

Pindolol Once Daily in the Treatment of Hypertension

GÖRAN FRITHZ

From the Department of Internal Medicine, Central Hospital, Eskilstuna, Sweden

ABSTRACT

The beta-adrenergic blocking drug pindolol has been used in the treatment of hypertension, using one single dose per day, given in the morning. 16 patients with mild to moderate hypertension were treated with doses which were increased if necessary up to 20 mg, and 14 patients achieved an adequate level of blood-pressure control. The trial was carried out as a single-blind cross-over study. The study shows that pindolol, a non-selective beta-blocker of high potency, may be given once daily as a hypotensive, offering advantages both for patients and physicians. Side-effects were infrequent.

INTRODUCTION

During the last decade, beta-adrenergic receptor blocking drugs have become an accepted form of treatment of arterial hypertension. An increasing number of different beta-blockers, with varying degrees of selectivity, potency and intrinsic sympathomimetic effect, have been introduced on the market.

Pindolol (Viskén®) belongs to the group of beta-blockers, which have an intrinsic sympathomimetic effect, and is characterized especially by its high potency (2). Its pharmacokinetics have been exhaustively described, particularly in relation to the liver-metabolism, by Gugler et al. (10). Its hypotensive effect has been documented, e.g. by Dunér (4), Collings & King (3) and Feltham et al. (5). Pindolol has usually been administered twice to three times daily in the treatment of hypertension. However, a recent study by Olsson & Varnauskas (14) showed that the betablocking effect after one single oral dose of 10 mg pindolol lasts for 24 hours. Even if the beta-blocking effect cannot be directly correlated to the hypotensive effect, these results suggest the possibility of a less frequent administration of pindolol in the treatment of hypertension.

Recently two Swedish studies have demonstrated that it is possible to maintain an adequate blood-pressure level, with one single dose of pindolol, in

patients, who have achieved an adequate pressure on multiple doses of either pindolol, alprenolol or propranolol (7, 13). With this background a study has been designed to investigate the possibility of initiating treatment of patients with hypertension with a single dose of pindolol which is gradually increased, as required.

MATERIAL AND METHODS

Out-patients with mild to moderate hypertension were selected for the study. All were previously untreated and referred from general practitioner for investigation of hypertension. They were all included in the routine examination scheme including e.g. ECG, fundoscopy, chest X-ray, electrolytes and creatinine in serum and urinary analysis for protein, glucose and blood cells. If necessary, further investigations were carried out, such as intravenous pyelography, angiography and hormone analysis. The investigations were carried out parallel with the treatment. The age and sex distribution is shown in Table I. In Table II the patients have been grouped according to the WHO-criteria of hypertension as well as to the fundoscopy changes according to Keith-Wagner-Baker.

Patients with the usual contraindications for treatment with beta-blockers such as asthma bronchiale, AV-block II and III, and heart failure, were excluded from the study.

Design of the trial

At least two blood-pressure measurements were taken, on two different occasions, before the treatment started. After that, a run-in period of three weeks on placebo was used. Patients, whose diastolic pressure fell below 105 mmHg during the placebo period were to be excluded from the study. The blood-pressure after the placebo period was recorded as the initial value in the calculations.

In the phase of active treatment, pindolol was given orally at 8 a.m., starting with a 5 mg dose. The blood-pressure was measured at four week intervals. The criterion for adequate pressure-control was considered to be a pressure under 165/95. The dose of pindolol was increased in steps of 5 mg up to a total single dose of 20 mg. Doses over 20 mg were not regarded as suitable in this study. The period of active treatment covered 4 months. Thus, patients requiring 20 mg were observed for one month on that dose. The blood-pressure was always

Table I. *Patients grouped according to age and sex*

	Age, years		
	30-39 (n)	40-49 (n)	50-59 (n)
Men	2	5	3
Women		3	3

measured by the same person, the author, with the same Mercury sphygmomanometer, with a 13 cm broad arm-cuff, after 10 minutes rest. The diastolic pressure was recorded as the end of phase 5, i.e. disappearance of the sounds. The pressure was always measured in the out-patient ward between 8-9 a.m. The patients were instructed not to take the morning dose of pindolol on that day. For the statistical evaluation, Student's two tailed *t*-test for paired differences has been used.

RESULTS

16 patients were treated on the one dose per day regime. No one had to be excluded due to pressure-fall during the placebo period. 14 responded in the study with a pressure-fall to under 165/95 mmHg. Two did not reach that level. Both non-responders belonged to WHO-group II and had a diastolic pressure of 100 mmHg after four months, i.e. after one month on 20 mg pindolol. One of these patients had FH (Fundus Hypertonicus) II in the eye-grounds, the other FH I.

