A comparison of dilevalol and placebo in the management of isolated systolic hypertension using ambulatory monitoring

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1 The antihypertensive effect of dilevalol, a compound which combines β -adrenoceptor blocking and vasodilating properties due to β_2 -adrenoceptor agonism, was studied in nineteen patients with isolated systolic hypertension (ISH). A randomized, double-blind, placebo-controlled, cross-over trial with two 4 week treatment periods was used to compare the efficacy of once daily dosing with dilevalol (in the range of 100–400 mg daily) against placebo. Assessment of response involved both casual blood pressure readings (amongst all patients) and 24 h ambulatory blood pressure monitoring (in ten of the nineteen patients).

2 A mean fall of 12/5 mm Hg (s.e. mean 3/2, $P < 0.05$) and 9/3 mm Hg (s.e. mean 3/2, $P < 0.05$) in supine and standing blood pressure respectively was observed with dilevalol. Mean heart rate was unchanged. The ambulatory monitoring profile demonstrated a smaller reduction in mean blood pressure (7/8 mm Hg) over the 24 h period and a reduction of 10/11 mm Hg over the daytime period. A blunting of the early morning increase in systolic pressure was observed with dilevalol.

3 The drug was well tolerated with light headedness and lethargy being reported more commonly than with placebo. Biochemical parameters were unaffected.

4 It is concluded that dilevalol in the doses used has a small but measurable antihypertensive effect as monotherapy in the treatment of ISH.

Keywords isolated systolic hypertension dilevalol ambulatory monitoring

Introduction

Dilevalol is a new antihypertensive agent which combines β -adrenoceptor blocking and vasodilator properties. It is one of the four optical isomers of labetalol but has three to five times the β -adrenoceptor blocking potency of this drug (Sybertz *et al.*, 1981). It has virtually no α -adrenoceptor blocking properties (Brittain *et al.*, 1982; Sybertz *et al.*, 1981) and its vasodilatory action is due to selective β_2 -adrenoceptor agonist properties (Baum & Sybertz, 1983; Matsunaga *et al.*, 1985). It is devoid of intrinsic

sympathomimetic activity on myocardial β_1 -adrenoceptors.

In previous clinical studies dilevalol has been shown to decrease mean arterial pressure and systemic vascular resistance at rest without changing cardiac output or stroke volume (Lund-Johansen, 1988). Although its blood pressure lowering effect has been demonstrated in moderate and severe hypertension (Abernathy *et al.*, 1987; Frick & Porsti, 1976; Ohman & Asplund, 1984) there have been no reported

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studies on the use of diltiazem in isolated systolic hypertension.

This study sought to compare the antihypertensive effect of diltiazem (in a dose range of 100 mg once daily to 400 mg once daily) and a placebo in patients with isolated systolic hypertension. Twenty-four hour ambulatory blood pressure monitoring was used to examine the 24 h blood pressure profile when the drug was administered on a once daily basis.

Methods

The study was a randomized, double-blind, placebo-controlled, cross-over trial with two treatment periods of 4 weeks separated by a 2 week single-blind placebo washout. Patients of either sex were eligible for inclusion provided their age was between 50 and 85 years and isolated systolic hypertension was recorded at two consecutive visits during a 3 week placebo run-in. All patients entered had a supine systolic blood pressure above 160 mm Hg in the presence of supine diastolic blood pressure less than 95 mm Hg, with the exception of one patient who had an entry blood pressure of 189/96 mm Hg. Exclusion criteria included; women of child bearing potential, weight outside the range of 50–95 kg, present or past history of congestive cardiac failure or heart block, stroke or myocardial infarction within the previous three months, presence of gastrointestinal disease or surgical procedure which might modify drug handling, concomitant therapy with other antihypertensive agents, or with other agents which might interfere with or potentiate the actions of the study drugs, conditions predisposing to hypoglycaemia, clinically significant abnormalities in pre-study biochemical or haematological profiles (serum creatinine above 1.2 mmol l^{-1} , AST greater than 45 iu l^{-1} , plasma bilirubin above 20 mmol l^{-1} , haemoglobin less than 12 g).

No other antihypertensive medication, investigational drugs or drugs which might affect blood pressure were permitted. If medications for conditions other than hypertension were considered essential for the patient's well-being while in the study, they were continued.

