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Effect of a new calcium antagonist, tiapamil, in hypertension of the elderly

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1 The antihypertensive effect of a single oral dose of tiapamil (450 mg) and placebo were compared in a single blind randomized cross-over study in 10 71–86 year old hypertensive patients. Blood pressure (BP) and heart rate (HR) were recorded every 15 min for 12 h by an automatic device.

2 Tiapamil led to a decrease in mean daytime systolic (SBP) and diastolic (DBP) BP from 171 ± 12/98 ± 10 mm Hg to 159 ± 11/90 ± 9 mm Hg ($P < 0.001$) without significant variation in HR.

3 Thereafter patients received tiapamil 450 twice daily; by the seventh day of treatment mean daytime SBP and DBP were 155 ± 13/85 ± 14 mm Hg ($P < 0.001$ *vs* placebo). The hourly mean values of SBP recorded for 8/12 h (first tiapamil day) and 10/12 h (seventh tiapamil day) were significantly lower than the corresponding values after placebo.

4 We conclude that tiapamil in the elderly exerts a sustained antihypertensive effect lasting 12 h or more, with only minor variations in HR. This effect predominates on systolic pressure and is significant from the first dose.

Keywords hypertension elderly patients calcium antagonists tiapamil

Introduction

The prognostic importance of hypertension in the elderly (Kannel & Gordon, 1973) and particularly that of systolic pressure (Kannel & Gordon, 1973; Kannel *et al.*, 1980a) are now well recognized. However, the demonstration that patients in this age group do benefit from long term treatment of their systolic hypertension is still missing. One epidemiological study currently in progress (Amery *et al.*, 1978) should hopefully answer this question.

The optimal therapy of hypertension in this age group is also a continuing debate. A recent study has demonstrated that the mechanism of systolic hypertension in the elderly differs markedly from that of systolic hypertension in young people (Simon *et al.*, 1979). This could explain the different response to β-adrenoceptor antagonists, in the former population (Buhler *et al.*, 1980) (Levenson *et al.*, 1983a). Diuretics, although effective in elderly patients, can cause an increase in their plasma creatinine concentration (Amery *et al.*, 1978). Centrally acting antihypertensive drugs could favour postural hypotension in the elderly, particularly those with cerebrovascular disease (Appenzeler & Descarries, 1974). Therefore both in terms of efficacy and tolerance the treatment of hypertension in the elderly requires a specialised approach. Despite these considerations and the high prevalence of hypertension in the elderly,

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only a small percentage of patients over 60 years are included in trials of antihypertensive drugs (Koch-Weser, 1978).

Recent observations that verapamil could be particularly effective in older patients, led Buhler *et al.* (1982) to propose the use of calcium antagonists as the first line treatment of hypertension in these patients. We report here one of the first trials of antihypertensive drugs conducted in a selected population of patients above 70 years. It assesses the acute and short term antihypertensive effect of tiapamil, a new calcium antagonist (Thorens & Hauesler, 1979).

Tiapamil is *N*-(3,4-dimethoxyphenethyl-2-(3,4 dimethoxyphenyl)-*N*-methyl-*m*-dithiane-2-propylamine 1,1,3,3-tetraoxide (Figure 1) and is similar in structure to verapamil. However, when compared in animal studies, tiapamil appears to differ from verapamil by the absence of negative inotropic effect in therapeutic doses or concentrations (Haeusler *et al.*, 1982). Both drugs are extensively metabolized, but whereas the metabolites of verapamil appear in urine the metabolites of tiapamil are mainly excreted in the faeces. Tiapamil is 78% bound to plasma proteins, its half-life of elimination ranges from 2 to 3 h and its oral bioavailability from 20 to 30% (Wendt, 1982).

