

6-1-1996

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Nonnuch Chaiyod

See next page for additional authors

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Recommended Citation

Itthipanichpong, Chandhanee; Kraisintu, Krisana; Panomvana Na Ayudhaya, Duangchit; Sirivong, Pairoj; Chaiyod, Nonnuch; and Nanthasomboon, Sirimas (1996) "The pharmacokinetics and pharmacologicaleffects of propranolol in normal subjects," *Chulalongkorn Medical Journal*: Vol. 40: Iss. 6, Article 4.

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The pharmacokinetics and pharmacologicaleffects of propranolol in normal subjects

Authors

Chandhanee Itthipanichpong, Krisana Kraisintu, Duangchit Panomvana Na Ayudhaya, Pairoj Sirivong, Nonnuch Chaiyod, and Sirimas Nanthasomboon

The pharmacokinetics and pharmacological effects of propranolol in normal subjects.

Chandhanee Itthipanichpong* Krisana Kraisintu**

Duangchit Panomvana Na Ayudhaya*** Pairoj Sirivong*

Nonnuch Chaiyod* Sirimas Nanthasomboon****

Itthipanichpong C, Kraisintu K, Panomvana Na Ayudhaya D, Sirivong P, Chaiyod N, Nanthasomboon S. The pharmacokinetics and pharmacological effects of propranolol in normal subjects. Chula Med J 1996 Jun;40(6): 451-463

Objective: *To evaluate the pharmacokinetics and pharmacological effects of propranolol in normal Thai subjects.*

Design: *Clinical trial*

Setting: *Department of Pharmacology, Faculty of Medicine, Chulalongkorn University.*

Subjects: *Five male and five female volunteers, ages ranging from 20 to 45 years. They were normal on physical, hematologic, biochemical and EKG examination. All of them were non smokers and had not taken any medication at least 5 day prior to the study.*

Methods: *Each subject took 80 mg propranolol orally after an overnight fasting. Propranolol plasma levels were determined prior to drug administration (time 0) and at 1,1.5,2,2.5,3,4,6,8 hours post dose. The following pharmacokinetic parameters were determined: C_{max} , T_{max} , AUC_{0-8} , K_a , K_{el} and $t_{1/2}$. During each time of blood drawing, the systolic blood pressure, diastolic blood pressure and pulse rate were measured.*

* Department of Pharmacology, Faculty of Medicine, Chulalongkorn University

** Department of Research and Development, The Government Pharmaceutical Organization

*** Department of Pharmacy, Faculty of Pharmaceutical Science, Chulalongkorn University

**** Department of Pharmacology, Faculty of Medicine, Khonkhaen University

Results: *After propranolol administration, the mean systolic blood pressure and pulse rate were reduced significantly from baseline value at two hours and one hour respectively. Pharmacokinetic data demonstrated that the mean peak plasma propranolol concentration (C_{max}) was 85.95 ± 16.67 ng/ml and the time to reach peak concentration (T_{max}) was 2.05 ± 0.17 hrs. The area under the plasma concentration-time curve from 0 to 8 hours (AUC_{0-8}) was found to be 422.78 ± 76.88 ng. ml⁻¹ hr. and the elimination half-life ($t_{1/2}$) was 3.75 ± 0.4 hrs. It was observed that the AUC_{0-8} values of the female volunteers were significantly higher than those of the male volunteers and the C_{max} value seemed to be greater in the former group as well, however, no significant change was observed in hemodynamic effects including blood pressure and pulse rate between the two groups of the subjects.*

Conclusion: *The pharmacokinetic parameters and pharmacological effects of propranolol were determined after an oral 80-mg dose. Although the difference in pharmacokinetic parameter among the male and female volunteers was found such as AUC, no significant difference was observed in hemodynamic effects including blood pressure and pulse rate. This may be due to the high therapeutic index of propranolol. Therefore the change in pharmacokinetic parameters didn't affect the pharmacological effects.*

Key words: *Pharmacokinetic, Pharmacological effect, Propranolol.*

Reprint request: Itthipanichpong C, Department of Pharmacology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.

Received for publication. April 15,1996.

