นิพนธ์ต้นฉบับ

A comparative bioavailability study of paracetamol suspensions.

Uthai Suvanakoot*
Yupa Chanyongworakul**

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The bioavailability of 5 paracetamol formulations (4 suspensions & 1 elixir) were determined in 8 normal healthy volunteers using a complete cross-over study. All subjects received a 25 ml equivalent of 600 mg of paracetamol as an single oral dose of each test product. Urine samples were collected at appropriate time intervals for 32 hr. The samples were assayed for paracetamol contents by a specifically spectrophotometric method. Data analysis showed that absorption of the drug from an elixir was faster than that from suspensions. The cumulative amount of paracetamol excreted into the urine from all formulations were not significantly different indicating bioequivalence in terms of the extent of absorption. The relative bioavailability of each paracetamol suspension to that of elixir was about 100%. All brands of paracetamol suspensions provided the same rates and the amount of drugs for absorption. This implied that all 4 suspensions were completely bioavailable.

Reprint request: Suvanakoot U, Department of Pharmacy, Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok 10330, Thailand.
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* Department of Pharmacy, Faculty of Pharmaceutical Sciences, Chulalongkorn University.
** Department of Pharmacy, Faculty of Medicine, Ramathibodi Hospital, Mahidol University.

อุทัย สุวรรณกูฏ, ยุพา จรรยงค์วรกุล. การเอื้อประโยชน์ในร่างกายของยาแขวนตะกอนพาราเซตามอล. จุฬาลงกรณ์เวชสาร 2533 ตุลาคม;34(10): 769-776

ศึกษาการเอื้อประโยชน์ในร่างกายของยาเตรียมพาราเซตามอล 5 ตำรับ (ยาแขวนตะกอน 4 ตำรับและยาอิลิกเซอร์ 1 ตำรับ) กระทำในอาสาสมัครที่มีสุขภาพดี 8 คนโดยใช้แบบแผนการทดลองข้าม อาสาสมัครทุกคนได้รับยาพาราเซตามอลจากยาเตรียมแต่ละตำรับจำนวน 600 มิลลิกรัมโดยการรับประทานเพียงครั้งเดียว ตัวอย่างปัสสาวะถูกเก็บในช่วงเวลาที่เหมาะสมตลอด 32 ชั่วโมงแล้วนำมาวิเคราะห์หาจำนวนพาราเซตามอลด้วยวิธีเฉพาะโดยใช้สเปคโตรโฟโตมิเตอร์จากการวิเคราะห์ข้อมูลพบว่าพาราเซตามอลจากยาอิลิกเซอร์ถูกดูดซึมได้เร็วกว่าพาราเซตามอลจากยาแขวนตะกอน จำนวนตัวยาสะสมที่ถูกขจัดออกมากับปัสสาวะหลังการให้ยาเตรียมพาราเซตามอลทั้ง 5 ตำรับมีค่าไม่แตกต่างกันอย่างมีนัยสำคัญ แสดงว่ายาเตรียมพาราเซตามอลทุกตำรับมีความสมมูลย์กันในร่างกายเมื่อพิจารณาจากจำนวนตัวยาที่ถูกดูดซึมเข้าสู่ระบบการไหลเวียนของโลหิต การเอื้อประโยชน์สัมพัทธ์ของยาแขวนตะกอนแต่ละตำรับเมื่อเทียบกับยาอิลิกเซอร์มีค่าประมาณ 100 เปอร์เซนต์ ยาแขวนตะกอนพาราเซตามอลของทุกบริษัทให้การเอื้อประโยชน์ในร่างกายเท่ากันทั้งอัตราเร็วและจำนวนตัวยาที่ถูกดูดซึม

