Br. J. clin. Pharmac. (1984), **17**, 547–552

Patients compliance in hypertension—the importance of number of tablets

J. ASPLUND, M. DANIELSON & P. ÖHMAN
Departments of Medicine, Central Hospital Falun, South Hospital Stockholm and Region Hospital Linköping, Sweden

1 The importance of number of tablets for patient compliance was investigated in 160 patients with mild–moderate essential hypertension treated with a β-adrenoceptor blocker and a thiazide diuretic. Mean BP at entry 146 ± 16/92 ± 8 mm Hg.

2 All patients were given pindolol 10 mg and clopamide 5 mg in one combination tablet or in separate tablets for 4 months respectively. Approximately 90% of the patients took > 90% of the prescribed dose throughout the study.

3 Mean BP decreased progressively and heart rate increased slightly.

4 Side effects were more frequently reported during the first month of the study than previously, and 30 patients discontinued the treatment. No differences in this respect were seen between 1 and 2 tablets daily.

5 Approximately 75% of the patients preferred 1 tablet daily, but combining two drugs in one tablet had no effect upon compliance.

Keywords compliance hypertension number of tablets

Introduction

Hypertension is a disorder that usually requires lifelong treatment, which therefore should be kept as simple as possible. Usually subjects with high blood pressure are given treatment, though sometimes with unsatisfactory result, and some are not treated at all despite the fact that the diagnosis is known (Berglund *et al.*, 1976; Hedstrand & Aberg, 1976). There could be many reasons, but it is known that patient compliance, and probably also the effectiveness of treatment, partly depends on the number of drugs and administrations per day (Gatley, 1968; Ayd Jr, 1972). The aim of this study was to evaluate the effects on blood pressure (BP) and heart rate (HR), patient compliance and patient preference of the number of tablets per day given to hypertensive patients under treatment with a β-adrenoceptor blocker and a thiazide diuretic.

Methods

In a multicentre, cross over study 25 physicians from 18 hospitals in Sweden participated. One hundred and sixty patients (98 men, 62 women) were recruited. Their mean age was 51 ± 10 years, 108 had mild and 52 moderately severe primary hypertension. The known duration of hypertension was 6 ± 5 years. All had normal renal function. Twenty-five per cent were smokers. Patients with alcohol abuse were excluded. Patients included had to be well controlled while treated with a β-adrenoceptor blocker and a thiazide diuretic. Their initial BP at rest supine was 146 ± 16/92 ± 8 mm Hg and HR 64 ± 10 beats/min.

During the entire study the patients were given pindolol 10 mg and clopamide 5 mg either in one combination tablet or in two separate tablets. Both drugs have a documented BP-

lowering effect and the side effects of both drugs are well known (Frithz *et al.*, 1978; Nyberg *et al.*, 1982). After randomization 80 patients began with one tablet containing pindolol 10 mg and clopamide 5 mg (= group A) while the others were given the same drugs in two separate tablets (= group B) in the morning = Period I. After 4 months the two groups changed treatment regimen and were followed for another four months = Period II. A standard surplus of tablets were supplied to the patients to provide flexibility in the appointment of return visits and methodological possibility of a tablet consumption > 100%. After the first and fourth month of each period BP and HR, plasma concentration of pindolol, serum potassium and uric acid, number of tablets returned, side effects and patients' experience of the treatment were registered.

BP was measured with a mercury sphygmomanometer after 5 or 10 min supine rest according to the standardized procedure for each investigator and after 2 min standing. HR was auscultated in connection with BP measurements. The patients returned the tablet bottles (1 or 2) at each visit and the number of tablets left were counted. Plasma concentration of pindolol at the time of BP measurement was analyzed according to Guerret *et al.* (1980). The time between drug intake and blood sampling was noted. Spontaneously reported side effects were registered. The patients' experience of the treatment during the two periods was evaluated by means of a questionnaire. Those who started with one tablet, group A, answered the questions after 4 (= 1 tablet once daily) and 8 months (= 2 tablets once daily), while those who started with two tablets, group B, answered the questions only after 8 months (= 1 tablet once daily).