Methods

Patients

Eight women and two men hospitalized in a medium stay hospital were included in this study. Informed consent was obtained from each patient prior to entry into the study; none of them had any cognitive impairment. Their average age was 79 years (71–86 years). All had mild to moderate arterial hypertension; in view of the known variability of the blood pressure in elderly subjects, a minimum of 20% of values higher than 160 mm Hg systolic or 95 mm Hg diastolic, at the first blood pressure recording was required as a criterion for definitive inclusion in the study. Obesity, cardiac insufficiency above NYHA Stage II, abnormal liver function tests (bilirubin SGOT, SGPT), sick sinus syndrome, second or third degree AV block and bifascicular block were criteria for exclusion. Mean creatinine clearance of the patients, calculated on the basis of the serum creatinine according to Cockcroft's formula (Cockcroft & Gault, 1976) was 35.5 ml/min.

The patients had been hospitalized for an average of 30 days and all previous antihypertensive medication was stopped at least 2 weeks before the start of the study, except in one case where clonidine was stopped only 3 days earlier, following gradual reduction of the dosage. During the whole period of the study the patients received a measured diet providing about 80 mmol of NaCl and 50 mmol of KCl per day and no other drug. Their customary daily activities including meals were maintained unchanged.

Arterial blood pressure was measured automatically by means of an oscillometric blood pressure recorder of the Dynamap 845 type (Johnson and Johnson). Briefly this apparatus uses, in addition to the cuff, two pressure indicators coupled with a microprocessor. Mean arterial pressure (MAP) is directly measured as the cuff pressure when maximum oscillations occur. Systolic blood pressure (SBP) is the cuff pressure when the amplitude of the oscillations suddenly grows larger, as the pulse pressure breaks through the occlusion. Diastolic blood pressure (DBP) is obtained similarly when the amplitude of the pulsations diminishes rapidly as the cuff pressure is further reduced (Borow *et al.*, 1982). The validity of the results obtained with this method has already been published (Silas *et al.*, 1980; Debru *et al.*, 1981).

The apparatus was programmed to measure and record SBP, DBP, MAP and the heart rate (HR) every 15 min. Each recording lasted for 12 h, from 08.00 h until 20.15 h, which corresponds to the active period of the day. Thus, in the course of each recording, 50 measurements were made of each parameter. The distance between the cuff and the apparatus gave the patient freedom of movement of about

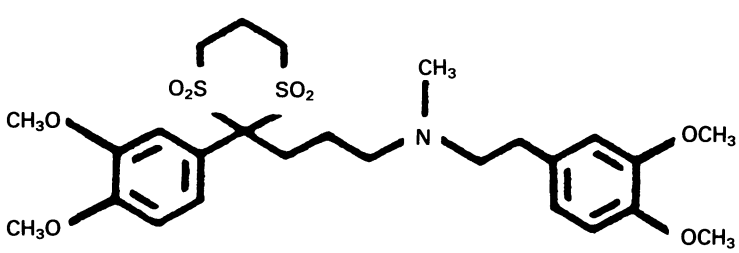

Figure 1 Chemical structure of tiapamil.

4 m and permitted the automatic measurements to be made either lying down, standing or sitting, but not in situations of exertion. In practice, almost all of the measurements were made in the recumbent or sitting positions.

Study procedure

The first recording was made after ingestion of placebo at 08.00 h. If the proportion of blood pressure values above 160/95 mm Hg was more than 20% the patient was included in the study.

The patients then received 1.5 placebo tablets at 08.00 h and at 20.00 h for 5 days. On day 6 and 7, the effect of a single oral dose of tiapamil 450 mg (1.5 300 mg tablet) and a matched placebo were compared in a single blind randomised cross-over study (second and third recording). Patients numbered 1, 3, 6, 7 and 10 received placebo first (group I), the remainder of the group received tiapamil first (group II). During these 2 days patients received only the single test dose in the morning and none in the evening. For the following 7 days patients received 1.5 tablets of tiapamil morning and evening (at 08.00 h and 20.00 h) that is a total of 900 mg tiapamil per day. A fourth 12 h BP recording was made on the seventh day of this treatment. The study design is summarized in Figure 2.

