Relative Bioavailability and Pharmacokinetics of Tylenol and GPO Paracetamol Tablets

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Two different brands of 500 mg paracetamol tablet : Tylenol and GPO Paracetamol, were evaluated for their relative bioavailability in 16 normal healthy Thai volunteers using a randomized crossover design with 2 weeks washout period. In each treatment, subjects received a single oral 1,000 mg dose of the test product following an overnight fast. Serial twelve venous blood samples of 10 ml were collected before each dose and during 10 hours period after drug administration. Plasma paracetamol concentrations were then analyzed by high performance liquid chromatography (HPLC). Pharmacokinetic parameters including peak plasma concentration (Cp_{max}), time-to- peak (T_{max}) and total area under the plasma concentration-time curve at 10 hours (AUC_0^{10}) and at infinity (AUC_0^{∞}) were calculated. Data analysis by ANOVA and Student's t test revealed that there were no statistically significant differences between Tylenol and GPO Paracetamol in all relevant pharmacokinetic parameters obtained. Therefore, it was concluded that Tylenol and GPO Paracetamol were bioequivalent.

Paracetamol was first used in medicine in 1893 by von Mering[1], but it has gained popularity only since 1949 after it was found that phenacetin were nephrotoxic whereas aspirin caused some unwanted complications including gastric irritation, abnormal blood coagulation, and increased risk of Reye's syndrome in children and adolescence[2,3]. However, paracetamol is not used for the treatment of rheumatoid arthritis as it has little or no anti-inflammatory action. At toxic doses, paracetamol also cause hepatotoxicity[4]. Paracetamol is especially indicated for persons who cannot tolerated or are allergic to aspirin[1].

At present, paracetamol is one of the most popular and widely used analgesic-antipyretics in Thailand and the less of the world[5,6]. This study was conducted to determine the relative bioavailability of two popular brands of paracetamol 2×500 mg oral tablet preparations (Tylenol and GPO Paracetamol) and also to investigate the pharmacokinetic features of paracetamol in healthy Thai volunteers

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GPO = The Government Pharmaceutical Organization

Materials and Methods

Materials

All chemicals used were analytical and/or HPLC grades. They were acetonitrile, methanol, glacial acetic acid which obtained from E. Merck, F.R. Germany; standard paracetamol and theophylline which obtained from Quality Control Devision of the Government Pharmaceutical Organization (GPO).

Test products were two brands of 500 mg paracetamol tablets. They were Tylenol (Olic Thailand Limited under the licence of McNeilab Inc), and the GPO Paracetamol.

Mobile phase was prepared from methanol and 1% acetic acid (1:3).

Internal standard was theophylline prepared as a stock solution (1000 ug/ml) in methanol. For calibration curves it was diluted to 10 and 30 ug/ml.

Standard paracetamol was prepared as a stock solution (1,000 ug/ml) in methanol. For calibration curves, it was diluted in plasma to concentration range of 0.5-12.0 ug/ml and 5-35 ug/ml.

Standard calibration curves for paracetamol in blank plasma were plotted from the ratio of the peak area of paracetamol to that of the internal standard against paracetamol concentrations.

Methods

1. Subjects

Sixteen drug-free, non-smoking, healthy volunteers (9 males, 7 females) aged ranging from 24 to 43 years (mean age 29.56 $\pm$ 5.2) and the body weight ranging from 46 to 72.8 kg (mean weight 57.75 $\pm$ 6.63 kg) participate in this complete crossover study.

All volunteers had good health condition which were screened by clinical and laboratory examinations. They all had a full physical examination with medical history review and blood chemical test prior to the study for approval of normal renal, hepatic, respiratory and cardiovascular functions. All subjects had no chronic and communicable diseases and had shown normal biochemical and hematological parameters. They did not received any other drug or alcohol for at least 1 week before and during the study. Informed consent was given by all the subjects entering the study which was approved by the Committee of Government Pharmaceutical Organization.

2. Study Design

The study, which consisted of 2 treatment phases, was conducted as single oral 1,000 mg dose trials with randomized complete crossover administration. Between the phases the subjects were allowed to have 2 weeks washout period.