จันทน์ อธิพานิชพงศ์, กฤษณา ไกรสินธุ์, ดวงจิต พนมวัน ณ อยุธยา, ไพโรจน์ ศิริวงษ์, นงนุช ไชยยศ, ศิริมาศ นันทสมบุรณ์. เภสัชจลนศาสตร์ และฤทธิ์ทางเภสัชวิทยาของยาโปรปราโนลอลในคนปกติ. จุฬาลงกรณ์เวชสาร 2539 มิถุนายน;34 (6): 451-463

วัตถุประสงค์	เพื่อศึกษาถึงเภสัชจลนศาสตร์และฤทธิ์ทางเภสัชวิทยาของยาโปรปราโนลอลในคนปกติ
รูปแบบการวิจัย	การวิจัยทางคลินิก
สถานที่	ภาควิชาเภสัชวิทยา คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
ผู้เข้าร่วมการศึกษา	อาสาสมัครชาย 5 คน และหญิง 5 คน มีอายุระหว่าง 20-45 ปี ทุกคนมีสุขภาพแข็งแรง โดยพิจารณาจากผลการตรวจร่างกาย การตรวจเลือด ค่าทางชีวเคมีและ อี เค จี นอกจากนี้อาสาสมัครเหล่านี้เป็นผู้ไม่สูบบุหรี่ และไม่รับประทานยาใดก่อนการศึกษาอย่างน้อย 5 วัน
วิธีการ	อาสาสมัครแต่ละคนรับประทานยาโปรปราโนลอลขนาด 80 มิลลิกรัม และเจาะเลือดหาระดับยาโปรปราโนลอลในเลือดก่อนรับประทานยา (เวลา 0) และภายหลังการรับประทานยา 1, 1.5, 2, 2.5, 3, 4, 6 และ 8 ชั่วโมงตามลำดับ หาค่า pharmacokinetic parameters ต่อไปนี้คือ C_{max} , T_{max} , $AUC_{0 \rightarrow 8}$, K_a , K_{el} และ $t_{1/2}$ ทุกครั้งที่เจาะเลือดจะวัดความดันโลหิต ทั้งซิสโตลิก และไดแอสโตลิก รวมทั้งอัตราการเต้นของชีพจรร่วมด้วย
ผลการศึกษา	พบว่าค่าเฉลี่ยความดันโลหิตซิสโตลิก และอัตราการเต้นของหัวใจลดลงอย่างมีนัยสำคัญที่เวลา 2 ชั่วโมงและ 1 ชั่วโมงตามลำดับภายหลังการรับประทานยาโปรปราโนลอล 80 มิลลิกรัม ส่วนค่าทางเภสัชจลนศาสตร์พบว่า ค่าเฉลี่ยระดับยาสูงสุดในเลือด คือ 85.95 ± 16.67 นาโนกรัมต่อมล. และเวลาที่ระดับยาขึ้นสูงสุดในเลือด (T_{max}) คือ 2.05 ± 0.17 ชั่วโมงภายหลังการรับประทานยา พื้นที่ภายใต้เส้นกราฟระหว่างความเข้มข้นของยาในพลาสมาที่เวลา 0 ถึง 8 ชั่วโมง ($AUC_{0 \rightarrow 8}$) เท่ากับ 422.78 ± 76.88 นาโนกรัม. มล ⁻¹ ชั่วโมง. ค่าครึ่งชีวิต (elimination half life) เท่ากับ 3.75 ± 0.4 ชั่วโมง นอกจากนี้ยังพบว่าอาสาสมัครหญิงมีค่า $AUC_{0 \rightarrow 8}$ สูงกว่าอาสาสมัครชายอย่างมีนัยสำคัญทางสถิติ และค่า C_{max} ของอาสาสมัครหญิงมีแนวโน้มสูงกว่าอาสาสมัครชาย ความแตกต่างทาง hemodynamic ไม่ว่าจะเป็ความดันโลหิตหรืออัตราการเต้นของชีพจร ไม่มีนัยสำคัญทางสถิติระหว่างอาสาสมัครชายและหญิง

สรุป

ได้ศึกษาค่าทางเภสัชจลนศาสตร์ และฤทธิ์ทางเภสัชวิทยาของยา โปรบราโนลอลในอาสาสมัครปกติ แม้ว่าจะพบความแตกต่างของค่าทางเภสัชจลนศาสตร์ระหว่างอาสาสมัครชายและหญิง คืออาสาสมัครหญิงมีค่า AUC สูงกว่าชายอย่างมีนัยสำคัญ แต่ความแตกต่างทาง hemodynamic ซึ่งได้แก่ ความดันโลหิต และอัตราการเต้นของชีพจร ไม่มีนัยสำคัญทางสถิติระหว่างอาสาสมัครทั้ง 2 กลุ่ม ทั้งนี้อาจเป็นเพราะโปรบราโนลอลเป็นยาที่มี therapeutic index สูง ดังนั้นการเปลี่ยนแปลงค่าทางเภสัชจลนศาสตร์ จึงไม่มีผลต่อฤทธิ์ทางเภสัชวิทยาของยา