The study was approved by the Research Advisory and Ethics Committee of the participating centre. It was performed in accordance with the Declaration of Helsinki and the Australian National Health and Medical Research Council guidelines for the conduct of clinical research. Patients were informed in writing and verbally about the method and purpose of the study, their rights to withdraw,

and that data would be subject to computer analysis. Written informed consent was obtained from all patients.

Methodology

Patients who met these criteria were randomized to either diltiazem (100 mg) or placebo administered once daily in the morning, and reviewed at weekly intervals. Patients were instructed not to take their medication on the morning of follow-up visits until they had been seen in the clinic. At each visit supine blood pressure was measured on three occasions following a period of 5 min recumbency and again following a period of 2 min standing. Korotkoff phase V was used to determine diastolic pressure. The three readings obtained in each position were then averaged. At the conclusion of each week those who had not reached their goal supine systolic blood pressure (defined as a decrease in the mean supine systolic blood pressure of at least 20 mm Hg from the last placebo visit *and* a supine systolic blood pressure less than or equal to 160 mm Hg) were titrated through the range 100 mg, 200 mg, 300 mg, and 400 mg daily; (this represented an increase of 1 tablet daily at each increment) provided there were no significant adverse effects present.

Baseline laboratory screening (full blood count, ESR, biochemistry profile and ECG) was performed on all patients who met the entry criteria. At the conclusion of week 4, an ECG and repeat biochemical profile was performed and active treatment or placebo was replaced by placebo medication for the 2 week mid trial washout period. At this time blood pressure was reassessed to ensure that the entry criteria were re-established for both systolic and diastolic values. Patients who did not meet these criteria were retested on up to two further occasions at 3 day intervals and those who failed to re-establish the criteria for systolic hypertension were discontinued and replaced by a new patient with the same treatment number in order to avoid an imbalance between the number of evaluable patients in the two treatment groups (diltiazem/placebo *vs* placebo/diltiazem). Patients continuing in to the second phase of the study received the alternative treatment to that given in the first 4 weeks, and identical conditions were used to titrate the medication dose. Adverse effects that were reported by the patients, both in response to active questioning and spontaneously, were recorded at each visit.

Throughout the study no specific dietary advice was given, and patients were instructed

to make no substantial changes in their salt or kilojoule intake during the course of the study.

Ambulatory monitoring

In ten patients ambulatory blood pressure monitoring was carried out at the end of each treatment period using an Accutrackers instrument (Suntech Medical Instruments, Raleigh, N.C., USA). This machine operates on an R-wave gating system and has been validated elsewhere (White *et al.*, 1987). The machine was programmed to measure blood pressure at 30 min intervals from 08.00–22.00 h and at 1 hourly intervals from 22.00–08.00 h.

Data analysis

All clinic data obtained were coded for computer entry and were analysed using the SAS statistical package. Mean blood pressures and heart rates were compared between the treatment groups, as was the mean fall in blood pressures. A two-way analysis of variance was used to test for period effects or treatment-period interactions. Paired *t*-tests were used in all of the other statistical evaluations. The data obtained from the 24 h ambulatory blood pressure and heart rate monitoring was transferred to an IBM compatible PC via an Accutrackers PC Interface Card, and then converted into a SAS data file.

The mean systolic, diastolic, mean arterial pressure and heart rates for the two treatment groups, were averaged over the whole 24 h period of observation and also as daytime and night time periods separately.

A General Linear Models regression (GLM) analysis was also used, of which analysis of variance (ANOVA) is a subset. In this analysis patients are assigned a number, from 1 to 10. These numbers are recoded into nine separate 'dummy' variables (patient number 1 has all values at zero). The daytime (08.01–22.00 h) and night time (22.01–08.00 h) periods, together with the treatment variables (placebo or dilevalol) are also recoded as dummy variables. When the analysis was performed the patient identifier dummy variables enter the regression equation first, and the treatment variables last.

The advantage of using dummy variables in a GLM analysis is that it allows the treatment effect level to be calculated, and a *t*-test to be performed to determine significance under the null hypothesis. A *P* value less than 0.05 was regarded as being statistically significant.

By placing variables such as patient identifiers first in the regression equation, these effects were removed before estimating treatment con-

tributions. The treatment effect level (parameter estimate) is therefore based on within-patient residuals, with all the between patient variance having been accounted for.