The patients were weighed every day and ECG and laboratory tests carried out before inclusion and on the first and seventh day of tiapamil treatment.

Analysis of the results

Fifty measurements per patient were collected from 08.00 h to 20.00 h for each of the four recordings. The average of these fifty values defines, for each patient, a mean daytime blood pressure value for each recording. The standard deviation of this value defined the within patient variability of BP. The mean of these standard deviations for the group were called s.d. SBP and s.d. DBP for systolic and diastolic BP respectively. In addition we used the mean BP measurements obtained during each of the twelve 1 h periods to show changes in BP occurring during the full time of each monitoring. An additional analysis was carried out on the mean of the last 10 measurements of the day, covering the period from 18.00 h to 20.15 h.

The percentage of blood pressure values above 160/95 mm Hg was calculated for each patient in the course of each of the four recordings. The means of these percentages for the 10 patients, for the different treatment days, were compared.

All the statistical calculations were carried out by means of the usual parametric tests (Student's *t*-test and analysis of variance).

For the central cross-over sequence we also followed the analytical method described by Hills & Armitage (1979). The threshold for statistical significance of $P < 0.01$ was chosen, except for the analysis of the hourly means, where the threshold of 0.05 was accepted because of the smaller number of data included. The results are expressed as mean values ± s.d.

Results

On the day of inclusion in the study mean daytime BP for the group was 174 ± 13/102 ± 14 mm Hg. The proportion of high BP values was 73.5% for SBP (above 160 mm Hg) and 60.1% for DBP (above 95 mm Hg). Three patients had isolated systolic hypertension and three additional cases had disproportionate systolic hypertension (Koch-Weser, 1975).

The analysis of variance shows the absence of

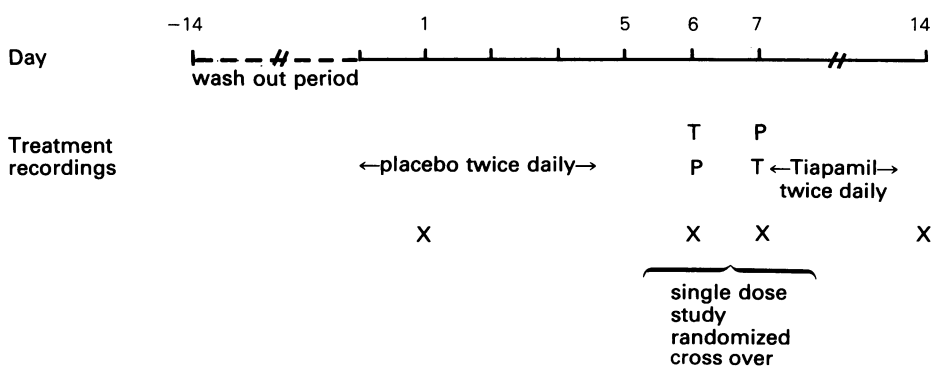

Figure 2 Study design. P placebo, T tiapamil.

an order effect ($F = 0.23$, NS) and of interaction ($F = 0.01$, NS) between the two days of the cross-over study. Therefore the first tiapamil intake led to a highly significant decrease of mean daytime blood pressure of an average 12 mm Hg for SBP, 8 mm Hg for DBP and 8 mm Hg for MAP (Table 1). The percentage of pathological SBP and DBP values also fell significantly. The fall in heart rate on the other hand was not significant and the variability of the blood pressure (s.d. SBP and s.d. DBP) was not affected (Table 1). The analysis for each individual patient showed that in only one patient did the SBP or DBP not fall significantly. The nine others had falls in SBP or DBP or both.

The hourly profile (Figure 3) revealed that the maximum effect occurred during the second hour, followed by a progressive rise in blood pressure in the course of the day. During this second hour of the recording the fall in blood pressure under tiapamil reached 12.97% and 10.31% for SBP and DBP respectively, as compared with the corresponding hour under placebo.