Propranolol is a non selective beta adrenergic blocking drug very widely used for the treatment of cardiovascular diseases, such as hypertension, cardiac arrhythmia and ischemic heart disease.^(1,2) It interacts with β_1 , and β_2 receptors with equal affinity and lacks intrinsic sympathomimetic activity. The drug is completely absorbed after oral administration. Much of the drug is metabolized by the liver during its first passage through the portal circulation and only about 25% reaches the systemic circulation system. Moreover, there is great interindividual variation in the presystemic clearance of propranolol by the liver and this contributes to enormous variability in plasma concentrations after oral administration and also to the wide range of doses in terms of clinical efficacy.⁽¹⁻⁴⁾ The effects of cirrhosis,⁽⁵⁾ renal diseases⁽⁶⁾, sex^(7,8), genetic or ethnic⁽⁹⁾ constitution have all been shown to alter the disposition of propranolol. Since propranolol is widely used in our country and the pharmacokinetic or pharmacodynamic data obtained before marketing of the drugs are usually performed in groups of patients in Western countries. It is essential to evaluate the pharmacokinetic and pharmacological effects of the drug among Thai subjects.

Material and Methods

Five male and five female volunteers participated in this study. They were found to be normal upon physical, hematologic, biochemical and EKG examination. The ages ranged from 20-45 years with an average body weight of 56.0 ± 8.6 kg. All subjects were non-smokers and had not taken any medications or alcoholic beverages for at least

5 days prior to the study. The protocol was approved by the Ethical Board of the Faculty Committee. After an overnight fasting, each subject took a single 80-mg oral dose of propranolol (two 40 mg tablets) in the morning. Breakfast was allowed 3 hours after the drug administration. Blood samples were obtained for measurement of the plasma propranolol levels before drug administration (time 0) and at 1, 1.5, 2, 2.5, 3, 4, 6, and 8 hours post-dose. Plasma propranolol levels were measured using a high performance liquid chromatographic assay with the method described by Drummer, et al.⁽¹⁰⁾ During each blood drawing, the systolic blood pressure, diastolic blood pressure and pulse rates were measured. The mean plasma concentration-time curve for propranolol was constructed and the pharmacokinetic parameters were determined. The peak plasma concentration (C_{max}) and the time to reach peak plasma concentration (T_{max}) were obtained from the data observed for each subject. The area under the plasma concentration-time curve from 0 to 8 hours (AUC_{0-8}) was calculated by the trapezoidal rule. The absorption rate constant (K_a) and elimination rate constant were obtained using an MK model computer program. The elimination half-life ($t_{1/2}$) of the propranolol was determined by the standard formula, $t_{1/2} = 0.693/K_{el}$. All pharmacokinetic and pharmacodynamic data were presented as mean \pm SEM. A comparison of the pharmacokinetic data between the male and female subjects was performed by using the Student's unpaired t test. Comparison of hemodynamic data of the subjects at baseline and at different times following propranolol administration were done using the analysis of variance. A p value of less than 0.5 was considered statistically significant.

Results

The mean plasma concentration-time profile of propranolol is demonstrated in Figure 1 with the mean peak concentration (C_{max}) of 85.95 ± 16.67 ng/ml and the time required to reach peak plasma concentration (T_{max}) was 2.05 ± 0.17 hrs after propranolol administration (Table 1). The area under the plasmaconcentration-time curve from 0 to 8 hours, (AUC_{0-8}) was 422.78 ± 76.88 ng ml⁻¹ hr. The absorption rate constant (K_a) and elimination rate constant (K_{el}) obtained from this study were 1.06 ± 0.12 and 0.20 ± 0.02 hr⁻¹ respectively. The elimination half-life ($t_{1/2}$) was 3.75 ± 0.40 hrs.

It was found that after two hours of propranolol administration, the mean systolic blood pressure reduced significantly ($p < 0.05$) and stayed reduced until the end of the sampling time as compared with the baseline values (Figure 2). No statistically significant difference was found in the diastolic blood pressures after the drug administration. A reduction in the pulse rate of the subjects was also observed during propranolol ingestion. It was significantly reduced from the baseline value one hour after oral administration of the drug (Figure 3).

