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COMPARATIVE ORAL BIOAVAILABILITY OF CONVENTIONAL PROPRANOLOL TABLETS AND A NEW CONTROLLED-ABSORPTION PROPRANOLOL CAPSULE

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ABSTRACT

The relative bioavailabilities of a new once-a-day propranolol formulation (Duranol) and conventional propranolol tablets (Inderal) were evaluated in six healthy male volunteers in a randomized balanced cross-over study. During the first treatment period, subjects were administered either a single 160 mg Duranol capsule at 9 a.m. or 80 mg Inderal at 9 a.m. and 9 p.m. Plasma propranolol concentrations were measured at 0, 2, 3, 4, 5, 6, 8, 10, 12, 13, 14, 15, 16, 24 and 36 hours after the 9 a.m. dose.

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Mean peak plasma propranolol concentrations (Cmax) of 92.7 ng/ml at 2 hours and 53.9 ng/ml at 2.8 hours were recorded after administration of the first and second Inderal doses, respectively. After Duranol dosing, the Cmax of 85 ng/ml was not significantly different than the Inderal values; however, Duranol's tmax of 8 hours was significantly greater ($p < 0.05$) than either tmax recorded for Inderal. Compared to data obtained after administration of conventional propranolol tablets, mean propranolol concentrations were significantly lower at 2, 3 and 4 hours ($p < 0.01$) and significantly higher at 8, 10 and 12 hours ($p < 0.05$) after Duranol administration. The lengths of time plasma levels remained at 5, 10, 20, 30, 40, 50, 60, 70 and 80 ng/ml were not significantly different between the two products. In addition, the mean AUCs for Inderal and Duranol after 12 hours (380.2 vs 434.0 ng $ml^{-1}h$, respectively), 24 hours (728.0 vs 728.8 ng $ml^{-1}h$, respectively), 36 hours (813.0 vs 826.8 ng $ml^{-1}h$, respectively), or from time 0 to infinity (838.6 vs 860.4 ng $ml^{-1}h$, respectively) were not significantly different.

These results indicate no loss in bioavailability despite a significantly prolonged absorption time for Duranol relative to conventional propranolol tablets. These results suggest that in the treatment of cardiovascular disorders an equivalent single dose of

Duranol can be substituted for the daily requirements of conventional propranolol administered in divided doses.

INTRODUCTION

Since their discovery[1], beta-adrenoceptor antagonists have been used with much success in the management of cardiovascular disorders such as hypertension, angina pectoris and cardiac arrhythmias[2-4]. Propranolol hydrochloride (Inderal, ICI) was the first of these drugs to demonstrate clinical effectiveness[5] and still remains one of the most widely prescribed beta-blocking agents. Because of its relatively short plasma half-life[6-9], patients are routinely asked to take propranolol in divided daily doses every 6 to 8 hours. Such frequent drug administration may reduce patient compliance, and thus therapeutic efficacy.

Recently, a long-acting propranolol formulation (Inderal LA, ICI) has been described which can be given as a single daily dose in the treatment of hypertension [10,11], and angina pectoris[12,13]. However, the oral bioavailability of Inderal LA relative to conventional propranolol tablets is reported to be only about 44%[14].

A novel multiparticulate form of propranolol hydrochloride (Duranol, Elan Corporation Limited) has been developed which is also designed for once daily

drug administration. This study compares plasma propranolol concentrations and areas under the concentration versus time curve in volunteers who received a single 160 mg dose of Druanol and 80 mg Inderal given every 12 hours for two doses. The results indicate that, while the absorption rates of the two products are quite different, the amounts of propranolol reaching the systemic circulation are equivalent.

