COMPARISON OF PROPRANOLOL AND INDERAL L.A. IN PATIENTS WITH ANGINA

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SUMMARY

TWELVE patients with moderately severe angina pectoris completed a double blind cross-over comparison of conventional propranolol (40 mg q.i.d.) and Inderal L.A. (160 mg once daily) with regard to therapeutic effectiveness, blood levels, compliance and patient acceptability.

Exercise tolerance was assessed using standardised treadmill testing at 1, 2, 4, 8, 12 and 24 hours after the morning dose. The double placebo technique was used. Patient compliance was excellent for both regimes and no serious side effects were reported. No significant differences in exercise tolerance or blood levels were observed between the two treatments at any time.

INTRODUCTION

The therapeutic effectiveness of propranolol in angina pectoris is well documented (Miller et al, 1975). The plasma half-life is 4-6 hours (Chidsey et al, 1975; McAinsh et al, 1978) and is usually administered 2-4 times daily. A long acting formulation (Inderal L.A. ICI) has been developed. Preliminary studies indicate that in healthy volunteers, Inderal L.A. given once daily produces blood levels comparable to those obtained by giving conventional propranolol 4 times daily in the same total dosage (Leahey et al, 1979). We compared conventional propranolol (40 mg q.i.d.) with once daily Inderal L.A. (160 mg) with regard to therapeutic effectiveness, blood levels, compliance and patient acceptability.

PATIENT SELECTION

Men aged under 70 years attending the cardiology clinic with angina pectoris were considered for the study. Those with overt heart failure, airways obstruction, heart block, unstable angina or evidence of myocardial infarction within six months were excluded. None was receiving digitalis preparations or anti-hypertensive drugs. Patients taking propranolol 40 mg q.i.d. for at least one month were tested on a treadmill linked to an Avionics stress monitor by the CM5 lead system (Sheffield and Roitman, 1976) Thirteen patients who could complete one but not three full stages of the Bruce protocol were studied. Informed consent was obtained.
METHOD

Each patient completed two weeks run-in followed by two 2-week study periods. During the run-in, patients continued to take conventional propranolol (40 mg q.i.d.). Before starting the treatment periods, six treadmill tests were performed 1, 2, 4, 8, 12 and 24 hours after the morning tablet. Resting heart rate, ST segment displacement and blood pressure were measured. They then walked at a constant 2.5 m.p.h. up a 12 per cent gradient. At the onset of pain, heart rate and ST segment displacement were recorded, blood pressure was measured and the treadmill stopped.

The patients were allocated randomly for two weeks treatment with propranolol tablets (40 mg q.i.d.) or Inderal L.A. 160 mg once daily. The treatments were then crossed over. The double placebo technique was used. Two weeks supply of one capsule daily (9 am) and one tablet q.i.d. (9 am, 1 pm, 5 pm and 9 pm) respectively was provided. Fifty trinitrin tablets were given, to be used only to relieve pain. After each treatment period tablet counts were performed. Diary cards were used to record the number and severity of anginal attacks, the number of trinitrin tablets consumed, subjective sense of well being and level of activity. The patients were seen weekly. Following each treatment period standardised treadmill tests were performed as before. Blood samples were taken following exercise. Plasma propranolol levels were measured by the fluorometric method (Shand et al, 1970). An analysis of variance was performed to compare differences between treatments.

RESULTS

One patient withdrew after the first study week because of epigastric burning attributed to the capsule, identified subsequently as placebo. Twelve completed the study. Their mean age was 54 years (range 43-57) and the mean duration of angina was 60.1 months.

Patient compliance as estimated by tablet count was excellent. Ninety eight per cent of the propranolol tablets and all of the Inderal L.A. capsules were taken. The number and severity of anginal attacks were similar in the two treatment periods. There were no statistically significant differences in patients' trinitrin consumption, subjective sense of well being or activity level between the two study periods. The mean observations and standard errors of heart rate, blood pressure and S.T. segment levels at each test are shown in Table 1 and Table 2.

Mean resting systolic and diastolic blood pressures were significantly lower at one hour while taking propranolol. Mean heart rate at the onset of pain was significantly lower at one hour and two hours while taking propranolol. No other statistically significant differences were observed.

The mean duration of exercise performed at each test for both regimes is shown in Figure 1 and Table 3. There was a slight improvement in exercise
tolerance with both drugs between one and two hours but no significant difference in exercise ability was observed between the two treatments at any time.

The mean blood levels are shown in Figure 2 and Table 3. There were no statistically significant differences at any time.

Fig. 1 Duration of exercise before symptoms in patients at various intervals after receiving propranolol or Inderal LA.

Fig. 2 Blood levels of propranolol and Inderal LA at intervals after administration.
**Table 1**

Resting Values of heart rate blood pressure and ST segment at various intervals after propranolol (Prop.) or Inderal L.A. (L.A.)