Results

Of the 30 patients originally entered in the study only 25 successfully completed it. Of the five patients discontinued from the study, only one was because of failure to meet the re-entry criteria after the first 4 week treatment period, three because of intercurrent medical illnesses unrelated to the study, and one due to non-compliance with the visits/dosing schedule. Of the 25 patients completing the study, 19 (11 males) were included in the analysis, the remaining six having protocol violations related to incorrect dosage titration whilst on the active phase of treatment. Amongst those included in the analysis, eight were in the group who had received dilevalol followed by placebo, whilst the remaining eleven had received the two drugs in the reverse order.

Analysis of the baseline demographic data revealed a mean age of 67 years (range 56–83), with the mean duration of hypertension being 10 years (range 0–40). Seventeen of the patients had been on previous antihypertensive therapy prior to entering the study. Five of these had been on monotherapy and the remainder on combination therapy (12 patients with two drugs, one patient with three drugs). The more commonly used classes of antihypertensive agents were diuretics (seven patients), β -adrenoceptor blockers and angiotensin converting enzyme inhibitors (six patients each) and peripheral vasodilators (five patients). Mean supine and standing blood pressures ($\pm$ s.e. mean) at the completion of the placebo run-in phase, immediately prior to randomization, were 175/85 (2/2) mm Hg and 172/99 (3/3) mm Hg respectively.

Casual blood pressure recordings measured at weekly intervals during the trial are shown graphically in Figures 1 and 2. During active dilevalol treatment only four patients achieved goal blood pressure at the lowest titration dose. Seven required dosage increases to the maximum level (400 mg once daily) and only two of these achieved goal blood pressure at the final evaluation. The remaining eight patients achieved goal blood pressure at doses of 200 or 300 mg day⁻¹.

Blood pressures were initially compared within, and between, the two treatment groups using a two way ANOVA test to determine

Figure 1 Comparison of supine blood pressures (dilevalol (▨) vs placebo (□))

Figure 2 Comparison of standing blood pressures (dilevalol (▨) vs placebo (□))

Table 1 Mean reductions from baseline in casual supine and standing blood pressures (mm Hg $\pm$ s.e. mean) for dilevalol vs placebo treatment

	Supine		Standing	
	Systolic	Diastolic	Systolic	Diastolic
Dilevalol	12 $\pm$ 3 <i>P</i> = 0.001	5 $\pm$ 2 <i>P</i> = 0.033	9 $\pm$ 3 <i>P</i> = 0.013	5 $\pm$ 2 <i>P</i> = 0.017
Placebo	1 $\pm$ 3 <i>P</i> = 0.789	1 $\pm$ 2 <i>P</i> = 0.704	2 $\pm$ 3 <i>P</i> = 0.546	2 $\pm$ 1 <i>P</i> = 0.308

whether any period effect or treatment-period interaction was present. In both cases there was no clinically or statistically significant change noticed. It was therefore considered appropriate to analyse the pooled data.

Table 1 compares the mean fall in blood pressure during the two treatment periods. The baseline is regarded as the blood pressure recorded immediately prior to commencing either active treatment or placebo. Dilevalol produced a mean fall of 12/5 mm Hg and 9/3 mm Hg in supine and standing blood pressures respectively ($P < 0.05$), whereas the corresponding falls during treatment with placebo were 1/1 mm Hg and 2/2 mm Hg ($P > 0.05$).

Mean heart rate remained constant in both the supine and standing positions whilst on dilevalol. Placebo had no effect on the standing heart rate but did increase the supine heart rate by 6 beats min^{-1} . This was statistically significant ($P < 0.05$).

Ambulatory monitoring

Ten of the nineteen patients underwent ambulatory monitoring at the end of each of the two 4 week treatment periods. Each of the patients had readings taken at regular intervals over a 24 h period. A total of 1109 readings were included in the analysis (range 70–108 per patient). The reason for the wide variation in the number of readings contributed by each patient is that those which were taken at the time of a machine error such as a loose cuff, disconnection of ECG leads or inability of the machine to detect the brachial pulse were excluded from analysis. In a small number of instances, patients self-activated the machine to take additional readings during the monitoring period. In order to overcome the problem of patients with different numbers of readings, we averaged all readings (for each patient) in 2 h time bands. This meant every patient contributed 12 average blood pressure readings throughout the 24 h period. The profile of blood pressure recordings obtained by ambulatory monitoring is recorded graphically in Figure 3.