METHODS

Subjects

Six healthy male volunteers aged between 20 and 35 years (mean age: 28 years) and within 10% of their ideal body weight (mean weight: 71 kg; range 61 to 74 kg) participated in this study. A medical history and complete physical examination, including a 12-lead electrocardiogram and laboratory screen (haematology, urinalysis and blood chemistries) were performed on each subject before drug administration. Subjects were excluded if there were clinically significant abnormalities noted during the physical examination or on laboratory tests results, a resting heart rate of less than 55 beats per minute, or if there was medical history of chronic disease, drug allergy, alcohol or drug abuse, or use of any medication within seven days of study enrollment.

Treatments

The following propranolol products were used:

(a) Inderal (Ayerst Lot I BX4) 40 mg tablets.

(b) Duranol (ECL Trial Batch 229/1) 160 mg capsules.

Experimental Design

This was a balanced two-period crossover investigation conducted under medical supervision at the Elan Clinical Pharmacology Centre. The study protocol was approved by the Institutional Review Board, and all subjects gave their informed consent for study participation. The trial was divided into two 36-hour treatment periods with 7 days separating each phase of the study. At the beginning of the study, subjects were randomly assigned to one of two treatment groups. During the first experimental period, Group 1 received 160 mg (1 capsule) Duranol at 9 a.m., while Group 2 received 80mg (2 tablets) Inderal at 9 a.m., and 9 p.m. The subjects in each group were crossed over to the alternate medication and drug administration schedule for the second treatment period. The morning dose of medication was taken after an 8-hour fast with approximately 5 oz. water. Diet was then standardized, and identical meals were served at 10 a.m., 1 p.m., and 6 p.m., on respective study days.

Plasma Propranolol Levels

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. During each treatment period, a 10 ml blood sample was collected at the following times: immediately before, and 2, 3, 4, 5, 6, 8, 10, 12, 13, 14, 15, 16, 24 and 36 hours after dosing. Immediately after collection, blood was transferred into 10 ml tubes containing lithium heparin as anticoagulant (Teklab 10 ml lithium heparin polysterene tubes, ML brand) and gently agitated. Plasma was extracted after centrifugation (1500 g x 10-15 minutes) and placed in 10 ml tubes (Teklab polysterene tubes, ML brand) for storage at - 20°C until analysis.

Concentrations of propranolol in heparinized plasma samples were determined by high-pressure liquid chromatography using fluorometric detection according to published methods[15]. The minimum concentration of propranolol that could be quantitated was 0.8 ng/ml. Spiked-plasma with concentrations of 5-200 ng/ml yielded a mean recovery of 88%, with excellent linearity and reproducibility (a correlation coefficient of 0.998, slope of 0.01001, and an intercept of 0.0026). For each subject, plasma samples for both periods of the trial were assayed on the same day.

Calculations

Area under the plasma level versus time curve from time zero through 12 (0-12 AUC), 24 (0-24) or 36 hours (0-36 AUC) was determined for each individual using the

trapezoidal rule. Area under the plasma level versus time curve from time 0 to infinity (AUC) was calculated for each subject using the following formula:

$$AUC = (0\text{-}t)\ AUC + C(t)/k$$

where:

t = the time of the last measurable plasma propranolol concentration on the terminal linear segment of the log plasma concentration versus time curve;

(0-t) AUC = area under the plasma concentration versus time curve from time 0 through t, calculated by the trapezoidal rule;

k = the elimination rate constant, calculated from the slope (determined by linear regression) of the terminal linear segment of the log plasma concentration versus time curve following Inderal administration.

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) plasma levels at each sampling point; and (d) duration of time (i.e. time coverage) at designated plasma levels. Wilcoxon's Signed Rank Test was used to evaluate

differences between Inderal and Duranol with respect to (a) the coefficient of variation (CV) of mean plasma levels at each of the sampling points and (b) time to peak plasma levels (tmax).