| INTERVAL AFTER ADMINISTRATION | 1 hour | 2 hours | 4 hours | 8 hours | 12 hours | 24 hours |
|-------------------------------|--------|---------|---------|---------|----------|----------|
| **Heart Rate**                |        |         |         |         |          |          |
| **(per minute)**              |        |         |         |         |          |          |
| Prop.                         | 57±1.7 | 56±1.6  | 60±2.0  | 54±2.2  | 58±2.5   | 59±1.8   |
| L.A.                          | 58±1.7 | 55±2.5  | 59±1.8  | 55±1.8  | 58±2.4   | 59±2.1   |
| **Systolic B.P.**             |        |         |         |         |          |          |
| **(mm Hg)**                   |        |         |         |         |          |          |
| Prop.                         | 110±3* | 109±8   | 112±4   | 114±4   | 124±5    | 116±4    |
| L.A.                          | 122±2* | 116±4   | 111±4   | 112±4   | 119±4    | 121±5    |
| **Diastolic B.P.**            |        |         |         |         |          |          |
| **(mm Hg)**                   |        |         |         |         |          |          |
| Prop.                         | 64±2.8†| 67±2.7  | 61±3.1  | 69±3.4  | 70±2.9   | 68±2.4   |
| L.A.                          | 73±2.0†| 68±3.5  | 63±2.2  | 70±2.1  | 69±2.5   | 72±3.1   |
| **S.T. Segment Depression (mm)** |        |         |         |         |          |          |
| Prop.                         | 0.6±0.2| 0.5±0.2 | 0.5±0.1 | 0.6±0.1 | 0.5±0.1  | 0.6±0.2  |
| L.A.                          | 0.5±0.2| 0.5±0.2 | 0.4±0.1 | 0.5±0.1 | 0.5±0.1  | 0.6±0.2  |

† P<0.01  * P<0.05   Other results not significantly different.

**Table 2**

Values of heart rate blood pressure and ST segment at the onset of pain at various intervals after propranolol (Prop.) and Inderal L.A. (L.A.)

| INTERVAL AFTER ADMINISTRATION | 1 hour | 2 hours | 4 hours | 8 hours | 12 hours | 24 hours |
|-------------------------------|--------|---------|---------|---------|----------|----------|
| **Heart Rate**                |        |         |         |         |          |          |
| **(per minute)**              |        |         |         |         |          |          |
| Prop.                         | 96±2.9†| 92±2.6* | 98±2.6  | 94±2.4  | 96±2.8   | 99±3.3   |
| L.A.                          | 100±3.1†| 94±2.9* | 96±3.1  | 93±2.8  | 97±3.0   | 96±3.8   |
Systolic B.P. (mm Hg)

|            | Prop. | Prop. | Prop. | Prop. | Prop. | Prop. |
|------------|-------|-------|-------|-------|-------|-------|
|            | 134± 4 | 131± 5 | 130± 5 | 136± 6 | 132± 6 | 136± 5 |
| L.A.       | 139± 5 | 135± 5 | 137± 7 | 136± 5 | 137± 4 | 137± 4 |

Diastolic B.P. (mm Hg)

|            | Prop. | Prop. | Prop. | Prop. | Prop. | Prop. |
|------------|-------|-------|-------|-------|-------|-------|
|            | 82± 2.9 | 85± 2.5 | 81± 3.6 | 79± 3.1 | 83± 4.2 | 86± 3.5 |
| L.A.       | 83± 2.3 | 80± 2.9 | 81± 2.4 | 81± 2.5 | 83± 2.3 | 85± 3.4 |

ST Segment Depression (mm)

|            | Prop. | Prop. | Prop. | Prop. | Prop. | Prop. |
|------------|-------|-------|-------|-------|-------|-------|
|            | 1.3± 0.3 | 1.2± 0.2 | 1.3± 0.2 | 1.4± 0.2 | 1.3± 0.2 | 1.5± 0.3 |
| L.A.       | 1.6± 0.3 | 1.2± 0.3 | 1.3± 0.3 | 1.4± 0.3 | 1.4± 0.3 | 1.4± 0.3 |

† P<0.01  * P<0.05  Other results not significantly different.

Table 3

Exercise duration and plasma propranolol concentration at various intervals after propranolol (Prop.) and Inderal L.A. (L.A.)

INTERVAL AFTER ADMINISTRATION

|            | 1 hour | 2 hours | 4 hours | 8 hours | 12 hours | 24 hours |
|------------|--------|---------|---------|---------|----------|----------|
| Exercise Duration (seconds) |        |         |         |         |          |          |
| Prop.      | 199± 24 | 202± 19 | 165± 19 | 188± 16 | 185± 20 | 173± 18 |
| L.A.       | 176± 18 | 204± 22 | 175± 17 | 188± 20 | 180± 24 | 197± 21 |

Plasma Concentration (ng/ml)

|            | Prop. | Prop. | Prop. | Prop. | Prop. | Prop. |
|------------|-------|-------|-------|-------|-------|-------|
|            | 24.1± 6.5 | 33.6± 7.4 | 33.0± 6.4 | 37.6± 8.2 | 37.9± 8.5 | 21.8± 7.2 |
| L.A.       | 21.2± 7.5 | 27.5± 8.5 | 32.1± 7.1 | 37.0± 7.3 | 37.8± 8.6 | 20.0± 6.7 |

No significant differences present.
Side effects were few and mild in both treatments. Apart from the patient who withdrew while taking the placebo capsule, only one patient had a complaint, fatigue while taking propranolol.

DISCUSSION AND CONCLUSIONS

This study has shown that in chronic dosage patients with angina achieved comparable plasma propranolol levels and had comparable exercise tolerance throughout the 24 hours after a single morning capsule of Inderal L.A. (160 mg) and after conventional propranolol 40 mg q.i.d. These findings support the kinetic studies on healthy volunteers (Leahey et al, 1979).

No important differences in blood levels or recorded clinical parameters were observed.

The excellent compliance on both regimes may be attributable to very close supervision and the patients’ enthusiastic co-operation.

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