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SUSTAINED ABSORPTION DOES NOT NECESSARILY REDUCE THE SYSTEMIC AVAILABILITY OF PROPRANOLOL

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ABSTRACT

The *in vitro* dissolution and *in vivo* pharmacokinetics of two marketed long-acting propranolol formulations, Duranol (D) and Inderal LA (LA) were examined. Dissolution rates were obtained using the USP rotating basket method, while the relative bioavailabilities of the products were evaluated in normal volunteers under single-dose (6 subjects) and steady-state (11 subjects) conditions in two separate crossover studies. Both LA and D demonstrated pH-independent dissolution profiles

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with T_{50} values of 4 and 6 hours, respectively. While the dissolution profile for D was sigmoidal and complete in 12 hours, data for LA suggested a log-linear profile and indicated only 85% dissolution at 12 hours. In pharmacokinetic studies the tmax was achieved in 7 to 8 hours for both products; however, Cmax values for D vs LA were 80.4 vs 49.9 ng/ml ($p < 0.05$) after a single dose and 76.6 vs 52.6 ng/ml ($p < 0.01$) at steady-state drug administration. The bioavailability of D was 55% and 44% greater than that of LA during single-dose and steady-state studies, respectively. Intersubject variability was lower for D than for LA during both studies. The data indicate that sustained absorption does not necessarily reduce the systemic availability of propranolol, and suggest that formulation-related factors may contribute to the low bioavailability of LA. The superior bioavailability and lower intersubject variability achieved with D compared to LA suggest that D should be at least as effective as LA in the treatment of cardiovascular disorders.

INTRODUCTION

Because of the anatomical arrangement and physiological role of the hepatic portal circulation, a large fraction of orally administered medication must pass through the liver before reaching the systemic circulation. Presystemic hepatic drug elimination,

commonly referred to as the "first-pass effect"[1], is particularly significant for drugs such as propranolol which are avidly extracted by the liver[2]. Thus, despite complete absorption from the gut[3], propranolol's systemic availability is low, and dose-dependent. Oral administration of a single 80 mg dose to healthy volunteers resulted in a bioavailability figure of 22%[4], which increased to approximately 35% during chronic administration[4,5]. Inderal LA (Ayerst, ICI) is a long-acting propranolol formulation that has demonstrated clinical efficacy when given once daily in the treatment of hypertension[6-9] and angina pectoris[10-12]. However, Inderal LA suffers from a significant bioavailability problem. The amount of systemically available propranolol from the long-acting preparation is reported to be 56% lower during single dose studies[13] and 31% lower after chronic administration[14] than that recorded with conventional tablets. Considering the poorer bioavailability and the higher unit dose cost of the LA product compared to conventional propranolol tablets, justification for the routine use of Inderal LA is debatable[15-19].

Recently, a new controlled absorption propranolol formulation (Duranol, Elan Corporation) has received marketing approval in Ireland. Data from this laboratory indicate that the systemic availability of propranolol following a single 160 mg Duranol capsule or 80 mg

of conventional propranolol tablets given at 12-hour intervals are equivalent, despite a significant difference in absorption rates[20]. We now extend these observations with Duranol (D) in comparative single-dose and steady-state bioavailability studies using Inderal LA (LA) as the reference formulation. The results indicate that while Duranol has a similar absorption profile, it provides considerably greater propranolol systemic availability than does the LA formulation.

METHODS

In Vitro Dissolution Studies

The dissolution rates of the formulations were measured at hourly intervals by the USP rotating basket apparatus at 75 rpm using dissolution medium maintained at pH levels ranging from 1.5 to 7.5. Drug content was determined by ultraviolet absorption at 290 nm.

In Vivo Bioavailability Studies

Two separate trials were conducted: one trial required the administration of a single 160 mg propranolol capsule (single-dose study); in the second study, 160 mg propranolol was administered every 24 hours for 5 days (steady-state study).

Subjects. All participants were males between the ages of 18 and 40 years and within 10% of their ideal body weight who were documented to be healthy during a pre-trial medical examination. After receiving

instructions concerning study procedures and potential risks, all subjects voluntarily consented to participate in the investigation. Six subjects with an average age of 29 years (range: 20-34 years) and mean weight of 79 kg (range: 70 to 87 kg) participated in the single-dose study. Twelve volunteers were selected for participation in the steady-state study. However, one volunteer was noncompliant with study instructions and was removed from further participation during the initial 5-day treatment period. Thus, 11 subjects with an average age of 22 years (range: 20 to 23 years) and mean weight of 73 kg (range: 57 to 84 kg) completed the steady-state trial.