When the hourly BP profile under placebo and after the first tiapamil intake were compared, statistical significance at the 5% level was reached during 8 out of 12 h for systolic, and only during 3 out of 12 h for diastolic blood pressure.

Loss of significance occurred mainly during the afternoon at a time when a spontaneous BP decrease was observed under placebo. The analysis of the SBP and DBP during the period 18.00 h to 20.15 h confirms that the antihypertensive effect remained significant 11 to 12 h after tiapamil intake (Figure 3).

After prolonged tiapamil treatment (recording on the seventh day of treatment) mean daytime BP was also significantly lower than under placebo; it was 155 ± 13/86 ± 14 mm Hg

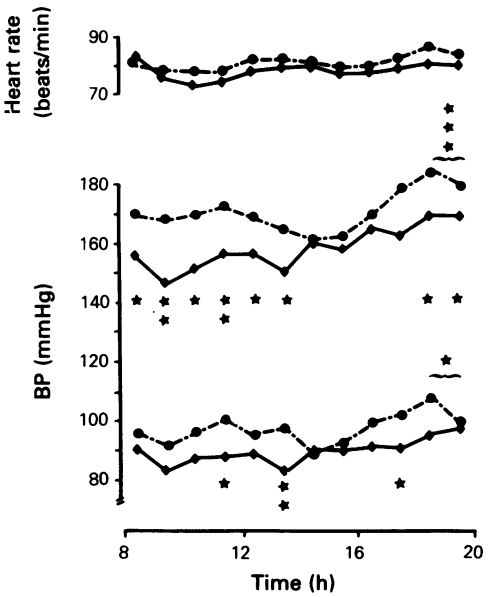

Figure 3 Comparison of the hourly profile of BP and HR after tiapamil 450 mg single oral dose (◆) and after placebo (●) $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

($P < 0.001$) which represents a decrease of on average 16, 12 and 16 mm Hg for SBP, DBP and MAP, respectively. These values tended to be lower than after the first tiapamil intake (Table 1) but were not significant. In the same way, the hourly mean values recorded on this seventh day were significantly lower than the corresponding values under placebo in 10 out of 12 h for SBP and 4 out of 12 h for DBP (Figure 4). For the pooled last 2 h of recording this difference reached significance at the 0.001 level for both SBP and DBP.

On the seventh day of treatment a slight non-significant decrease in HR was observed (Table

Table 1 Mean ± s.d. daytime BP standard deviation, heart rate and percentage of systolic values above 160 mm Hg and of diastolic values above 95 mm Hg during the cross-over phase of the study and on the seventh day of tiapamil treatment

	Cross-over phase				*Seventh day of tiapamil treatment*	Δ (vs *placebo*)	P (vs *placebo*)
	Placebo	*Tiapamil*	Δ	P			
SBP (mm Hg)	171 ± 12	159 ± 11	− 12	< 0.001	155 ± 13	− 16	< 0.001
DBP (mm Hg)	98 ± 11	90 ± 9	− 8	< 0.001	86 ± 14	− 12	< 0.01
MAP (mm Hg)	122 ± 7	113 ± 6	− 9	< 0.01	106 ± 15	− 16	< 0.01
s.d. SBP (mm Hg)	17 ± 3	16 ± 2	− 1	NS	18 ± 4	+ 1	NS
s.d. DBP (mm Hg)	18 ± 6	17 ± 3	− 1	NS	18 ± 4	+ 1	NS
HR (beats/min)	82 ± 10	79 ± 9	− 3	NS	76 ± 8	− 6	NS
% SBP > 160 mm Hg	68 ± 21	47 ± 23	− 25	< 0.01	41 ± 23	− 27	< 0.001
% DBP > 95 mm Hg	50 ± 28	33 ± 22	− 17	> 0.01	28 ± 17	− 22	< 0.01

*s.d. SBP and s.d. DBP are the average of s.d. to mean daytime BP values calculated for each patient.

