A study of the bioavailability of four brands of propranolol tablet in normal Thai volunteers.*

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A study of the bioavailability of four brands of propranolol tablet in normal Thai volunteers.

This study was performed in order to evaluate both in vivo and in vitro bioavailability of four brands of propranolol tablet marketed in Thailand. One of the four was the original brand and the others were locally manufactured brands.

The in vitro study demonstrated that the disintegration time, dissolution rate, propranolol content, the content uniformity and weight variation of all four products employed in this study met USP XXII specifications.

The bioavailability study was carried out in 10 normal volunteers (five males and five females, ranging in age from 20 to 45 years), using a randomized, double blind and cross-over study design. After fasting overnight, each subject was administered two 40 mg tablets of propranolol orally, for a total dose of 80 mg each. Plasma propranolol was determined by specific high-performance liquid chromatography analysis. No significant difference was observed in the extent and rate of propranolol absorption. Therefore, it could be concluded that all four propranolol tablets were bioequivalent.

The mean peak plasma propranolol concentration ($C_{max}$) and the time required to reach the peak ($T_{max}$) obtained from this study were $87.79 \pm 8.32$ ng/ml and $1.99 \pm 0.12$ hrs, respectively. The area under the plasma concentration-time curve from 0 to 24 hrs ($AUC_{0-24}$) was $498.50 \pm 50.39$ ng.ml$^{-1}$ hr. The elimination half-life of propranolol in the Thai volunteers was $2.78 \pm 0.16$ hrs. It was found that the absorption rate constant ($K_a$) and the elimination rate constant ($K_e$) were $1.05 \pm 0.03$ hr$^{-1}$ and $0.28 \pm 0.01$ hr$^{-1}$

**Key words**: Bioavailability study, Propranolol.

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

Received for publication. January 25, 1993.

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*This work was supported by the Government Pharmaceutical Organization.

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งานวิจัยนี้มีวัตถุประสงค์ เพื่อศึกษาการผลิตประโยชน์ในเร่งกายของยาเม็ด propranolol สีท่าน้ำ โดยมีกลุ่มควบคุมทั้งหมดที่มีและผลิตภัณฑ์ทางยาในประเทศไทยที่รับ ทำการประเมินคุณภาพทั้งในทดลองทดลองและในเร่งกาย พบว่า ผลิตภัณฑ์ทั้งหมดที่รับมีคุณสมบัติทางยาของเร่งกาย ทำให้การเฉลี่ยการผลิต รายวัน  ani ตราสิ่งผลิตภัณฑ์ ความแน่นแบบของพยาบาลาสัมพันธุ์ ความแตกต่างของน้ำหนักยา และมวลสารคงที่ ที่กำหนดในผลิตภัณฑ์ (USP XXII)

ผลการศึกษาในเร่งกาย เมื่อให้ยาทั้งหมด 10 คน เป็นเพศชาย 5 คน และเพศหญิง 5 คน อายุระหว่าง 20-45 ปี รับยาในยาเม็ด propranolol ขนาด 40 มิลลิกรัม ที่มีมวลสารคงที่ ผลการผลิต propranolol ในเร่งกาย โดยใช้ High performance liquid chromatography พบว่ายาเม็ด propranolol ทั้งหมดมีการผลิตประโยชน์ในเร่งกายเท่ากันที่น้ำหนักยา เพราะทั้งหมดมีน้ำหนักยาและปริมาณยาที่ถูกคำตอบในน้ำหนักยาเท่ากันอย่างมีน้ำหนักทางสถิติ (p>0.05)