Figure 3 24 h ambulatory monitoring profile in isolated systolic hypertension: dilevalol (■ diastolic, ● systolic BP) vs placebo (□ diastolic, ○ systolic BP)

The mean ambulatory blood pressure ($\pm$ s.e. mean) for patients throughout the 24 h period whilst on placebo was 152/93 $\pm$ 2/1 mm Hg compared with 146/83 $\pm$ 2/1 mm Hg whilst on treatment with dilevalol ($P < 0.01$).

The ambulatory monitoring blood pressure data was then analysed in two ways. Firstly when subjected to GLM regression analysis the parameter estimate (a measurement of the treatment effect level) demonstrated that dilevalol reduced blood pressure by 7/8 mm Hg ($P < 0.05$) over the whole 24 h period and by 10/11 mm Hg over the day-time period alone ($P < 0.05$). The data was then analysed by dividing the 24 h period into daytime (08.01–22.00 h) and night time (22.01–08.00 h). During the day time mean ambulatory blood pressures ($\pm$ s.e. mean) on dilevalol were 150/87 mm Hg (1/1) compared with 160/98 mm Hg (2/1) on placebo ($P < 0.05$). During the night time mean ambulatory blood pressures ($\pm$ s.e. mean) on dilevalol were 142/80 mm Hg (3/3) and 139/83 mm Hg (2/2) on placebo (NS). Mean heart rate was also consistently lower during the day time period (73 beats min^{-1}) on dilevalol compared with 67 beats min^{-1} on placebo ($P < 0.05$).

When subjected to analysis of variance, both the treatment and time of measurement variables produced independently statistically significant

Table 2 Adverse effects

	<i>Dilevalol</i> n = 8 patients	<i>Placebo</i> n = 11 patients
Headaches	3	5
Dizziness/light headedness	3	1
Fatigue/lethargy	3	1
Nightmares	1	—
Gastric pains on waking	1	—
Swelling of ankles	1	3
Back pain	—	1

effects ($P < 0.01$) on systolic and diastolic blood pressure as well as heart rate. An interaction of treatment and time of measurement also produced statistically significant results although these were much less than occurred as a result of these variables independently.

Biochemistry

There was no clinically or statistically significant change in serum creatinine, uric acid, cholesterol, glucose or SGOT levels between the two treatment periods.

Treatment with dilevalol did produce a slight fall in potassium levels compared with placebo (mean difference dilevalol–placebo of $-0.16 \text{ mmol l}^{-1}$ s.e. mean 0.07) which was statistically significant at the 0.05 level ($P = 0.043$).

Adverse effects

Eight patients reported adverse effects whilst on treatment with dilevalol (see Table 2). Four of these patients all reported mild headaches as being the principal symptom. Other symptoms reported were dizziness and light-headedness (three patients), fatigue/lethargy (three patients), nightmares, gastric pains on waking and swelling of the ankles (one patient). None of the adverse effects was reported as being severe and none resulted in the patient's being withdrawn from the study.

Discussion

Isolated systolic hypertension has traditionally been defined on the basis of casual blood pressure readings. Ambulatory blood pressure monitoring has been noted in previous studies to record consistently lower mean blood pressures, when averaged over the whole 24 h or just over the day-time period (O'Brien *et al.*, 1989). This phenomenon was observed again in this study. This may represent an overdiagnosis of the condition in an office setting where blood pressure

is raised in response to the presence of a physician, a situation analogous to 'white coat hypertension' in younger patients (Mancia *et al.*, 1983). Whether the mean ambulatory blood pressure in these patients would also fall with repeated monitoring remains unanswered.

Epidemiological evidence from Framingham, and other studies, indicates an increased risk of cardiovascular mortality in patients with the isolated systolic hypertension (Kannel *et al.*, 1980, 1981). However there is currently a lack of clinical trials demonstrating either an appropriate therapeutic agent or the benefit of treatment. The use of a single agent given in a once daily dosage, in order to avoid problems with compliance that occurs often in the elderly, would provide the optimal solution. Ideally the drug should have a preferential effect on systolic blood pressure and be able to maintain its effective action throughout the whole day-time period, without causing undue side effects (in particular postural hypotension).