Paracetamol is a nonprescription analgesic and antipyretic drug. Due to its poor solubility in water (1 : 70), liquid dosage from of[1] paracetamol was prepared using mixtures of alcohol, propylene glycol and glycerol as vehicle. The presence of alcohol in pediatric medication is of major toxicological interest with respect to both acute ingestion and passive exposure which would occur during therapy. Thus, the Committee on Drug of the American Academy of Pediatrics has stated that "It is desirable that no ethyl alcohol be included in medicinal products intended for use in children"[2]

Recently, paracetamol suspensions have been formulated and has been available in Thailand for a few year now. The question arose as to whether paracetamol suspensions were of biological equivalence to paracetamol elixirs. Therefore, the present study was conducted to evaluate the relative bioavailability of paracetamol suspensions to paracetamol elixir and to compare the bioavailability of 4 paracetamol suspensions commercially available in Thailand. Results obtained could provide information for selecting and using an appropriate dosage form.

Materials and Methods

Materials :

Test Products : An original brand of paracetamol elixir and four commercially available paracetamol suspensions (one was an original product) were bought from the drug stores. The concentration of paracetamol in both dosage form was 125 mg/ 5 ml. All chemical were analytical grade and used as received.

Methods :

Subjects : Eight healthy volunteers, 4 females and 4 males, aging range from 20-30 years and weighing between 45-65 kg. participated in this study. They were taking no other medications and having no history of gastro-intestinal, liver and renal diseases (Table 1). Written informed consent was obtained from all subjects before entering the experiment.

Table 1. Demographic Data of the Subjects.

Subject No	Sex	Age (yr)	Weight (kg)	Height (cm)	RBC (cell/mm^3)	WBC (cell/mm^3)	SGOT (iu/l)	SGPT (iu/l)	S_c (mg%)	BUN (mg%)
1	F	30	45	157	4,300,000	6900	15	20	0.8	14
2	F	24	45	161	4,200,000	9000	12	10	1.0	11
3	F	26	48	152	4,500,000	6000	13	15	1.0	15
4	F	25	56	164	5,000,000	8000	16	12	0.9	17
5	M	19	63	164	5,500,000	6500	10	9	0.9	12
6	M	20	50	162	5,000,000	7000	8	11	1.0	12
7	M	21	65	175	6,000,000	6500	12	14	1.1	16
8	M	20	48	166	4,800,000	6800	14	18	0.9	13

Dose and Drug Administration : All subjects received a 25 ml. equivalent to 600 mg of paracetamol as an single oral dose of each test products. The doses were given in the morning after an overnight fast. No food was allowed until two hours postdose.

Experiment Design : The study was conducted in a crossover design. The dose was administered one week apart.

Sample Collection : Urine samples for paracetamol analysis were collected quantitatively prior to dosing and at 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 12.0, 16.0, 24.0 and 32 hours following drug administration. Subjects were carefully instructed to deliver a complete urine specimen (i.e. completely empty the bladder). Aliquots of 15 ml from urine samples were stored at-4°C until subsequent assay.

Determination of Paracetamol in Urine Samples : Paracetamol in each urine sample was analyzed triplicately using the specifically modified colorimetry of Novotny and Elser.[4] The sensitivity of the method was

5 mcg/ml and the method also correlated linearly with paracetamol concentration from 0 upto 250 mcg/ml. Analytical recovery of paracetamol from pooled urine ranged from 98 to 107%. Neither urea nitrogen plus creatinine nor unmeasured anions interfered with paracetamol determination by this modified analysis. The concentration of paracetamol was quantified using a standard curve.

Statistical Evaluation of Bioavailability Results : The relative bioavailability (F_{rel}) was calculated using the following equation

$$F_{rel} = \frac{[D_{uoo}] \text{ suspension}}{[D_{uoo}] \text{ elixir}} \times \frac{\text{Dose elixir}}{\text{Dose suspension}} \times 100$$

where D_{uoo} is the maximum cumulative amount of paracetamol excreted into the urine. The comparative bioavailability of paracetamol suspensions with paracetamol elixir and among themselves were evaluated using the following parameters ; (a) the maximum cumulative amount of drug excreted into the urine, D_{uoo}, (b) the maximum rate of drug excretion, $(dD_u/dt)_{max}$, (c) the time for maximum urinary excretion, t_{oo}, and (d) the absorption rate constant, K_a. A one-way analysis of variance and t-test were used through a computerized statistical program ABSTAT for data analysis.

