Clinical Pharmacokinetics and Relative Bioavailability of Oral Procaterol

Michael A. Eldon,[1,4] Michele M. Battle,[2] Michael J. Coon,[2] Gerald D. Nordblom,[2] Allen J. Sedman,[1] and Wayne A. Colburn[2,3]

Received June 4, 1992; accepted October 5, 1992

The pharmacokinetics and relative oral bioavailability of procaterol, an orally active β_2-adrenergic agonist bronchodilator were evaluated in healthy volunteers. Procaterol was rapidly absorbed after oral administration. Mean plasma procaterol concentration–time profiles and pharmacokinetic parameters for both formulations were essentially superimposable. Following tablet administration, the mean C_{max} was 358 pg/mL and the corresponding mean t_{max} was 1.6 hr. Mean renal clearance was 163 mL/min and accounted for approximately one-sixth of the mean apparent oral plasma clearance (988 mL/min). The mean apparent elimination half-life of procaterol was 4.2 hr. Hepatic metabolism appears to be the primary mechanism for elimination of procaterol from the body, and first-pass metabolism may limit systemic bioavailability.

KEY WORDS: procaterol; bronchodilator; healthy volunteers; pharmacokinetics; bioavailability.

INTRODUCTION

Procaterol hydrochloride (Pro-Air, Parke-Davis), (±)-(R*, S*)-8-hydroxy-5-[1-hydroxy-2-[(1-methylethyl)amino]-butyl]-2(1H)-quinolinone monohydrochloride hemihydrate, is an orally effective selective β_2-adrenergic receptor agonist. Procaterol has potent bronchodilating action at microgram doses, a rapid onset and long duration of action, and a higher selectivity for bronchial smooth muscle than for cardiovascular muscle (1–4). Bronchodilating effects of procaterol appear to be exerted by increasing intracellular cyclic AMP as a result of β-receptor stimulation of adenyl cyclase in bronchial cells, thereby mediating smooth muscle relaxation (5,6). The relatively long-lasting bronchodilation seen with procaterol, as compared to that of isoproterenol and albuterol, is due primarily to persistent elevation of cyclic AMP (7). In large, double-blind comparative studies, procaterol was found to be an effective, well-tolerated, long-acting, oral bronchodilator suitable for the treatment of reversible bronchospastic disease (8,9).

Since procaterol is efficacious at microgram doses, concentrations of drug in plasma and urine are low relative to those of less potent β_2-adrenergic agonists such as albuterol, metaproterenol, and terbutaline. In a previous study of procaterol disposition in humans, ^{3}H-procaterol was used to quantify drug in plasma and urine. Recently, specific and sensitive radioimmunoassay methods capable of detecting picomolar amounts of procaterol in plasma and urine were developed. The purpose of this study was to assess the pharmacokinetics of procaterol in healthy subjects and to compare the bioavailability of procaterol tablets and solution after administration of single 100-μg doses.

METHODS

Subjects. Eighteen healthy volunteers participated in the study conducted at the Parke-Davis Community Research Clinic, Ann Arbor, Michigan. All subjects were healthy as determined by medical history, clinical laboratory profiles, and physical examinations. Mean (range) weight, age, and height for the subjects were 72.0 kg (55.6 to 100.7 kg), 31 years (20 to 46 years), and 174 cm (159 to 187 cm), respectively. The protocol was approved by the Community Research Clinic Institutional Review Board and subjects provided informed consent.

Protocol. The study used a single-dose, nonblinded, randomized, two-way crossover design. Subjects received two oral 100-μg procaterol doses administered as 20 mL of a 5 μg/mL solution (Pro-Air Syrup, Parke-Davis, Lot CI-144065) and a 100-μg tablet (Pro-Air commercial tablets, Parke-Davis, Lot CI-144065), with a 1-week washout separating the doses. All doses were administered with 8 oz of water after a 10-hr overnight fast, and subjects continued fasting for an additional 4 hr after dosing.

Blood samples (5 mL) were drawn into heparinized tubes before dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 14, and 16 hr after dosing. Plasma was harvested and stored frozen until assayed for procaterol. Urine was collected prior to dosing and quantitatively during the intervals 0–2, 2–4, 4–6, 6–8, 8–10, 10–12, 12–16, 16–24, 24–36, and 36–48 hr postdose. Total urine voided was measured for each collection period and a 20-mL aliquot was stored frozen until assayed for procaterol.

