Solid Dispersions of Testosterone with Reduced Presystemic Inactivation

ALMAS BABAR and C. I. JAROWSKI ×

Received April 1, 1982, from *St. John's University, College of Pharmacy & Allied Professions, Jamaica, NY, 11439.* Accepted for publication June 10, 1982.

Abstract □ Dissolution rates of solid dispersions of testosterone in various lipids or polyethylene glycol 6000 with and without surfactants were determined. In a limited study, selected dispersions were evaluated for oral absorption efficiency in a 32-year-old male. Significant reductions in urinary testosterone metabolites to testosterone ratios were observed with a 1:4 weight ratio of testosterone–polyethylene glycol 6000 and a 1:4:0.25 weight ratio of testosterone–cholesteryl stearate–sorbitan monolaurate.

Keyphrases □ Testosterone—solid dispersions with reduced presystemic inactivation, dissolution, absorption efficiency □ Dissolution—solid dispersions of testosterone with reduced presystemic inactivation, absorption efficiency □ Presystemic inactivation—reduced, solid dispersions of testosterone, absorption efficiency □ Absorption—efficiency, solid dispersions of testosterone with reduced presystemic inactivation

Solid dispersions and eutectic mixtures of drugs with inert carriers such as urea and succinic acid have been used to enhance the rate of dissolution and oral absorption of therapeutic agents poorly soluble in water (1). Previous work (2, 3) has dealt with the *in vitro* dissolution characteristics of such systems. In *in vivo* studies griseofulvin dispersions in polyethylene glycol 6000 were found (4) to be completely and rapidly absorbed after oral administration to humans, and a morphine–tristearin dispersion in a weight ratio of 1:1 exhibited reduced presystemic inactivation in rats (5).

When testosterone therapy is indicated, parenteral administration is preferred, since oral administration is inefficient due to presystemic inactivation (6). Hepatic enzymes were predominantly responsible for the chemical modification of testosterone. It has been reported that twice as much testosterone (I) was required to match the androgenic effect of methyl testosterone when administered sublingually (7). It was recently demonstrated (8) that clinical efficacy upon oral administration required 400-mg doses of I.

The purpose of this investigation was to study the oral absorption efficiency of I from various solid dispersions. The dissolution rates of the dispersions were evaluated *in vitro*, and selected dispersions were chosen for evaluation *in vivo*. The urinary recovery of I and its principal metabolites was used as a measure of oral absorption efficiency in a 32-year-old male.

EXPERIMENTAL

Materials—The following were obtained from commercial sources: I (NF grade)[1], polyoxyethylene (20) sorbitan monooleate (II)[2], sorbitan monolaurate (III)[2], sodium cholate (IV)[3], sodium deoxycholate (V)[3], β-sitosterol (VI)[3], cholesteryl stearate (VII)[3], lactose (VIII)[3], cholesterol (IX)[4], polyethylene glycol 6000 (X)[5], chloroform[6], hydrochloric acid[6], β-glucuronidase (beef liver)[7], androsterone (XI)[8], etiocholanolone (XII)[8], and tripalmitin (XIII)[8].

Equipment—The following equipment was used: spectrophotometer[9], thermal analyzer with differential scanning colorimeter[10], USP dissolution apparatus with basket assembly[11], and a GC equipped with an electronic integrator[12].

Preparation of Solid Dispersions—Micronized I and various surfactants were weighed in ratios of 1:0.05. The mixtures were dissolved in 50 ml of chloroform. The solvent was evaporated in a stream of air while the solution was stirred with a magnetic stirrer. The residue was dried in a vacuum oven at 40°, ground in a mortar, and then passed through an 80-mesh screen. After blending to ensure homogeneity, aliquots were assayed. Only samples assaying 100 ± 5% of I were used in the dissolution and absorption studies. Dispersions containing I–lipid in weight ratios of 1:4, 1:6, and 1:8 as well as I–lipid–surfactants in weight ratios of 1:4:0.05 were prepared in a similar fashion. Polyethylene glycol 6000 dispersions also used chloroform. The I–lipid–lactose dispersions in weight ratios of 1:4:4 were prepared by evaporating the chloroform in the presence of lactose.