Treatments. The following propranolol products were used:

(a) Commercially-available Inderal LA (ICI Lot NI 537) 160 mg capsules.

(b) Duranol (ECL Trial Batch 229/2) 160 mg capsules.

Experimental Design. Both studies were conducted under medical supervision using a balanced two-period crossover design with at least 5 days between treatment periods. The study protocols were approved by an internal ethical review committee, and all subjects gave their informed consent for study participation. All medication was administered after an 8 hour fast with approximately 8 oz water. After dosing,

blood was aseptically obtained by venepuncture from an antecubital vein using Becton-Dickinson (BD-Plastipak polypropylene) syringes equipped with a Yale microlance 21 gauge, 1.5 inch needle. Immediately after collection, blood was transferred into 10 ml tubes containing lithium heparin as anticoagulant (Medlabs 10 ml lithium heparin polysterene tubes) and gently agitated. Plasma was extracted after centrifugation (1500 g x 10-15 minutes) and placed in 10 ml tubes (Medlabs polysterene tubes) for storage at - 20°C until analysis.

In the single-dose study, plasma was collected at the following times after administration of a single 160 mg propranolol dose: 0, 1, 2, 3, 4, 6, 8, 12 and 24 hours.

During the steady-state trial, subjects were administered 160 mg propranolol at 8 a.m. for 5 days. Plasma was obtained before the morning dose on days 1, 4, and 5, and at the following times after dosing on day 5: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16 and 24 hours.

Plasma Propranolol Levels

Concentrations of propranolol in heparinized plasma samples were determined by high-pressure liquid chromatography using fluorometric detection according to published methods[21]. The minimum concentration of propranolol that could be quantitated was 0.8 ng/ml.

Calculations

Area under the plasma concentration versus time curve from zero through 24 hours (0-24 AUC) was determined for each individual using the trapezoidal rule.

Statistical Analysis

A two-way analysis of variance procedure was used to assess differences between the two products in terms of: (a) peak plasma concentrations (Cmax); (b) mean AUC values; (c) propranolol levels at each dissolution and blood sampling point; (d) duration of time (i.e. time coverage) at designated plasma levels; (e) trough plasma levels on Days 4, 5 and 6 for each product on the multiple dose schedule. Results are expressed as mean $\pm$ s.e.m. unless otherwise stated.

RESULTS

In Vitro Dissolution Profiles

Because dissolution rates of Inderal LA and Duranol were pH-independent, mean results are presented in Figure 1. The dissolution of Inderal LA was apparently log-linear, and incomplete after 12 hours. In contrast, the dissolution of Duranol was sigmoidal in shape and was complete by 12 hours. The times for 50% dissolution (i.e., T_{50}) for Inderal LA and Duranol were approximately 4 and 6 hours, respectively. Compared to Inderal LA results, Duranol's dissolution rate was initially slower from 0 to 4 hours, and faster during 4 to 9 hours (Figure 1).