The comparison of the results is based on 130 patients since there were 30 drop-outs for different reasons (see below). Routine statistical methods for the calculation of mean values and standard deviations were used. Students two tailed *t*-test for paired observations was used and significance was considered at the 5% level. The study protocol was approved by the local ethical committee of the University of Gothenburg. All patients gave their informed consent.

Results

Blood pressure and heart rate

Mean systolic and diastolic BP decreased during the study (Figures 1 and 2) and after 8 months of treatment all changes in BP mean values were significant, except for diastolic BP in group A, i.e. patients who took 2 tablets daily during the last period. The numerical differences between group A and B and period I and II were not statistically significant due to the marked inter-

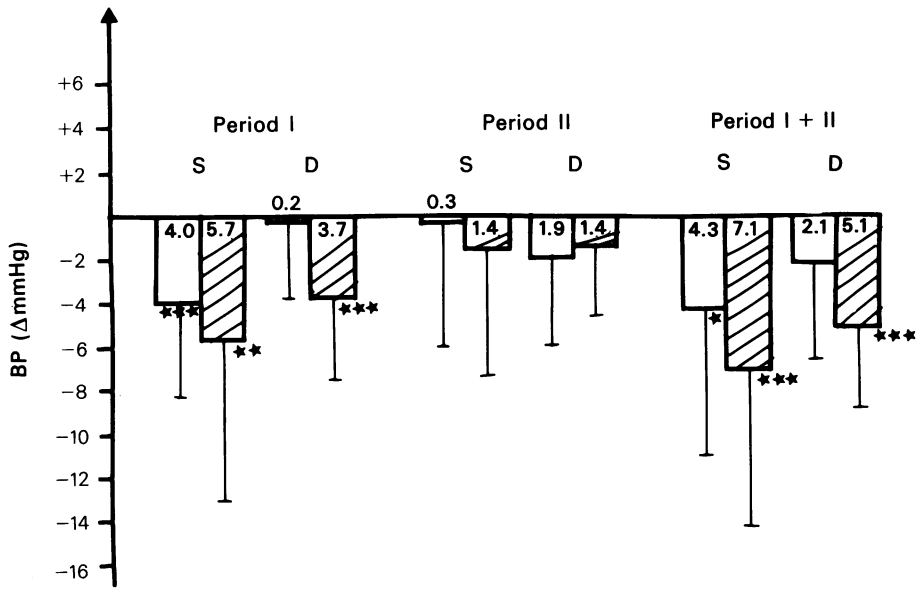

Figure 1 Changes in supine blood pressure (S systolic, D diastolic) during period I (= month 1–4) and period II (= month 5–8). Group A (□) = 1 combination tablet, Group B (▨) = 2 separate tablets. Mean ± s.d. $n = 130$. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