Sample Analysis. Procaterol in plasma and urine was assayed using sensitive, specific, and validated radioimmunoassays (10). Plasma (100-μl) and urine (10-μl) samples were incubated with fixed amounts of antibody and ^{125}I-labeled procaterol. The antibody bound fraction was precipitated with sheep anti-rabbit immunoglobulin antibody and counted in a gamma counter. In plasma, cross-reactivities of the three major procaterol metabolites, procaterol glucuronide, *N*-desisopropyl procaterol, and 5-formyl-8-hydroxycarbostyril, were 0.46% or less. Logit-log standard curves in plasma were linear over the calibration range of 15 pg/mL to 2 ng/mL. The lower limit of quantitation for procaterol in plasma was 15 pg/mL and values below this concentration were reported as zero. Precision of plasma control standards (N = 8 at each of four concentrations) assayed during sample analysis range from 10.1 to 24.9% and accuracy ranged from −1.8 to 6.0% of procaterol concentrations determined during validation. In urine, cross-reactivities of the procaterol metabolites described above were 0.029% or less. Logit-log standard curves in urine were linear over the calibration range of 800 pg/mL to 50 ng/mL. The lower limit of

[1] Clinical Pharmacology Department, Parke-Davis Pharmaceutical Research Division, Warner-Lambert Co., 2800 Plymouth Road, Ann Arbor, Michigan 48105.

[2] Pharmacokinetics/Drug Metabolism Department, Parke-Davis Pharmaceutical Research Division, Warner-Lambert Co., 2800 Plymouth Road, Ann Arbor, Michigan 48105.

[3] Current address: Harris Clinical Development, 7432 East Stetson Drive, Scottsdale, Arizona 85251.

[4] To whom correspondence should be addressed.

0724-8741/93/0400-0603$07.00/0

quantitation for procaterol in urine was 800 pg/mL and values below this concentration were reported as zero. Precision of urine quality control standards ($N = 8$ at each of four concentrations) assayed during sample analysis ranged from 11.4 to 21.7% and accuracy ranged from −5.7 to 18.0% of theoretical procaterol concentrations.

Data Analysis. Noncompartmental pharmacokinetic parameters were calculated from plasma procaterol concentration–time data using established methods (11) (see Table I for parameter definitions). The cumulative amount of procaterol excreted unchanged in urine (A_e), expressed as percentage of dose (A_e%), was determined from urine drug concentration and urine volume data. Apparent plasma clearance (Cl/F) was calculated as Dose/AUC(0–∞). Renal clearance (Cl_r) was calculated as A_e/AUC(0–∞). Nonrenal clearance (Cl_{nr}) was obtained as the difference between apparent plasma clearance and renal clearance.

The terminal phase of drug disposition was not determined for Subject 16 after the solution treatment because of a lack of data in the latter portion of the plasma concentration-time profile. Subjects 17 and 18 did not receive the tablet treatment. Subject 17 withdrew from the study for personal reasons, whereas Subject 18 was unable to complete the trial due to a viral illness. Data from these subjects for completed treatments were included in the statistical analyses, requiring use of statistical methods for unbalanced data.

Procaterol pharmacokinetic parameters and urinary excretion parameters were analyzed using an analysis of variance (ANOVA) model with sequence, subject (within sequence), period, and treatment main effects to evaluate the statistical significance of differences between treatment means. To assess the pharmacokinetic performance of the tablets relative to the solution, 90% confidence intervals for the differences between treatment mean C_{max} and AUC values were calculated and expressed as a percentage of the solution mean values (12).

Table I. Mean Procaterol Pharmacokinetic Parameters Following Administration of Single 100-μg Oral Doses of Procaterol as a Solution and as a Tablet to 18 Healthy Subjects

Pharmacokinetic Parameter	Treatment mean[a] (%RSD)	
	Tablet	Solution
C_{max}	358 (38.8)	368 (47.0)
t_{max}	1.6 (30.9)	1.7 (51.1)
AUC(0–16)	1780 (39.2)	1800 (35.0)
AUC(0–∞)	1960 (37.3)	1980 (31.7)
λ_z	0.23 (48.0)	0.19 (40.0)
$t_{1/2}$	4.2 (78.5)	4.3 (50.1)
Cl/F	988 (43.5)	922 (31.5)
Cl_r	163 (34.7)	169 (33.0)
Cl_{nr}	825 (48.7)	753 (36.3)
A_e%	17.9 (31.4)	19.3 (39.2)

[a] Mean of 17 observations for solution treatment and 16 observations for tablet treatment. %RSD, relative standard deviation expressed as percentage of mean; C_{max}, maximum observed plasma concentration (pg/mL); t_{max}, time of C_{max} (hr); AUC(0–16), area under the plasma concentration–time curve from time 0 to 16 hr (pg·hr/mL); AUC(0–∞), area under the plasma concentration–time curve from time 0 to infinity (pg·hr/mL); λ_z, apparent elimination rate constant (hr^{-1}); $t_{1/2}$, apparent elimination half-life (hr); Cl/F, apparent plasma clearance (mL/min); Cl_r, renal clearance (mL/min); Cl_{nr}, nonrenal clearance (mL/min); A_e%, percentage of dose excreted in urine as unchanged procaterol.