Dissolution Studies—The dissolution rates of I and its dispersions were conducted in simulated gastric fluid, without pepsin, by the procedure described in the USP (9). Simulated gastric fluid (900 ml) was placed in a 1-liter beaker and maintained at 37 ±0.5° in a constant-temperature bath. A sintered-glass immersion filter (medium porosity) was placed in a medium for aliquot withdrawals. The basket was lowered to 1 cm above the bottom of the beaker and rotated at 300 rpm. Accurately weighed samples equivalent to 20 mg of I were spread over the surface of the medium. Any aggregates that formed at this stage were submerged by a microspatula within 10 sec after sample addition. Five-milliliter aliquots were removed at intervals of 15, 30, 45, 60, 90, and 120 min using a 5-ml pipet. A constant volume of dissolution medium was maintained by additions of preheated medium. The filtered aliquots were passed through a micropore filter (0.45-μm) and read directly for their absorbance at 248 nm. A cumulative correction was made for the previously removed samples to determine the total quantity of I that had dissolved (10). Sink conditions were maintained, since the solubility of I was determined to be 44 mg/900 ml.

Assay Procedure for Testosterone—Plots of absorbance *versus* wavelength for solutions of I in water, simulated gastric fluid, and methanol were developed. The maximum absorbance values observed were 248 nm for water and simulated gastric fluid and 244 for methanolic solutions of I. Beer's law was followed for 1–20-μg/ml concentrations. The stability of I in simulated gastric fluid was determined. After 24 hr at 37° no potency change was noted.

Assay of Urinary Testosterone and its Metabolites—Selected test samples were evaluated in a healthy, adult male, 32 years of age. Each sample was tested on at least three occasions. The subject was administered an equivalent of 50 mg of I in a hard gelatin capsule after an overnight fast, with 240 ml of water. Food was avoided for at least 2 hr. Urine samples were collected for 24 hr, pooled, and frozen until assayed. One week or more was allowed to elapse between oral dosings. Free I and XI and XII were determined by a modification of published procedures (11, 12). Essentially, the derivatization step was eliminated since adequate quantities of I, XI, and XII were present. In addition, the GC procedure was altered to afford more efficient separation of the components. Details of the assay procedure will be presented in a separate publication.

RESULTS AND DISCUSSION

Dissolution Rate Studies—Only 54.6% of I had dissolved after 2 hr

[1] Roussel Corporation, New York, N.Y.
[2] ICI, Atlas Chemical Corp., Wilmington, Del.
[3] Aldrich Chemical Co., Milwaukee, Wis.
[4] Croda Inc., New York, N.Y.
[5] Union Carbide, Tarrytown, N.Y.
[6] Fisher Scientific Co., Springfield, N.J.
[7] Worthington Biochemicals Inc., Freehold, N.J.
[8] Pfaltz and Bauer, Inc., Stamford, Conn.
[9] Model 25, Beckman Instruments Inc., Mountainside, N.J.
[10] Model 990, E.I. DuPont, Instrument Division, Wilmington, Del.
[11] Hanson Research Corp., Northridge, Calif.
[12] Model 5840-A, Hewlett-Packard Co., Avondale, Pa.

0022-3549/83/0600-0708$01.00/0

Table I—Dissolution Rate of Testosterone Dispersions in Simulated Gastric Fluid at 37°