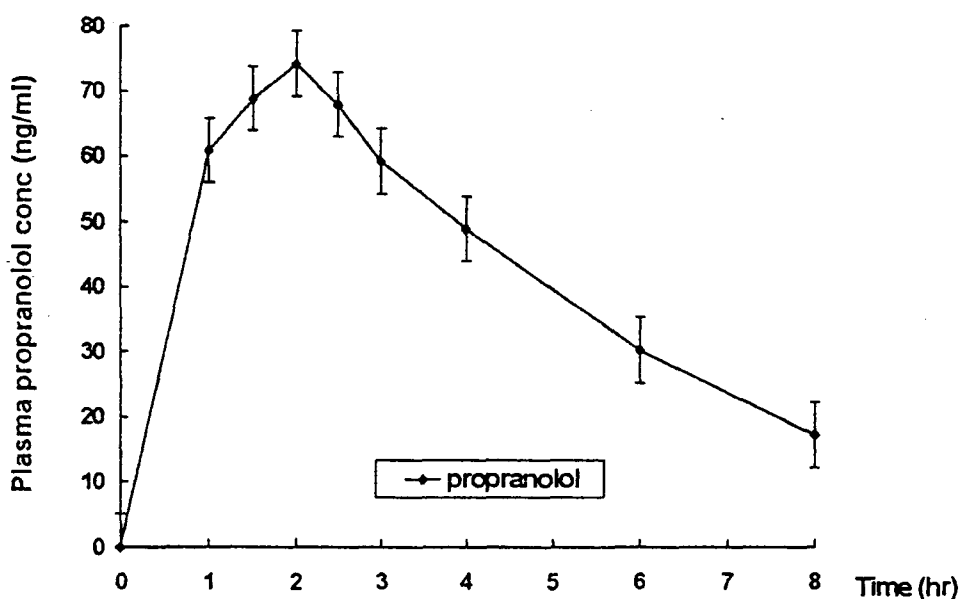


Figure 1. Mean (\pm SEM) plasma concentration of propranolol from 10 subjects following an oral 80-mg dose of propranolol.

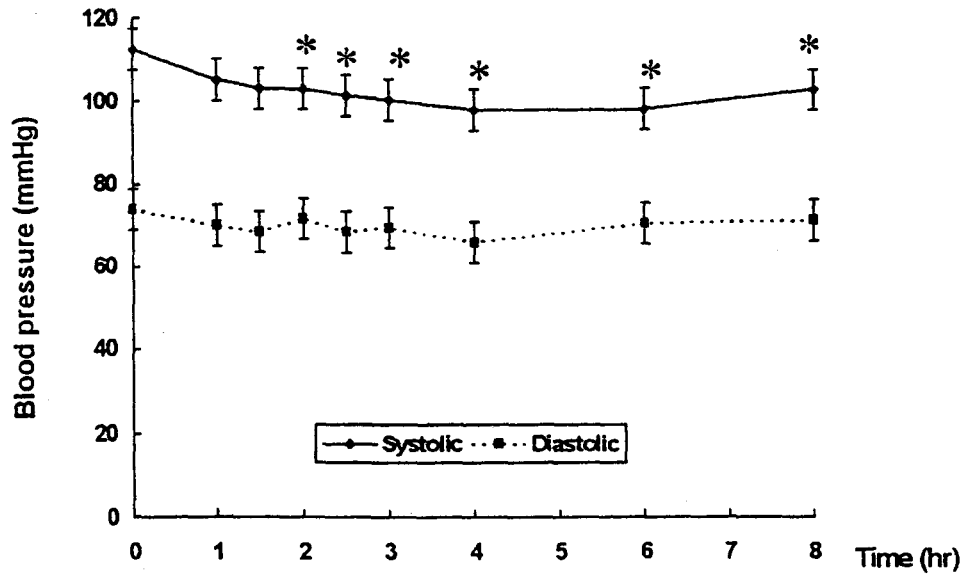


Figure 2. Mean (\pm SEM) systolic and diastolic blood pressure of 10 subjects following an oral 80-mg dose of propranolol. * $p < 0.05$ compared with the baseline value. (at time zero)