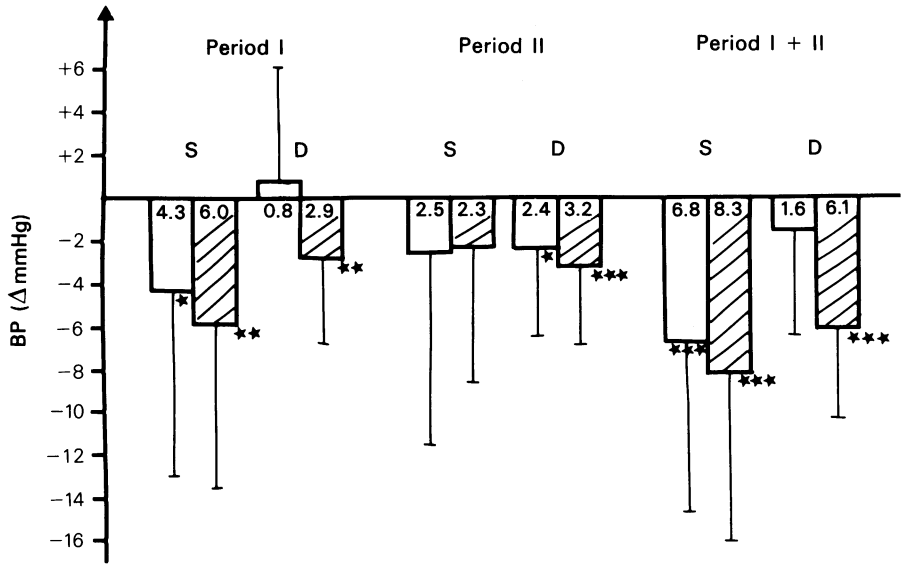

Figure 2 Changes in standing blood pressure during period I (= month 1–4) and period II (= month 5–8). Group A (□) = 1 combination tablet, Group B (▨) = 2 separate tablets. Mean ± s.d. $n = 130$. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

individual variation in BP change. Heart rate increased at the transfer to pindolol and clopamide (Figure 3) but without any difference between group A and B or period I and II.

Tablet count

The tablets returned were counted at each visit. The percentages of patients who had taken < 90% of the prescribed dose at 1, 4, 5 and 8 months of treatment were 12.5, 9.2, 6.1 and 11.5% respectively. Between 2.4 and 6.5% of the patients had used more than one tablet extra per month (= 3.3%) during the study, irrespective of treatment period. Thus, adherence to therapy was not affected by treatment duration or the number of tablets prescribed per day. In group A, 33 (51%) patients claimed that they had never forgotten a tablet during period I. This was true in 80%. During period II, when the patients in group A took two tablets daily, 69%

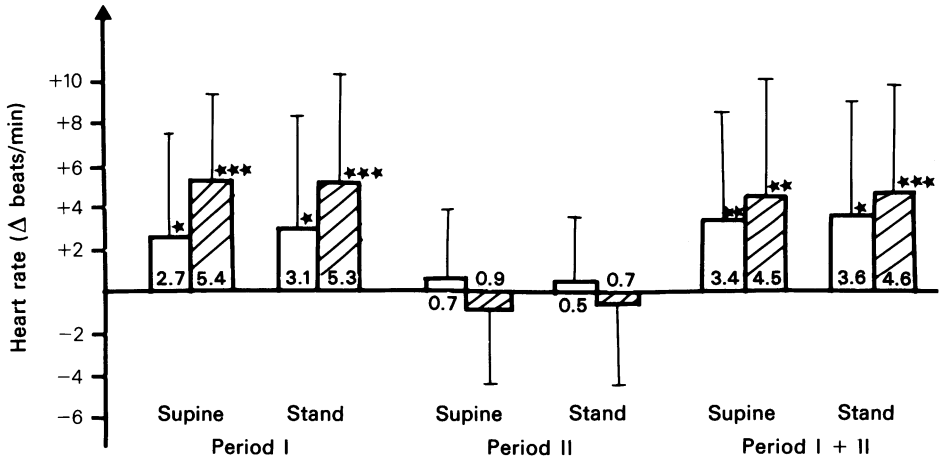

Figure 3 Changes in supine and standing heart rate during period I (= month 1–4) and period II (= month 5–8). Group A (□) = 1 combination tablet, Group B (▨) = 2 separate tablets. Mean ± s.d. $n = 130$. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

of the 34 patients who considered themselves strictly adherent to therapy in fact were. Patients in group B answered the questionnaire only after the 4 months when they had taken 1 tablet daily. Thirty-three of them claimed that they had never forgotten any tablet, which was true for 88%.

Pindolol in plasma

Blood samples for the determination of plasma concentration of pindolol were drawn at different numbers of hours after the intake of pindolol 10 mg. This resulted in a great variation of plasma concentration (Figure 4). Only a few patients had a concentration < 10 ng/ml and at a single visit. The plasma concentrations did not differ between the periods with the drugs combined or in separate tablets. Neither were there any difference in plasma concentration in different age groups 2–4 h after drug intake.

