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BIOPHARMACEUTICAL CHARACTERISTICS OF A NEW PROPRANOLOL/ HYDROCHLOROTHIAZIDE TABLET COMBINATION

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ABSTRACT

Experiments have been carried out in dogs and man to determine the effect of hydrochlorothiazide (HCT) on the pharmacokinetics of propranlol and to evaluate the bioavailability of two dosage forms containing both propranolol and HCT (40/25 and 80/25 mg, respectively). In adult male beagles, 50 mg of HCT had no apparent effect on AUC, C_{max}, T_{max}, and $T_{\frac{1}{2}}$ of propranolol administered concurrently. In man, INDERIDE® (40/25 mg) and INDERIDE® (80/25 mg) were shown to be similar in bioavailability to the reference formulations, i.e. the same amount of drugs administered as the separate tablets of INDERAL® plus HYDRODIURIL®.

KEY WORDS Bioavailability Propranolol Hydrochlorothiazide Human Interaction Dog

INTRODUCTION

Propranolol is widely used in the treatment of hypertension because of its efficacy and relative safety.[1] When administered as sole therapy, it can effectively control blood pressure in a majority of hypertensive patients.[1-4] Propranolol in combination with a diuretic will provide control of blood pressure for approximately 90 per cent of patients with mild to moderate hypertension.[4-6] This paper deals with pharmacokinetic and bioavailability studies carried out with INDERIDE®, a propranolol/hydrochlorothiazide (HCT) combination, in both animals and man.

MATERIALS AND METHODS

Materials

HCT in the form of 25 mg HYDRODIURIL® tablets (Merck, Sharp, and Dohme) was purchased from a retail pharmacy outlet. Propranol in the form of

INDERIDE® Ayerst Laboratories.

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40 or 80 mg INDERAL® tablets was obtained from commercial lots (Ayerst Laboratories, Rouses Point, N.Y.). The new propranolol/HCT combination dosage forms (40/25 or 80/25 mg) were prepared by the Clinical Supply Group, Ayerst Laboratories, Rouses Point, N.Y.

Interaction study in dogs

The effect of HCT on the pharmacokinetics of propranolol was investigated in 10 adult male beagles, weighing about 10 kg. The animals were randomly separated into two equal groups and were given, p.o., either two 40 mg propranolol tablets or two 40 mg propranolol tablets together with two 25 mg HCT tablets (commercial lots). A small amount of food was given with the drugs to counter possible emesis. Blood samples were taken (Vacutainers, Becton Dickinson, No. 4720) at 0, 0·5, 1, 1·5, 2, 3, 4, 5, 6, and 8 h after dosing. After clotting, the serum was separated and frozen prior to determination of propranolol concentrations. After an interval of 1 week, the crossover was carried out.

Bioavailability studies in man

Three studies were carried out with normal adult male volunteers between the ages of 18 and 40. Each volunteer was made aware of the nature of the study and signed a consent form. Details concerning the investigator, site, dosage, number of subjects and duration of the study are given in Table 1. After a 12 h fast (8 h in Study 2), one-half of the randomly selected subjects were given the propranolol and HCT tablets separately, and the other half received the same amount of drugs combined in a single dosage form. The tablets were taken with 200 ml of water (100 ml in Study 2). Blood samples were taken (EDTA Vacutainers, Becton Dickinson, No. 4713) at 0, 0·5, 1, 2, 4, 6, 8, 10, 12, 16, 24, and 48 h after dosing. In Study 2, the tablets were administered twice a day, with a 12 h interval, for 7 consecutive days; the bleeding schedule on Day 1 was therefore curtailed to 0–12 h and the complete bleeding schedule was followed on Day 7. Plasma was obtained by centrifugation and frozen until analysis of both propranolol and HCT. After an interval of 7 days (9 days in Study 2), the crossover was carried out. On the study days when blood samples were being taken, all subjects refrained from lying down or smoking and consumed no food or beverages for a period of 4 h after drug administration.