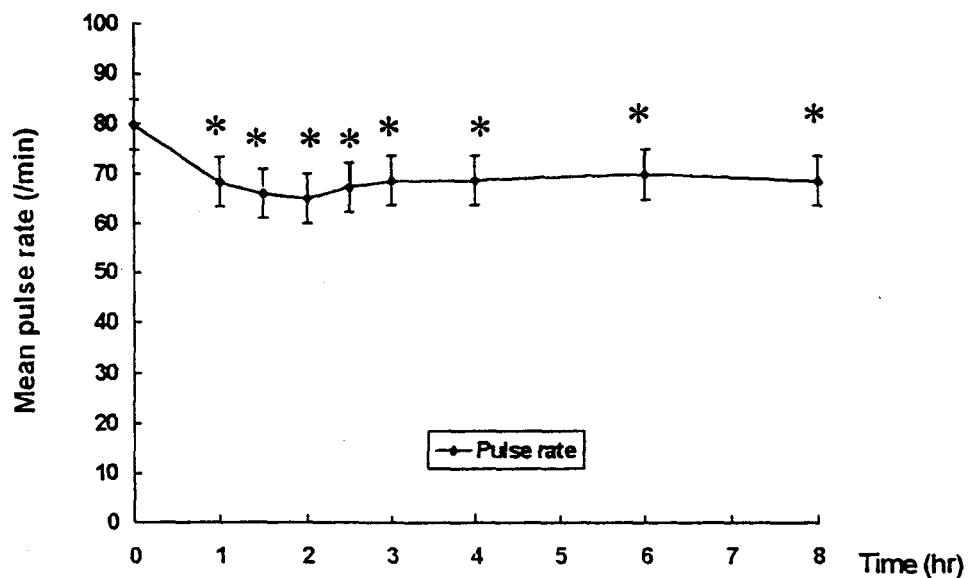


Figure 3. Mean (\pm SEM) pulse rate obtained from 10 subjects after an oral 80-mg dose of propranolol. * $p < 0.05$ compared with the baseline value. (at time zero)

Table 1. Pharmacokinetic parameters obtained from 10 subjects after taking 80 mg oral dose of propranolol. (Mean \pm SEM)

Pharmacokinetic parameters	Value
C_{max} (ng/ml)	85.95 \pm 16.67
T_{max} (hr)	2.05 \pm 0.17
AUC_{0-8} (ng.ml ⁻¹ hr)	422.78 \pm 76.88
K_a (hr ⁻¹)	1.06 \pm 0.12
K_{el} (hr ⁻¹)	0.20 \pm 0.02
$t_{1/2}$ (hr)	3.75 \pm 0.40

Furthermore, as shown in table 2 and figure 4, it was observed that female volunteers had greater AUC_{0-8} as compared with the male volunteers (616.34 \pm 54.81 and 229.21 \pm 69.73, $p < 0.05$) and the mean C_{max} of the females tended to be

higher than among the males (109.56 \pm 18.76, 62.35 \pm 24.89). No significant change was observed in hemodynamic effects, including systolic blood pressure, diastolic blood pressure and pulse rate, between the two groups of subjects (Figures 5,6).

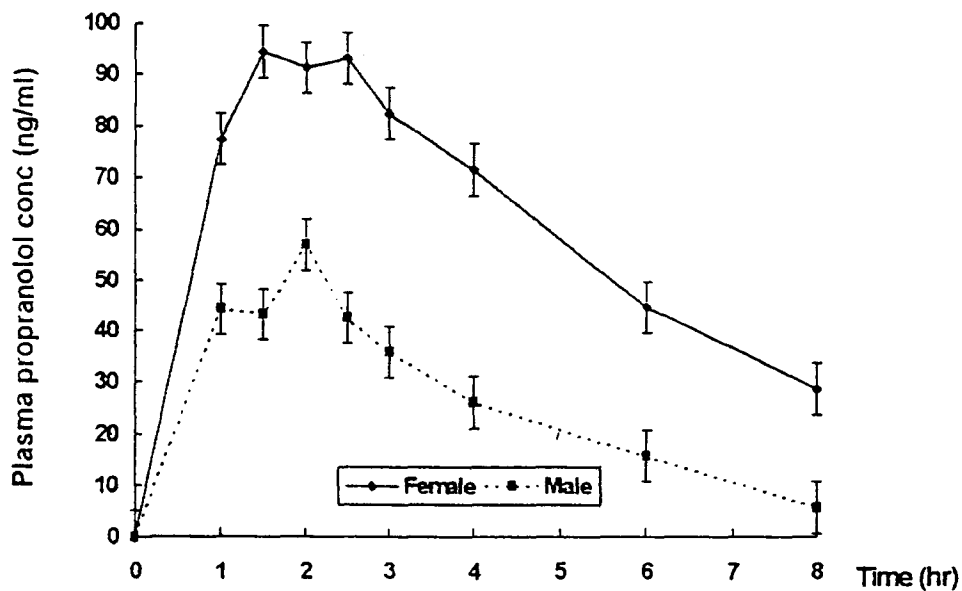


Figure 4. Mean (\pm SEM) plasma concentration of propranolol of the female and male subjects after an oral 80-mg dose of propranolol.