สำหรับค่าเฉลี่ยของความเร็วเชิงยางกลับของน้ำหนักยาในยาเม็ด propranolol 10 คน พบว่าความเร็วเชิงยางกลับในน้ำหนักยา (Cmax) คือ 87.79±8.32 นาทีมีผลิตภัณฑ์ ส่วนเวลาที่ระบายยาในน้ำหนักยา (Tmax) คือ 1.99±0.12 ชั่วโมง ค่าที่รับ (T1/2) คือ 2.78±0.16 ชั่วโมง ที่นั้นก็ได้ส่งผลทั้งค่า ความเชิงยางกลับ propranolol ในน้ำหนักยา (AUC) ค่าค่าที่ 498.50±58.39 นาทีมีผลิตภัณฑ์ และค่าที่รับที่ดีกว่าการดูแลขั้นต่ำคือ 1.65±0.03 ชั่วโมง 1 ชั่วโมง 1 สำหรับค่าที่ถูกต้องการวิเคราะห์ที่คิด (Kd) ที่ประมาณ 0.28±0.01 ชั่วโมง 1
Propranolol, a beta-adrenergic blocking drug, is widely used throughout the world as antihypertensive, antianginal and antiarrhythmic drugs. A large number of propranolol products are available in the market where the price competition between the original product and the locally manufactured ones is keen. Physicians have questioned the therapeutic equivalency of the differences brands, which led us to study the bioavailability of each product. Moreover, great inter-individual variability in the disposition of propranolol has been observed and differences in propranolol plasma levels between patients receiving identical oral doses have been reported.1-3 Through study of the pharmacokinetic process, the individual and inter-individual variability in absorption, distribution and excretion of the drug can be defined.4

This study was performed to evaluate the bioavailability of four commercial brands of propranolol tablet marketed in Thailand and also the pharmacokinetic profile of propranolol in normal Thai volunteers.

Materials and Methods

Materials

Four brands of propranolol hydrochloride tablet marketed in Thailand were designated as drugs A, B, C, D. One of them was the original product; the others locally manufactured products.

DL-propranolol hydrochloride, labetalol and 1-heptane-sulfonic acid were purchased from Sigma Co U.S.A. Diethyl ether and methanol were obtained from May and Baker (UK) and sodium metabisulfite was purchased from Merck Co. (Germany). All of the reagents used in this study were HPLC grade except diethyl ether and sodium metabisulfite.

Study subjects

Ten healthy Thai volunteers (five males and five females) gave written consent to participate in this study, which was approved by the Ethical Board of the Faculty Committee. None of the subjects had any abnormal finding on routine laboratory testing, history taking, physical examination and electrocardiography. All subjects were non-smokers and had not taken any medication or alcoholic drink for at least three days prior to the study. The mean age of the subjects was 28.96 ± 5.56 years (range 20 to 45). Their mean weight was 55.95 ± 8.56 kg (range 40-75 kg).

Methods

In vitro study

The following tests were carried out in order to determine whether or not all the propranolol hydrochloride tablets used in this study met the requirement of the United States Pharmacopeia (XXII)5:

1. weight variation
2. disintegration
3. dissolution
4. propranolol content of each tablet
5. content uniformity

In vivo study

Bioavailability study

After an overnight fast, blood samples (8 ml each) were drawn from the subject for control purposes (time 0). They then were administered 80 mg of propranolol hydrochloride (2 × 40 mg tablets) each with a glass of water (250 ml). Blood samples were taken at 1, 1.5, 2, 2.5, 3, 4, 6, 8, and 24 hours after dosing. The subjects were allowed to have breakfast two hours after drug administration. Blood samples were collected in heparinized tubes and centrifuged at 2,500 rpm for five minutes. Then the plasma was separated and frozen at −20°C until the time of sample analysis. The study was a double-blind, randomized and cross-over design.

Plasma propranolol determination was done by modified HPLC method described by Drummer OH.6 To the aliquot portion of the plasma sample (900 μl) was added 100 μl of internal standard labetalol (400 μg/ml) and 100 μl of 20% sodium metabisulfite. The solution was then alkalized by adding 1 ml of 1 M sodium carbonate and extracted by diethyl ether (7 ml). The organic phase was separated by centrifugation and evaporated to dryness in a nitrogen atmosphere. The residue was then dissolved in 0.8 ml of the mobile phase and 50 μl of each sample was injected into the chromatograph.

The high-performance liquid chromatography system consisted of a radial pack cartridge (C18) 8 mm ID plastic column and the radial compression separation system (RCM 100) from Water Associated Pty. Ltd. U.S.A. The absorbance of the eluent was determined using spectrofluorometer (Jasco Model FP210) with the excitation and emission wavelengths at 296 and 340 nm, respectively. The mobile phase was 0.006 M 1 heptane-sulfonic acid sodium salt in 1% glacial acetic acid : methanol 40 : 60. The flow rate was 1.2 ml/min.

