Absorption of Propranolol in Humans Following Oral, Jejunal, and Ileal Administration

Akshay Buch[1,2,3] and William H. Barr[1]

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INTRODUCTION

Recently, dosage form development has been directed toward longer acting dosage forms which prolong delivery of drug over the entire gastrointestinal tract. In order to evaluate feasibility and optimize the performance of controlled release dosage forms, it is critical to obtain information about regional differences in specialized absorption processes and luminal and mucosal metabolism, and other regionally specific processes (1). The intubation technique provides the capability in humans to compare the absorption characteristics in different regions of the G.I. tract by directly delivering the drugs to the regions of interest (2,3). Compared to the methods that utilize remote controlled drug delivery devices (4), the intubation method is versatile and allows a variety of drug inputs such as bolus or continuous infusion. Moreover, using specialized multi-leumen tubes (e.g. Loc-I-Gut), drug absorption and the permeability determinations from different regions of the intestine could be evaluated (5). Propranolol, a widely used β-blocker, is commonly used as a controlled release product and has been extensively studied due to its significant inter- and intra-subject variability in the absorption and metabolism upon oral administration. The objective of this study was to evaluate differences in absorption and metabolism of propranolol when delivered to proximal and distal intestine in humans.

MATERIALS AND METHODS

Subjects

Seven subjects (3 males and 4 females) completed the clinical portion of this study. The mean age was 31.9 years and the mean body weight was 70.3 kg. All the subjects gave a written consent and were judged as healthy by a pre-study clinical examination. Since fluoroscopic observations were required for the study procedures, the female subjects selected for the study were confirmed hysterctomized. The study protocol was approved by the local Institutional Review Board.

[1] Department of Pharmacy and Pharmaceutics, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia.
[2] Present address: Procter and Gamble Pharmaceuticals, Cincinnati, Ohio.
[3] To whom correspondence should be addressed. (e-mail: buch.ab@pg.com)

Study Design

The study was designed as an open-label, three period crossover design. All the subjects received an aqueous solution containing 80 mg propranolol hydrochloride either as an oral dose or directly through the tube to the proximal and distal small intestine. The dose level (80 mg) and the infusion duration (4 hr) were selected to simulate the controlled release tablet delivery within practical limits.

Oral Dosing

The oral dose was administered as four divided doses (at 0, 1, 2 and 3 hours) each consisting of 20 mg of propranolol hydrochloride as aqueous solution. The subjects fasted overnight (at least 10 hr) prior to receiving the first dose. This "staircase" input function was intended to approximate the zero order intestinal infusion.

Intestinal Infusions

Intestinal doses were delivered through an intestinal tube, as a zero-order infusion over 4 hours. Intubation procedure was carried out on the evening before the first intestinal dose. The tube tip, lubricated with a jelly, was inserted through the nostril. The movement of the tube within the stomach and into the duodenum was monitored by periodic fluoroscopic visualization. The position of the tip of the tube was confirmed prior to dose administration by fluoroscopy, and the tube was externally anchored. The propranolol dose was delivered as 20 mg/hr infusion using a pump. The total volume of fluid for the oral dosing and the intestinal infusions was the same.

At the end of the infusion to the proximal site, the tube was allowed to migrate to the distal site by the peristaltic waves. Just prior to administering the distal dose (24 hr after the proximal dose), the position of the tip of the tube was again verified under fluoroscopy. The propranolol solution was delivered to the distal region by exactly the same procedure as described under the proximal dose. The tube was removed about an hour after the dose to the distal region was delivered.

Sample Collection

A total of 17 blood samples were collected for pharmacokinetic analysis during each treatment period. Each sample (7 mL) was collected in heparinized vacutainer tube, centrifuged and the separated plasma was stored in labeled tubes under frozen condition (−20°C) until analyzed.