Serum potassium and uric acid

At entry mean serum potassium was 3.9 ± 0.43 mmol/l and 3.9 ± 0.37 mmol/l in group A and B respectively and serum uric acid 343 ± 61 mmol/l and 343 ± 87 mmol/l respectively. These values were not significantly altered during the observation periods.

Complaints

Among specific tolerance complaints, tiredness, vertigo, sleep disturbance and headache dominated. Whether the patients started with one or two tablets daily, the number of complaints during the first month increased compared to the pre-investigational situation, also with drop-outs excluded, whereafter it returned to approximately the previous level for the rest of the observation period. After 4 months of treatment, one tablet daily seemed to give less complaints, but this impression was not confirmed at the 8 months control.

Drop-outs

Thirty patients discontinued the study for the following reasons: subjective complaints 20 (tiredness, dizziness, sleep disturbances, headache, palpitations, nausea/abdominal discomfort, bronchial obstruction, sweating and unspecified uneasiness); hypokalaemia 4; occurrence of concomitant disease 4 (diabetes mellitus, gastric cancer, dermatitis, allergy) and non-compliance 2 (1 patient after 1 month due to a marked increase in BP, 1 due to misunderstanding of drug dosage—continued also previous medication—withdrawn after 4 months). The majority (n = 20) dropped from the study during

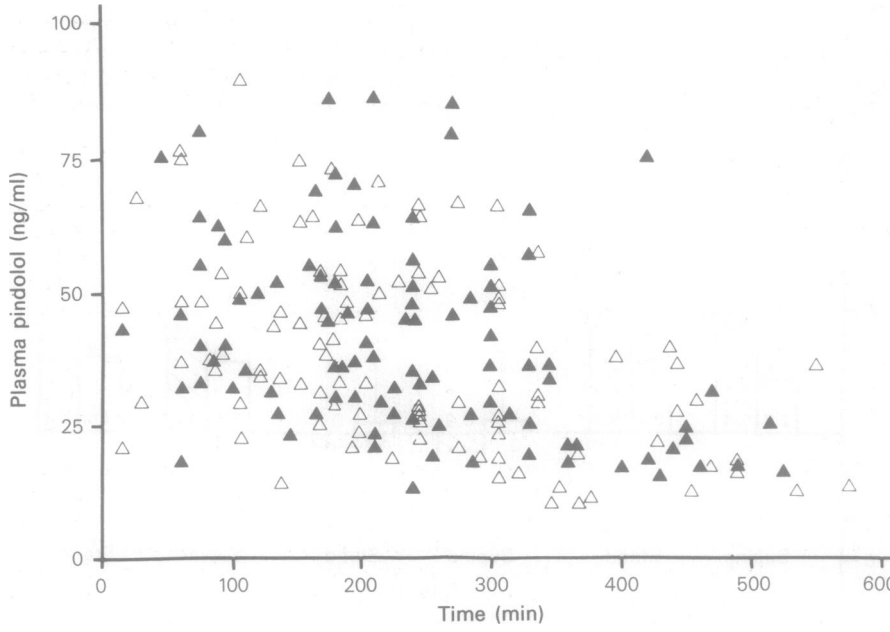

Figure 4 Plasma concentration of pindolol (ng/ml) in relation to minutes after drug intake. ▲ = 1 combination tablet, △ = 2 separate tablets.

the first month of treatment, 26 during the first 4 months. There were no differences in this respect between one and two tablets daily.

Patient experience

Question 1: Do you experience any difference in taking one tablet compared to taking two tablets in the morning?—After having taken one tablet for 4 months 54% of the patients in group A and 50% in group B answered yes. All of them considered one tablet better. After having changed to two tablets every morning the patients in group A answered: Worse with two tablets 45%, better with two tablets 16% and no difference 39%.