RESULTS

Plasma Propranolol Concentrations

The mean plasma propranolol concentrations obtained after administration of Duranol and Inderal are listed in Table 1 and graphically displayed in Figure 1. The plasma concentration versus time curves for each subject are shown in Figure 2. Rapid absorption of conventional propranolol tablets produced a mean peak propranolol concentration of 92.7 ng/ml at 2 hours after the first Inderal dose, and of 53.9 ng/ml at 2.8 hours after the second dose. In contrast, Duranol demonstrated a delayed and sustained absorption rate, producing mean peak concentrations of 85.0 ng/ml at 8 hours after drug administration.

A comparison between the two products of the mean plasma propranolol concentrations at each sampling point reveals significantly higher values with Inderal at 2, 3 and 4 hours, and with Duranol at 8, 10 and 12 hours after dosing. Drug concentrations at other collection times were not statistically different between the two products.

TABLE 1

Summary of Plasma Propranolol Concentrations (mg/ml)

in 6 Subjects (mean ± s.e.m.)

Sampling time (hrs)	Inderal	Duranol
Pre	ND	ND
2	92.7 ± 16.0	4.9 ± 1.7**
3	66.8 ± 15.4	7.5 ± 2.0**
4	51.3 ± 11.7	11.2 ± 3.5**
5	33.9 ± 8.6	23.4 ± 4.5
6	24.9 ± 6.2	49.6 ± 14.0
8	16.8 ± 12.0	58.4 ± 9.0**
10	7.3 ± 3.1	70.4 ± 23.6*
12	3.6 ± 1.9	52.8 ± 15.4*
13	26.5 ± 10.7	40.5 ± 11.6
14	46.9 ± 14.0	33.2 ± 8.0
15	43.3 ± 5.5	30.1 ± 8.8
16	39.3 ± 5.2	27.5 ± 6.6
24	13.2 ± 4.0	10.3 ± 1.9
36	1.0 ± 0.6	6.1 ± 3.8

ND Not detected.

* $p < 0.05$.

** $p < 0.01$.

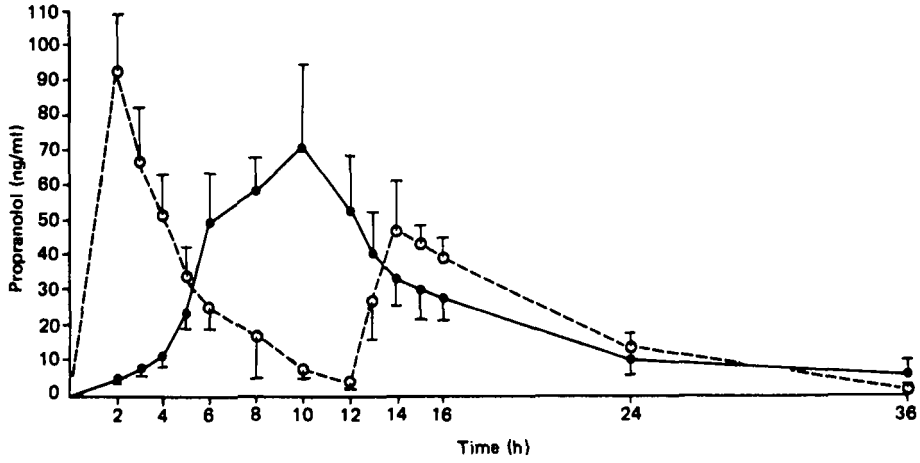

FIGURE 1

Plasma levels of propranolol following administration of Inderal (ICI) 80 mg at 0 and 12 hours (o—o) and Duranol (ECL) 160 mg single dose at 0 hours (●—●) (mean ± s.e.m. n = 6).

Time Coverage at Designated Plasma Concentrations

An important objective of any long-acting formulation is to maintain plasma drug concentrations at therapeutic levels for the same period as that obtained with divided daily doses of a conventional product. We examined the time coverage at various plasma propranolol levels after administration of a single 160 mg dose of Duranol and compared the data to results observed with 80 mg of Inderal given at 0 and 12 hours (Table 2). At each of the selected plasma concentrations, Duranol achieved a time coverage that was equivalent to the value obtained with divided doses of conventional propranolol tablets.