Analysis of Propranolol in Plasma Samples

The plasma samples were analyzed for propranolol using a validated HPLC method. Briefly, propranolol and the internal standard were extracted into diethyl ether and then back extracted into an acid The acid phase was injected onto a phenyl column. The mobile phase consisted of 25% acetonitrile in a pH 3.0 buffer The separated analytes were detected by using a fluorescence detector. The calibration curve was linear over 1–50 ng/mL range. During the analysis, the recovery was within 6% and the inter-day variability was less than 10%.

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Analysis of Propranolol Glucuronide

The plasma samples were hydrolyzed with β-glucuronidase enzyme from bacterial origin (Sigma Chemicals, St. Louis, MO), to quantitate total propranolol in the samples. The difference in the propranolol concentration measured before and after the hydrolysis provided the glucuronide content of the samples. During the analysis, the recovery was within 7% and the inter-day variability was less than 12%.

Pharmacokinetic Analysis

Plasma concentration versus time data of propranolol and glucuronide were evaluated by noncompartmental methods. The maximum plasma concentration, Cmax, and time to achieve maximum plasma concentration, Tmax, were the observed values. The terminal elimination rate constant, K, was calculated from the linear regression of the terminal phase of the log concentration-time profile. The terminal elimination half-life, T-HALF, was determined from the relationship: T-HALF = 0.693/K. The area under the plasma concentration versus time curve from 0 to 24 hr, AUC(0–24), was calculated by linear trapezoidal rule, and extrapolated to infinity to obtain AUC(INF).

Statistical Analysis

The pharmacokinetic parameters of propranolol and glucuronide were evaluated using the analysis of variance method suitable for a three period study. The model included terms for subject, treatment and residual error. The bioavailability of propranolol from the proximal and distal intestinal infusions relative to the oral dose was evaluated by constructing 90% confidence intervals for the ratio of the log transformed AUC (INF) for the treatments (6).

RESULTS

Study Conduct and Subject Safety

In general, the subjects tolerated the intubation procedure and dosing of propranolol without any significant adverse events. There were no drug or procedure related dropouts from the study. The dose to the proximal region was administered in the duodenum to proximal jejunum region and the distal dose was administered in the distal ileum (near the ileocecal junction) region.

Pharmacokinetics of Propranolol

The mean plasma concentration-time profiles for propranolol following the three treatments are shown in Figure 1-A, and the pharmacokinetic parameters are listed in Table I. Plasma concentrations from the distal dose were higher than those for proximal and oral doses. The individual subject AUC(INF) following each treatment are shown in Figure 1-B. In most subjects, the distal dose exhibited an increase in AUC compared to the proximal and oral doses.

The mean (±SD) Cmax for propranolol following the dose to the distal region was 73.3 ± 29 ng/mL and was significantly higher than the value following proximal dose 58.4 ± 23 ng/mL and the oral dose, 60.8 ± 33 ng/mL. Similarly, the AUC(INF) for the distal dose (564.5 ± 202 ng.hr/mL) was significantly higher (30%) than that following oral route (433.3 ± 214 ng.hr/mL). There were no significant differences for Tmax and T-HALF values among treatments.

Pharmacokinetics of Glucuronide

The mean plasma levels of propranolol glucuronide following each of the three treatments are shown in Figure 2-A and the mean pharmacokinetic parameters are listed in Table II. There were no significant differences for any of the pharmacokinetic parameters for glucuronide. The individual subject AUC(INF) values for glucuronide for the three treatments are shown in Figure 2-B. Similar to the case for propranolol, there was an increasing trend in the AUC(INF) values for the distal dose, relative to the proximal dose in most subjects.

DISCUSSION

The information on absorption differences in the regions of the G. I. tract would be critical for the success of controlled release formulations. Regional differences in absorption have been reported for drugs such as amoxicillin (7), benazepril (8), ranitidine (9), sumitriptan (10) and danazol (11), and this information has direct relevance in designing controlled release formulations of these drugs. All of the drugs cited above exhibit decreasing availability as they progress down the G.I. tract, in contrast to propranolol which demonstrated an increase in availability from distal regions. Similar increase in availability from the distal dose has also been observed for gepirone in humans (12) and diltiazem in rabbits (13).