Dilevalol possesses a combination of β -adrenoceptor blockade and vasodilatory properties (Sybertz *et al.*, 1981) due to β_2 -adrenoceptor agonist effect and no α -adrenoceptor blockade, and therefore may provide an approach which considerably simplifies treatment and improves compliance by avoiding the need for combination therapy. Labetalol possesses similar properties, however with vasodilation mainly due to α -receptor blockade, and was the first of such agents to be developed (Frisk & Porsti, 1976). In long term studies with this compound it has been shown to be an effective antihypertensive agent (Abernathy *et al.*, 1987; McNeil *et al.*, 1988; Ohman & Apslund, 1984; Rugsley *et al.*, 1976).

In a single-blind study of labetalol in a group of elderly patients with isolated systolic hypertension, a mean blood pressure fall (based on 24 h ambulatory readings) of 10/3 mm Hg was observed (De Quattro *et al.*, 1988). The 24 h blood pressure profile of labetalol demonstrated a blunting of the early morning surge in systolic pressure (De Quattro *et al.*, 1988). However

orthostatic hypotension is one of the well known side effects of labetalol and this is attributed to its α -adrenoceptor blocking properties.

Dilevalol, like its parent compound, has a combination of non-selective β -adrenoceptor blockade together with β_2 -adrenoceptor agonist activity (Baba *et al.*, 1988; Lund-Johansen, 1988). However unlike labetalol it is almost devoid of α -adrenoceptor blocking activity. This might be expected to result in fewer orthostatic problems.

The difference between the mean casual supine blood pressure on placebo and active treatment at the end of the two 4 week periods was 11/5 mm Hg. However, the mean difference in blood pressure noted on ambulatory monitoring during the day time period (between dilevalol and placebo) was less at 7/8 mm Hg.

The 24 h ambulatory recordings provide a dynamic evaluation of the efficacy of dilevalol. They demonstrate a single dose of the dilevalol significantly reduces systolic blood pressure for approximately 5 to 7 h after dosing and diastolic pressure for 7 to 10 h after dosing. This effect is abolished, relative to placebo, during the late afternoon and early evening. Although doses of 300 or 400 mg were required in 68% of patients to achieve this, the remainder achieved successful blood pressure control with lower doses.

There was a statistically significant difference between daytime and night-time pressures, consistent with the natural diurnal variation in blood pressure. In addition a treatment-measurement period (daytime or night-time) interaction was also observed, i.e. the effect of dilevalol was again more marked during daylight hours.

The lower heart rate seen in patients on dilevalol during the day time period would be consistent with the β -adrenoceptor blocking properties of the drug. This was also observed in studies using labetalol (Baba *et al.*, 1988; Lund-Johansen, 1988).

Dilevalol was generally well tolerated with the rate of adverse symptoms similar to that observed in other studies using the drug (McGrath *et al.*, 1989). Light headedness and fatigue were the symptoms reported most commonly on dilevalol but not on placebo. None of these resulted in patient withdrawal from the study. Postural hypotension was not encountered with the drug doses used.

With the exception of the decline in potassium levels, there were no significant adverse effects on laboratory parameters as a result of treatment with dilevalol. In particular there were no significant changes in serum creatinine, lipids, glucose or urate. The decline in potassium was small and of doubtful clinical significance. Liver function tests were unaffected by dilevalol.

The results of this study suggest that dilevalol is effective as monotherapy in the treatment of isolated systolic hypertension. However it needs to be compared against other antihypertensive agents in the treatment of this condition. When this study is taken together with the results of other studies in patients with mild to moderate hypertension, it would suggest that dilevalol is a useful and well tolerated antihypertensive agent for use in elderly patients.