Results and Discussion

The cumulative amount of paracetamol excreted into the urine as a function of time for all products are presented in Table 2 and Figure 1. This parameter is directly related to the total amount of drug absorbed. In this study the cumulative amount of drug excreted into the urine at the time 32 hours postdose was read as the maximum values. This is because the concentration of the drug in urine samples after that are too low to be correctly determined by the method used. The highest value is that from a suspension Brand S2 followed by those from an elixir and suspension Brands S1 and S3, respectively. This may be due to suspension Brand S2 containing more drug in the formula than any other brands. However, no statistically significant difference in this value among the five brands was observed ($p>0.05$). The total paracetamol recovery studied here was about 70-75% of the dose which was less than those of approximately 80-90% as reported previously.[5,6] However, the total recovery of paracetamol in urine of about 67-80% has also been published.[7]

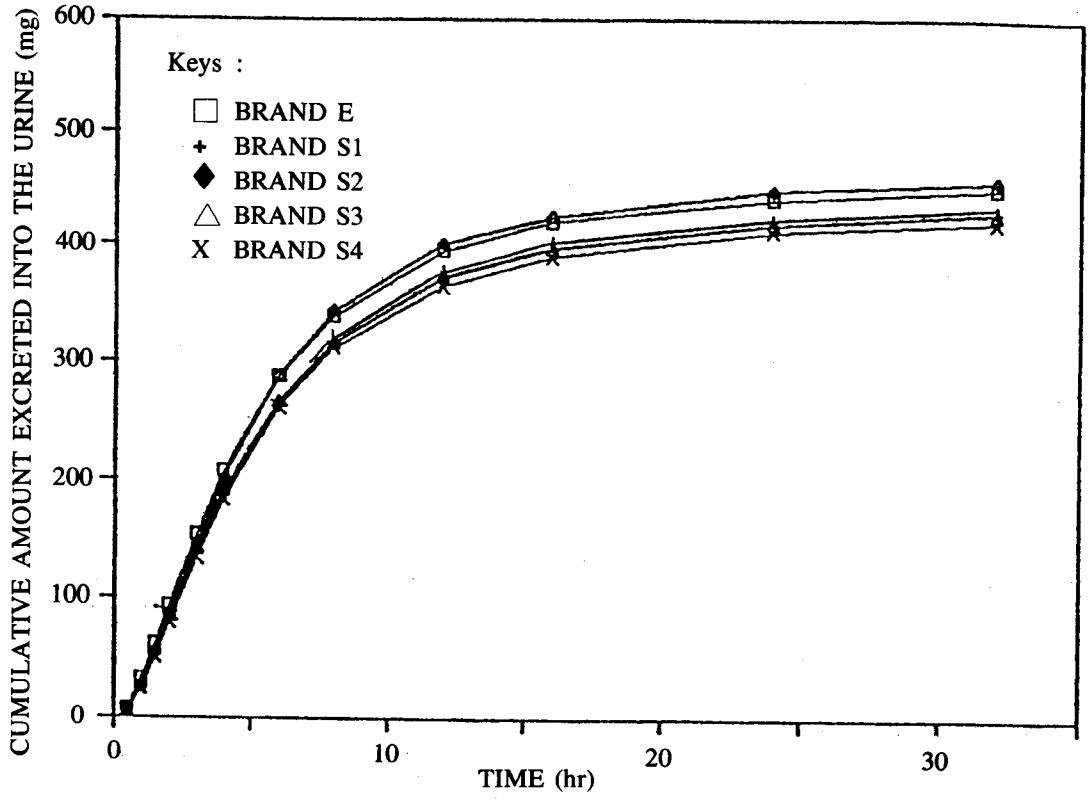

Figure 1. Mean cumulative amount of paracetamol excreted into the urine from 8 subjects following single oral dose of 600 mg paracetamol from paracetamol elixir and paracetamol suspensions.

