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PENBUTOLOL OR HYDROCHLOROTHIAZIDE ONCE A DAY IN HYPERTENSION. A CONTROLLED STUDY WITH HOME MEASUREMENTS

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1 The hypotensive effect of single daily dosing with 80 mg penbutolol was compared to 100 mg hydrochlorothiazide and placebo in a double-blind cross-over controlled trial with daily home measurements in ten hypertensive patients.

2 Penbutolol, 80 mg once a day, reduced significantly the supine and standing blood pressure.

3 This hypotensive effect was more potent than hydrochlorothiazide 100 mg particularly in the evening.

4 The hypotensive effect remained for 24 h as shown by the evening (14 h after dose) and morning (24 h after dose) blood pressure readings.

5 No relevant subjective or physical side effects were recorded. There was no significant change nor individual noticeable variation in biochemical data during penbutolol treatment. However, during hydrochlorothiazide treatment, the expected electrolyte changes were observed (symptom-free hypokalemia and hyperuricemia).

6 Penbutolol serum concentration showed no cumulation after one month of treatment.

7 Sudden withdrawal of penbutolol after 1 month of therapy resulted in a slow return to baseline blood pressures over a 2-week period without rebound.

Introduction

The choice between diuretics and β-adrenoceptor blocking agents as the first drug in the treatment of hypertension remains difficult. Adequate comparison between the two drugs should provide an answer to this problem.

The present study has been designed to compare the hypotensive effect of a diuretic, hydrochlorothiazide and a β-adrenoceptor blocking agent, penbutolol. This latter drug is a potent long acting non-cardioselective β-adrenoceptor blocker. It possesses some intrinsic sympathomimetic activity and weak membrane stabilizing properties. Its potency in man is approximately four times that of propranolol. Penbutolol is almost completely absorbed and does not undergo first pass metabolism. Plasma half-lives after oral administration are 2.5 and 27 h for the fast and slow dispersion phases, respectively (Vallner *et al.*, 1977). Furthermore, the methodology employed i.e. self measurements of blood pressure by the patient has allowed a precise definition of the duration of action as well as withdrawal effects of both drugs.

Methods

Patients selection

Adult patients less than 65 year old were selected. They had mild or moderate hypertension defined as a diastolic blood pressure in the supine position of 95 to 120 mm Hg. Patients with grade III or IV retinopathy were excluded as well as those with renal or hepatic dysfunction or obesity. Those patients in whom β-adrenoceptor blockers are normally contraindicated, that is second or third heart block, a history of bronchospasm or of cardiac failure, were excluded.

Before the beginning of the study, patients were trained in hospital to record their own blood pressures.

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The validity of these measurements was controlled by one of the authors (J.F.D.P.) and the patients were included in the study only when they had demonstrated their competence. They were then asked to record systolic and diastolic pressures every morning and every evening in the supine and standing positions with the same anaeroid sphygmomanometer. Informed consent was obtained from each participant.

Trial design

The trial was a double-blind cross over study, consisting of 4-week periods of treatment, namely placebo, penbutolol or hydrochlorothiazide, then hydrochlorothiazide or penbutolol, and again placebo. The order of the active treatments was selected according to a predetermined random code.

Both active drugs and placebo were available in capsules of identical size, shape and colour. A dose of two capsules equalled 80 mg penbutolol or 100 mg hydrochlorothiazide. Compliance was encouraged by use of special weekly packages containing seven daily dosage boxes of the trial medications.

Patients were seen at two weekly intervals for the first month (baseline placebo period) and then at monthly intervals at the end of each treatment period.

Blood pressure (measured by mercury sphygmomanometer), pulse rate, body weight were recorded at each visit. At the end of each 4-week period of clinical evaluation, 12-lead ECG, serum electrolytes, blood samples for pharmacokinetic studies and a 24 h urine collection for sodium determination were obtained. Plasma renin activity was determined from blood samples taken at the same occasion in the sitting position.

Blood pressure was measured by the same physician in the early afternoon between 13.00 h and 15.00 h (approximately 6 h after drug intake), in the dominant arm after 5 min recumbency (mean of 3 readings) and 1 min standing (mean of 2 readings).

Blood pressure was also recorded at home by the patient with an anaeroid sphygmomanometer at awakening before arising and immediately thereafter in the standing position. At the end of the day, measurements were repeated just before going to bed while standing and again after 5 min rest in bed.