Analysis of propranolol and HCT

Propranolol concentrations in serum or plasma were determined fluorimetrically using our modification[7] of the method of Shand *et al.*[8]. Based on a 4·0 ml sample volume, the method had a detection limit of 5 ng ml^{-1}. The method is specific and little, if any, interference is caused by propranolol metabolites.[7,9] Because additives in some Vacutainers may result in displacement of propranolol from protein binding sites and cause eventual losses to the red cells,[10]

Table 1. Bioavailability studies in man

Study No.	Investigator	Site	Dosage	Lot No.	Subjects	Duration (days)
1	Dr. J. Arnold	Quincy Research Centre, Kansas City, Mo.	HCT, 2 × 25 mg propranolol, 2 × 40 mg HCT + propranolol, 2 × (25 + 40 mg)	W2425 2GAR 2FXG	22	1
2	Dr. C. S. Crawford	Techni-Med Consultants, Wyncote, Penn.	HCT, 2 × 25 mg propranolol, 2 × 40 mg HCT + propranolol, 2 × (25 + 40 mg)	W3940 4HFV 1JJH	16 19	1 7*
3	Dr. J. Bessent	Pharmacokinetics Laboratory Inc., Baltimore, Md.	HCT, 2 × 25 mg propranolol, 2 × 80 mg HCT + propranolol, 2 × (25 + 80 mg)	W3940 4HFX 1JTG	24	1

* From Day 1–7, the subjects were dosed b.i.d., q. 12 h.

care was taken to prevent the contact of the whole blood with the stoppers and serum or plasma were separated as quickly as possible.

HCT concentrations were measured by the high pressure liquid chromatography (HPLC) procedure of Robinson and Cosyns.[11] Based on a 3·0 ml sample volume the detection limit for the method was 3 ng ml^{-1}.

Data analysis

All studies were carried out according to a 2 × 2 Latin-square design.[12] All parameters were subjected to a Type II analysis of variance (ANOVA) for crossover experiment, provided sufficient data were available.[13] For unbalanced groups, due to problems with recruitment of participants or missing data points, the sums of squares were calculated according to Grizzle.[14] Calculations were performed on a CDC Cyber 172/2 computer using a program which provided: the areas under the drug concentration/time curves (AUC_{0-T}), calculated by the trapezoidal rule; the half-life ($T_{\frac{1}{2}}$), calculated from the non-weighted linear least squares analysis of the log–linear terminal portions of the drug concentration/time curves; the peak concentrations (C_{max}); the 'time-to-peak' (T_{max}); and the required ANOVAs.

RESULTS

Interaction study in dogs

Similar profiles of mean serum propranolol concentrations were obtained in dogs given, p.o., 80 mg of propranolol either alone or together with 50 mg of HCT (Figure 1). The differences between the four parameters calculated for

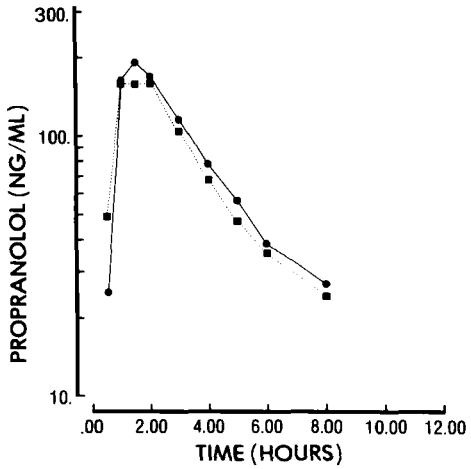

Figure 1. Serum propranolol concentrations in dogs given 80 mg of propranolol (■) or 80 mg of propranolol plus 50 mg of HCT (●), orally

Table 2. Effect of HCT on the pharmacokinetics of propranolol in dogs

Parameter	Propranolol, 80 mg, p.o. Alone	+50 mg HCT	p
C_{max} ($ng\,ml^{-1}$)	203±31*	208±33	NS
T_{max} (h)	1·50±0·15	1·40±0·10	NS
AUC†	590±60	645±81	NS
$T_{\frac{1}{2}}$ (h)	2·85±0·21	2·74±0·26	NS

* Mean ± S.E., $n = 10$. NS = Not significant.
† 0–8 h, $ng \times h\,ml^{-1}$.

each treatment, i.e. C_{max}, T_{max}, AUC_{0-8}, and $T_{\frac{1}{2}}$ were not statistically significant (Table 2).