The following pharmacokinetic parameters were determined:

\[ C_{\text{max}} \] = peak plasma concentration
\[ T_{\text{max}} \] = time of peak plasma concentration
\[ T_{1/2} \] = half-life
AUC = area under plasma concentration-time curve

\( K_e \) = elimination rate constant

\( K_a \) = absorption rate constant

Mean and standard deviation were used for the in vitro data presentation. Mean and standard error were for the in vivo.

Comparison of each parameter of the four individual products was done by analysis of variance.

Results

In vitro study

The in vitro study demonstrated that the four preparations of propranolol tablet employed in this study (A, B, C, D) fulfilled the requirements of the United States Pharmacopeia XXII. The disintegration time, dissolution rate, propranolol content, the content uniformity and weight variation of each preparation are shown in tables 1 and 2.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Weight variation (x ± SD, n = 10) (mg)</th>
<th>Disintegration time (min, n = 6) (% LA ± SD, n = 10)</th>
<th>Dissolution at 30 min (% LA ± SD, n = 10)</th>
<th>Propranolol content LA ± SD, n = 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>206.18 ± 2.66</td>
<td>6</td>
<td>106.26 ± 2.09</td>
<td>96.57 ± 1.18</td>
</tr>
<tr>
<td>B</td>
<td>190.90 ± 2.08</td>
<td>8</td>
<td>100.48 ± 1.74</td>
<td>96.35 ± 0.93</td>
</tr>
<tr>
<td>C</td>
<td>195.70 ± 3.63</td>
<td>12</td>
<td>105.34 ± 3.13</td>
<td>100.60 ± 0.95</td>
</tr>
<tr>
<td>D</td>
<td>202.74 ± 5.38</td>
<td>20</td>
<td>97.80 ± 2.55</td>
<td>95.37 ± 0.83</td>
</tr>
</tbody>
</table>

\( \% LA = \% \) of labelled amount

Labelled amount = the amount of drug labelled in each tablet

Table 2. The content uniformity study of the four preparations of propranolol tablets. (n = 10).

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>% LA</td>
<td>% LA</td>
<td>% LA</td>
<td>% LA</td>
<td>% LA</td>
</tr>
<tr>
<td>1</td>
<td>96.20</td>
<td>102.80</td>
<td>106.44</td>
<td>99.26</td>
</tr>
<tr>
<td>2</td>
<td>96.20</td>
<td>103.63</td>
<td>104.07</td>
<td>102.96</td>
</tr>
<tr>
<td>3</td>
<td>96.08</td>
<td>106.11</td>
<td>106.38</td>
<td>99.38</td>
</tr>
<tr>
<td>4</td>
<td>92.54</td>
<td>106.70</td>
<td>102.79</td>
<td>97.38</td>
</tr>
<tr>
<td>5</td>
<td>97.38</td>
<td>100.09</td>
<td>107.59</td>
<td>99.38</td>
</tr>
<tr>
<td>6</td>
<td>95.49</td>
<td>101.03</td>
<td>103.95</td>
<td>102.92</td>
</tr>
<tr>
<td>7</td>
<td>100.92</td>
<td>105.76</td>
<td>106.02</td>
<td>99.03</td>
</tr>
<tr>
<td>8</td>
<td>98.91</td>
<td>101.62</td>
<td>113.63</td>
<td>101.27</td>
</tr>
<tr>
<td>9</td>
<td>94.19</td>
<td>101.39</td>
<td>103.28</td>
<td>104.46</td>
</tr>
<tr>
<td>10</td>
<td>96.20</td>
<td>99.85</td>
<td>105.41</td>
<td>99.03</td>
</tr>
<tr>
<td>X</td>
<td>96.42</td>
<td>102.90</td>
<td>105.96</td>
<td>100.28</td>
</tr>
<tr>
<td>SD</td>
<td>± 2.32</td>
<td>± 2.54</td>
<td>± 3.11</td>
<td>± 2.08</td>
</tr>
<tr>
<td>% CV</td>
<td>2.41</td>
<td>2.47</td>
<td>2.94</td>
<td>2.07</td>
</tr>
</tbody>
</table>

\( \% CV = \% \) coefficient of variation.
In vivo study
The bioavailability study of four propranolol preparations

Figure 1 shows the chromatogram of propranolol and labetalol (the internal standard). The retention time for labetalol and propranolol were 4.33 and 6.76 minute respectively. The limit of detection was 10 ng/ml. The precision was high as the mean coefficient of variation was less than 7% and the percentage of recovery of propranolol in the plasma was between 92 and 105%.