The 12 lead ECGs were interpreted by a blinded observer according to the Code of Minnesota. Sodium, chloride, potassium, calcium, bicarbonate, serum creatinine, uric acid and blood glucose were measured in the routine laboratory. Plasma renin activity (PRA) was determined according to the method of Valloton (1971), and values are expressed in ng ml^{-1} h^{-1}. Free and conjugated penbutolol were determined in serum samples after completion of the study by the method of Hajdu & Damm (1979). The 24 h urine collections were obtained immediately before the visit to the clinic.

Statistical analysis

The physician's measurements recorded at the end of each 4-week period of the study were investigated using an analysis of variance structured for treatments and order effects (Scheffe, 1959; Cochran & Cox, 1957).

The home measurements were reduced to weekly averages and subjected to a similar analysis which also took account of possible time and treatment × time interaction effects.

Such an analysis provides a sensitive test for differences between treatments by adjusting for systematic variation introduced by the other factors.

Where a treatment effect was found to be significant at the 5% level, comparisons among the four treatment means (two active treatments, initial and final placebo) were made using Duncan test. This allows a simple overall significance level to be quoted for a systematic comparison of all pairs of means. Results designated significant were associated with a probability (P) of less than 0.05.

Results

Patients

Sixteen patients entered the study. Six patients did not complete the study; two did not return after the initial visit; two were withdrawn in the initial placebo period: one because his blood pressure returned to normal and one because of concomitant diuretic use. Two patients were excluded during active treatment: one had unreliable home measurements despite a satisfactory initial validation and one developed tachycardia, fatigue and hypertension during the hydrochlorothiazide period.

Ten patients completed the study: eight males and two females (age range: 30–56 years). Six were classified as Keith-Wagener Eye Fundus Grade I and four as Grade II. Eight patients had essential hypertension, one renovascular hypertension and one had hypertension secondary to a polycystic kidney.

Physician measurements

The mean values for blood pressure, pulse and body weight are shown in Table 1. The blood pressure values obtained during the second placebo period were not different from those recorded during the initial placebo period; our baseline was thus not affected by time.

Table 1 Mean (± s.e.mean) blood pressure, pulse rate and body weight measured by the physician under different treatment.

		Placebo 1	*Hydrochlorothiazide*		*Penbutolol*	*Placebo 2*
Blood pressure (mm Hg)						
supine	systolic	167.8±5.4	155.4±8.0 ○	NS	150.9±7.0 ●○	176.3±7.5
	diastolic	109.9±3.2	105.8±4.8 ○	*	98.0±3.4 ●○	114.4±4.0
standing	systolic	163.9±6.7	140.4±6.8 ●○	NS	145.9±6.8 ●○	162.3±6.7
	diastolic	117.1±3.7	107.1±5.0 ●○	NS	106.0±3.2 ●○	114.6±4.5
Pulse rate (beats/min)	supine	76.8±2.2	79.2±3.5	*	62.5±1.5 ●○	77.2±3.2
	standing	88.8±4.4	96.6±5.2	*	69.1±2.3 ●○	89.5±4.7
Body weight (kg)		83.2±2.9	81.4±2.7		82.4±2.9	82.0±2.9

● indicates a significant difference with placebo 1 period
○ indicates a significant difference with placebo 2 period
* indicates a significant difference between active treatments
NS indicates no significant difference between active treatments

Systolic and diastolic blood pressure in the standing position were significantly reduced by both drugs (mean difference −18/11 mm Hg for penbutolol and −23/10 mm Hg for hydrochlorothiazide). By contrast in the supine position only penbutolol produced a significant decrease of systolic and diastolic blood pressure (−17/12 mm Hg for penbutolol and −12/4 mm Hg for hydrochlorothiazide). When the hypotensive effect of both drugs was compared, supine diastolic blood pressure was significantly lower with penbutolol than with hydrochlorothiazide.

The pulse rate (beats/min) was significantly reduced during penbutolol therapy from 76.8 to 62.5 but remained practically unaltered with hydrochlorothiazide (79.2).

Table 2 Mean (± s.e.mean) blood pressure (mm Hg) measured by the patients at home

	Placebo 1	*Hydrochlorothiazide*		*Penbutolol*	*Placebo 2*
Morning supine					
systolic	138.8±2.8	133.9±3.3 ●○	*	130.7±3.0 ●○	137.3±3.2
diastolic	89.7±1.8	84.6±1.8 ●	*	80.9±1.5 ●○	85.0±1.7 ●
standing					
systolic	149.8±3.1	142.5±3.7 ●○	NS	139.5±3.0 ●○	146.9±3.6
diastolic	101.8±2.0	96.0±2.6 ●	*	92.9±2.1 ●○	97.5±2.8 ●
Evening supine					
systolic	145.8±2.9	141.6±3.2 ●	*	135.0±2.8 ●○	141.4±2.9 ●
diastolic	91.4±1.6	87.5±1.8 ●	*	82.1±1.3 ●○	85.4±1.5 ●
standing					
systolic	157.8±3.3	149.3±3.8 ●	*	142.2±2.8 ●○	152.0±3.5 ●
diastolic	103.3±1.9	98.8±2.7 ●	*	94.2±2.1 ●○	97.4±2.3 ●