Bioavailability of the (40/25 mg) propranolol/HCT tablet

The bioavailability of propranolol and HCT from the (40/25 mg) combination tablet was assessed in two studies, one comprising 22 subjects (Study 1) and the other 19 subjects (Study 2). The AUC, C_{max}, and T_{max}, and $T_{\frac{1}{2}}$ were estimated for both propranolol and HCT. The mean plasma drug concentration/time curves are depicted in Figure 2a and b, and the pharmacokinetic parameters are presented in Table 3. The only statistically significant changes ($p < 0·05$) recorded with the propranolol/HCT combination were an

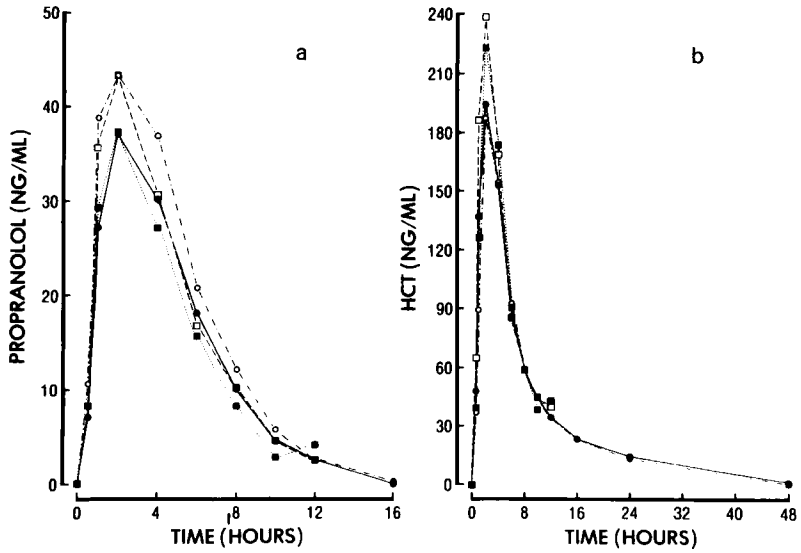

Figure 2. Plasma propranolol (a) and HCT (b) concentrations in subjects given propranolol (2 × 40 mg) and HCT (2 × 25 mg) as separate tablets or the combination (2 × 40/25 mg) formulation. Separate tablets: Study 1, (○), Study 2 (■); combination tablets: Study 1 (●). Study 2 (□)

18·1 per cent reduction in AUC and a 19·8 per cent reduction in C_{max} for propranolol in Study 1. In Study 2, the reverse was found and the AUC and C_{max} for propranolol were increased by 14·9 and 9·0 per cent respectively. The changes were, however, not statistically significant. Half-life values for propranolol in plasma could only be calculated from the mean concentration profiles. No statistical treatment of the data was possible but the values of 2–3 h were as expected.

Table 3. Single dose pharmacokinetic data for the 40/25 mg dosage form

Parameter	Study	Prop*+HCT	Combination	%	*p*
		Propranolol data			
AUC†	1	259±40	212±30	−18·1	<0·05
	2	194±32	223±26	+14·9	NS
C_{max}	1	50·5±8·6	40·5±5·5	−19·8	<0·05
(ng ml^{-1})	2	42·1±8·0	45·9±5·4	+9·0	NS
T_{max} (h)	1	2·64±0·29	2·11±0·22	−20·1	NS
	2	2·00±0·22	1·81±0·19	−9·5	NS
$T_{\frac{1}{2}}$ (h)	1	2·3 —	2·2 —	−4·3	
	2	2·8 —	2·1 —	−25·0	
		HCT data			
AUC‡	1	1544±96	1598±91	+3·5	NS
	2	1226±95	1296±75	+5·7	NS
C_{max}	1	201±12	212±13	+5·5	NS
(ng ml^{-1})	2	238±24	256±18	+7·6	NS
T_{max} (h)	1	2·55±0·19	2·14±0·21	−16·1	NS
	2	2·13±0·20	2·06±0·27	−3·3	NS
$T_{\frac{1}{2}}$ (h)	1	8·32±0·60	9·44±0·85	+13·5	NS
	2	—	—		

*prop = propranolol.
† In ng × h ml^{-1}; Study 1: 0–16 h; Study 2: 0–12 h.
‡ Study 1: 0–48 h; Study 2: 0–12 h.
NS = Not significant.