![Chromatogram](image)

**Figure 1.** The chromatogram of propranolol and the internal standard (labetalol)

- a. plasma blank with internal standard
- b. propranolol and labetalol in plasma

Figure 2 shows that the mean plasma propranolol concentration and the time profile after oral administration of four propranolol preparations gave quite similar patterns (table 3). The pharmacokinetic parameters, $C_{\text{max}}$, $T_{\text{max}}$, AUC$^{0\rightarrow\infty}$, $K_{a}$, $K_{e}$ and T$_{1/2}$ are demonstrated in table 4.

The mean peak propranolol concentration ($C_{\text{max}}$) of the four preparations of the drug was between 82.34 and 96.96 ng/ml. The mean peak time concentration was between 1.90 and 2.05 hours. By using the trapezoidal rule, it was found that the area under the plasma concentration-time curve from 0 to 24 hours (AUC$^{0\rightarrow\infty}$) was between 429.83 and 557.42 ng.ml$^{-1}$ hr. The elimination half-life (T$_{1/2}$) was between 2.27 and 3.14 hrs.

The absorption rate constant (K$_{a}$) and the elimination rate constant (K$_{e}$) obtained from the computerized CSTRIP program were between 0.98 and 1.10 hr$^{-1}$, 0.23 and 0.32 hr$^{-1}$, respectively. There was no significant difference between the four preparations in all the pharmacokinetic parameters studied.
Table 3. The mean plasma propranolol concentration and time profile after 80 mg oral dose of the four brands propranolol tablet. (mean ± SE) in 10 subjects.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Time (hr)</th>
<th>0</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
<th>2.5</th>
<th>3</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
<td>51.49</td>
<td>64.06</td>
<td>67.26</td>
<td>71.10</td>
<td>65.79</td>
<td>51.77</td>
<td>30.45</td>
<td>20.59</td>
<td>0.73</td>
<td>±12.61 ±10.12 ±11.79 ±19.61 ±15.23 ±11.13 ±5.94 ±4.06 ±0.61</td>
</tr>
<tr>
<td>B</td>
<td></td>
<td>60.86</td>
<td>68.86</td>
<td>74.24</td>
<td>67.98</td>
<td>59.26</td>
<td>48.95</td>
<td>30.31</td>
<td>17.24</td>
<td>1.36</td>
<td>±15.04 ±15.61 ±13.22 ±11.51 ±10.58 ±9.29 ±5.59 ±3.92 ±0.98</td>
</tr>
<tr>
<td>C</td>
<td></td>
<td>44.07</td>
<td>56.62</td>
<td>70.41</td>
<td>70.79</td>
<td>55.21</td>
<td>45.23</td>
<td>26.99</td>
<td>13.15</td>
<td>2.05</td>
<td>±11.12 ±13.34 ±12.19 ±13.46 ±11.38 ±10.80 ±5.85 ±3.36 ±1.27</td>
</tr>
<tr>
<td>D</td>
<td></td>
<td>67.60</td>
<td>72.27</td>
<td>81.38</td>
<td>77.95</td>
<td>66.04</td>
<td>55.26</td>
<td>32.26</td>
<td>19.38</td>
<td>2.45</td>
<td>±19.24 ±18.98 ±16.48 ±16.09 ±12.89 ±11.87 ±6.63 ±4.02 ±1.57</td>
</tr>
</tbody>
</table>

Table 4. The pharmacokinetic profile from 10 subjects following the oral administration of 80 mg propranolol. (mean ± SE).