Table 2. Mean Cumulative Amount of Paracetamol Excreted into the Urine from 8 Subjects Following. Single Oral Dose of 600 mg. of Paracetamol from Elixir and Suspensions.

Time (hours)	Cumulative Amount of Paracetamol Excreted (mg) $\bar{X}$ (SD)				
	Elixir	Suspension (brands)			
		S1	S2	S3	S4
0.5	7.7(1.9)	5.3(1.2)	5.9(2.3)	7.3(2.7)	6.2(2.1)
1.0	32.8(5.0)	25.5(6.7)	26.1(8.4)	29.8(7.7)	25.4(6.5)
1.5	61.2(6.2)	52.6(8.5)	55.1(13.4)	57.1(11.7)	51.5(11.4)
2.0	94.0(7.8)	81.8(11.3)	86.7(18.3)	85.7(13.6)	80.0(14.5)
3.0	153.3(15.0)	138.2(16.3)	145.1(29.0)	141.7(19.5)	133.7(22.1)
4.0	208.2(21.0)	189.1(17.8)	201.1(36.8)	191.9(25.9)	183.5(27.8)
6.0	288.1(21.5)	263.1(20.6)	287.9(45.8)	267.1(32.6)	262.0(38.9)
8.0	338.7(21.9)	316.4(21.3)	343.2(49.3)	316.5(35.7)	312.2(43.4)
12.0	394.8(22.3)	371.9(26.1)	401.3(52.2)	373.2(36.1)	364.8(45.4)
16.0	420.8(26.1)	397.4(31.2)	426.5(53.5)	398.0(35.8)	390.1(46.9)
24.0	441.1(27.8)	419.0(38.0)	448.8(57.4)	418.9(37.0)	411.8(48.7)
32.0	450.1(28.1)	430.9(39.2)	457.0(58.5)	429.2(40.7)	420.9(51.2)
Frel	-	**95.7%**	**101.5%**	**95.4%**	**93.5%**

The rate of drug excretion, dD_u/dt could not be determined experimentally for any given instance. Thus, an average urinary excretion was calculated for the collection period (Table 3). The plots of average rate of drug excretion for each brand on a semilogarithmic scale versus the time at the midpoint of the collection period are shown in Figure 2. Generally, the rate of drug excretion is dependent on the concentration of that drug in plasma. Hence, the maximum rates of drug excretion should be identical with the maximum concentration of the drug.[8] The study demonstrates that the maximum rates of drug excretion for all products can be ranked as E > S2 > S1 > S3 > S4. An analysis of variance indicated that there were no statistically significant difference among the five brands ($p > 0.05$) where as the t-test showed difference between Brand E and Brand S4 ($p < 0.05$) according to the maximum rates of drug excretion.

The time for maximum urinary excretion, t_{oo} obtained from all formulations are about the same indicating that the total time required after drug administration for the drug to be absorbed and completely excreted from all products tested are equal.

From the semilogarithmic plots of the average rates of paracetamol excreted into the urine versus time at the midpoint of the collection period, the data were well described by a mean of one compartment open model with first-order absorption and elimination. The data from each brand were analyzed for the pharmacokinetic parameters employing CSTRIP and NONLIN computer programs.[9] Results obtained are displayed in Table 4.