Generally, it is believed that because of a large surface area, the proximal intestine has the largest absorptive capacity, and the absorption goes down with transit to the distal regions. This is probably true for low permeability drugs, however, there is also evidence that intestinal metabolism decreases down the small intestinal tract (11,14) which would tend to increase systemic availability of drugs metabolized by the intestine. All subjects in the present study exhibited an increase in propranolol AUC at the distal site (Figure 1-B). The mean bioavailability of the distal dose was 130% of the oral dose. These results are consistent with the results of previous studies that have indicated an increased rate and extent of propranolol absorption from the lower G. I. tract. Taylor et al. (15) found that propranolol was absorbed at a faster rate from dog ileum than from jejunum. In humans, Castleden et al. (16) concluded that propranolol plasma levels were higher and faster from a dose coadministered with a G. I. transit accelerating agent, metoclopramide, compared to a dose with a transit slowing agent, propenthaline. The results of the current study showed no significant differences for elimination T-HALF of propranolol suggesting that there was no difference in the systemic disposition of propranolol from any of the treatments.

Propranolol is a highly metabolized drug. Approximately 40% of the dose is reported to be metabolized by ring hydroxylation to form 4-hydroxy-propranolol, another 35–40% by side-chain oxidation and remaining 20–25% by direct conjugation (17). The formation of the oxidative metabolites is associated with cytochrome P450 family of enzymes including CYP2D6. To examine the possibility that the increased propranolol AUC from the distal dose is due to a reduced metabolism in that

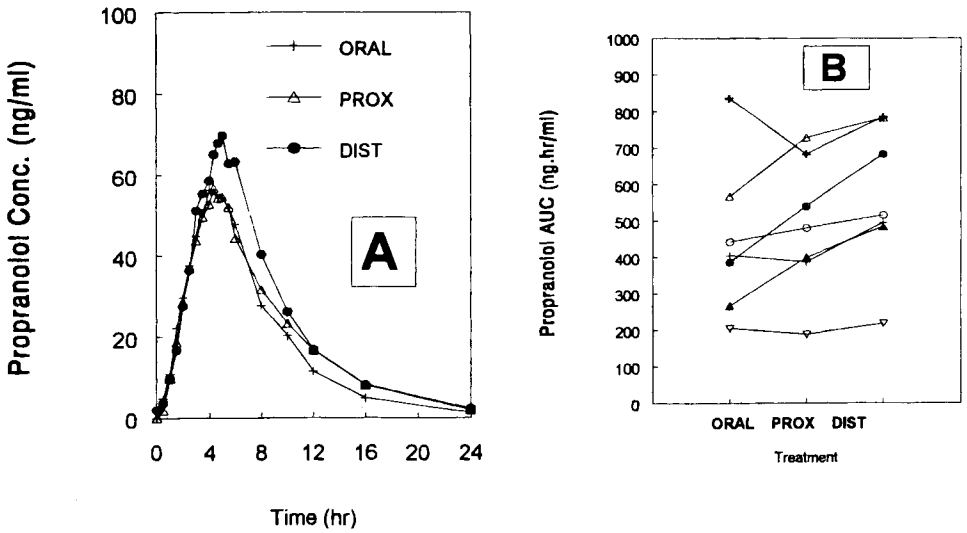

Fig. 1. Mean propranolol plasma concentration time profiles following propranolol doses administered by the oral route and by intestinal infusions to the proximal and the distal regions (Figure 1-A), and the individual subject AUC values for propranolol following the 3 treatments (Figure 1-B).

