² in either aqueous or hydroalcoholic solution. Therapeutically optimum concentrations occurred usually at 60 min and only occasionally as early as 10 min after drug administration.

Considering the desirability of achieving optimum plasma theophylline concentrations rapidly in case of an acute asthma attack, there is a rational basis for attempting to enhance the rate of theophylline absorption beyond that which can usually be achieved by oral administration of the drug in aqueous solution. While low concentrations of ethanol were found to enhance theophylline absorption in rats when a solution of the drug was introduced directly into the small intestine (5), a similar effect was not apparent upon oral administration to human subjects under the conditions of this study. It is possible that the absorption-enhancing effect of ethanol on theophylline may have been dampened by the process of gastric emptying in this study. The amount of ethanol taken by the subjects may even have been sufficient to inhibit gastric emptying (10, 11) and thereby to decrease actually the rate of theophylline absorption. Use of smaller amounts of ethanol or of one of the other absorption-enhancing agents recently discovered in this laboratory[1] may be more rewarding.

There have been reports (12, 13) of a feeling of mild inebriation in some subjects after oral administration of 75 ml of a hydroalcoholic solution of theophylline containing 20% ethanol. The results of this study, using similar doses of ethanol, indicate that the concentrations in plasma are well below those found to elicit a noticeable pharmacological effect (14, 15). Interestingly, none of the subjects complained of nausea after taking theophylline in hydroalcoholic solution but three subjects, all women, reported nausea after taking theophylline in aqueous solution. Since the theophylline concentration in the plasma of these three subjects was

Table II—Theophylline Concentration in Plasma of Healthy Adults after Oral Administration of a Hydroalcoholic Solution of Theophylline[a]

Subject	Minutes 10	30	60	120	240	360	480
	Theophylline Concentration in Plasma, μg/ml						
1	2.70	3.45	10.91	13.15	12.30	6.07	4.37
2	5.13	8.88	11.33	11.72	9.89	7.86	7.00
3	7.88	11.01	11.09	11.35	8.69	6.60	5.07
4	5.73	8.69	10.51	11.11	9.88	7.79	6.74
5	8.10	11.12	12.15	11.70	8.94	7.99	7.19
6	9.26	8.51	13.23	10.41	8.54	7.55	6.22
7	2.91	9.82	14.08	12.90	10.59	7.99	7.61
Mean	5.96	8.78	11.90	11.76	9.83	7.41	6.31
SD	2.58	2.58	1.32	0.97	1.32	0.76	1.19

[a] Two hundred milligrams of theophylline/m² of body surface area.

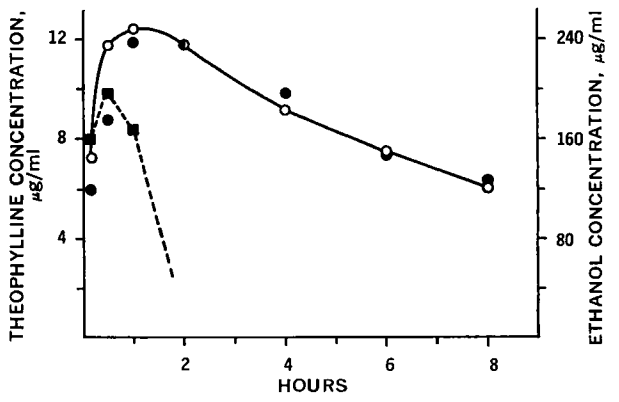

Figure 1—*Mean plasma theophylline concentrations in seven normal adult subjects after oral administration of 200 mg of theophylline/m² of body surface area in aqueous solution* (○) *and hydroalcoholic solution* (●). *The ethanol content of the latter was equivalent to 10 ml/m² of body surface area and produced the plasma concentrations represented by* ■ *and the dashed line.*

[1] J. B. Houston and G. Levy, to be published.

Table III—Ethanol Concentration in Plasma of Normal Adults after Oral Administration of a Hydroalcoholic Solution of Theophylline[a]

Subject	Minutes 10	30	60	120
Ethanol Concentration in Plasma, μg/ml				
1	193.0	204.2	165.9	—[b]
2	82.2	132.8	21.5	—[b]
3	180.3	190.7	223.0	—[b]
4	73.3	204.3	172.1	53.0
5	229.8	206.7	89.4	—[b]
6	229.5	221.3	143.2	38.7
7	140.0	222.6	342.0	69.2
Mean	161.2	197.5	166.7	
SD	64.8	30.6	102.3	

[a] Ten milliliters of ethanol/m² of body surface area. [b] Less than 20 μg/ml.

not unusually high and not higher than that of the other subjects in the study, the nausea probably was due to a local rather than central effect of the drug. The observations are at best suggestive, but they are in agreement with those of a previous investigation (2). Jørgensen and Møller reported that two subjects who took 400 mg theophylline in water suffered from severe abdominal colic and nausea while no such effects were noted in 16 patients when theophylline was administered in hydroalcoholic solution containing 20% ethanol (2).

The apparent biological half-life of theophylline found in this study ranged from about 4 to 9 hr and averaged slightly less than 7 hr. These results are well within the range of previous studies on adult subjects but somewhat longer on the average than the mean values of 4.4 and 5.2 hr observed by Mitenko and Ogilvie (16) and Jenne *et al.* (17), respectively, after intravenous injection. It is possible that protracted absorption affected the biological half-life estimates in this study and they have therefore been designated as apparent half-lives.

Table IV—Apparent Biological Half-Life of Theophylline in Normal Adults after Oral Administration of Aqueous and Hydroalcoholic Solutions

Subject	Apparent Half-Life, hr: Aqueous Solution	Hydroalcoholic Solution
1	3.78	4.19
2	8.03	7.80
3	7.06	5.15
4	5.71	7.23
5	8.56	8.81
6	7.09	8.31
7	5.30	7.43
Mean	6.50	6.98
SD	1.67	1.69

Table V—Incidence of Nausea after Administration of Theophylline in Aqueous and Hydroalcoholic Solutions

Subject	Aqueous Solution	Hydroalcoholic Solution
1	−	−
2	+	−
3	+	−
4	+	−
5	−	−
6	−	−
7	−	−

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