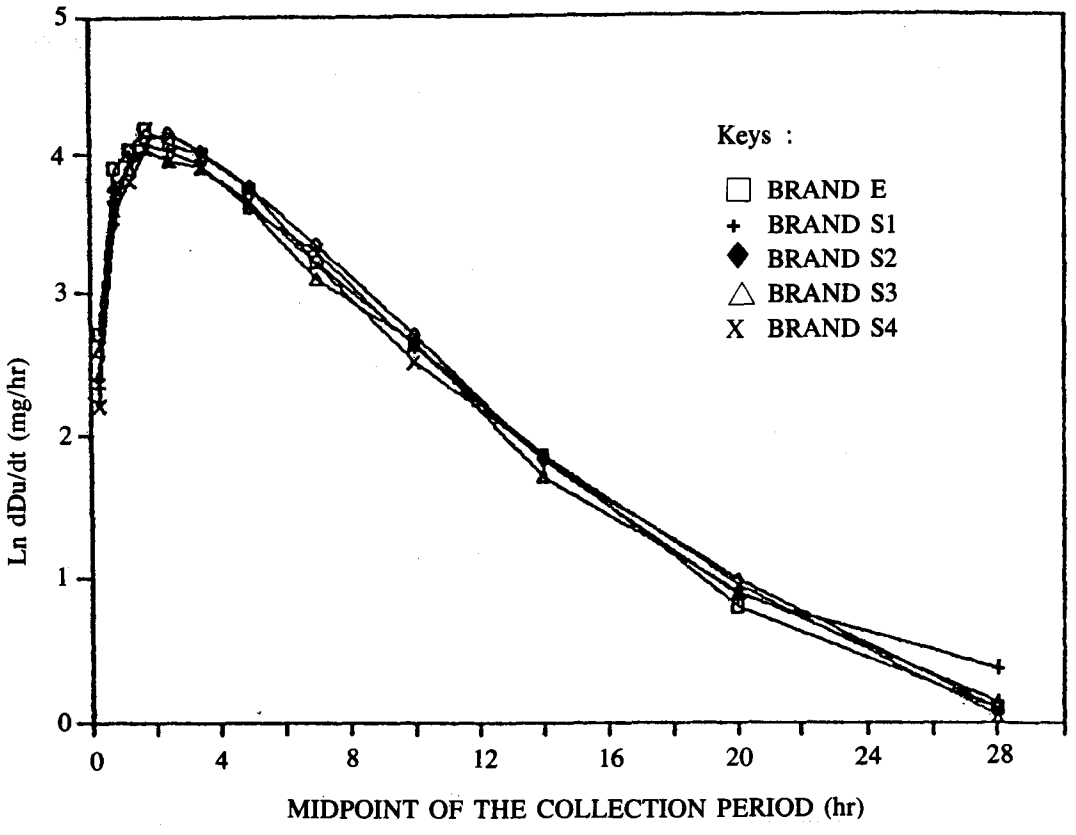

Figure 2. Mean rate of paracetamol excretion from 8 subjects following single oral dose of 600 mg paracetamol from elixir and suspensions.

Table 3. Mean Rate of Paracetamol Excretion from 8 Subjects Following Single Oral Dose of 600 mg. of Paracetamol from Elixir and Suspensions

Time (hours)	Rate of Paracetamol Excretion (mg/hr) $\bar{X}$ (SD)				
	Elixir	Suspension (brands)			
		S1	S2	S3	S4
0.25	15.4(3.8)	10.6(2.4)	11.8(4.6)	14.6(5.4)	10.9(4.6)
0.75	50.2(9.1)	40.5(11.8)	40.5(13.4)	44.9(10.3)	39.8(8.9)
1.25	56.9(4.6)	54.0(5.5)	58.0(15.2)	54.6(8.4)	52.4(10.4)
1.75	65.7(5.0)	59.7(6.1)	64.4(12.5)	59.2(4.6)	58.1(9.8)
2.50	59.3(7.9)	56.3(6.3)	58.4(11.5)	56.0(7.3)	53.6(8.6)
3.50	54.9(7.6)	50.9(3.0)	55.9(8.7)	50.2(8.6)	49.8(6.5)
5.00	39.9(2.9)	37.0(2.9)	43.5(5.7)	37.6(5.6)	39.2(6.1)
7.00	25.3(3.9)	26.6(4.0)	27.6(3.1)	24.7(3.1)	25.1(4.5)
10.00	14.0(2.5)	13.8(2.8)	14.5(2.1)	14.2(2.3)	13.2(2.3)
14.00	6.5(1.4)	6.3(1.7)	6.3(1.6)	6.2(1.4)	6.3(1.4)
20.00	2.6(0.6)	2.7(1.0)	2.8(0.8)	2.6(0.7)	2.7(0.7)
28.00	1.1(0.2)	1.5(0.3)	1.0(0.4)	1.3(0.7)	1.2(0.5)