Area Under the Plasma Concentration versus Time Curve

Because Inderal was administered at 0 and 12 hours, AUC figures were calculated at three time points for

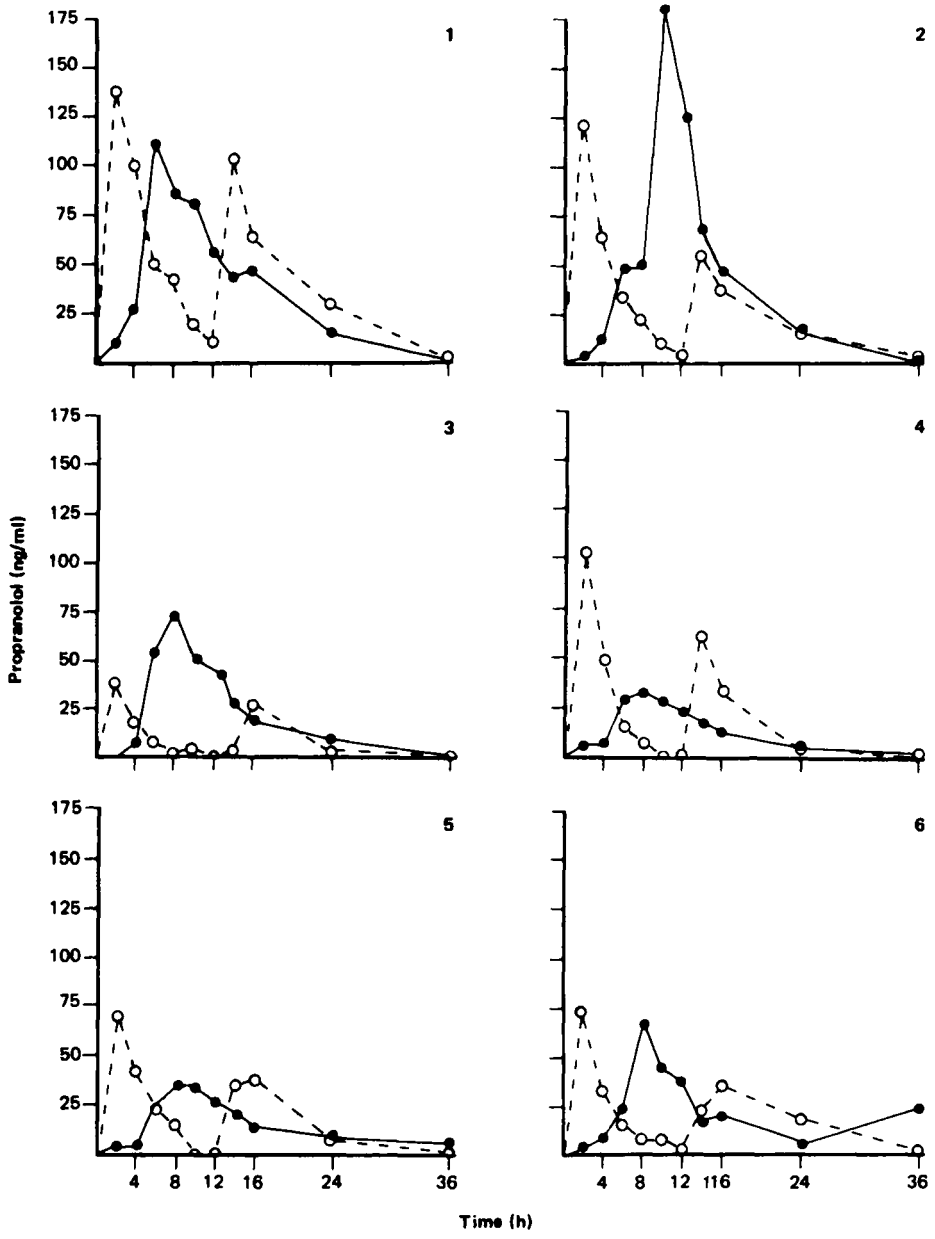

FIGURE 2

Plasma levels of propranolol in six subjects following administration of Inderal (ICI), 80 mg at 0 and 12 hours (○ — ○) and Duranol (ECL) 160 mg single dose at 0 hours (● — ●).