With respect to HCT, for all four pharmacokinetic parameters tested, the combination tablets and the propranolol plus HCT provided virtually identical data. Differences in AUC and C_{max} were < 10 per cent and even the largest difference, i.e. the 16 per cent reduction in T_{max}, for the combination, was not statistically significant.

Bioavailability of the (80/25 mg) propranolol/HCT tablet

The assessment of the bioavailability of propranolol and HCT from the (80/25 mg) tablets was carried out in 24 volunteers (Study 3). Mean plasma drug concentrations are depicted in Figures 3a and b and the pharmacokinetic parameters are presented in Table 4. For propranolol, no statistically significant differences were found for any of the parameters tested. For HCT, significant

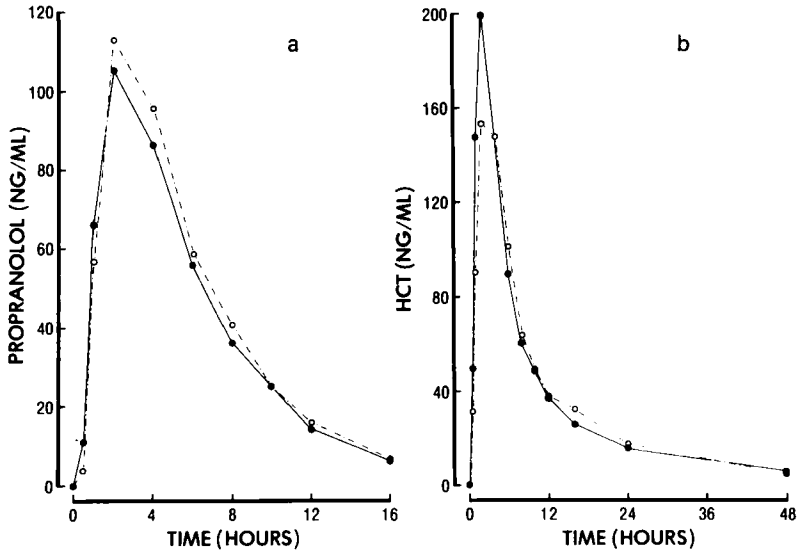

Figure 3. Plasma propranolol (a) and HCT (b) concentrations in subjects given propranolol (2 × 80 mg) and HCT (2 × 25 mg) as separate tablets or as the combination (2 × 80/25 mg) formulation. Separate tablets: (○); combination tablets (●)

Table 4 (Study 3). Single dose pharmacokinetic data for the 80/25 mg dosage form

Parameter	Drug	Prop*+HCT	Combination	%	p
AUC†	Prop	716±86	679±84	−5·2	NS
	HCT	1683±87	1729±136	+2·7	NS
C_{max}	Prop	117±13	110±13	−6·0	NS
(ng ml^{-1})	HCT	185±11	217±14	+17·3	<0·05
T_{max} (h)	Prop	2·46±0·19	2·38±0·24	−3·3	NS
	HCT	3·35±0·33	2·26±0·25	−32·5	<0·05
$T_{\frac{1}{2}}$ (h)	Prop	3·27±0·20	3·53±0·21	+8·0	NS
	HCT	13·9±2·2	12·6±1·4	−9·4	NS

* Prop = propanolol.
† In ng × h ml^{-1}, 0–16 h; Prop: 0–48 h HCT.
NS = Not significant.

changes ($p < 0·05$) of 17·3 per cent and −32·5 per cent were noted for C_{max} and T_{max} with the (80/25 mg) combination tablet.