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References

- Abernathy, D. R., Bartos, P., Placketka, J. R. (1987). Labetalol in the treatment of hypertension in elderly and younger patients. *J. clin. Pharmacol.*, **27**, 902–906.
- Baba, T., Murayashi, S., Aoyagi, K. & Ishaizaki, T. (1988). Effects of dilevalol, an R,R-isomer of labetalol, on blood pressure and renal function in patients with mild to moderate essential hypertension. *J. clin. Pharmacol.*, **35**, 9–15.
- Baum, T. & Sybertz, E. J. (1983). Antihypertensive properties of an isomer of labetalol and other vasodilator β -adrenoceptor blockers. *Fed. Proc.*, **42**, 176–181.
- Brittain, R., Drew, G. & Levy, G., (1982). The α - and β -adrenoceptor properties of labetalol and its individual stereoisomers in anaesthetized dogs and in isolated tissues. *Br. J. Pharmacol.*, **77**, 105–114.
- Bugni, W. J., Ayers, C. W., Ashby, R., Bittle, P. A. & Ramirez, G. (1989). Effects of dilevalol on rest and supine exercise haemodynamics in mild to moderate systemic hypertension. *Am. J. Cardiol.*, **63**, 452–456.
- DeQuattro, V., De-Ping Lee, D., Allen, J., Sirgo, M. & Placketka, J. (1988). Labetalol blunts morning pressure surge in systolic hypertension. *Hypertension* [Suppl. 1], **1**, I-1988–I201.
- Frick, M. M. & Porsti, P. (1976). Combined α - and β -adrenoreceptor blockade with labetalol hypertension. *Br. med. J.*, **1**, 1046–1048.
- Kannel, W. B., Dawber, T. R. & Gee, D. L. (1980). Perspectives on systolic hypertension. The Framingham Study. *Circulation*, **61**, 1179–1182.
- Kannel, W. B., Wolf, P. A., McGee, D. L., Dawber, T. R., McNamara, P. & Castelli, W. P. (1981). Systolic blood pressure, arterial rigidity and risk of stroke. The Framingham Study. *J. Am. med. Ass.*, **245**, 1225–1229.
- Lund-Johansen, P. (1988). Haemodynamic effects of β -blocking compounds possessing vasodilating activity: a review of labetalol, prizidilol and

- ditalol. *J. cardiovasc. Pharmac.*, 1988, II (suppl 2): 512-517.
- Mancia, G., Grassi, G., Pomidissi, G., Gregorini, L., Bertinieri, G., Parati, G., Ferrari, A. & Zanchetti, A. (1983). Effects of blood pressure measurement by the doctor on patient's blood pressure and heart rate. *Lancet*, ii, 695-697.
- Matsunaga, K., Nakamura, K. & Ueda, M. (1985). Intrinsic β -sympathomimetic activity of dilevalol, R-R isomer of labetalol. *J. Pharmacobio-Dyn.*, 8, 785-787.
- McGrath, B. P., Matthews, P. G. & Louis, W. (1990). Double blind study of dilevalol and captopril, both in combination with hydrochlorothiazide, in patients with moderate to severe hypertension. *J. clin. exp. Hypertension* (in press).
- McNeil, J. J., Anderson, A. E. & Louis, W. J. (1988). An analysis of the blood pressure response to labetalol in hypertensive patients. *Clin. Sci.*, 61, 449s-452s.
- O'Brien, E., Cox, J. P. & O'Malley, K. (1989). Ambulatory blood pressure measurement in the evaluation of blood pressure lowering drugs. *Hypertension*, 7, 243-247.
- Ohman, K. P. & Asplund, J. (1984). Labetalol in primary hypertension: A long-term effect and tolerance study. *Curr. Ther. Res.*, 35, & 277-286.
- Rugsley, D., Armstrong, B., Nassim, M. & Beilin, L. J. (1976). Combined α - and β -adrenoceptor blockade in hypertension: a controlled trial of labetalol (AM 5158) compared with propranolol and placebo. *Clin. Sci. mol. Med.*, 51, 5015-5033.
- Sybertz, E. J., Crawford, S., Sabin, K. K., Pula, G., Van der Vliet, G., Glennon, J., Gold, E. H. & Baum, T. (1981). α - and β -adrenoceptor blocking properties of labetalol and its R-R isomer, Sch 19927. *J. Pharmac. exp. Ther.*, 218, 435-443.
- White, W. B., Schulman, P., McCanbe, E. J. & Nardone, M. B. (1987). Clinical validation of the Accutacker, a novel ambulatory blood pressure monitor using R-wave gating for Korotkoff sounds. *J. clin. Hypertension*, 3, 500-509.

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