TABLE 2

Summary of Time Coverage at a Range of Plasma Propranolol Levels (mean ± s.e.m.)

Propranolol level (ng/ml)	Time (h) Inderal	Duranol
5.00	27.1 ± 3.1	29.4 ± 1.6
10.00	22.1 ± 2.9	21.9 ± 2.3
20.00	15.0 ± 2.6	13.0 ± 2.1
30.00	9.6 ± 2.5	9.1 ± 2.3
40.00	6.0 ± 2.4	6.2 ± 2.4
50.00	4.3 ± 1.7	3.9 ± 1.5
60.00	2.7 ± 1.3	2.8 ± 1.2
70.00	1.6 ± 0.9	2.0 ± 1.1
80.00	1.2 ± 0.7	1.6 ± 1.0

both products (Table 3). The mean 0-12 AUC for Duranol (434.0 ng $ml^{-1}h$) was not statistically different than the value calculated for Inderal (380.2 ng $ml^{-1}h$). Similarly, at 24 and 36 hours, the mean AUCs for Duranol were within 2% of those computed for Inderal, and there were no statistical significance detected between the two products. Calculation of the mean AUC from time 0 to infinity yielded figures of 860.4 ng $ml^{-1}h$ for Duranol and 838.6 ng $ml^{-1}h$ for Inderal respectively, and these values were not significantly different.

TABLE 3

Summary of Pharmacokinetic Parameters

(mean ± s.e.m.)

	Inderal	Duranol
Cmax (ng/ml)	92.7 ± 16.0, 53.9 ± 11.0*	85.0 ± 22.9
tmax (h)	2.0 ± 0, 2.8 ± 0.4*	8.0 ± 0.5**
0-12 AUC	380.2 ± 84.6	434.0 ± 86.8
0-24 AUC	728.2 ± 147.1	728.8 ± 156.6
0.36 AUC	813.0 ± 170.6	826.8 ± 159.5
AUC	838.6 ± 167.8	860.4 ± 164.7

* Results after the first and second doses, respectively.

** Significantly different ($p < 0.05$) than the Inderal data obtained after the first and second doses.

DISCUSSION

Patient compliance is a recognized component in the treatment of cardiovascular disorders[16,17]. Among those factors affecting compliance, the daily frequency of drug administration and the number of tablets or capsules that must be taken appear to be important[16,18].

Based on pharmacokinetic observations of an elimination half-life of 2 to 6 hours[6-9], dosage

recommendations for propranolol include frequent periodic drug administration, especially in patients with angina pectoris[19-21]. Yet conventional propranolol tablets administered every 12 hours have been shown to have therapeutic effects in the treatment of hypertension[22-25] and angina pectoris[26]. These reports indicate that the pharmacological activity of propranolol may be longer than its apparent plasma half-life and that it may be possible to give the total daily amount of propranolol in larger, but less frequent, daily doses. However, conventional propranolol tablets produce peak plasma concentrations approximately two hours after dosing[6,7,9], and large doses may result in unwanted or even hazardous effects. Thus, there is a need for a propranolol formulation which can be conveniently administered once daily and still avoid potential risks associated with excessively high plasma drug levels. A long-acting form of propranolol (Inderal LA, ICI) has been developed which is reported to be effective when taken once daily in the treatment of hypertension[10,11,27], and angina pectoris[12,13]. However, Floras and coworkers[11] required doses as high as 640 mg (mean dose: 457 mg; n = 7) to produce a significant reduction in mean blood pressure for 22 of 24 hours. It is possible that the large doses used by Floras is a reflection of the poor bioavailability of the slow-release form of propranolol

used in the study. The relative bioavailability of Inderal LA compared with a conventional propranolol tablet has been reported to be only about 44%[14].