Question 2: For your future antihypertensive treatment, would you prefer (a) one tablet in the morning? (b) two different tablets in the morning? or (c) does the number of tablets not bother you?—After having taken one tablet in the morning for 4 months, 74% of the patients in group A and 76% in group B preferred one tablet while 26 and 24% respectively said that it did not matter. Of the patients in group A who had changed to two tablets in the morning 72% wanted one tablet in the morning and 28% said that it did not matter.

Discussion

Compliance with drug treatment in hypertension has been the subject of extensive studies concerning anything from psychological aspects to different drug dosage prescriptions (Podell, 1975; O'Hanrahan & O'Malley, 1981; Haynes *et al.*, 1982). The aim of this study has primarily been to investigate the importance of a simplified therapy for patient compliance, one tablet instead of two tablets once daily, and which effects this might have on blood pressure, heart rate, different biochemical parameters and on tolerability. Despite a clear patient preference for one tablet daily, the effects on the studied parameters of the two types of drug administration in this patient material did not differ. The results could therefore be said to be 'negative'. Anyhow, we have found it important to report them, since a number of problems related to studies of patient compliance are illustrated.

The patient material consists of individuals with established hypertension on concomitant therapy with a β-adrenoceptor blocker and a duiretic. The material is highly selected, since at the beginning of the study all patients had a normal blood pressure and had thereby demonstrated an adequate compliance to the antihypertensive treatment with two drugs. They had also accepted to participate in a study of a new tablet, though with well known components, and had become aware of the investigational situation. It is difficult to study patient compliance, because once you start to measure it, it is already affected. We did not try to withhold the aim of the study. The patients were initially informed about the antihypertensive drugs given and they have continuously reported 'side effects' (= complaints) and via a questionnaire been asked which drug regimen they preferred and how they have adhered to given prescriptions. The investigational situation probably activated the patients who become more aware of the treatment. Thereby most probably compliance was improved (McKinney *et al.*, 1973). To obtain more optimal investigational premises, previously untreated patients should be studied, with the investigational procedure incorporated in the regular routines of the general practitioner to avoid awareness and activation of the patient by the investigation in itself.

Before the study, the patients were treated with different drugs in a variety of doses. When changing to pindolol and clopamide, all patients were given the same dose without aiming at equipotency with prior treatment. Despite this, we found that for the patients who completed the study we could maintain and even improve their BP control (as a mean) by giving them pindolol 10 mg and clopamide 5 mg daily in one tablet or separately. Since the BP reduction was independent of the number of tablets; it could be the result of a generally improved management induced by the investigational situation, or a better blood pressure reducing effect of the drugs given. With the questionnaire it was also shown that, if the patients had any preferences, they were in favour of a simple drug administration with a combination tablet. Rather many patients were indifferent to the number of tablets, however, which probably was due to the selection of patients who were well controlled while treated with several tablets.

Many complaints and drop-outs were registered. This is notable since the patients had been given a similar pharmacological treatment earlier. On the other hand, the further BP reduction acquired could result in more patients getting symptoms of unspecific nature like tiredness, dizziness and headache. The investigational situation in itself also implies a greater awareness and suspiciousness from the patient, that may increase the complaints and be the cause of the 13 drop-outs due to unspecific side effects.

Withdrawal of long-term β-adrenoceptor blockade without intrinsic sympathomimetic

activity (ISA) might give a rebound phenomenon due to an increase in the number of β-adrenoceptors and/or their sensitivity during β-adrenoceptor blockade without ISA (Prichard & Walden, 1982). This may explain the circulatory related complaints, i.e. palpitations that caused five drop-outs when changing to a β-adrenoceptor blocker with ISA. Hypokalaemia (four cases) could be due to a better adherence to the therapy or an individual variation in the sensitivity to the hypokalaemic effect of different diuretic agents. The other drop-outs have specific causes; two patients lost BP control, four developed a concomitant disease and two did not want to continue the study.

The patients' opinion about their drug intake is rather adequate, but as expected, the number of tablets missed was slightly underestimated. Deterioration of compliance with time was not noted during the study and no difference existed between the periods with one and two tablets. The patient selection, as discussed above, may have contributed to this good result. Measurements of plasma levels of pindolol did not reveal any notorious uncompliant patient.