RESULTS AND DISCUSSION

Mean plasma procaterol concentration–time profiles following administration of tablets and solution were comparable (Fig. 1). Procaterol was rapidly absorbed after administration of both formulations as indicted by mean t_{max} values of 1.6 and 1.7 hr for the tablets and solution, respectively. Inspection of individual subject data showed that after reaching a peak, concentrations declined with time in a monoexponential fashion. Mean $t_{1/2}$ values were 4.2 and 4.3 hr for the tablet and solution, respectively. Although variation in plasma concentration–time profiles and pharmacokinetic parameters was evident among subjects (see %RSD values, Table I), data were generally comparable between formulations within a given subject.

Mean C_{max} and AUC values were comparable for both formulations (Table I) indicating that drug absorption following tablet administration was rapid and complete relative to that of solution. No statistically significant differences were found between the tablet and solution dosage forms for any pharmacokinetic parameter. Confidence intervals (90%) for between-formulation differences in C_{max} and AUC(0–∞) relative to solution mean values were 82.8 to 115 and 85.2 to 110.9%, respectively, demonstrating that the rate and extent of procaterol absorption are equivalent for both formulations.

Approximately 70% of an oral procaterol dose is absorbed after administration to rats and beagle dogs, but first-pass metabolism results in a systemic bioavailability of approximately 10 to 30% (13,14). Following administration of a 100-μg oral dose of ^{3}H-procaterol to humans, 70% of the dose was excreted in urine (20% unchanged) and 24% of the dose was recovered in feces (21% unchanged) within 24 hr postdose (unpublished data). These findings, in conjunction with the results of the present study (Table I), indicate that procaterol is reasonably well absorbed, rapidly eliminated from the systemic circulation, extensively metabolized, and probably subject to first-pass metabolism. The high mean values for apparent plasma clearance (988 mL/min) and nonrenal clearance (825 mL/min) after tablet administration support the concept that the systemic bioavailability of procaterol is limited by first-pass metabolism.

Procaterol undergoes extensive conjugative and oxidative metabolism in humans, with the glucuronide conjugate being the major metabolite formed (15). Desisopropylprocaterol, 5-formyl-8-hydroxycarbostyril, and, to a lesser extent, 8-hydroxycarbostyril are also formed. None of these metabolites are significantly active as β-adrenergic agonists (16,17). The metabolic pattern in humans is qualitatively similar to those of laboratory animals, which show evidence of extensive absorption from the intestine, first-pass metabolism, biliary excretion of procaterol and metabolites, and enterohepatic recycling of procaterol (13–15). In summary, absorption of procaterol is rapid after oral administration of tablets or solution, first-pass metabolism may limit systemic bioavailability, and hepatic metabolism appears to be the primary mechanism for elimination of procaterol from the body.

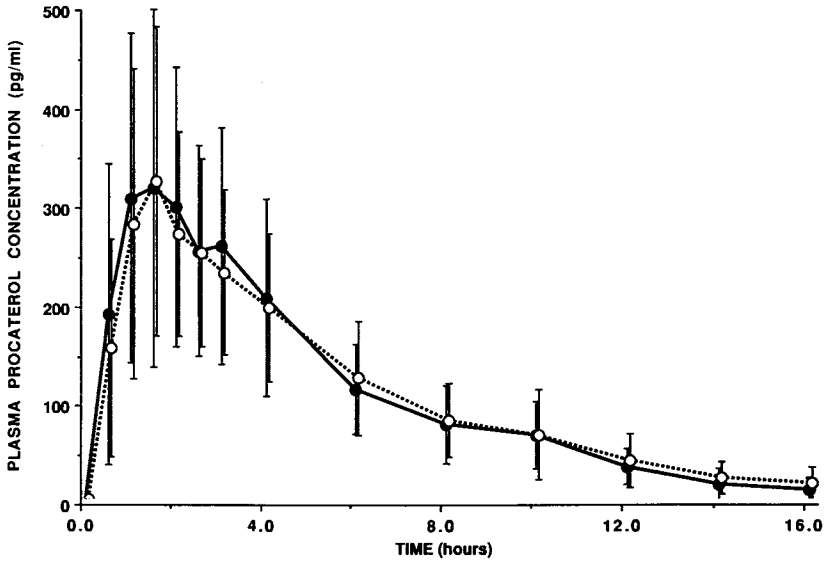

Fig. 1. Mean (±SD) plasma procaterol concentration–time profiles following administration of single 100-μg oral doses of procaterol as a solution (○) and as a tablet (●) to healthy subjects.