Table I. Mean (S.D.) Pharmacokinetic Parameters of Propranolol Following Oral Dosing (ORAL), and Intestinal Infusions to the Proximal (PROX) and the Distal (DIST) Regions

Parameter	ORAL	PROX	DIST	Statistical Analysis
Cmax (ng/mL)	60.80 (33.3)	58.42 (23.0)	73.33 (28.9)	DIST > ORAL
Tmax (hr)*	5.0	5.0	4.7	DIST > PROX
AUC(0-24) (ng.hr/mL)	433.30 (213.9)	472.82 (184.0)	549.55 (200.6)	
AUC (INF) (ng.hr/mL)	442.86 (209.5)	485.66 (185.8)	564.50 (201.7)	DIST > ORAL
T-HALF (hr)	3.92 (1.4)	4.39 (0.9)	4.10 (1.0)	DIST > ORAL
REL. BA**	—	1.11 (0.97,1.27)	1.30 (1.13,1.49)	NS[a]

[a] NS - No significant difference ($p > 0.05$).
*Median reported.
**Bioavailability relative to the oral dose. Values reported are point estimate (90% confidence interval).

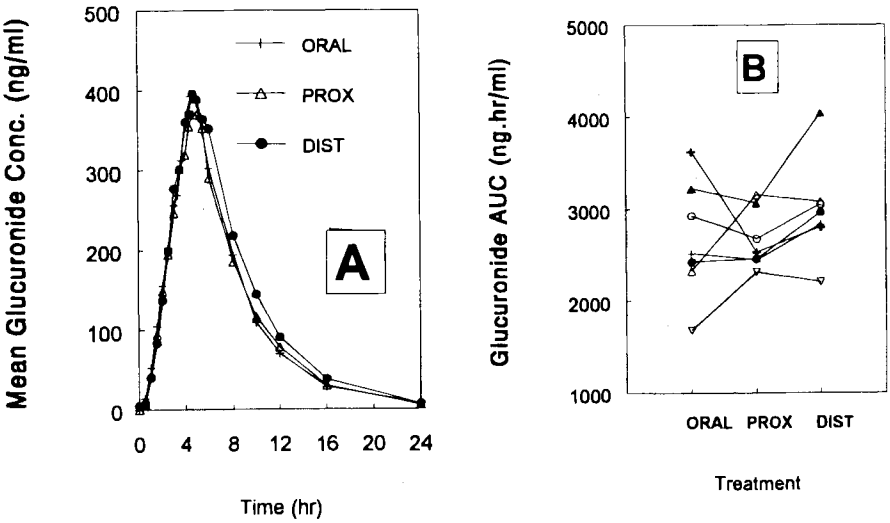

Fig. 2. Mean propranolol glucuronide concentration-time profiles following propranolol dosing by the oral route and infusions to the proximal and distal regions of the intestine (Figure 2-A), and the individual subject AUC data for the 3 treatments (Figure 2-B).

Table II. Mean (±s.d.) of Propranolol Glucuronide Pharmacokinetic Parameters Following Oral Dosing (ORAL), and Intestinal Infusions of Propranolol to the Proximal (PROX) and the Distal (DIST) Regions

Parameter	ORAL	PROX	DIST	Statistical Analysis
Cmax (ng/mL)	409.64 (86.3)	391.72 (48.1)	411.67 (55.4)	NS[a]
Tmax (hr)*	5.0	5.0	5.0	
AUC(0-24) (ng.hr/mL)	2621.29 (604.9)	2631.57 (300.1)	2959.00 (499.8)	NS
AUC (INF) (ng.hr/mL)	2672.08 (639.1)	2658.97 (322.4)	2990.90 (545.3)	NS
T-HALF (hr)	3.49 (1.3)	3.44 (1.1)	3.33 (1.0)	NS

[a] NS - No significant difference ($p > 0.05$).
* Median reported.

