Comparative Bioavailability Study of Acetaminophen Solutions Used in Hospital Formulary

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To learn the influence of polyethylene glycol (PEG) on bioavailability, this study compared the bioavailability of acetaminophen in the presence of 10% ethanol (acetaminophen–ethanol liquid) to that in the presence of 10% PEG (acetaminophen–PEG liquid) since these two preparations are commonly used in hospital formulary. The results in Thai male volunteers showed there was not significantly different.

Keywords acetaminophen; bioavailability; paracetamol; polyethylene glycol

Introduction

Acetaminophen (paracetamol), a common antipyretic and analgesic drug, is poorly soluble in water, and solutions in which it is used usually contain ethanol to solubilize the drug. Most hospitals in Thailand formerly used acetaminophen elixir which contains ethanol in their formularies; however, the presence of ethanol (10% (v/v)) in the formulation caused some undesirable effects. Polyethylene glycol (PEG), a powerful solubilizer for acetaminophen,¹⁾ has therefore replaced ethanol in the formulation. Since PEG retards absorption and decreases bioavailability of certain drugs,²⁾ its effects on acetaminophen were of interest.

The present study was aimed at comparing the bioavailability of acetaminophen in the presence of 10% (v/v) ethanol to that in the presence of 10% (w/v) PEG.

Experimental

Materials Acetaminophen was obtained from Rhone-Poulenc. Methanol and acetonitrile were HPLC grade. All other chemicals used in this study were commercial reagent grade.

Preparation of Acetaminophen Liquids Acetaminophen–ethanol (aceta–EtOH) liquid and acetaminophen–polyethylene glycol (aceta–PEG) liquid, both containing 24 mg/ml of acetaminophen, were prepared according to the following formulas:

	aceta–EtOH	aceta–PEG
acetaminophen	2.4 g	2.4 g
ethanol	10.0 ml	—
PEG 4000	—	10.0 g
propylene glycol	10.0 ml	10.0 ml
glycerin	5.0 ml	5.0 ml
Syrup USP	47.0 ml	47.0 ml
saccharin	0.1 g	0.1 g
conc. paraben	1.0 ml	1.0 ml
raspberry flavor	qs.	qs.
purified water qs.	100.0 ml	100.0 ml

Subjects and Study Design Twelve Thai male volunteers participated after given written informed consent. They were required to be free of serious cardiovascular, hepatic, renal, and gastro-intestinal diseases.

The study was performed in randomized crossover design. The subjects were instructed to take no other medications at least one week prior to the study and not to drink caffeine or ethanol-containing beverages for at least 5 d before and during the period of medication. They were randomly allocated to receive either aceta–EtOH and then aceta–PEG, or aceta–PEG and then aceta–EtOH with a washout period of at least one week. After fasting overnight, each subject ingested 500 mg of acetaminophen followed by 180 ml of water and he was permitted to have a normal diet 2 h later.

Blood Collection Before drug administration, an intravenous catheter was inserted into a forearm vein of each subject for blood sampling. Patency of the catheter was maintained by periodic flushing with small injection of 10 units/ml of heparin in normal saline. Blood samples (8 ml) were

collected at 0, 5, 10, 15, 20, 30, 45, 60, 90, 120, 240, 360, and 480 min after drug administration.

Each sample was centrifuged at 3000 rpm (International Equipment Co.) for 5 min. The supernatant liquid was transferred to a screw capped test tube and stored at -10°C until analysis.

HPLC Assay Extraction: Five-tenths ml of serum was mixed with 0.1 ml of 0.03 M HCl and 0.1 ml of theophylline (80 $\mu\text{g}/\text{ml}$) as internal standard. Four ml of acetonitrile was added to this mixture and then mixed for 3 min by a vortex mixer. The mixture was centrifuged at 3000 rpm for 5 min. Three ml of the supernatant was transferred to a 15 ml conical glass tube and evaporated under a stream of air until dried. The residue was reconstituted in 75 μl of water and an aliquot (10 μl) was injected into the column.

Chromatography: A Waters model 6000 A pump (Waters Associates, Mass., U.S.A.) equipped with an injection loop of 10 μl and a Waters model 481 variable UV spectrophotometric detector were used. Samples were chromatographed with spherisorb 5-ODS (4.6 i.d. $\times$ 250 mm). The mobile phase was a mixture of methanol and 0.05 M sodium acetate buffer (pH 4.3) at a ratio of 22:78. The flow rate was 1 ml/min. The eluate was monitored at 254 nm with attenuation of the signal integrator of 16.

Calibration Graph: Standard samples were prepared by spiking 0.5 ml blank serum with 0.1 ml of acetaminophen standard solution. Acetaminophen standard solutions used ranged from 2.5 to 125 $\mu\text{g}/\text{ml}$ and contained 80 $\mu\text{g}/\text{ml}$ of theophylline as internal standard. A calibration graph was obtained from linear regression of the peak area ratio against the concentration of the spiked serum.

Data Analysis and Statistics Data of individual serum acetaminophen concentration from each treatment was analyzed using the PCNONLIN. The best fit was suggested by maximum likelihood and least squares. The pharmacokinetic parameters obtained from each preparation were compared using *t*-test. Statistical significance was defined as $p < 0.05$.

Results and Discussion

Analysis of Acetaminophen Figure 1 shows the representative chromatogram for a serum blank, serum spiked with standard acetaminophen and theophylline, and serum sample from a subject 2 h after ingestion of aceta–EtOH with theophylline added as internal standard. The two acetaminophen and theophylline peaks were well separated with the retention time of 6.0 and 10.0 min, respectively. No interfering peaks from serum extracted components were detected. The optimum pH of acetate buffer used as mobile phase in this study was 3.9–4.3 giving good separation between the endogenous substance peaks and the acetaminophen peak.