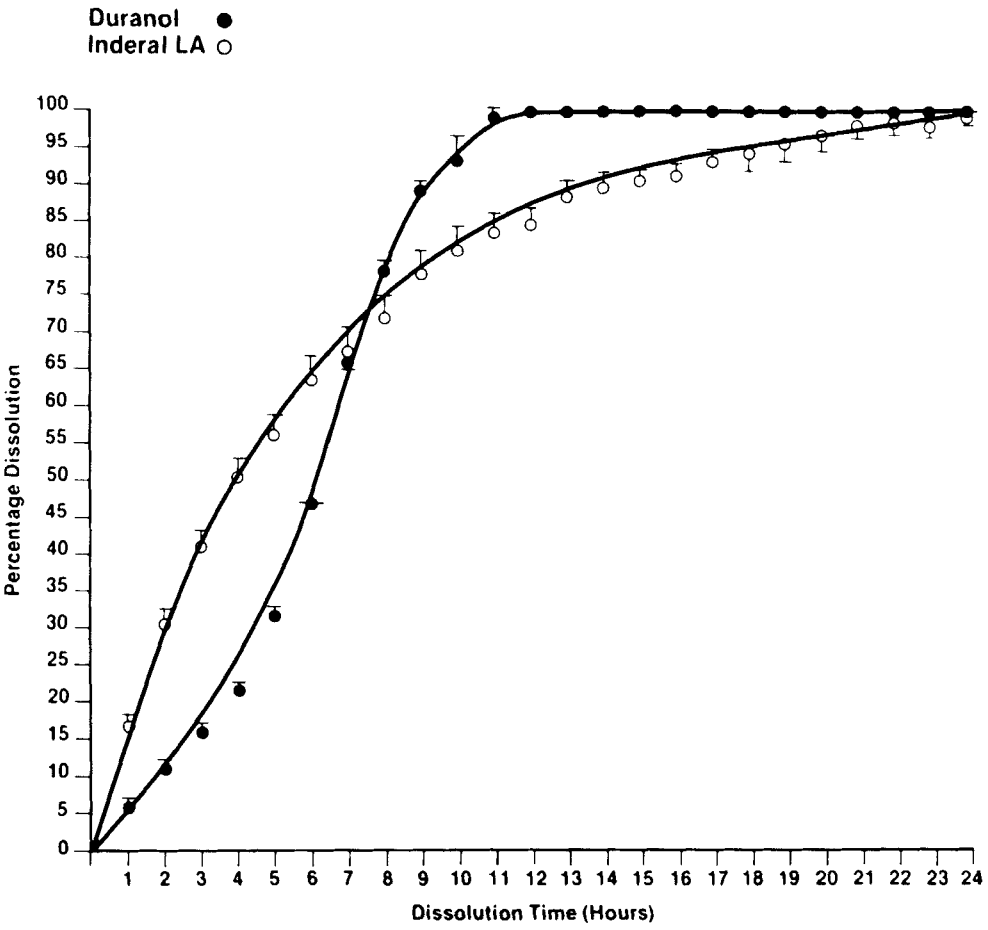

FIGURE 1

In vitro dissolution profiles for Inderal LA and Duranol (mean ± s.d.)

In Vivo Results

Plasma propranolol concentrations: Mean plasma propranolol concentrations obtained during the single and multiple-dose studies are listed in Table 1 and graphically displayed in Figure 2. After administration of a single 160 mg propranolol dose (Table 1, Figure

TABLE 1

Summary of Plasma Propranolol Concentrations and % CV (in parentheses) After Administration of Duranol (D) and Inderal LA (LA)

Time After Dosing (h)	Plasma Propranolol Concentrations (ng/ml)			
	Single-Dose (N=6)		Day 5 Steady-State (N=11)	
	D	LA	D	LA
Baseline	ND	ND	13.9 ± 1.2 (28.6)	12.8 ± 2.1 (53.1)
1	10.8 ± 2.5 (57.3)	11.6 ± 6.8 (143.3)	18.3 ± 2.8 (50.0)	18.5 ± 2.8 (51.0)
2	17.1 ± 3.6 (51.1)	28.4 ± 11.1 (95.4)	21.8 ± 2.9 (44.2)	24.7 ± 3.3 (44.1)
3	23.0 ± 5.0 (53.5)	33.0 ± 10.2 (75.9)	23.3 ± 3.0 (43.4)	28.6 ± 3.8 (43.9)
4	24.3 ± 4.6 (46.3)	32.7 ± 10.4 (78.1)	33.9 ± 5.4 (52.6)	37.9 ± 4.6 (40.4)
5	---	---	38.5 ± 4.9 (41.8)	37.8 ± 5.2 (45.5)
6	48.4 ± 4.4 (22.3)	39.9 ± 11.2 (68.9)	52.1 ± 5.4 (34.2)	44.4 ± 4.6 (34.5)
7	---	---	57.3 ± 5.2 (30.2)	44.6 ± 4.6 (34.3)
8	80.4 ± 13* (39.6)	38.2 ± 7.6 (48.5)	57.3 ± 4.2*. (24.2)	38.7 ± 4.2 (35.7)
9	---	---	68.9 ± 5.5* (26.2)	34.1 ± 3.9 (38.2)
10	---	---	61.5 ± 5.1* (27.7)	31.3 ± 3.3 (34.7)
12	62.7 ± 11.3 (44.4)	35.4 ± 9.2 (63.8)	52.5 ± 4.6* (29.2)	30.0 ± 3.3 (36.0)
16	---	---	37.0 ± 4.8* (42.7)	21.3 ± 3.1 (48.5)
24	27.0 ± 3.3 (30.4)	16.9 ± 7.2 (104.9)	15.4 ± 1.2 (26.2)	13.3 ± 1.9 (47.6)

* $p < 0.05$, D vs LA; within-study comparison.