ACKNOWLEDGMENTS

The authors thank the staff of the Parke-Davis Community Research Clinic for conducting the clinical component of the study. Expert analytical assistance was provided by Ms. Debbie S. Blake. Dr. P. Klockowski, and Oneida Research Services are acknowledged for their contribution to the preparation of the manuscript. This material was presented in part at the 89th Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics, March 1988.

REFERENCES

1. T. Yagura and Y. Yamamura. A new selective beta-receptor stimulant, OPC-2009 (procaterol): Its bronchodilator potency and characteristics in asthmatic patients. *Curr. Ther.* 10:1499–1507 (1978).
2. A. Hamada, T. Shida, K. Ito, T. Yagura, and Y. Yamamura. Bronchodilatory effects of single dose procaterol (OPC-2009) tablets—multicenter study at 29 institutions. *Curr. Ther.* 11: 225–236 (1979).
3. Y. Wagatsuma, K. Togashi, and A. Umezu. Therapeutic effect of procaterol by dose frequency in a repetitive dose study. *Basic Pharmacol. Ther.* 8:3857–3862 (1980).
4. C. L. Zanetti, H. H. Rotman, and A. J. Dresner. Efficacy and duration of action of procaterol, a new bronchodilator. *J. Clin. Pharmacol.* 22:250–253 (1982).
5. H. Hashimoto, S. Shintani, S. Tei, M. Takai, M. Tsutsui, K. Kaawamura, T. Ohkawa, T. Hiyama, and Y. Yabuuchi. Pharmacological properties of procaterol hydrochloride, a newly synthesized, specific β_2-adrenoceptor stimulant. I. Effects on the central nervous system. *Folia Pharmacol. Jpn.* 75:271–289 (1979).
6. K. Hashimoto, S. Shintani, S. Tei, *et al.* Pharmacological properties of procaterol, a newly synthesized β-adrenoceptor specific stimulant. II. Effects on peripheral organs. *Folia Pharmacol. Jpn.* 75:333–364 (1979).
7. T. Inamizu, M. Yamakido, K. Ohnari, T. Ikuta, and Y. Nishimoto. Assessment of therapeutic effect of procaterol (OPC-2009) based on biochemical changes: a comparison with salbutamol. *Clin. Med.* 20:2243–2253 (1978).
8. S. C. Siegel, R. M. Katz, G. S. Rachelefsky, M. L. Brandon, and L. A. Borgen. A placebo-controlled trial of procaterol: A new long-acting oral beta$_2$-agonist in bronchial asthma. *J. Allergy Clin. Immunol.* 75:698–705 (1985).
9. R. P. Baughman and R. G. Loudon. The utility of a long-acting sympathomimetic agent, procaterol, for nocturnal asthma. *Chest* 93:285–288 (1988).
10. G. D. Nordblom, M. J. Coon, M. J. Suto, T. Chang, L. A. Pachla, and W. A. Colburn. Development of Radioimmunoassays for the measurement of the specific bronchodilator procaterol in human plasma and urine. *J. Clin. Immunoassay* 15:258–264 (1992).
11. M. Gibaldi. *Biopharmaceutics and Clinical Pharmacokinetics,* 3rd ed., Lea and Febiger, Philadelphia, 1984, pp. 17–28.
12. D. J. Schuirmann. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. *J. Pharmacokin. Biopharm.* 15:657–680 (1987).
13. Y. Yasuda, N. Fujisawa, S. Morita, and H. Kohri. Metabolic fate of a new β_2-adrenergic stimulant procaterol (OPC-2009). *Arzneim-Forsch/Drug Res.* 29:261–265 (1979).
14. M. Ishigami, K. Saburomaru, K. Niino, M. Kido, S. Morita, G. Miyamoto, and H. Kohri. Pharmacokinetics of procaterol in the rat, rabbit, and beagle dog. *Arzneim-Forsch/Drug Res.* 29:266–270 (1979).
15. T. Shimizu, H. Mori, E. Tabusa, and K. Nakagawa. The metabolites of procaterol HCl in urine and feces of dog and man. *Xenobiotica* 8:705–710 (1978).
16. M. Takai, S. Yamashita, S. Tei, K. Kawamura, and Y. Yabuuchi. β-Adrenergic stimulant properties of procaterol hydrochloride (OPC-2009) metabolites in various organs of guinea pigs, dogs, and cats. *Pharmacometrics* 17:345–354 (1979).
17. S. Shintani, M. Takai, S. Yamashita, K. Kawamura, M. Tsutsui, Y. Saitoh, T. Hiyama, and Y. Yabuuchi. Pharmacological properties of metabolites of procaterol hydrochloride (OPC-2009). *Pharmacometrics* 17:639–661 (1979).