Effect of chronic dosing on the bioavailability of the combination tablet

Mean plasma drug concentration/time curves obtained: (a) after administration of single doses (80 mg propranolol, 50 mg HCT) as separate tablets or the (40/25 mg) combination, or (b) after b.i.d. (q. 12 h) administration of the

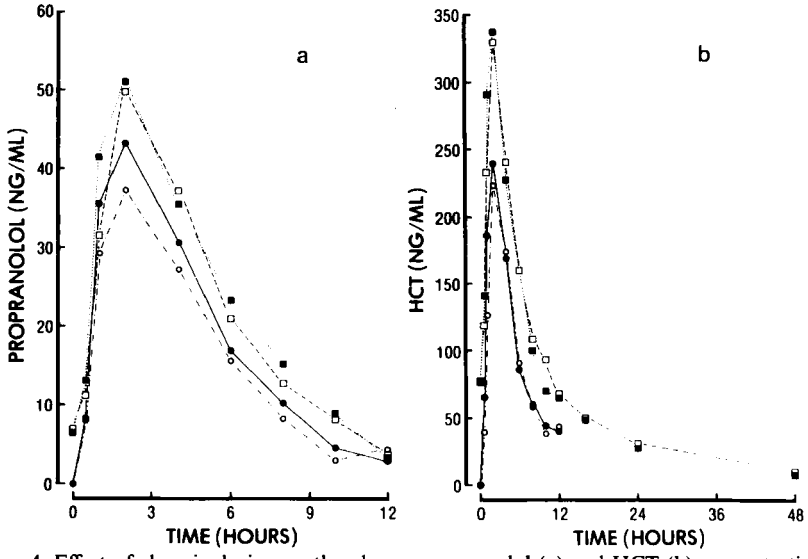

Figure 4. Effect of chronic dosing on the plasma propranolol (a) and HCT (b) concentrations in subjects given separate propranolol (2 × 40 mg) and HCT (2 × 25 mg) tablets or the combination (2 × 40/25 mg) formulation. Separate tablets: Day 1 (○). Day 7 (■); combination tablets: Day 1 (●), Day 7 (□)

Table 5 (Study 2). Chronic dose study with the 40/25 mg dosage form

Parameter	Day	Prop* + HCT	Combination	%	*p*
		Propranolol data			
AUC†	1	194 ± 32	223 ± 26	+14·9	NS
	7	285 ± 30	268 ± 28	−6·0	NS
C_{max}	1	42·1 ± 8·0	45·9 ± 5·4	+9·0	NS
(ng ml^{-1})	7	54·7 ± 6·5	51·8 ± 5·2	−5·3	NS
T_{max} (h)	1	2·00 ± 0·22	1·81 ± 0·19	−9·5	NS
	7	1·79 ± 0·10	1·89 ± 0·20	+5·6	NS
$T_{\frac{1}{2}}$ (h)	1	2·8 —	2·1 —	−25.0	
	7	3·25 ± 0·33	2·95 ± 0·18	−9·2	NS
		HCT data			
AUC†	1	1226 ± 95	1296 ± 75	+5·7	NS
	7	2931 ± 162	3074 ± 153	+4.9	NS
C_{max}	1	238 ± 24	256 ± 18	+7·6	NS
(ng ml^{-1})	7	367 ± 17	359 ± 20	−2·2	NS
T_{max} (h)	1	2·13 ± 0·20	2·06 ± 0·27	−3·3	NS
	7	1·95 ± 0·24	2·37 ± 0·29	+21·5	NS
$T_{\frac{1}{2}}$ (h)	1	—			
	7	12·3 ± 0·8	13·4 ± 1·0	+8·9	NS

* Prop = propanolol.
† In ng × h ml^{-1}, 0–12 h.
‡ Day 1: 0–12h; Day 7: 0–48 h.
NS = Not significant.

same doses for 7 days are depicted in Figure 4a and b. The pharmacokinetic parameters are presented in Table 5. On either Day 1 or Day 7, for both propranolol and HCT, both dosage regimens provided a similar bioavailability as none of the parameters tested showed any statistically significant differences. After chronic dosing, only minor increase in the $T_{\frac{1}{2}}$ of propranolol were noted, the mean for both formulations being 3·1 h.

Because of the difference in the number of subjects available for the assessments at Day 1 and 7, direct comparison of the AUC and C_{max} was not possible. Data based on the 16 common subjects are presented in Table 6. For propranolol, the mean increases in AUC and C_{max} after 7 days of b.i.d. dosing were 24 and 12 per cent, respectively. The increases were not stastistically significant. In contrast, for HCT, statistically significant ($p<0·001$) increases of 61 and 47 per cent were recorded.