In each phase, the subjects took the drug at about 7.00-8.00 a.m. after previous overnight fast. They were allowed to have breakfast at 3 hours postdose. Serial twelve venous blood samples (10 ml) were taken from a forearm vein at the following time : 0 (predose), 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0 hours after drug administration. The blood samples were mixed with 30 mg EDTA and immediately contrifuged for 10 minutes at 3,500 rpm. The plasma was collected and stored frozen at -10 to -20°C until analysis.

3. Assay Procedure

Plasma concentrations of paracetamol were determined by HPLC consisting of a Constametric 3,000 pump (Milton Roy) equipped with a reverse phase (μ Bondapak C_{18}) 30 cm x 3.9 mm. i.d. analytical column with the guard column (Waters Associate), a Spectromonitor 3,100 UV detector operating at 254 nm, a CI 10 B data processor (integrator), and a Rheodyne manual injector with 20 μl loop.

Paracetamol in the plasma sample was extracted by mixing 500 μl plasma obtained from each subject with 3 ml acetonitrile in a 15 ml screw-capped tubes. The tubes were

vortexed for 1 minute and then were centrifuged for 10 minutes. The separate organic phase of each tube was removed and evaporated to dryness under N_2 stream at 45 °C. The residue was reconstituted with 1 ml internal standard solution, vortexed and centrifuged for 10 minutes. After centrifugation, 20 μl of the supernatant was injected onto the column of HPLC system for determining the paracetamol concentration from the previous constructed standard curves. The pharmacokinetic parameters and the relative bioavilability were then determined. The mobile phase was pumped at the flow rate of 1.2 ml/min. The UV detection was carried out at 254 nm.

The precision of assay was determined by analyzing in triplicate all the control standard plasma samples in a day (Intraday variability) for 3 days (Interday variability) and then calculating percent coefficient of variation (C.V.) (% C.V. = 100 S.D./x). Percent C.V. value less than 10% indicated that the method had good precision.

The accuracy of assay was determined by comparing the measured concentration with the theoretically true concentration and calculating for the percentage error.

The efficiency of the assay was determined by comparing the peak area ratio of the extracted plasma to that of the equivalent concentrations of standard paracetamol and calculating the percentage recovery.

4. Statistical Analysis

The data was statistically analyzed employing ANOVA and the Student's t test. P-value of less than 0.05 was regarded as statistically significant.

Results of all parameters were expressed as mean values ± standard error of the mean (s.e.m.)

Results

The chromatogram of standard paracetamol in plasma showed the retention time for paracetamol was 4.64 minutes and for the internal standard was 6.32 minutes. The relative retention time (RRT) was 0.734.

Two calibration curves plotted from peak area ratio against standard paracetamol concentrations were linear over the two concentration ranges of paracetamol (0.5-12.0 and 5-35 μg/ml).

Table 1. Percent recovery of paracetamol after extraction

Standard conc (µg/ml)	% Recovery	%C.V.	Standard conc (µg/ml)	% Recovery	%C.V.
0.5	101.23	8.40	5	99.08	1.01
1	101.64	2.36	10	97.26	2.70
2	95.85	2.39	15	104.76	4.81
4	98.30	0.19	20	101.11	3.08
6	106.32	4.20	25	97.82	5.12
8	95.94	4.34	30	100.42	2.84
10	99.93	0.62	35	100.06	1.32
12	99.47	2.56			
	99.84 ± 3.40			100.07 ± 2.49	

a = 3; value expressed as mean ± s.e.m.