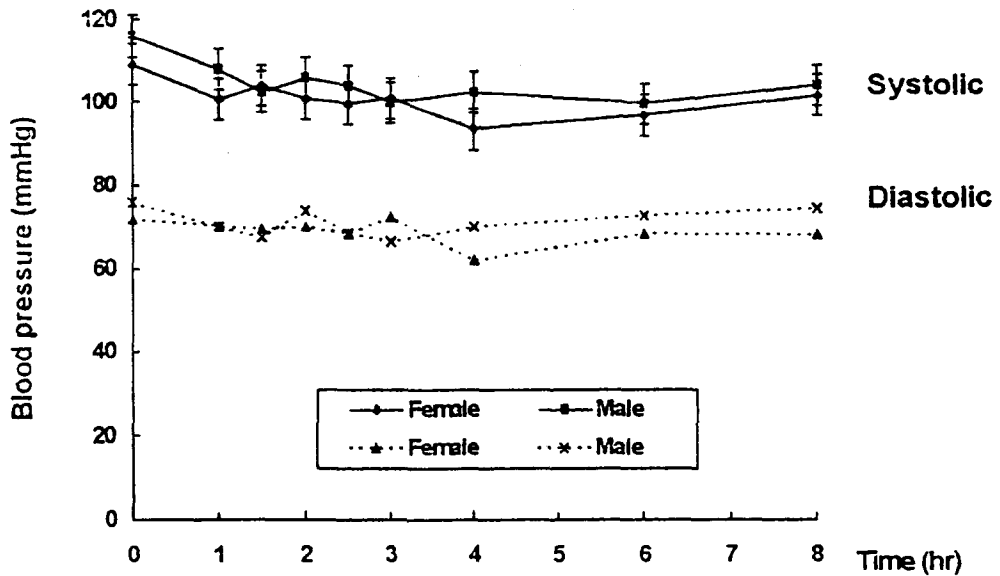


Figure 5. Mean (\pm SEM) systolic and diastolic blood pressure of the male and female volunteers following an oral 80-mg dose of propranolol.

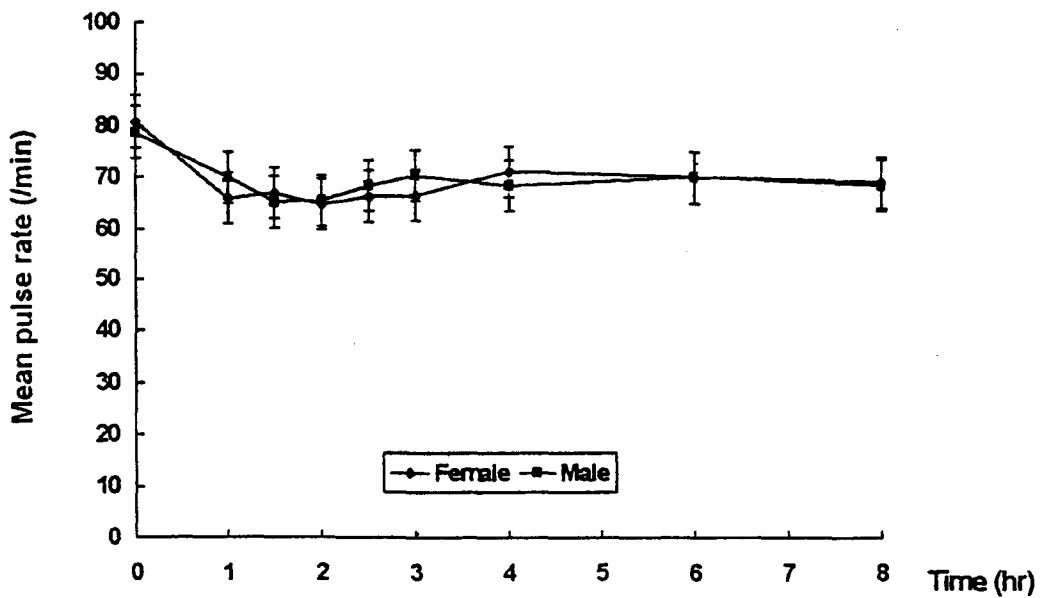


Figure 6. Mean (\pm SEM) pulse rate of the male and female volunteers following an oral 80-mg dose of propranolol.