Table 4. Mean Pharmacokinetic Parameters ($\bar{X}$ (SD)) from 8 Subjects Following Single Oral Dose of 600 mg. of Paracetamol from Elixir and Suspensions.

Parameters	Elixir	Suspension (brands)				Statistical Test
		S1	S2	S3	S4	
Maximum cumulative amount of drug excreted into the urine, D_{uoo} (mg)	450.1(28.1)	430.9(39.2)	457.0(58.5)	429.2(40.7)	420.9(51.2)	NS
Maximum rate of drug excretion, $(dD_u/dt)_{max}$, (mg/hr)	65.7(5.0)	59.7(6.1)	64.4(12.5)	59.2(4.6)	58.1(9.8)	S, E>S4
Time for maximum urinary excretion, t_{oo}, (hr)	29.7(1.4)	31.0(4.1)	29.0(1.4)	30.6(3.0)	30.3(2.))	NS
Absorption rate constant, K_a, (hr^{-1})	2.5(0.5)	2.3(1.1)	1.5(0.3)	2.0(0.6)	1.7(0.4)	S, E>S2, E>S4
Half-life, t½, (hr)	4.2(0.2)	4.4(0.6)	4.1(0.2)	4.4(0.4)	4.3(0.4)	NS

The average absorption rate constant of paracetamol from an elixir is greater than those from suspensions. This is expected because an elixir contains drug in soluble form which is readily and easily absorbed. The lowest value is that of suspension Brands S2. It may be because the dispersed drug particles are aggregated or agglomerated into larger ones resulting in slower absorption. However, there were no statistically significant difference among the absorption rate constants of Brand E versus those of Brands S1 and S3 ($p>0.05$) except those of Brand E versus Brands S2 and S4 ($p<0.05$).

The mean half-life, t½ of all products studied as presented in Table 4 are similar and no differences are observed among these parameters. The half-life received here is longer than those of approximately 1.62 to 2.83 hours as reported previously.[5,10] However, the half-lives from urine data of up to 4 hours in adults were also published by other investigators.[6,11]

Bioequivalent Evaluation. Relative bioavailability of paracetamol suspensions to that of elixir were calculated. They were 95.7, 101.5, 95.4 and 93.5% for Brands S1, S2, S3 and S4, respectively. Brand S1 and Brand E were completely bioequivalent. Brand S2, S3, S4 were bioequivalent with Brand E according to only the total amount of drug absorbed. Comparative bioavailability of paracetamol suspensions was also studied. Paracetamol suspension Brand S1 was assigned as reference standard against Brands S2, S3 and S4. It was interesting that all brands were of complete bioequivalence.

Conclusion

Bioavailability of paracetamol from an original brand of suspension and an elixir was similar. This is shown by there were no statistically significant differences in any measured parameters. Bioequivalence was also established for any other brands of suspension and an elixir in term of the extent of absorption. This is demonstrated by statistical equivalence of the total amounts of paracetamol excreted into the urine following a dose in elixir and suspensions. In addition, the data also showed that all brands of paracetamol suspensions tested were completely bioequivalent with respect to both the rate and the amount of paracetamol absorption. Therefor any brand of paracetamol suspension can be used interchangeably. However, for a faster onset of action, an original brand of paracetamol suspension is recommended.

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