Sample	Weight Ratio	Percent Dissolved (Min) 15	30	45	60	90	120
I		4.3	11.3	25.3	37.7	45.6	54.6
I-II	1:0.05	4.0	24.6	36.0	54.3	56.3	66.7
I-III	1:0.05	5.0	27.0	42.6	50.6	58.7	67.0
I-IV	1:0.05	4.3	14.6	23.3	34.3	44.6	50.3
I-V	1:0.05	2.0	8.3	16.0	26.0	34.6	44.3
I-IX	1:4	3.0	8.7	14.3	19.6	24.0	30.6
I-IX	1:6	3.3	7.0	8.6	10.6	16.3	21.6
I-IX	1:8	2.3	6.3	13.0	16.0	20.6	25.6
I-VI	1:4	1.0	6.6	13.6	17.0	20.0	21.6
I-VI	1:6	2.6	4.3	4.6	6.3	7.0	7.3
I-VI	1:8	0.3	2.0	3.6	5.0	5.6	6.3
I-VII	1:4	1.0	14.0	17.6	21.0	24.6	31.0
I-VII	1:6	2.6	8.6	17.3	23.6	31.3	39.0
I-VII	1:8	1.3	9.6	21.6	26.0	20.6	35.0
I-XIII	1:4	3.6	8.6	11.3	15.3	19.0	24.3
I-XIII	1:6	3.0	6.0	8.6	10.0	12.0	16.0
I-XIII	1:8	2.3	6.0	7.3	12.0	15.6	18.3
I-IX-II	1:4:0.25	8.0	25.6	38.3	45.0	49.0	58.6
I-IX-III	1:4:0.25	3.3	14.0	22.0	28.0	31.3	38.6
I-IX-IV	1:4:0.25	6.3	13.0	19.0	25.3	27.3	36.0
I-IX-V	1:4:0.25	3.6	15.0	20.6	21.6	26.3	31.3
I-VI-II	1:4:0.25	2.0	29.0	38.0	42.0	43.0	48.6
I-VI-III	1:4:0.25	4.0	9.6	11.6	16.0	19.0	22.3
I-VI-IV	1:4:0.25	0.6	9.0	17.3	25.6	34.6	43.3
I-VI-V	1:4:0.25	4.6	12.3	19.6	26.0	29.3	39.0
I-VII-II	1:4:0.25	5.3	21.6	35.6	43.3	49.0	58.0
I-VII-III	1:4:0.25	10.3	30.6	47.0	61.3	69.6	79.3
I-VII-IV	1:4:0.25	3.3	21.6	37.0	48.0	57.6	67.3
I-VII-V	1:4:0.25	9.6	19.3	27.0	35.6	39.6	48.3
I-XIII-II	1:4:0.25	4.6	33.0	55.0	65.0	71.0	77.0
I-XIII-III	1:4:0.25	6.6	33.6	49.3	56.3	62.0	73.6
I-XIII-IV	1:4:0.25	4.3	21.6	31.0	41.6	49.0	60.0
I-XIII-V	1:4:0.25	4.6	19.0	34.0	46.0	53.6	64.3
I-IX-VIII	1:4:4	2.3	17.6	29.3	34.6	43.6	49.0
I-VI-VIII	1:4:4	7.0	15.6	20.3	23.6	24.6	27.6
I-VII-VIII	1:4:4	4.0	15.3	26.0	36.3	46.3	57.3
I-XIII-VIII	1:4:4	1.7	11.6	22.0	31.0	37.6	44.3
I-X	1:4	9.0	58.3	84.6	96.0	97.6	99.3

Table II—Urinary Recovery of Testosterone and its Principal Metabolites after Oral Administration of Selected Dispersions (50-mg equivalent) to a Male Subject

Sample	Experiment No.	Recovered, % XI plus XII	I	Ratio of Metabolites-I
I	1	27.4	1.6	17:1
	2	27.3	1.3	21:1
	3	17.4	0.7	25:1
	Average	24.1	1.2	21:1
I-VII[a]	1	24.5	1.4	17:1
	2	28.6	1.6	18:1
	3	31.7	2.8	11:1
	Average	28.3	1.9	15:1
I-VII-III	1	27.4	3.1	9:1
	2	37.4	1.6	23:1
	3	41.6	4.7	9:1
	Average	35.5	3.1	13:1
I-X	1	37.2	8.2	4.5:1
	2	32.1	2.2	14.6:1
	3	39.9	7.3	5.5:1
	4	46.4	10.6	4.4:1
	Average	38.9	7.1	7:1

[a] Weight ratio 1:4.

(Table I). A slight increase was observed when synthetic surfactants were added(I-II, I-III); however, the two bile salts were ineffective (I-IV, I-V). The lipid dispersions of I with 1:4–1:8 weight ratios released the hormone more slowly (I-IX, I-VI, I-VII, and I-XIII). The addition of the various surfactants increased the release rate. The most rapid dissolution rate for the lipid–surfactant dispersions was exhibited by I-VII-III (79.3%). Solvent dispersion of I on lactose with the various lipids resulted in an improvement in the dissolution rates: whereas I-IX released 30.6% of I after 2hr, I-IX-VIII released 49%. The sample exhibiting the fastest rate of dissolution was I-X (99.3%).