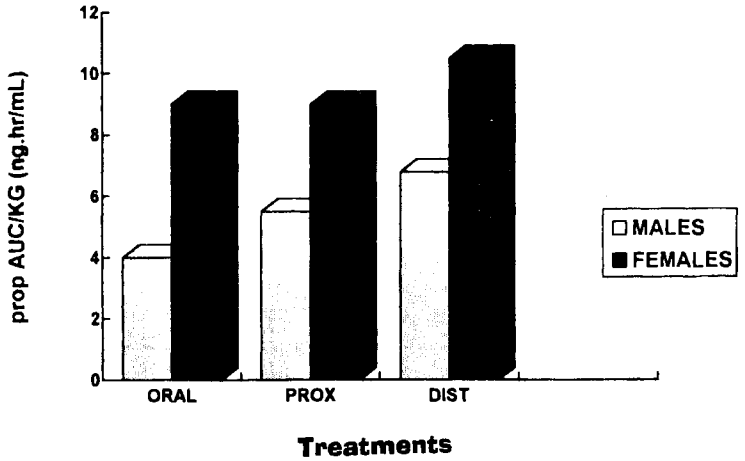

Fig. 3. Mean body weight adjusted AUC of propranolol following the 3 treatments for male (N = 3) and female (N = 4) subjects.

region, we evaluated regional differences in propranolol glucuronidation. Regional differences in intestinal glucuronidation of estrogens have been reported earlier (18). The results of propranolol glucuronide exhibited increasing trends for the distal dose compared to the oral and proximal doses (Figure 2-B) but, the differences were not statistically significant. Also, the ratio of the glucuronide AUC to propranolol AUC either remained similar or showed an increase for the distal dose in 6 out of 7 subjects (data not shown). This indicated that the increased AUC of propranolol from the distal dose was not as a result of compromised metabolism to the glucuronide pathway. This is consistent with the results of Du Souich et al. (19) that propranolol glucuronide is hepatic rather than intestinal in origin. Several other metabolites of propranolol have been identified which were not evaluated here. It is quite possible that other metabolic pathways may be involved, particularly those that involve CYP2D6, that account for the observed regional differences in propranolol bioavailability. It has been shown that CYP2D6 is present in human intestine and its content decreases from the proximal to the distal intestine (20).

Figure 3 shows the values of AUC(INF) corrected for body weight for the 4 females and 3 male subjects. The mean values for the females were about 50% higher than men for each of the 3 treatments. Due to a small number of subjects in each gender category, additional statistical analyses were not carried out.

The results of the present study has direct implications in the design of controlled release propranolol formulations. The results showed good propranolol absorption from both the proximal and distal doses, indicating that the dosage forms releasing the drug over an extended period would be suitable. While a 30% difference in the bioavailability between distal and oral dose may not have great clinical significance, it could significantly increase the variability in bioavailability studies with propranolol formulations, making bioequivalence determination more difficult. The greater variability of the oral administration compared to the proximal or distal dose is probably due to differences in the transit times and provides a source of intra-subject variability. The differences between men and women represents a potential source for inter-subject variability and should be further evaluated in a larger group with emphasis on reasons for the observed differences.

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REFERENCES

1. J. T. Fell and G. A. Digenis. Imaging and behaviour of oral dosage forms in vivo. *Int. J. Pharm.* **22**:1–15 (1984).
2. G. Jobin, A. Corot, J. Godbillon, M. Duval, J. P. Schoeller, J.