The coefficient of variation (*CV*) of peak area ratios obtained from five replicate injections of 11.16 $\mu\text{g}/\text{ml}$ acetaminophen standard solution was 1.60% which was less than 2.0%. The system met the requirements of the system suitability test of the United States Pharmacopeia.

Fig. 1. HPLC Chromatogram of Extracts from (a) Blank Human Serum, (b) Human Serum Spiked with Acetaminophen and Theophylline, and (c) Serum Sample 2 h after of Drug Administration Spiked with Theophylline. Peak 1 = acetaminophen; peak 2 = theophylline.

The standard graph was constructed from the peak area ratios of the spiked serums and the concentrations of standard acetaminophen. The linear regression line of the standard graph was $Y = 0.014 + 0.026 X$, and the correlation coefficient was 0.9996.

The repeatability of the assay was determined in a set of 5 blank serum spiked with acetaminophen standards to the concentrations of 1.116, 11.6 and 22.32 $\mu\text{g/ml}$. The coefficient of variation of the determined concentration was calculated to be 3.17%, 2.67% and 1.49%, respectively. The method of analysis is suitable for the present study.

Pharmacokinetic Analysis Vital statistics of the 12 healthy Thai subjects participating in the study were: mean age 25.8 years (range 17–37), mean weight 58.8 kg (range 52–76), and mean height 167.3 cm (range 162–177).

The mean (S.E.M.) of acetaminophen serum concentration–time profile of the two groups of preparations is shown in Fig. 2. It can be seen that the serum acetaminophen concentration increased rapidly after administration. After the peak serum level was reached, the serum level decreased rapidly and then more slowly. This behavior may be fitted to a two-compartment open model. The triexponential equation of absorption, intercompartment distribution and elimination may be described by the following equation:

$$F = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-K_{01}t}$$

where F is the serum concentration at time t ; t is the time after drug administration minus the lag time; A , B , C are hybrid intercept constants; α , β , K_{01} are hybrid exponents representing apparent distribution rate constant, apparent elimination rate constant and apparent absorption rate constant, respectively. The results from PCNONLIN analysis were best described by a two-compartment open model with lag time.

Statistical comparison of pharmacokinetic parameters of the two test preparations are shown in Table I. The means

Fig. 2. Mean Serum Acetaminophen–Time Profile of the 12 Subjects Following Oral Administration of 500 mg of Acetaminophen

Liquids, —, mean + S.E.M. aceta–EtOH, ···, mean – S.E.M. aceta–PEG.

TABLE I. Comparison between the Mean of Pharmacokinetic Parameters for Acetaminophen–EtOH and Acetaminophen–PEG Oral Liquids Using t -Test

	Mean (S.D.) pharmacokinetic parameter		Probability	Significance level
	Aceta–EtOH	Aceta–PEG		
K_{01} (h^{-1})	6.916 (5.260)	5.312 (1.841)	0.330	N.S.
α (h^{-1})	3.592 (2.278)	3.380 (1.440)	0.788	N.S.
β (h^{-1})	0.253 (0.071)	0.292 (0.082)	0.223	N.S.
T_{lag} (h)	0.088 (0.026)	0.065 (0.028)	0.056	N.S.
K_{10} (h^{-1})	0.706 (0.306)	0.647 (0.147)	0.553	N.S.
K_{12} (h^{-1})	1.838 (1.449)	1.522 (0.793)	0.514	N.S.
K_{21} (h^{-1})	1.303 (0.859)	1.506 (0.834)	0.563	N.S.
$t_{1/2, \beta}$ (h)	3.016 (1.123)	2.516 (0.576)	0.184	N.S.
Volume (l)	27.83 (9.22)	31.12 (10.94)	0.434	N.S.
C_{max} ($\mu\text{g/ml}$)	12.76 (2.63)	11.43 (3.31)	0.287	N.S.
T_{max} (min)	25.83 (14.43)	23.33 (10.30)	0.630	N.S.
$AUC_{0-\infty}$ ($\mu\text{g} \cdot \text{h/ml}$)	32.76 (7.64)	31.37 (8.34)	0.673	N.S.

K_{01} = first order absorption rate constant. K_{10} = first order elimination rate constant. K_{12} , K_{21} = first order intercompartment transfer rate constant. $t_{1/2, \beta}$ = half live. C_{max} = maximum serum concentration. T_{max} = time to reach maximum concentration. T_{lag} = lag time.

(S.D.) of these parameters were used to compare the test preparations at the significant level $p < 0.05$ by t -test.

The bioavailability of the two test preparations was compared from the rate and extent of absorption. The values of C_{max} and T_{max} were obtained from individual serum profile. The extent of absorption was compared using area under the serum concentration–time curve ($AUC_{0-\infty}$), and the rate of drug absorption was judged by comparing of C_{max} and T_{max} . In the present study, the values of $AUC_{0-\infty}$, C_{max} , and T_{max} of acetaminophen–EtOH and acetaminophen–PEG oral liquids were not significantly different (t -test, $p < 0.05$). Thus, the two formulas of acetaminophen oral liquids which have been used in the hospitals were bioequivalent and that PEG had no significant effect on the bioavailability of acetaminophen.

The pharmacokinetic parameters of the two test preparations were also compared to previous reports³⁾ in Caucasian subjects and found to be of no statistically significant difference.

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