The rapid dissolution of I-X is likely due to the release of microcrystalline I as the water-soluble X dissolves. The lipid dispersions without surfactants were dissolution-rate retarding. However, inclusion of surfactants would again ensure the release of microcrystalline particles. The lipids in such preparations would be readily dispersed because of the presence of the surfactants. The beneficial effect of lactose with the solvent-deposited lipid dispersions is most likely the result of greater surface exposure to the aqueous dissolution medium.

Oral Absorption Studies—On the basis of the dissolution data in Table I three dispersions were selected for the oral absorption studies. The urinary excretion data are presented in Table II. The recovery of I ranged from 0.7 to 1.6% following a 50-mg dose of micronized particles. The lipid dispersion plus surfactant produced levels of I ranging from 1.6 to 4.7%. The best recovery of I, as anticipated from the *in vitro* data, was shown by I-X (range: 2.2–10.6%). Metabolite recovery followed a similar progressive increase. The ratios of metabolites-I showed significant decreases with the more efficiently absorbed samples. Thus, the ratio was 21:1 for I alone, whereas for I-X the ratio was reduced to 7:1.

The results of the very limited oral absorption studies correlate very well with the dissolution data. The data suggest that rapid oral absorption of I is a desirable goal, since metabolite formation was reduced. Although a clear advantage was shown by using X as the excipient, a combination of VII and III may be indicated when acid-labile drugs are used. The latter would be expected to release the drugs more slowly in acidic media as compared with the former.

REFERENCES

(1) K. Sekiguchi and N. Obi, *Chem. Pharm. Bull.*, **9**, 866 (1961).

(2) A. H. Goldberg, M. Gibaldi, and J. L. Kanig, *J. Pharm. Sci.*, **55**, 482 (1966).

(3) A. H. Goldberg, M. Gibaldi, J. L. Kanig, and M. Mayersohn, *ibid.*, **55**, 581 (1966).

(4) W. L. Chiou and S. Riegelman, *ibid.*, **59**, 973 (1970).

(5) K. S. Chang and C. I. Jarowski, *ibid.*, **69**, 466 (1980).

(6) E. B. Estwood, "Pharmacological Basis of Therapeutics," Goodman and Gilman, 4th ed., Macmillan, New York, N.Y., 1970, p. 1571.

(7) G. L. Foss, *Lancet*, 502 (March, 1939).

(8) S. G. Johnsen, *ibid.*, 1473 (1974).
(9) "The United States Pharmacopeia," 18th rev., U.S. Pharmacopeial Convention, Rockville, Md., p. 934.
(10) D. Wurster and P. Taylor, *J. Pharm. Sci.*, **54**, 670 (1965).
(11) H. Ibayashi, M. Nakamura, and K. Nakao, *Steroids*, **2**, 559 (1964).
(12) W. Futterweit, N. L. McNiven, and R. I. Dorfman, *ibid.*, **1**, 628 (1963).

COMMUNICATIONS

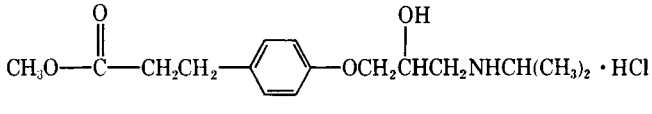
Esmolol: A Pharmacokinetic Profile of a New Cardioselective β-Blocking Agent

Keyphrases □ β-Adrenergic blocking agents—esmolol hydrochloride, pharmacokinetic profile, metabolism □ Pharmacokinetic profile—cardioselective β-adrenergic blocking agent, methyl 3-[4-(2-hydroxy-3-(isopropylamino)propoxy]phenylpropionate hydrochloride □ Esmolol—cardioselective β-adrenergic blocking agent, pharmacokinetic profile

To the Editor:

β-Adrenergic receptor blocking drugs exert their effects by competitively inhibiting the binding of catecholamines to β-adrenergic receptors. To attain therapeutic levels rapidly, intravenous bolus or infusions of β-blockers are usually instituted. However, since these agents have cardiac depressant properties, they are initially used at low doses, and slowly increased until the desired effects are obtained. Because currently available β-adrenergic blocking agents are long acting, the emergence of side effects, especially acute cardiac failure, poses a significant problem in their use because their action cannot be readily terminated. Therefore, there is a need for a β-adrenergic blocking drug with a short onset of action which can be rapidly terminated if side effects develop.