In this study, the relative bioavailability of a single 160 mg Duranol capsule was equivalent to that calculated for 80 mg Inderal given at 12 hour intervals. Maximum plasma propranolol concentrations were observed 8 hours after Duranol administration and 2-3 hours after Inderal dosing, which would indicate that the rate at which propranolol is presented to the systemic circulation (i.e. effective propranolol absorption) is much slower for Duranol relative to Inderal. McAinsh et al[14] have reported a correlation between the fall in Inderal LA AUC and the increase in in-vitro dissolution time and postulated that for propranolol, the bioavailability is directly related to the absorption rate such that as the absorption rate constant is lowered, increased presystemic metabolism of propranolol results in reduced bioavailability. The results of the present study, however, demonstrated no loss in AUC for Duranol despite an approximate four-four delay in peaking time relative to Inderal.

Although the relationship of propranolol plasma concentrations and therapeutic effects have not been clearly defined, the results of the present study suggest that an equivalent daily dose of Duranol may

be as efficacious as divided daily doses of Inderal in the treatment of cardiovascular disorders. It is generally accepted that cardiac beta receptors are completely (but reversibly) blocked by propranolol concentrations in the range of 75 to 100 ng/ml[28,29]. A 50% reduction in exercise tachycardia and plasma renin activity has been observed with plasma propranolol concentrations in the range of 8 to 30 ng/ml[28-32], although propranolol levels of 30 ng/ml or more have been recommended in the treatment of angina pectoris[29,32,33]. In 50 normal male volunteers, plasma propranolol concentrations above 20 ng/ml reduced exercise heart rate by at least 20 beats per minute in 50% of the subjects[34]. Plasma propranolol levels of 15 to 40 ng/ml have been proposed to be optimal for the treatment of essential hypertension[35].

Regardless of the range of plasma propranolol concentrations which are considered to be therapeutic, the results of the present single-dose bioavailability study indicate that a single 160 mg Duranol capsule maintains plasma concentrations at 5 to 80 ng/ml for a time period that is equivalent to that obtained with 80 mg Inderal given at 0 and 12 hours.

An interesting observation in this study was the reduced Cmax and a tendency towards a delayed tmax after the second Inderal dose (relative to the first

dose) which was observed in all 6 volunteers. Although the reason for this consistent phenomenon is unclear, Markiewicz and coworkers[36] have reported chronobiological fluctuations in propranolol plasma concentrations, with a lower Cmax and delayed tmax following drug administration at 1400 and 2000 hours when compared to data obtained after dosing at 0200 and 0800 hours.

In summary, the results of this study indicate that a single 160 mg dose of Duranol has the equivalent bioavailability of two 80 mg doses of Inderal given at 12 hour intervals, and that it is possible to prolong the absorption of propranolol without loss of AUC. In addition, plasma propranolol concentrations of 5 to 80 ng/ml were maintained for the same length of time with either Duranol or Inderal, and suggests that the therapeutic effects obtained with 80 mg of conventional propranolol tablets administered every 12 hours should be achieved with a single 160 mg dose of Duranol.