The results after four months treatment are shown in Table III, together with the dosages of pindolol at that time. The mean dosage of pindolol is somewhat lower for patients belonging to WHO I group than that for the WHO II group.

In three cases mild side effects, for which pindolol may have been responsible, were registered. One patient complained of palpitations, one of dizziness and one of slight nausea after the tablet intake. Two patients were receiving 15 mg, and the third 20 mg. None reported sleep-disturbances.

DISCUSSION

Most of the patients responded well, with adequate pressure-control on one single, moderate dose of pindolol, given in the morning. It would perhaps have been possible to go further with an increased dosage. However, it was judged as not advisable, partly due to the possibility of subjective symptoms, and partly because a paradoxal effect on the

pressure could be expected. It has recently been discussed, that, with beta-blockers which have an intrinsic sympathicomimetic property, the stimulating effect may counteract the hypotensive effect and give a rise in the blood-pressure (15). Therefore, after the study was ended, it was considered preferable to treat the two cases who did not achieve a fully acceptable pressure-control on pindolol alone, with a combination of a single daily dose of pindolol with one tablet of the fixed combination of 50 mg hydrochlorothiazide and 5 mg amiloridchloride (Moduretic®) given simultaneously. On that combination both patients achieved a diastolic pressure of 90 mmHg after one month's further treatment.

The study demonstrates the clinical application of the earlier experimental observations by Olsson & Varnauskas (14). However, it must be born in mind, that the action of beta-blockers in hypertension is complex and that no direct correlation between the beta-blockade, measured as the inhibition of isoprenaline-induced tachycardia, and the hypotensive effect can be quoted.

The blood-pressure was measured in the morning to obtain an interval of 24 hours from the last tablet intake. It could naturally be argued, that it is of more interest to measure the pressure during the day to see, whether the pressure control could be maintained in active life. However, it is well-known that the effect of a peroral dose of pindolol reaches its peak after about 3 hours (1), so there is little reason to believe, that the pressure control should be less satisfactory during the day. The ideal must, of course, be to make repeated measurements during the day, which in this study was impossible for practical reasons, since the patients were in active employment. Telemetric measurements in selected cases offer one possibility in such situations, another is measurements by the patients themselves at repeated intervals during the day. Gordon (9) recently reported three patients who cooperated in such a study, and he found little difference in the

Table II. *Patients grouped according to WHO and Keith-Wagner-Baker hypertension classification*

Classi- fication ...	WHO I (n)	WHO II (n)	FH 0 (n)	FH I (n)	FH II (n)
Men	7	3	5	2	3
Women	5	1	3	2	1

Table III. Blood-pressure before and after 4 months treatment and the dose of pindolol in the 4th month

Before treatment	Range	After treatment	Range	Diff.
Mean systolic BP, mmHg 181.2±7.1	210–170	150.1±8.3	165–120	31 $p<0.001$
Mean diastolic BP, mmHg 110.5±3.2	120–105	91.0±3.0	100–80	19 $p<0.001$
Dose in the 4th month	10 mg	15 mg	20 mg	
Patients, WHO I	3	7	2	
Patients, WHO II		1	3	

overall blood-pressure control whether pindolol was administered once, twice or three times daily.

The difficulties in maintaining patients with known hypertension on continuous treatment are documented in many studies (6, 8, 11). It is also known, that the chances of missing tablet in-takes increase with the dosage frequency (12). Therefore the administration of pindolol once daily can be useful in helping patients to comply with the prescribed treatment. If an adequate response is not obtained on a tolerable dose of the beta-blocker, it is reasonable to suggest the coprescription of a long acting diuretic, which can also be administered once daily, rather than a drug which requires administration at more frequent intervals. This matter, however, needs further investigation.

The material is too small to draw any certain conclusions regarding the side-effects. It is worth noting that no patients had sleep disturbances or nightmares. This is in agreement with earlier observations on once a day dosage (8, 13) and perhaps these well-known side-effects can be avoided when the tablets are given once daily in the morning. It is also unlikely that undesirable beta-blocker-induced bradycardia would occur with drugs having a sympathicomimetic effect.

In a study like the present one, which is not performed with a double-blind technique, the bias-risk has to be considered. However, the aim has been to investigate a simple treatment regime and not to prove the hypotensive effect of pindolol, which is already documented (3, 4, 5). Furthermore, it is debatable whether there is any possibility of performing a strict double-blind trial with beta-blockers, in view of their effect on the pulse rate both at rest and under work load.

Summarising, the once daily dosage regime with pindolol seems to be a simple and effective way to

treat mild to moderate hypertension with relatively few side-effects. It offers advantages, both for the patient and the physician, which are of great importance in view of the very long duration of therapy.

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Address for reprints:

Göran Frithz, M.D.
Department of Internal Medicine
Central Hospital
S-631 88 Eskilstuna
Sweden