Table 2. Pharmacokinetic parameters of the male and female volunteers following an oral 80-mg dose of propranolol. (Mean \pm SEM)

Pharmacokinetic parameters	Female subjects	Male subjects
C_{max} (ng/ml)	109.56 \pm 18.76	62.35 \pm 24.89
T_{max} (hr)	2.30 \pm 0.25	1.80 \pm 0.20
AUC_{0-8} (ng.ml ⁻¹ .hr)	616.34 \pm 54.81	229.21 \pm 69.73*
K_a (hr ⁻¹)	0.92 \pm 0.12	1.20 \pm 0.20
K_{el} (hr ⁻¹)	0.22 \pm 0.03	0.19 \pm 0.30
$t_{1/2}$ (hr)	3.30 \pm 0.36	4.19 \pm 0.71

* P < 0.05 compared with female subjects.

Discussion

Propranolol is commonly used as a beta adrenergic blocking drug because of its effectiveness in the treatment of various cardiovascular diseases. The price of the drug is not as high as newer agents in the same therapeutic category. These qualifications are selection criteria for drugs in The National List of Essential Drugs of Thailand. Propranolol has a high hepatic extraction ratio and is almost completely eliminated by hepatic metabolism.⁽¹¹⁾ A large number of routes of metabolism have been identified in man,⁽¹²⁾ including ring oxidation to form 4-hydroxypropranolol (4-OH propranolol) which has β -blocking activity of the same order as that of the parent drug. Side chain oxidation also yields N-dealkylated products that are subsequently further metabolized to propranolol glycol and naphthoxylic acid. Glucuronidation of parent drug and metabolites also occurs to a significant extent.

It was found that after an 80-mg oral dose of propranolol was taken by the subjects, the mean pulse rate was reduced from the baseline value one hour after drug administration and continuing to the end of the sampling time. A reduction in the mean systolic blood pressure was noted significantly from the baseline value at 2 hours after drug administration ($p < 0.05$) and this lasted to the end of the study period, but no significant difference was found in the diastolic blood pressure. These pharmacological effects of propranolol are due to the occupancy and blockade of beta receptors. The prominent effect is on the heart and the negative inotropic and chronotropic effects are predictable. The effects on the blood pressure may result from the effect on the heart.⁽¹⁾

Considering the pharmacokinetic data it was observed that plasma concentration of propranolol appeared as ng.ml in circulation with a maximum concentration (C_{max}) of 85.95 \pm 16.67 ng/ml. It

Table 3. Mean (\pm SEM) systolic, diastolic blood pressure and pulse rate of 10 subjects at different times following an oral 80-mg dose of propranolol.

Parameter	Time (hrs)								
	0	1	1.5	2	2.5	3	4	6	8
systolic BP (mm Hg)	112.60 ± 2.68	105.25 ± 2.67	103.25 ± 4.29	103.11 $\pm 3.27^*$	101.56 $\pm 4.34^*$	100.50 $\pm 3.58^*$	98.09 $\pm 2.62^*$	8.20 $\pm 1.17^*$	102.8 $\pm 2.95^*$
diastolic BP (mm Hg)	74.0 ± 3.06	70.0 ± 1.89	68.50 ± 3.50	71.78 ± 3.39	68.44 ± 3.52	69.50 ± 3.52	66.0 ± 1.96	70.6 ± 2.39	71.20 ± 2.27
pulse rate (/min)	79.80 ± 2.36	68.29 $\pm 3.74^*$	66.0 $\pm 2.40^*$	65.11 $\pm 1.89^*$	67.33 $\pm 2.08^*$	68.86 $\pm 3.14^*$	68.89 $\pm 2.11^*$	70.0 $\pm 1.86^*$	68.67 $\pm 1.97^*$