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REFERENCES

1. C.E. Powell and I.H Slater, J. Pharmacol. Exp. Ther., 122, 480 (1958).

2. W. Freshman and R. Silverman, Am. Heart J., 98, 119 (1979).

3. M.E. Connolly, F. Kersting and C.T. Dollery, Prog. Cardiovasc. Dis., 19, 203 (1976).

4. L.H. Opie, Lancet, 1, 693 (1980).

5. F.J. Zacharias, K.J. Cowen, J. Prestt, J. Vickers and B.G. Wall, Am. Heart J., 83 755 (1972).

6. C.A. Chidsey, P. Morselli, G. Bianchetti, A. Morganti, G. Leonetti and A. Zanchetti, Circulation, 52, 313 (1975).

7. R. Gomeni, G. Bianchetti, R. Sega and P.L. Morselli, J. Pharmacokinet. Biopharm., 5, 183 (1977).

8. D.M. Kornhauser, A.J.J. Wood, R.E. Vestal, G.R. Wilkinson, R.A. Branch and D.G. Shand, Clin. Pharmacol. Ther., 23, 165 (1978).

9. D.G. Shand, E.M. Nuckolls, J.A. Oates, Clin. Pharmacol. Ther., 11, 112 (1970).

10. A.P. Douglas-Jones, N.S. Baber and A. Lee. Europ. J. Clin. Pharmacol., 14, 163 (1978).

11. J.S. Floras, J.V. Jones, M.O. Hassan and P. Sleigh, Br. Med. J., 285, 1387 (1982).

12. H. Halkin, I. Vered, A. Saginer and B. Rabinowitz, Eur. J. Clin. Pharmacol., 16, 387 (1979).

13. F.H.H. Leenen and A.B. Van Der Vijgh, Curr. Ther. Res., 30, 113 (1981).

14. J. McAinsh, N.S. Baber, B.F. Holmes, J. Young and S.H. Ellis. Biopharm Drug Disp., 2, 39 (1981).

15. G. Nygard, W.H. Shelver and S.K.W. Khalil. J. Pharm. Sci., 68, 379 (1979).

16. D. Hamblin, F.O. Wells, and S. Ellis, J. Clin. Pharm. 4, 41 (1979).

17. B. Blackwell, N. Eng. J. Med., 289, 249 (1973).

18. M.S. Gatley, J. Roy. Coll. Gen. Practit., 16, 39 (1968).

19. P.M.S. Gillam, and B.N.C. Prichard, Am. J. Cardiol, 18, 366 (1966).

20. W.M. Bennett, I. Singer and C.J. Coggins, J. Am. Med. Assoc., 230, 1544 (1974).

21. Inderal (Ayerst) product information, In Physicians' Desk Reference, 36th Edition (1982). Medical Economics Company Inc, Oradell, pp 624 (1982).

22. G. Berglund, O. Andersson, L. Hansson and R. Orlander, Acta Med. Scand., 194, 513 (1973).

23. P.R. Wilkinson, N. Dixon and K.R. Hunter. J. Intern. Med. Res., 2, 220 (1974).

24. J. Kanto, T. Kleimola, R. Mantyla and E. Syvalahti, Acta Pharmacol. Toxicol., 39, 573 (1976).

25. A.R. Lorimar, F.G. Dunn, J.V. Jones and T.D.V. Lawrie, Am. J. Med., 60, 877 (1976).

26. U. Thadani, and J.O. Paker, Am. J. Cardiol., 46, 117 (1980).

27. J.C. Petrie, T.A. Jeffers, O.J. Robb, A.K. Scott and J. Webster, Br. Med. J., 281, 1573 (1980).

28. D.J. Coltart and D.G. Shand, Br. Med. J., 3, 731 (1970).

29. M. Pine, L. Favrot, S. Smith, K. McDonald and C.A. Chidsey. Circulation, 52, 886 (1975).

30. C.A. Chidsey, M. Pine, L. Favrot, S. Smith, G. Leonetti, P. Morselli and A. Zanchetti. Postgrad. Med. J., 52, 26 (1956).

31. D.G. Shand, A.J.J. Wood, R.E. Vestal, G.R. Wilkinson and R.A. Branch. International series number 446, Amsterdam, Excerpta Medica. Eds. Braunwall, E. (1978).

32. D.G. Shand, Med. Clin. N. Amer., 58, 1063 (1974).