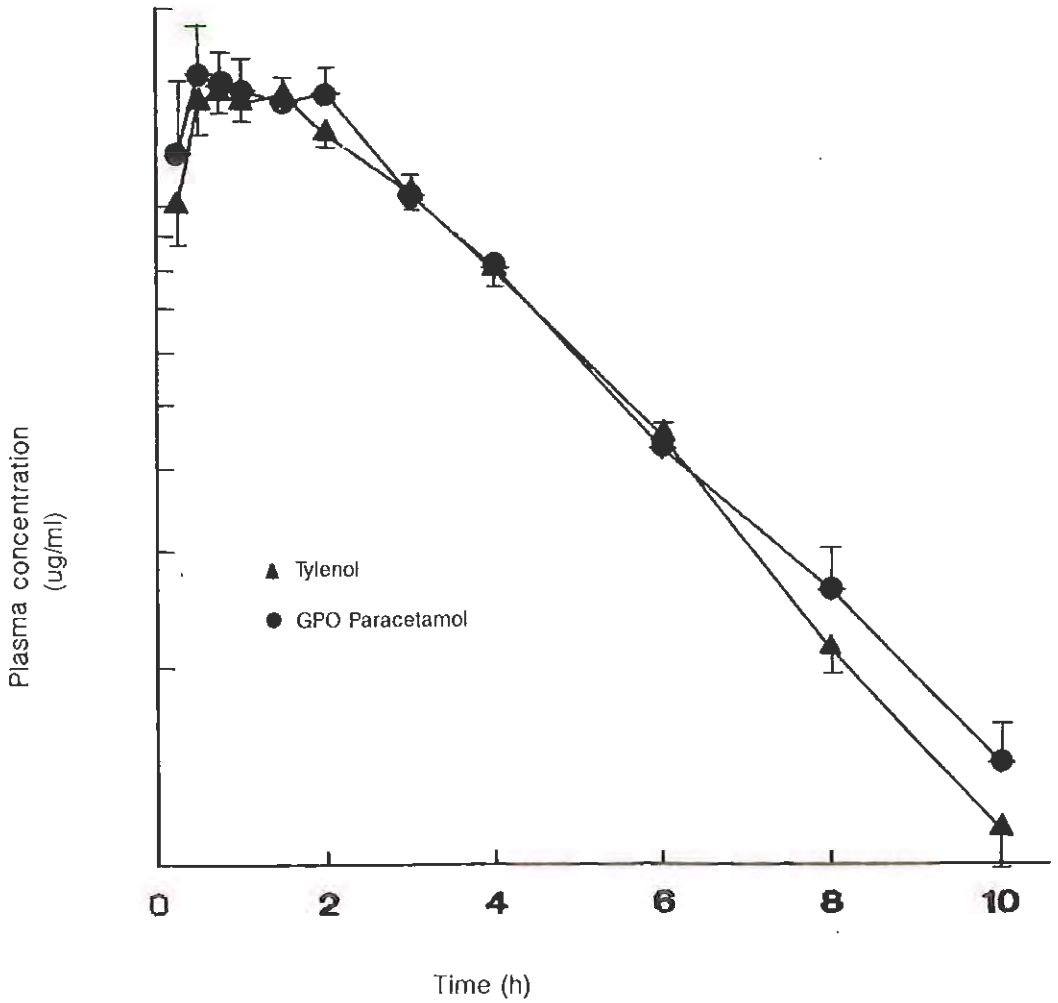

Figure 1. Mean paracetamol concentration at various times following oral administration of 2×500 mg paracetamol tablets, Tylenol and GPO Paracetamol.

Percent C.V. of intraday and interday assay varied from 1.86-3.81 % and 0.92-3.87 % ,respectively, at peracetamol concentration ranging from 0.5-12.0 μg/ml and varied from 0.55-3.50% and 0.56-4.71% respectively, at paracetamol concentration ranging from 5.0-35.0 μg.ml.

Percent errors were found to be 0.4-3.0% when standard paracetamol concentrations in plasma, ranging from 1-30 mg-ml, were assayed.

Percent recovery of paracetamol in tripicate assays of standard paracetamol concentrations were shown in Table 1. In these assays percent recoveries were ranging from 95.85% to 106.32 % (mean 99.84 ± 3.40 %) and from 97.26 % to 104.76 % (mean 100.07 ± 2.49 %), when standard paracetamol concentrations were varied from 0.5-12.0 μg/ml and 5.0-35.0 μg/ml, respectively.

Mean plasma concentration time curves of Tylenol and GPO Paracetamol were shown in Figure 1 and Table 2. Peak plasma concentrations were reached within 0.5-1.0 hours

Table 2. The mean value of Pharmacokinetic parameters of paracetamol from 16 subjects following 2×500 mg oral administration.