● indicates a significant difference with placebo 1 period
○ indicates a significant difference with placebo 2 period
* indicates a significant difference between active treatments
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Body weight averaged 83.2 kg at the end of the first placebo period, 82.4 kg after penbutolol and 81.4 kg after hydrochlorothiazide; none of these differences are significant.

Home measurements

Table 2 gives the mean value of the self-recorded blood pressures for each treatment period. Since the analysis of variance shows that neither the time effect nor the treatment × time interaction effect were statistically significant, the means were derived from the combined data of the 4 weekly values of each treatment period.

Both active treatments produced a significant fall in blood pressure. Penbutolol was significantly more effective than hydrochlorothiazide in all parameters except for the systolic BP recorded standing in the morning. The evening values were systematically higher (up to 6%) than those recorded in the morning and this observation was verified for all treatment periods. Similarly, the standing values were also consistently higher (5 to 8%) than the supine values. Finally, as expected, the home measurements were consistently lower (about 15%) than the physician's measurements (Silverberg & Rosenfeld, 1980).

Duration of action

Both penbutolol and hydrochlorothiazide were given as a single dose in the morning. Blood pressure was still reduced in both supine and standing position 24 h after dosing.

Withdrawal

After interruption of both active treatments the blood pressure rose slowly and approached the baseline values within 2 weeks. Figure 1 illustrates the gradual return to baseline values of the five patients who received penbutolol in the last treatment period. None of the patients had any side effect as a result of sudden withdrawal.

Biochemical data

The effects of the treatment regimen on serum electrolytes, creatinine, uric acid, bicarbonates, blood glucose and urine 24 h sodium excretion are shown in Table 3. During hydrochlorothiazide therapy there was a significant decrease in serum potassium and chloride.

There was also a significant increase in serum uric acid, calcium and bicarbonate. No significant differences from control were noticed during penbutolol treatment. Blood glucose and 24 h sodium urine excretion did not change significantly.

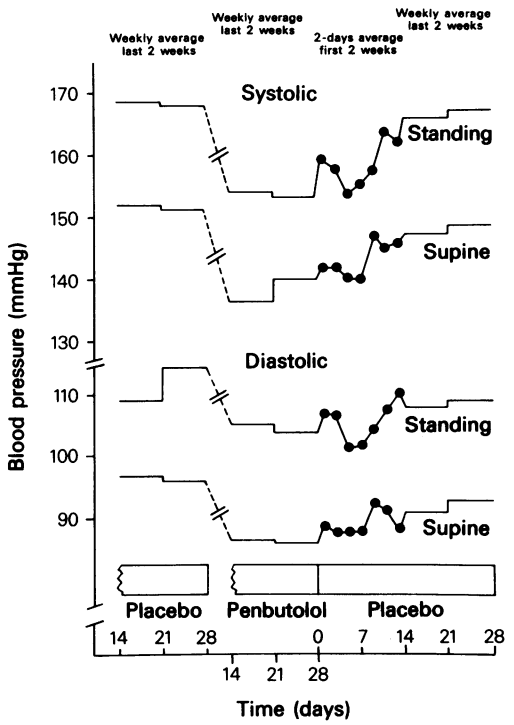

Figure 1 Home blood pressure recordings: effects of penbutolol withdrawal ($n = 5$). Weekly averages of the last 2 weeks of each treatment period have been presented for comparative purposes. For the first 2 weeks of withdrawal, the average of two days has been calculated.

Plasma renin activity (PRA)

As shown in Table 3, plasma renin activity rose during hydrochlorothiazide but failed to decrease significantly during penbutolol. No correlation was found between initial plasma renin activity and the magnitude of the hypotensive effect of penbutolol and hydrochlorothiazide.

Penbutolol serum concentrations

Serum concentrations of free and total penbutolol of blood obtained approximately 6 h after the last dose at the end of the 4-week treatment period averaged 0.12 ± 0.03 μg/ml and 3.56 ± 0.54 μg/ml respectively.

Side effects

Both drugs were well tolerated. One patient reported transient dizziness during hydrochlorothiazide, another transient muscle spasm during penbutolol. As mentioned in methods, one patient dropped out

Table 3 Biochemical data at the end of each treatment period. Mean ± s.e.mean.