ND - Not Detected.

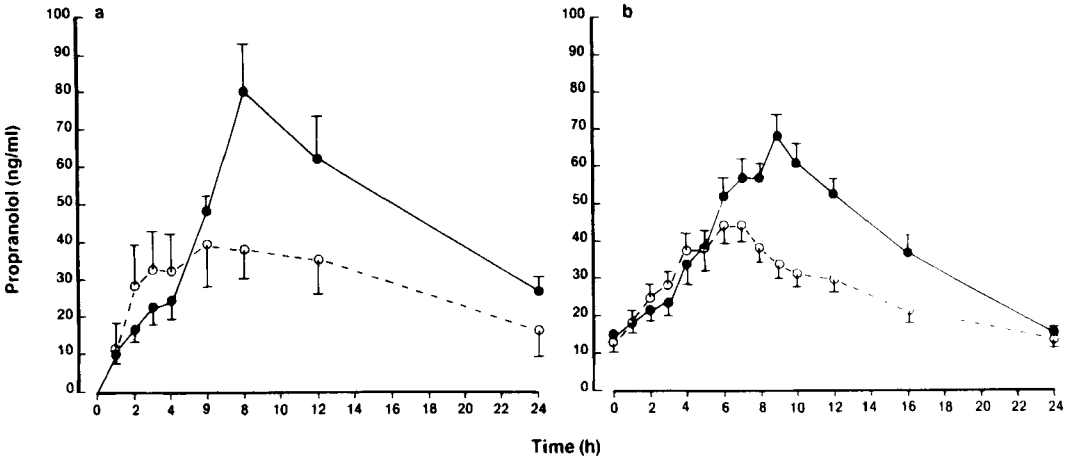

FIGURE 2

Plasma levels of propranolol following administration of Inderal LA 160 mg (o---o) and Duranol 160 mg (●---●)

2a), Duranol produced mean plasma levels from 1 to 4 hours that were lower than those of Inderal LA, although the differences between products were not statistically significant. However, plasma concentrations recorded at subsequent times were consistently higher for Duranol compared to Inderal LA values, and a significant difference in mean 8-hour values was noted ($p < 0.05$) (Figure 2).

Administration of 160 mg every 24 hours for 5 days achieved steady-state plasma levels for each of the propranolol formulations. Plasma levels recorded before dosing on days 4 and 5 and 24 hours after the last dose on day 5, were similar for both products (Table 2).

TABLE 2

Trough Plasma Propranolol Concentrations (ng/ml)
In 11 Subjects Receiving 160 mg/day Propranolol
Daily

	Day 4 0 Hr	Day 5 0 Hr	Day 5 24 Hr	p value
Inderal LA	12.2 ± 2.2	12.8 ± 2.1	13.3 ± 1.9	NS
Duranol	18.4 ± 2.9	13.9 ± 1.2	15.4 ± 1.2	NS

During steady-state, plasma propranolol concentrations recorded for Duranol from 8 to 16 hours after dosing were significantly higher ($p < 0.05$) than those of Inderal LA (Table 1, Figure 2b).

Absorption variability. Consistency in drug absorption was estimated by comparing the coefficients of variation (CV) of mean plasma levels at each of the sampling points for both products. In both the single-dose and steady-state studies (Table 1), Duranol demonstrated a significantly lower % CV ($p < 0.05$) when compared to Inderal LA data. A graphical display of individual plasma concentration-time curves obtained in the single-dose study illustrates the absorption variability obtained with each product (Figure 3). Maximum plasma concentrations were achieved at 8 hours after administration of Duranol in all 6 subjects, while