Parameter	Brand		
	Tylenol	GPO paracetamol	Statistical Significance
Peak plasma concentration (Cp_{max} μg/ml)	20.43 ± 2.26	22.72 ± 2.04	NS
Time to peak plasma level (T_{max} h)	1.05 ± 0.19	1.08 ± 0.22	NS
Area under the plasma concentration (AUC_0^{10} μg.h/ml)	69.35 ± 5.85	72.40 ± 4.83	NS
Area under the plasma concentration (AUC_0^{∞} μg.h/ml)	73.64 ± 6.62	78.18 ± 5.20	NS
Half life ($t_{1/2}$,h)	2.16 ± 0.18	2.33 ± 0.24	NS

NS = not significant difference at $p < 0.05$
value expressed as mean ± s.e.m.

in both preparations and then declined in a linear manner when the plasma paracetamol concentrations were plotted on a logarithmic scale indicating the first-order process of elimination (Figure 1) with elimination half lives of 2.16 ± 0.18 hours for Tylenol and 2.33 ± 0.24 hours for GPO Paracetamol (Table 2). Figure 1 is here

Pharmacokinetic parameters summarized in Table 3 were mean peak plasma concentrations (Cp_{max}), mean time-to-peak (T_{max}), and mean total area under the plasma concentration-time curves at 10 hours and at infinity (AUC_0^{10} and AUC_0^{∞}) of Tylenol and GPO Paracetamol. ANOVA and the Student's t test were used to test for statistical significant differences and found that there were no significant differences in all parameters.

Discussion

This analytical method was specific and sensitive with good precision, good accuracy and very efficiency as chromatograms of paracetamol and internal standard theophylline were clearly separated (RRT = 0.734) with % C.V. of Intraday and Interday assays and % errors of measurement were less than 5% together with % recovery of paracetamol analysis were close to 100% (>95%).

From the mean plasma concentration at various time (Table 2) Tylenol and GPO Paracetamol were rapidly absorbed when given orally, reaching peak concentrations at about 1 hour and the plasma concentrations were maintained above therapeutic level (10-20 μg/ml) for at least 3 hours after drug administration. The peak concentrations

(Cp_{max}) after oral 1,000 mg dose of Tylenol and GPO Paracetamol were 20.43 ± 2.26 μg ml and 22.72 ± 2.04 μg/ml, repectively. The peaks were attained within 1.05 ± 0.19 hours and 1.08 ± 0.22 hours (T_{max}) respectively. No statistically significant differences were observed ($P > 0.05$) between Cp_{max} and T_{max} of Tylenol and GPO Paracetamol.

The extent of paracetamol absorption can be determined by the total area under the plasma concentration-time curve (AUC). In this study, the AUC at 10 hours (AUC_0^{10}) of Tylenol and GPO Paracetamol plasma concentration-time curves were 69.35 ± 5.85 μg.h/ml and 72.40 ± 4.83 μg.h/ml, respectively, and at infinity (AUC_0^{∞}) were 73.64 ± 6.62 μg.h/ml and 78.18 ± 5.20 μg.h/ml, respectively. There were no statiscally significant differences ($P > 0.05$) in AUC_0^{10} and AUC_0^{∞} between these two commercial preparations.

The bioavailability of Tylenol and GPO Paracetamol appeared to be relatively equal as indicated by statistically non-significant differences in Cp_{max}, T_{max}, AUC_0^{10} and AUC_0^{∞} between both commercial tablets. These results indicated that Tylenol and GPO Paracetamol were bioequivalent.[7-10]

Conclusion

Tylenol and GPO Paracetamol, when given to sixteen drug-free, non-smoking, healthy Thai volunteers as a single oral 1,000 mg dose after an overnight fast, were rapidly absorbed into systemic circulation with statistally bioequivalent as indicated by no significant differences in Cp_{max}, T_{max}, AUC_0^{10} and AUC_0^{∞} between each preparation. It was concluded that these two preparations were relatively bioequivalent in term of the rate and extent of drug absorption.

Acknowledgements

The authors gratefully appreciate the valuable suggestion from Dr. Samranchit Prateepasen during this study.

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