Table 6 (Study 2). Single and multiple dose bioavailability comparisons in 16 subjects for the 40/25 mg dosage form

Parameter	Dosage	Day 1	Day 7	%	p
		Propranolol data			
AUC*	Prop†+HCT	194±33	264±33	+36·1	NS
	combination	233±26	250±28	+12·1	NS
				(24)‡	
C_{max}	Prop+HCT	42·1±8·0	48·0±5·0	+14·0	NS
(ng ml^{-1})	combination	45·9±5·4	50·2±6·0	+9·4	NS
				(12)	
		HCT data			
AUC*	Prop+HCT	1296±75	2013±113	+55·3	<0·001
	combination	1226±113	2048±98	+67·0	<0·001
				(61)	
C_{max}	Prop+HCT	256±18	357±24	+39·5	<0·001
(ng ml^{-1})	combination	238±24	369±19	+55·0	<0·001
				(47)	

* In ng × h ml^{-1}, 0–12 h.
‡ Mean percentage change for both formulations.
† Prop = propanolol.
NS = Not significant.

DISCUSSION

The interaction between HCT and propranolol was investigated in dogs. Under our experimental conditions, simultaneous administration of 50 mg HCT and 80 mg propranolol had no appreciable effect on the pharmacokinetic parameters of propranolol (Table 2) that were estimated. A similar finding with other β-blockers has been reported previously.[15,16] Our results are in agreement with a recent report on the lack of effect of HCT and triamterene on propranolol kinetics in man following administration of the drugs in a new 3-drug combination dosage form.[17]

When the bioavailability of propranolol from the (40/25 mg) combination dosage form was first compared to that obtained with equimolar doses of propranolol and HCT given separately, the only statistically significant differences were 18–20 per cent decreases in AUC and C_{max} (Table 3). However, no differences in the bioavailability of HCT were detected. Since the combination formulation represents an intimate mixture of propranolol and HCT, it is unlikely that the dosage forms were bioequivalent with respect to HCT but not for propranolol. Upon oral administration, within the same subject and especially between subjects, considerable variations are found in the serum concentrations of propranolol that are achieved.[8, 18–20] The variability is caused by the difference in the rate and extent of metabolism, mainly during the first pass through the liver.[21, 22] In contrast, HCT is uniformly well absorbed and not extensively metabolized.[23] This would suggest HCT as the more reliable index for bioequivalence assessment. Indeed, when the study was repeated in another group of subjects, the AUC and C_{max} of propranolol from the combination tablets were actually slightly increased while the pharmacokinetic parameters for HCT remained unaltered. Based on the combined results from the two studies, we consider the combination dosage form to be similar in bioavailability to the conventional tablets used as reference, for both propranolol and HCT.

Essentially identical findings were obtained with the (80/25 mg) combination tablets in Study 3 (Table 4). Despite the minor increase in C_{max} (from 185 to 217 ng ml^{-1}) and a slightly faster rate of absorption for the HCT component in the combination formulation, no significant differences in AUC were noted.

We have investigated the effect of 7-day administration of drug on the relative bioavailability of the (40/25 mg) combination formulation in 16 normal volunteers. On day 7, no differences were found for either propranolol or HCT (Table 5). Multiple dosing, for 7 days, did not result in any significant differences in bioavailability parameters between the combination dosage form and the separately administered tablets, a finding agreeing with those of the one day study in 16 subjects.

The extent of drug accumulation at steady state depends on the $T_{\frac{1}{2}}$ and the frequency of dosing. Because of its longer $T_{\frac{1}{2}}$,[23] the increases in AUC and C_{max} for HCT (Table 6) were as high as 67 per cent ($p < 0{\cdot}001$). For propranolol they were less marked (up to 34 per cent) and not statistically significant.

The new combination dosage forms, Inderide 40/25 and 80/25 mg, are similar in bioavailability to the same dosages of propranolol and HCT taken together as separate tablets. This suggests that, when desired, they may be substituted for the individual drugs in patients who have been titrated to acceptable dose levels.

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