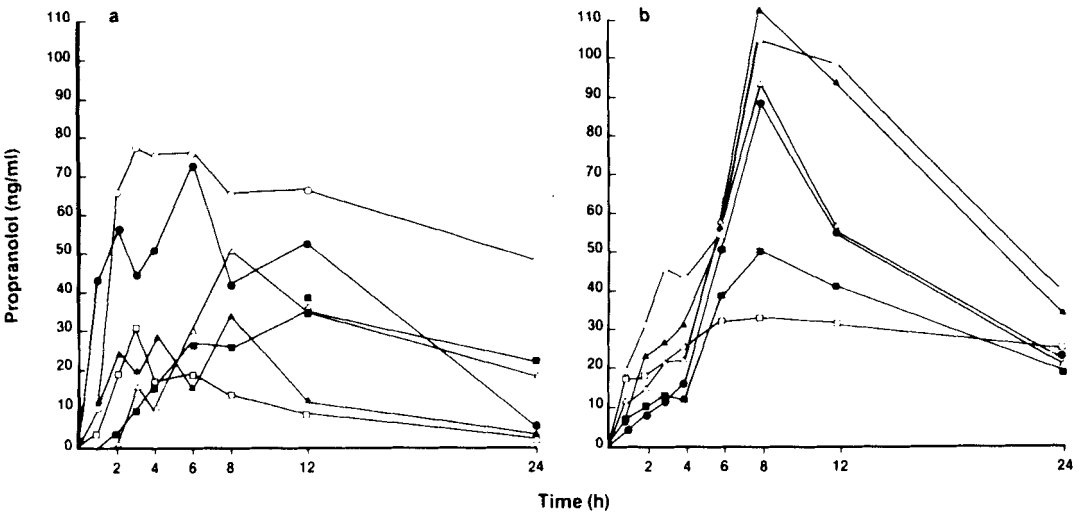

FIGURE 3

Individual plasma propranolol levels in six subjects following administration of a single 160 mg dose of Inderal LA (a) and Duranol (b)

individual tmax values ranged from 3 to 12 hours after Inderal LA dosing (Figure 3).

Pharmacokinetic comparison. Peak plasma concentrations (Cmax) recorded after Duranol administration were significantly greater than Inderal LA values, although times to peak levels (tmax) were similar (Table 3).

Identification of a terminal log-linear elimination phase was not possible because continued absorption masked the true elimination of propranolol. Thus, the relative bioavailability of Duranol compared to Inderal LA in each study was estimated from the area under the plasma concentration versus time profile

TABLE 3

Summary of Pharmacokinetic Parameters

	Single 160 mg (n = 6)		160 mg/day x 5 days (n = 11)	
	Inderal LA	Duranol	Inderal LA	Duranol
Cmax (ng/ml)	49.9± 8.5	80.4± 13.0*	52.6± 4.9	76.6± 4.7**
tmax (hrs)	6.7± 1.4	8.0± 0.0	7.3± 0.8	8.3± 0.4
0-24 AUC (ng/ml x h)	700.8±179.5	1088.0±162.9	633.7±63.5	911.4±67.1*
Frel	100%	155%	100%	144%

* $p < 0.05$ ** $p < 0.01$ Frel = relative bioavailability

from 0 to 24 hours (0-24 AUC). Calculated in this way, the bioavailability of Duranol was 55% greater in the single-dose study and 44% greater during chronic dosing than that of Inderal LA.

Time coverage at designated plasma concentrations. Although the relationship between plasma propranolol concentrations and therapeutic efficacy is still under question, we examined the length of time propranolol blood levels remained at various concentrations during administration of both long-acting formulations (Table 4). After a single 160 mg dose, the average time coverage was greater for Duranol than for Inderal LA, although there were no statistically significant differences detected

TABLE 4

Summary of Time Coverage at a Range of Plasma Propranolol Concentrations During a 24 Hour Dosing Interval

Propranolol level (ng/ml)	Time Coverage (h)			
	Single 160 mg (n = 6)		160 mg/day x 5 days (n = 11)	
	Inderal LA	Duranol	Inderal LA	Duranol
5.0	21.8 ± 0.9	23.4 ± 0.2	23.1 ± 0.9	24.0 ± 0.0
10.0	18.7 ± 2.2	22.7 ± 0.4	22.2 ± 1.1	23.9 ± 0.1
20.0	14.8 ± 3.4	21.1 ± 0.6	15.7 ± 1.9	18.9 ± 1.0
30.0	9.7 ± 3.7	16.1 ± 2.0	7.9 ± 1.7	13.7 ± 1.3**
40.0	6.8 ± 3.9	11.7 ± 3.2	3.7 ± 1.1	9.7 ± 1.4***
50.0	4.7 ± 3.5	8.1 ± 2.9	1.6 ± 0.7	6.0 ± 1.3*
60.0	2.7 ± 2.4	6.1 ± 2.4	0.6 ± 0.3	3.8 ± 1.1*