1). The hourly mean heart rate was significantly reduced in 5 out of the 12 h (Figure 4).

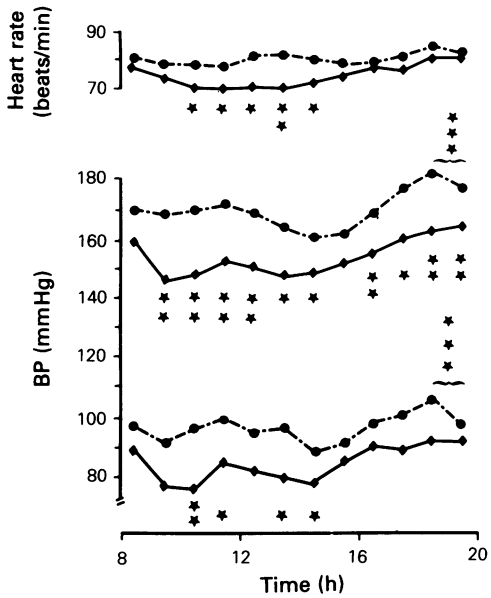

Figure 4 Comparison of the hourly profile of BP and HR after treatment of tiapamil 450 mg twice daily for 7 days (◆) and after placebo (●) $*P < 0.05$, $**P < 0.01$, $***P < 0.001$.

Tolerance of tiapamil was good in every case, the appearance of a vague sleepiness being the only side effect observed in two patients in the course of the study. No significant alteration in the PR interval was observed in the repeated ECG.

In no case was there any appearance of oedema during treatment and the body weight of the patients remained stable. There was only a non-significant tendency to haemodilution, suggested by simultaneous reductions of plasma proteins (from 71.2 ± 2.3 to 69.1 ± 3.3 g/l, NS), uric acid concentrations (from 310.5 ± 35.3 to 284 ± 47.0 μmol/l, NS) and haematocrit (from 41.5 ± 4.5 to 40.5 ± 3.7, NS). No alteration in plasma creatinine, GOT, GPT, bilirubin, ions or blood count occurred in the course of the study.

Discussion

The antihypertensive effect of tiapamil was determined by comparison with the blood pressure profile while on placebo. Since we used an automatic method of measuring and recording the arterial blood pressure it was not necessary to conduct this study according to a double blind procedure. However, the fact of having a cuff inflated every 15 min over a period of 12 h could represent an important element of stress; we therefore carried out a 'dummy' recording, before the start of the study proper, in order to select patients, to accustom them to this inconvenience, and to verify the reproducibility of the method.

The reproducibility was considered excellent since from this preliminary recording to the placebo day of the cross-over phase mean day time BP decreased only by an average of 3 mm Hg, that was not significant at the threshold of $P < 0.05$.

From the first dose, tiapamil led to a significant fall in the blood pressure, reaching its maximum during the second hour after administration, and lasting 10–12 h.

For the first and seventh days of tiapamil treatment, the extent of the reduction in blood pressure was less at the beginning of the afternoon, as compared with the placebo day. The main reason for this was the spontaneous fall in blood pressure due to a period of sleep (Drayer *et al.*, 1982) that was observed in most of these old patients, at this time of the day.

After repeated doses of tiapamil, there was only a trend towards an additional decrease in BP which was especially marked in the last few hours of the day.

This last phase of the study was not controlled; therefore a spontaneous BP decrease from the first to the last day of active treatment cannot be excluded. However the prolonged hospitalization of the patients before inclusion, and the reproducibility of the method observed during the placebo phase made a spontaneous BP decrease very improbable. On the contrary a longer duration of action after prolonged treatment would be in agreement with an increase in bioavailability recently observed after repeated doses of tiapamil (Eckert *et al.*, 1984).