Esmolol (ASL-8052, Scheme I) is a new cardioselective intravenous β-receptor blocking agent with a very short duration of action in humans (unpublished data) and dogs (1). It is extensively metabolized in blood and liver by hydrolysis of the methyl ester functionality to form its major metabolites, ASL-8123 and methanol.



Esmolol (ASL-8052)

Methyl 3-[4-(2-Hydroxy-3-(isopropylamino)propoxy]phenylpropionate hydrochloride

Scheme I

To study the pharmacokinetics of esmolol, eight healthy male subjects (21–27 years old) weighing 62.4–76.2 kg received constant intravenous infusions of 50, 150, and 400 μg/kg/min for 2 hr on three different days. Each subject received an intravenous dose of isoproterenol, which had previously been determined to produce a 50% increase in heart rate. The suppression of the isoproterenol-induced increase in heart rate and blood pressure was determined on several occasions during and up to 60 min after the cessation of the esmolol infusion. At each dose level, blood samples were collected for determinations of esmolol and ASL-8123 by gas chromatography–mass spectrometry and high performance liquid chromatography, respectively (2). Esmolol and ASL-8123 concentrations, as a function of time during and after the infusion, were fitted to equations describing a two-compartment open model (3, 4) and modified one-compartment open model, respectively, by nonlinear least-squares regression analysis.

Esmolol infusion significantly blocked the isoproterenol effects with its action being most evident at the 400-μg/kg/min dose. The duration of action of esmolol was, however, very short with no significant effect evident 30 min after cessation of the infusion at all three doses. There was a significant correlation between the reduction of the isoproterenol-induced increase in heart rate and blood pressure and the logarithm of esmolol blood concentrations. Blood levels of 0.3 and 1 μg/ml esmolol were associated with 50 and 80%, respectively, reduction in heart rate and 30 and 50%, respectively, reduction in blood pressure.

The steady-state concentrations of esmolol increased proportionally with the dose ($r = 0.866$, $p < 0.001$, $n = 24$). The mean concentrations (±*SD*) were 0.164 ± 0.068, 0.569 ± 0.204, and 1.59 ± 0.605 μg/ml, respectively, after 2-hr infusions of 50, 150, and 400 μg/kg/min. The respective values for the total clearance were 363 ± 184, 298 ± 112, and 285 ± 104 ml/min/kg, which were not correlated with dose ($r = 0.210$, $p > 0.3$, $n = 24$). These findings suggest that the elimination of esmolol is linear within the 50–400 μg/kg/min dosing range given for 2 hr.

Table I summarizes several of the key pharmacokinetic parameters for esmolol and ASL-8123 after the 400

Table I—Summary of Some Pharmacokinetic Parameters of Esmolol and its Metabolite after Administration of 400 μg/kg/min infusion of the Drug for 2 hr in Normal Subjects

Pharmacokinetic Parameters	Esmolol	ASL-8123
Steady-state concentration, μg/ml	1.59 ± 0.605[a]	—
Peak concentration, μg/ml	—	77.9 ± 3.93
Peak time, min	—	146 ± 11.1
Terminal half-life, min	9.19 ± 3.51	223 ± 14.0
Half-life of formation of metabolite(s), min	—	2.82 ± 0.592
Total clearance, ml/min/kg	285 ± 104	1.28 ± 0.19
Volume of distribution, liters/kg	3.43 ± 1.42	0.411 ± 0.057
Calculated fraction of metabolite formed[b]	—	0.829

[a] Mean ± *SD*; $N = 8$. [b] Ratio of formation and elimination rate constants (k_f/k_{10}).

0022-3549/83/0600-0710$01.00/0