* $p < 0.05$ ** $P < 0.01$ *** $p < 0.001$

between the two products at any of the selected plasma concentrations . During steady-state drug administration, Duranol achieved significantly greater time coverage at 30, 40, 50 and 60 ng/ml levels than did Inderal LA

DISCUSSION

Controlled-release medications offer a number of potential therapeutic advantages: improved patient compliance, continuous therapeutic effects and reduction in side effects. However, regulatory marketing approval has been difficult to obtain for many controlled-release products because of their large intersubject variability or inability to demonstrate bioequivalence to a reference product.

Inderal LA (Ayerst, ICI) was the first long-acting propranolol formulation to receive marketing approval in the United States and many European countries, primarily (if not exclusively) because of clinical efficacy data[6-12]. Nevertheless, Inderal LA has a significant bioavailability problem[13,14] which may influence therapy. Dosage guidelines advise physicians that an escalation in the daily propranolol dose may be required when substituting Inderal LA for conventional tablets (Ayerst Product Information). Results of a recent double-blind comparative study support the need for large doses (457 $\pm$ 194 mg; n = 7) of slow-release propranolol in the treatment of patients with mild to

moderate hypertension[9]. It has been suggested that LA propranolol may be 20-30% more costly to patients than conventional tablets or other similar preparations, partly as a result of its poor bioavailability[17,18]. Indeed, one reviewer has failed to recommend Inderal LA as an addition to his hospital formulary[19].

Duranol is a new controlled absorption formulation of propranolol. Previously, a single dose of Duranol has been shown to provide as much systemically available propranolol as two doses of conventional tablets[20]. In the present report we extend this information on Duranol to include comparisons with Inderal LA. The systemic availability of Duranol was 55% and 44% greater than that of Inderal LA under single-dose and steady-state conditions, respectively. The increase in Duranol's relative bioavailability can be correlated with peak propranolol concentrations. Cmax values for Duranol were 61% and 41% greater than those for Inderal LA during single-dose and chronic drug administration, respectively. Moreover, the significantly lower coefficient of variation for Duranol indicates a reduction in intersubject variability relative to LA propranolol.

Many drugs which suffer from poor bioavailability either undergo extensive presystemic elimation, have formulation deficiencies, or both. McAinsh and coworkers[13] concluded that the low bioavailability of LA

propranol is caused by its lowered absorption rate constant, thus decreasing the fraction of absorbed propranolol that escapes presystemic hepatic elimination. However, results of the present study with Duranol dispute this premise. The *in vitro* T_{50} and *in vivo* tmax values for Duranol and Inderal LA were similar; however, the relative systemic availability of Duranol was superior to that of LA propranolol. It is possible that the low relative bioavailability of Inderal LA is related to formulation characteristics which impair absorption. Thus, the *in vitro* release rate of LA was such that only 85% was dissolved in 12 hours. In contrast, Duranol was completely dissolved in 12 hours.

The greater bioavailability and more consistent absorption of the Duranol formulation suggest that Duranol should be at least as effective as Inderal LA in the treatment of cardiovascular disorders. Recent data by Mullane and co-workers[22] indicate that propranolol levels above 20 ng/ml induce significant beta blockade. These authors recommend adjustment of propranolol therapy to maintain plasma concentrations in the 20 to 50 ng/ml range. Current results indicate that Duranol provides more sustained plasma propranolol levels within the range quoted by Mullane *et al* than does Inderal LA.

In summary, the results of these studies indicate that sustained absorption does not necessarily reduce

the systemic availability of propranolol. Although T_{50} and tmax values (a reflection of in vitro and in vivo absorption rates) were similar for both products, the relative bioavailability of Duranol was greater than that of Inderal LA. In the absence of metabolite data,the poor systemic availability of Inderal LA can be explained by formulation-related factors rather than increased hepatic elimination. The data also suggest that Duranol should be at least as effective as Inderal LA in the treatment of cardiovascular disorders.

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