Hirtz, and J. J. Bernier. Investigation of drug absorption from the gastrointestinal tract of man. I. Metoprolol in stomach, duodenum and jejunum. *Br. J. Clin. Pharmacol.* **19**:97S–105S (1985).
3. N. Vidon, D. Evard, J. Godbillon, M. Rongier, M. Duval, J. P. Schoeller, J. J. Bernier, and J. Hirtz. Investigation of drug absorption from the gastrointestinal tract of man. II. Metoprolol in the jejunum and ileum. *Br. J. Clin. Pharmacol.* **19**:107S–112S (1985).
4. D. Gardner, R. Casper, F. Leith, and I. Wilding. Noninvasive methodology for assessing regional drug absorption from the gastrointestinal tract. *Pharm. Technol.* **21**:82–89 (1997).
5. H. Leneernas, O. Ahrenstedt, R. Hallgren, L. Knutson, M. Ryde, and L. K. Paalzow. Regional jejunal perfusion, a new in vivo approach to study oral drug absorption in man. *Pharm. Res.* **10**:1243–1251 (1992).
6. D. J. Schuirmann. A comparison of the two one-sided tests procedure and the power approach for assessing equivalence of average bioavailability. *J. Pharmacokinetic Biopharm.* **6**:657–680 (1987).
7. W. H. Barr, E. M. Zola, E. L. Candler, S-M. Hwang, A. V. Tendolkar, R. Shamburek, B. Parker, and M. Hilty. Differential absorption of amoxicillin from the human small and large intestine. *Clin. Pharm. Ther.* **56**:279–285 (1994).
8. K. K. H. Chan, A. B. Buch, R. D. Glazer, V. A. John, and W. H. Barr; Site-differential gastrointestinal absorption of benazepril hydrochloride in healthy volunteers. *Pharm. Res.* **11**:432–437 (1994).
9. M. F. Williams, G. E. Dukes, W. Heizer, Y.-H. Han, D. J. Hermann, T. Lampkin, and L. J. Hak. Influence of gastrointestinal site of drug delivery on the absorption characteristics of ranitidine. *Pharm. Res.* **9**:1190–1196 (1992).
10. P. E. Warner, K. L. R. Brouwer, E. K. Hussey, G. E. Dukes, W. D. Heizer, K. H. Donn, I. M. Davis, and J. R. Powell. Sumitriptan absorption from different regions of the human gastrointestinal tract. *Pharm. Res.* **12**:138–143 (1995).
11. W. N. Charman, M. C. Rogge, A. W. Boddy, W. H. Barr, and B. M. Berger. Absorption of danazol after administration to different sites of the gastrointestinal tract and the relationship to single- and double-peak phenomena in the plasma profiles. *J. Clin. Pharmacol.* **33**:1207–1213 (1993).
12. L. K. Tay, F. Dixon, Jr., M. B. Sostrin, W. H. Barr, R. H. Farmen, and K. A. Pittman. The site differential gastrointestinal absorption of gepirone in humans. *J. Clin. Pharmacol.* **32**:827–832 (1992).
13. W. Homsy, G. Caille, and P du Souich. The site of absorption in the small intestine determines diltiazem bioavailability in the rabbit. *Pharm. Res.* **12**:1722–1726 (1995).
14. W. H. Barr. The role of intestinal metabolism on bioavailability. In P. G. Welling, F. L. S. Tse, and S. V. Dighe (eds). *Pharmaceutical Bioequivalence*, Marcel Dekker, New York, 1991, pp. 149–168.
15. D. C. Taylor, R. Grundy, and B. Loveday. Chronic dog intestinal loop model for studying drug absorption as exemplified by beta-adrenoreceptor blocking agents, atenolol and propranolol. *J. Pharm. Sci.* **70**:516–521 (1981).
16. C. M. Castleden, C. F. George, and M. D. Short. Contribution of individual differences in gastric emptying to variability in plasma propranolol concentrations. *Br. J. Clin. Pharmacol.* **5**:121–122 (1978).
17. T. Walle, U. K. Walle, and L. S. Olanoff. Quantitative account of propranolol metabolism in urine of normal man. *Drug Metab. Disp.* **13**:204–209 (1985).
18. E. Diczfalusy, C. Franksson, and B. Martinsen. Oestrogen conjugation by the human intestinal tract. *Acta Endocrin.* **38**:59–72 (1961).
19. P. Du Souich, H. Maurice, and L. Heroux. Contribution of the small intestine to the first-pass uptake and systemic clearance of propranolol in rabbits. *Drug Metab. Disp.* **23**:279–284 (1995).
20. D. R. Krishna and U. Klotz. Extrahepatic metabolism of drugs in humans. *Clin. Pharmacokinet.* **26**:144–160 (1994).