* $p < 0.05$ compared with the baseline value (at time zero)

took 2.05 ± 0.17 hours for the drug to reach the peak concentration (T_{max}). The area under the plasma concentration-time curve 0 to 8 hours (AUC_{0-8}) was shown to be 422.78 ± 76.88 ng.ml⁻¹ hr. The half-life ($t_{1/2}$) was 3.75 ± 0.4 hours. In comparing the pharmacokinetic parameters among the male and female volunteers, there was a statistically significant difference in the area under the plasma concentration-time curve (AUC_{0-8}). The female volunteers had a greater AUC_{0-8} than the male volunteers and the mean C_{max} of the female volunteers tended to be higher than for the males. These results were in accordance with Matangkasombat et al.⁽¹³⁾ and Bonate⁽⁷⁾ who had reported sex difference was one of the contributing factors in propranolol drug disposition. Woman exhibited steady-state serum level about 80% higher than men.⁽¹⁴⁾ The oral clearance of this drug

is higher in men than in women, a difference is due to the metabolic pathway specific. Where as cytochrome P-450 mediated side-chain oxidation was 137% higher in men than in women, there was no sex-based difference in other cytochrome P450 pathways, i.e ring oxidation. In addition, glucuronidation was 50% higher in men.⁽⁸⁾ Moreover, circulating levels of testosterone play important roles in gender-related differences in the metabolic pathways of men.⁽¹⁵⁾

Genetic polymorphism of drug metabolizing enzyme would be considered as one important factor involved in drug metabolism especially ring oxidation of propranolol to form 4-OH propranolol which is equipotent with propranolol in beta-adrenergic blocking activity. Although the poor metabolizer (PM) of debrisoquine oxidation phenotype showed about 500% decrease in 4-OH

Table 4. Mean (\pm SEM) systolic and diastolic blood pressure of the male and female volunteers at different times following an oral 80-mg dose of propranolol.

Blood pressure (mmHg)	Time (hrs)								
	0	1	1.5	2	2.5	3	4	6	8
systolic (male)	116.0 ± 4.0	108.0 ± 3.74	102.5 ± 2.5	106.0 ± 3.83	104.0 ± 7.70	100.0 ± 4.08	102.50 ± 2.50	99.60 ± 0.98	104.0 ± 2.45
systolic (female)	109.2 ± 3.26	100.67 ± 1.76	104.0 ± 8.91	100.8 ± 5.16	99.6 ± 5.49	101.0 ± 6.56	93.50 ± 3.50	96.80 ± 2.06	101.60 ± 5.71
diastolic (male)	76.0 ± 4.0	70.0 ± 3.16	67.50 ± 2.50	74.0 ± 4.0	68.50 ± 4.35	66.50 ± 3.50	70.0 ± 0.0	72.80 ± 2.80	74.4 ± 2.04
diastolic (female)	72.0 ± 4.90	70.0 ± 0.0	69.50 ± 7.09	70.0 ± 5.48	68.40 ± 5.78	72.50 ± 6.29	62.0 ± 2.71	68.4 ± 3.92	68.0 ± 3.74

Table 5. Mean (\pm SEM) pulse rate of the male and female volunteers at different times following an oral 80-mg dose of propranolol.

Pulse rate (/min)	Time (hrs)								
	0	1	1.5	2	2.5	3	4	6	8
male	78.80 ± 4.54	70.0 ± 6.38	65.20 ± 3.88	65.50 ± 3.59	68.50 ± 3.30	70.5 ± 3.20	68.50 ± 3.86	70.0 ± 3.34	68.4 ± 2.71
female	80.80 ± 1.96	66.0 ± 3.46	67.00 ± 3.0	64.8 ± 2.25	66.40 ± 2.93	66.67 ± 6.67	71.2 ± 3.14	70.0 ± 2.10	69.0 ± 3.32

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propranolol AUC in comparison with the extensive metabolizer (EM), the plasma concentrations of propranolol in the two groups of subjects did not differ overall from each other.⁽¹²⁾ This would suggest metabolic pathways other than 4-hydroxylation are more important in the overall clearance process. Despite 4-OH propranolol plasma concentration was 500% higher in extensive metabolizer, there was no difference in the extent of β -blockade as judged by pulse rate while standing and after exercise. The result obtained from our study also showed that although the AUC of propranolol in the female subjects increased significantly in comparison with the male subjects, it did not enhance hemodynamic effects (beta-adrenergic receptor blocking effects), such as the alterations in blood pressure or pulse rate as shown in figure 5,6. This pharmacodynamic implication indicates that propranolol has a quite high therapeutic index. The change in pharmacokinetics didn't affect the pharmacodynamics of the drug in this study. Therefore, adjustment of propranolol dosage based on gender seems to be unnecessary from this study but further study including more subjects need to be done to clarify this.

Conclusion

In summary, the pharmacokinetic parameters of propranolol in normal subjects were determined after a single 80-mg oral dose. The change in hemodynamic effects after propranolol administration included decreasing of the systolic blood pressure and pulse rate. The AUC₀₋₈ of the female subjects was higher than among the males

but there was no significant difference in hemodynamic effects between the male and female subjects.

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