Parameter		*Placebo 1*	*Hydrochlorothiazide*		*Penbutolol*	*Placebo 2*
Serum	creatinine (μmol/l)	90±6	88±5		83±4	85±4
	sodium (mmol/l)	142.2±0.5	140.8±0.8 ○	*	143.0±0.5	143.2±0.5
	chloride (mmol/l)	101.9±0.8	96.1±0.1 ●○	*	102.3±0.5	102.0±1.1
	potassium (mmol/l)	3.9±0.1	3.2±0.1 ●○	*	3.9±0.1	3.8±0.1
	calcium (mmol/l)	2.39±0.33	2.48±0.38 ●○	*	2.36±0.23	2.41±0.40
	HCO_3 (mmol/l)	27.1±0.8	29.7±0.8 ●○	*	28.1±0.6	27.1±1.0
	uric acid (mmol/l)	0.29±0.01	0.38±0.04 ●	*	0.31±0.02	0.33±0.03
Blood glucose (mmol/l)		4.95±0.17	5.17±0.24		5.09±0.41	5.20±0.37
Urine 24 h sodium excretion (mmol/l)		120.1±38.3	137.3±31.4		111.0±22.6	125.9±30.8
Plasma renin activity ($ng\ ml^{-1}\ h^{-1}$)		1.49±0.25	5.67±1.51 ●○	*	1.22±0.24	1.63±0.35

● indicates a significant difference with placebo 1 period
○ indicates a significant difference with placebo 2 period
* indicates a significant difference between active treatments
NS indicates no significant difference between active treatments

as a result of tachycardia and fatigue developed during hydrochlorothiazide administration.

Discussion

Our study confirms the efficacy of penbutolol as a hypotensive agent (Sainani *et al.*, 1977; Frick, Hartikainem & Pörsti, 1978). With 80 mg daily for 1 month a mean fall of 17/12 mm Hg supine and 18/11 mm Hg standing was observed for systolic and diastolic blood pressure respectively. These results are of the same order of magnitude as those observed by Hanson & Hökfelt (1976) and by Holti (1979) with a 40–60 mg daily dosage.

The efficacy and the excellent tolerance of β-adrenoceptor blockers has led to the proposal that these hypotensive drugs rather than diuretics should be used as the first choice in the treatment of hypertension. A critical assessment of this attitude hinges upon an adequately designed comparison between the two types of drugs given in optimal amount. In our study we have used a double-blind cross-over design, comparing penbutolol and hydrochlorothiazide. Our data demonstrate that penbutolol is more efficient than hydrochlorothiazide given once daily. All patients had a significant decrease of blood pressure when given penbutolol whereas only 7 out of 10 demonstrate a hypotensive effect when given the diuretic. Furthermore, the net fall in blood pressure for the whole group was slightly but significantly greater with penbutolol than with the thiazide. The clinical relevance of this difference remains to be determined.

This conclusion is largely based on home blood pressure measurements; the question might arise whether this apparent difference is due to the fact that these data were weighted also by readings taken during the first, second and third week when hypotensive efficacy, especially with the thiazide, would not have reached a maximum. If this had been the case, the interaction treatment × time effect in the analysis of variance would have been statistically significant. This was not so for any of the eight variables tested.

It is not surprising that home blood pressure measurements are more sensitive to statistical differences since the average readings are based on a larger amount of data than the physician's.

The difference of effect does not seem to be related to a suboptimal dosage of hydrochlorothiazide; 50 mg twice daily or 100 mg once daily is optimal in adult patients (MacMahon, 1978). Furthermore, the fact that 24 h urinary sodium excretion was similar during both treatment periods makes it unlikely that changes in sodium intake were responsible for the difference in the efficacy of the two drugs.

All the patients had a normal plasma renin activity and were not therefore expected to be specially sensitive to β-adrenoceptor blockers or resistant to diuretics.

The two drugs were clinically well tolerated except for dizziness in one patient. During thiazide period hypokalemia was present in most patients and severe in three of them; serum uric acid was moderately increased in eight patients but did not result in an attack of gout. By contrast, during the β-adrenoceptor blocker period, the potassium and uric acid levels were practically unchanged.

The levels of serum penbutolol achieved after 4 weeks of treatment fall in the same range of those observed at the end of 1 week (Müller, Hundt, Bromley, Torres & Vanderbeke, 1979). These data demonstrate the absence of cumulation of the drug after prolonged administration. Furthermore, the low coefficient of variation of the serum levels (15% and 25%) reflects an homogeneous absorption and is compatible with the absence of first pass effect.