On average the decrease in systolic BP was more pronounced than that in diastolic BP. When hourly BP profile was considered, the lowering effect of tiapamil on SBP was more significant than its effect on DBP. To discuss this observation one must consider both the mechanism of hypertension in the elderly and the mechanism of action of calcium entry blockers. In older patients, the reduced arterial distensibility is the main mechanism of systolic hypertension (Simon *et al.*, 1979). Arterial compliance, which is a quantitative evaluation of elasticity is a major determinant of systolic hypertension (Simon *et al.*, 1982). It is decreased in systolic hypertension of old patients and inversely related to the increase in the systolic

pressure (Simon *et al.*, 1979) (Levenson *et al.*, 1982). Any drug increasing arterial compliance by a direct effect on the arterial wall may thus cause a predominant decrease in systolic BP. This type of action was already demonstrated for nitroprusside (Simon *et al.*, 1979) and nitroglycerine (Levenson *et al.*, 1980, 1982) which cause an increase in arterial compliance and a predominant decrease in systolic BP. More recently the calcium entry blocker nifedipine was found to cause an increase in systemic arterial compliance (Levenson *et al.*, 1983b); and this effect was more strongly related to the decrease in systolic than in diastolic pressure (Levenson *et al.*, 1983b).

In addition both nifedipine (Levenson *et al.*, 1983b) and diltiazem (Safar *et al.*, 1983) markedly increase the diameter of the brachial artery. Such an effect, in spite of the fall in blood pressure, demonstrates their direct action on peripheral large arteries. Tiapamil also causes vasorelaxation of the isolated artery by interfering with calcium influx (Thorens & Hauesler, 1979). It could act similarly on peripheral large arteries of elderly patients to correct predominantly their systolic hypertension. The direct relationship found by Buhler & Hulthen (1982) between age and the antihypertensive effect of another calcium entry blocker verapamil could also reflect the above mentioned development in the mechanism of hypertension.

Another noteworthy feature was the slight reduction in the pulse rate after prolonged treatment, which is in contrast with the tachycardia consistently produced by nifedipine (Henry, 1980). It was less pronounced than the bradycardia which has been reported in certain studies with verapamil (Gould *et al.*, 1982).

The absence of signs of reflex sympathetic activation under tiapamil, in spite of the lowered blood pressure, might be explained by its direct action on the heart (Levy *et al.*, 1982). The lack of baroreflex activation by calcium entry blockers, has also been discussed in the light of their effect on large artery diameter and subsequent decrease in tangential tension of the arterial wall (Levenson *et al.*, 1983b; Safar *et al.*, 1983). On the other hand, reflex tachycardia is always less pronounced in elderly patients (Chrystant *et al.*, 1977).

The variability of the blood pressure in elderly subjects is well known, and the standard deviation from the mean of the blood pressure values can be used to express it (Drayer *et al.*, 1982). In a group of hypertensive patients aged from 60 to 64 years, observed in an outpatient clinic, the Framingham study reports a standard deviation of 16 mm Hg for the SBP (Kannel *et al.*, 1980b).

In our hospitalized patients, whose average age was 79 years, this variability was also of 17 mm Hg for the SBP, on average. No 'regularizing' effect of tiapamil on the arterial blood pressure was observed in these patients. However the risk of cardiovascular disease is not affected by the variability when it is adjusted for the mean level of pressure (Kannel *et al.*, 1980b).

The pharmacokinetics of tiapamil in elderly patients are still not known. The marked reduction in glomerular filtration observed in these elderly patients cannot be responsible for a reduction of the total clearance of tiapamil, since only 10% of tiapamil and its main metabolite are eliminated by the kidney (Wendt, 1982). On the other hand, since tiapamil is subject to extensive first pass metabolism, its oral bioavailability could be affected by changes in hepatic blood flow and diminished enzyme activity. It is therefore necessary to await the results of the pharmacokinetic study in elderly patients which is at present in progress.

In conclusion, by their action on systolic pressure, calcium entry blockers show promise for the treatment of hypertension in the elderly. Since their short duration of action is presently a main limitation for their use in hypertension, the sustained effect of tiapamil suggests that larger trials should be performed with this drug.

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