<table>
<thead>
<tr>
<th>Drugs</th>
<th>$C_{\text{max}}$ (mg/ml)</th>
<th>$T_{\text{max}}$ (min)</th>
<th>$\text{AUC}_{0\rightarrow t}^{24}$ (ng.mL$^{-1}$.hr)</th>
<th>Ka (hr$^{-1}$)</th>
<th>$K_{\text{el}}$ (hr$^{-1}$)</th>
<th>$t_{1/2}$ (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>85.95 ± 15.82</td>
<td>2.05 ± 0.17</td>
<td>495.71 ± 94.22</td>
<td>1.06 ± 0.06</td>
<td>0.23 ± 0.02</td>
<td>3.14 ± 0.20</td>
</tr>
<tr>
<td>B</td>
<td>85.96 ± 19.09</td>
<td>2.00 ± 0.25</td>
<td>510.10 ± 105.10</td>
<td>1.03 ± 0.05</td>
<td>0.27 ± 0.03</td>
<td>2.83 ± 0.38</td>
</tr>
<tr>
<td>C</td>
<td>82.34 ± 12.67</td>
<td>1.90 ± 0.22</td>
<td>429.83 ± 96.30</td>
<td>0.98 ± 0.08</td>
<td>0.32 ± 0.02</td>
<td>2.27 ± 0.21</td>
</tr>
<tr>
<td>D</td>
<td>96.90 ± 17.14</td>
<td>2.00 ± 0.22</td>
<td>557.42 ± 117.85</td>
<td>1.10 ± 0.05</td>
<td>0.28 ± 0.04</td>
<td>2.87 ± 0.40</td>
</tr>
</tbody>
</table>

$X$ ± SE 87.79 ± 8.32 1.99 ± 0.12 498.50 ± 50.39 1.05 ± 0.03 0.28 ± 0.01 2.78 ± 0.16

Figure 2. The mean plasma concentration-time curve from 10 subjects after the oral administration of 80 mg propranolol. (Drug A, B, C, D)
Discussion

The four preparations of propranolol tablets met the specification of the United States Pharmacopeia XXII including the disintegration time which was less than 30 minutes, the dissolution rate in 30 minute was more than 75% of the labelled amount, the content of propranolol was not less than 90% and not more than 110% in each tablet. The content uniformity was in the range 90-110% labelled amount and the weight variation was less than 7.5%. It indicated that the four products of 40 mg propranolol tablets were equivalent in both qualitative and quantitative study in vitro.

The bioavailability study in vivo was considered from the extent and rate of drug absorption into the body. Thus the pharmacokinetic parameters concerned were $T_{\text{max}}$, $C_{\text{max}}$, AUC and Ka.

The maximum plasma drug concentration ($C_{\text{max}}$) represented the highest plasma concentration achieved after drug administration and it also reflected both the rate and extent of drug absorption. The result shown in table 4 indicated that drug A, B, C and D displayed the same rate and extent of propranolol absorption since there was no significant difference in $C_{\text{max}}$ between the four products. The other parameters, $T_{\text{max}}$ which reflected the rate of propranolol absorption into the body and $\text{AUC}_{0}^{\text{m}}$, which determined the extent of the drug absorption also showed no significant difference between each preparations.

On the assumption that the pharmacokinetics of propranolol was one-compartment model, the elimination rate constant ($K_{u}$), and the absorption rate constant ($K_{a}$); then from this study no statistical difference was observed between drugs A, B, C, D. Therefore it could be concluded that the four preparations of propranolol 40 mg tablets were bioequivalent since the extent and rate of drug absorption of each product were equivalent.

Considering of the elimination rate constant ($K_{u}$) of the four preparations in 10 volunteers, it was $0.28 \pm 0.01 \text{ hr}^{-1}$ ($0.23-0.32 \text{ hr}^{-1}$) and the elimination half life was $2.78 \pm 0.16 \text{ hr}$ ($2.27 - 3.14 \text{ hr}$). Since the elimination half life was the time taken for the concentration to halve, its value was inversely proportional to the elimination rate constant ($t_{1/2} = 0.693/K_{u}$). Any drug with a low value of $K_{u}$ will be eliminated more slowly and the elimination half life will be prolonged. The elimination half life of propranolol obtained in this study was found to be a little bit shorter than that reported by Walle et al.\(^{(9)}\) in Europeans whose elimination half life was between 3 and 4 hours. However the elimination half life of propranolol in Indians reported by Biswas NR et al\(^{(10)}\) was $2.41 \pm 0.65 \text{ hr}$ which was quite similar to that of Thai volunteers. This variability resulted from the difference in drug metabolising enzyme which depended on many factors such as genetics, diet, environment\(^{(11,12)}\).

Conclusion

The result of the bioavailability study of four propranolol tablets demonstrated that all drugs were bioequivalent in vivo and all of them met the USP XXI specification for tablets in vitro. The therapeutic effect of the four propranolol tablets should be similar and they may be used instead of each other.

References

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