Several papers have documented a rebound phenomenon after sudden withdrawal of β-adrenoceptor blockers. An exacerbation of a pre-existing coronary artery disease was described by Miller, Olson, Amsterdam & Mason (1975) whereas a more benign syndrome of sympathetic hyperactivity including an abrupt rise in standing blood pressure was reported by Lederballe-Pedersen, Mikkelsen, Lanng-Nielsen & Christensen (1979). In our patients, withdrawal of penbutolol did not elicit any such symptom. Blood pressure returned gradually to placebo values within 2 weeks.

The absence of a rebound phenomenon in our series might be due to the small number of patients. Indeed, rebound has been observed only in a minority of patients: 3 out of 27 (O'Brien & MacKinnon, 1972) and 5 out of 20 (Lederballe-Pedersen, 1976).

The multiple home determinations have allowed a detailed monitoring of the hypotensive effect of both drugs on the circadian rhythm of the blood pressure. With hydrochlorothiazide, as well as with penbutolol, a significant hypotensive effect is noted throughout the 24 h after a single dosage. Our data provide further support to the idea that once daily, β-adrenoceptor blockers control adequately blood pressure (Douglas-Jones & Cruickshank, 1976; Reybrouck, Amery, Fagard, Jousten, Lijnen & Meulepas, 1978).

Interestingly, it is mainly in the evening that the hypotensive effect of penbutolol is superior to that of diuretics (Figure 2). Whether this difference is due to a high evening sympathetic tone remains to be demonstrated.

In conclusion, in the dosage given in this study, the hypotensive effect of penbutolol was more marked than that of hydrochlorothiazide. The duration of the blood pressure control with a single daily dose was 24 h and no rebound effect after sudden cessation of the treatment was observed. With these characteristics, penbutolol appears to be an effective and well tolerated once-a-day treatment for mild and moderate hypertension.

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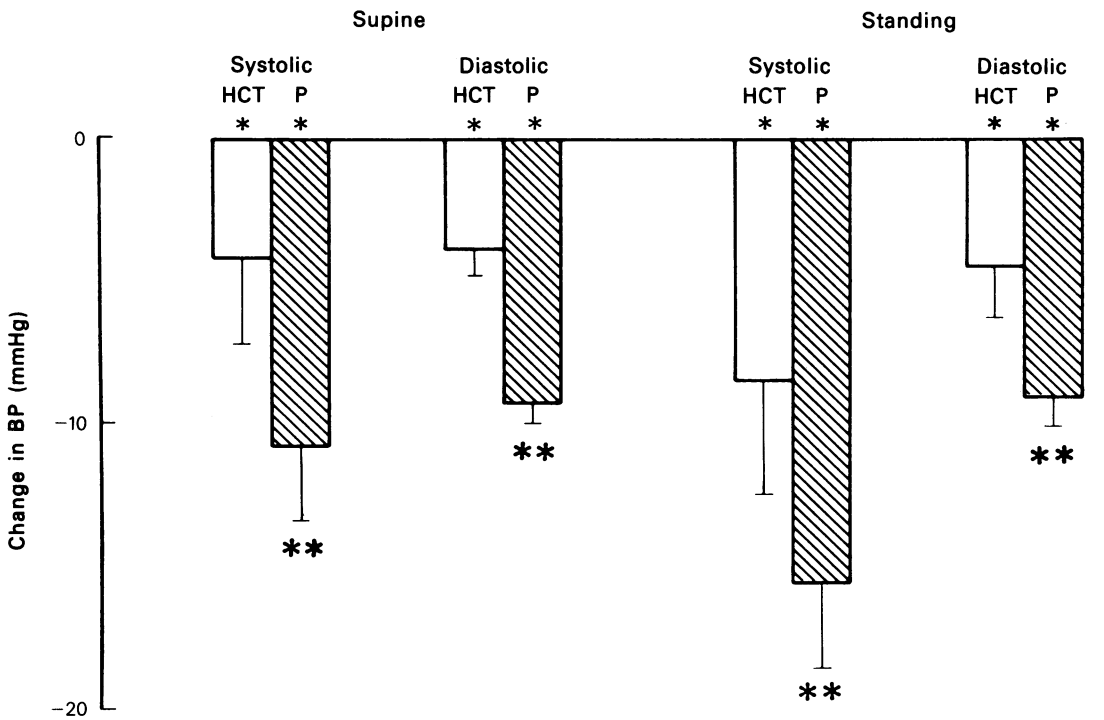

Figure 2 Mean (±s.e.mean) blood pressure differences from baseline (home recording – evening) during active treatments.
*Significant difference from the placebo period. **Significant difference from the preceding column.

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