This study has demonstrated the positive value of a good management for BP control in hypertensive patients. A simple treatment, rather frequent visits to the clinic and activation of the patient has improved BP control, but the relative importance of the separate factors cannot be exactly defined. At the same time a high number of complaints and drop-outs were noted in patients already treated with similar drugs when changed to the investigational drugs. The importance of the mode of drug administration for the patients' adherence to therapy needs further evaluation.

The following physicians participated in the study: Johan Asplund, Falun; Ragnar Bergström, Härnösand; Mats Danielson, Stockholm; Anna Engström-Laurent, Uppsala; Sven-Erik Fagerberg, Örebro; Göran Frithz, Eskilstuna; Bengt-Göran Hansson, Halmstad; Lennart Hansson, Göteborg; Nels Christian Henningsen, Malmö; Björn Hole, Kalix; Frit Huhtasaari, Kalix; Bengt E. Karlberg, Linköping; Jerzy Leppert, Västeras; Hans Liedholm, Lund; Ingvar Liljefors, Stockholm; Bengt Möller, Sundsvall; Sven Nilsson, Jönköping; Ola Ohlsson, Kristianstad; Claes Ringqvist, Sundsvall; Olof Svensson, Jönköping; Tomas Thulin, Lund; Kerstin Tolagen, Karlstad; Hans Aberg, Uppsala; Brage Aström, Västeras; Peter Öhman, Linköping.

References

Ayd Jr., F. J. (1972). Once-a-day neuroleptic and tricyclic antidepressant therapy. *Int. Drug Ther. Newsletter*, **7**, 33–40.

Berglund, G., Andersson, O. & Wilhelmsen, L. (1976). Prevalence of primary and secondary hypertension: studies in a random population sample. *Br. med. J.*, **2**, 554–556.

Frithz, G., Danielson, M., Henningsen, N. C., Malmborg, R. O., Nordström-Öhrberg, G. & Schröder, G. (1978). Long-term blood pressure control with pindolol given once daily. *Eur. J. Cardiol.*, **7**, 131–136.

Gatley, M. S. (1968). To be taken as directed. *J. Roy. Coll. Gen. Practit.*, **16**, 39–44.

Guerret, M., Lavene, D. & Kiechel, J. R. (1980). Determination of pindolol in biological fluids by electron capture GLC. *J. pharm. Sci.*, **69**, 1191–1193.

Haynes, R. B., Mattson, M. E., Chobanian, A. V., Dunbar, J. N., Engbretson, Jr. T. O., Garrily, T. F., Leventhal, H., Levine, R. J. & Levy, R. L. (1982). Management of patient compliance in the treatment of hypertension. Report from the NHLBI Working group. *Hypertension*, **4**, 415–423.

Hedstrand, H. & Aberg, H. (1976). Detection and characterization of middle-aged men with hypertension. *Acta med. Scand.*, **199**, 273–280.

McKinney, J. M., Slining, J. M., Hendersson, H. R., Devins, D. & Barr, M. (1973). The effect of clinical pharmacy service on patients with essential hypertension. *Circulation*, **48**, 1104–1111.

Nyberg, G., Asplund, J., Anagreus, N., Astrom, B., Leppert, J., Bergström, R., Övermo, J., Kullman, S. & Lessem, J. (1982). New design for clinical trial of antihypertensive drugs applied to pindolol, clopamide and combinations thereof. *Lancet*, **i**, 355–358.

O'Hanrahan, M. & O'Malley, K. (1981). Compliance with drug treatment. *Br. med. J.*, **3**, 298–300.

Podell, R. N. (1975). *Physician's guide to compliance in hypertension.* Merck & Co Inc.

Prichard, B. N. C. & Walden, R. J. (1982). The syndrome associated with the withdrawal of β-adrenergic receptor blocking drugs. *Br. J. clin. Pharmac.*, **13**, 337S–343S.

(Received September 30, 1983, accepted December 14, 1983)