Dose requirement and effect of nicardipine on lipid profile in mild to moderate essential hypertensives

A R Tariq, MRCP
K Maheendran, MBBS
J Kamsiah, MD
P Christina, MBBS

Department of Pharmacology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Jalan Raja Muda, Kuala Lumpur

Summary

Twenty eight patients who satisfied the entry criteria and had completed an initial 2 weeks treatment with placebo were titrated fortnightly with doses of Nicardipine ranging from 30mg to 90mg daily in two or three divided doses. Nicardipine treatment significantly reduced blood pressures both in the supine and standing positions ($p<0.0004$) when compared with placebo treatment. Heart rates however did not change significantly. Forty six percent (13/28) of patients on 20mg twice daily, 25% (7/28) on 10mg three times daily, 18% (5/28) of patients on 20mg three times daily and 11% (3/28) on 30mg three times daily achieved supine diastolic blood pressures <90mmHg. Nicardipine treatment at 16 weeks and at 24 weeks did not significantly alter the lipid profile when compared to the end of placebo treatment period. No other biochemical abnormalities were reported during the study period. Except for 2 cases of mild pedal oedema and 2 cases of transient headaches, no serious side-effects were encountered.

Key words: Nicardipine, lipid profile, hypertension.

Introduction

Calcium channel blockers are now being increasingly used for the treatment of hypertension. The currently available calcium channel blockers are similar in their anti-hypertensive efficacy but differ in their effects on the AV node and the degree of peripheral vasodilatory action[1].

Nicardipine is a dihydropyridine derivative which is a peripherally selective slow calcium channel blocker. It causes both a systemic arteriolar vasodilatation and a significant reduction in left ventricular afterload[2]. It is remarkably free of any adverse metabolic or endocrine effects[3]. The responsiveness to this drug is little affected by race or age and because of its mild natriuretic action, the concommitant use of diuretics or dietary sodium restriction may not be necessary.

The dose range used in the treatment of mild to moderate, uncomplicated essential hypertension is 30 – 120mg Nicardipine daily in three divided doses[4].

Side effects which are not severe and easily reversible, are well tolerated by the patients. These appear to be mainly due to excessive vasodilatation i.e. headache, flushing and pedal oedema.

Nicardipine has been recently approved by the Drug Control Authority of Malaysia for the treatment of hypertension.

Materials and Methods

a. Patient selection

Patients were recruited from the Hypertension Clinic Medical Faculty, University Kebangsaan Malaysia (UKM). Patients of either sex aged 40 - 65 years with a resting supine diastolic blood pressure (SpDBP) of 95 - 115 mmHg when not on treatment for at least two weeks were eligible to enter the study.

They must have a normal fasting serum total cholesterol of <7.0 mmol/L, fasting serum triglyceride of < 1.8 mmol/L, relatively normal renal function with a serum creatinine level < 140 umol/L and relatively normal liver function with a serum SGOT < 80 U/L. Informed consent was obtained from each patient before entry into the study and the protocol was passed by the Ethical Committee of the Institution.

The protocol excluded malignant hypertension, resistant or secondary hypertension (including estrogen-induced hypertension), grade III or IV retinopathy, acute myocardial infarction within the last three months, congestive heart failure, unstable angina pectoris, diabetes mellitus, known hepatic, gastro-intestinal or haematologic diseases, excessive alcohol intake and all concomitant drugs known to affect the serum lipids, in particular hypolipidaemic agents and diuretics.

b. Trial design

This study was conducted in three phases with a total duration of twenty-six weeks for each patient. This consisted of two weeks placebo phase, eight weeks of titration phase and sixteen weeks of maintenance phase. Newly diagnosed patients or patients who had not been on any treatment for at least two weeks were recruited into the study. After careful screening and after completing all investigations, patients who qualified to enter the study were given placebo for two weeks. The supine and standing blood pressures and heart rates were recorded and all laboratory and clinical investigations were performed. Patients proceeded to the titration phase, if the SpDBP were 95 to 115 mmHg.

During phase II (eight weeks) the patients were titrated with doses of Nicardipine starting with 30 mg to 90 mg daily in two or three divided doses until their SpDBP were ≤ 90 mmHg. Patients were examined in the morning at least two hours after taking their morning medication. Clinic visits were scheduled every two weeks during this phase. Those patients not achieving SpDBP of ≤ 90 mmHg at the maximum dose of 30 mg three times daily were deemed to be treatment failures and were withdrawn from the study and given alternative treatments. Patients who exhibited postural hypotension (i.e. a fall of diastolic blood pressure ≥ 20 mmHg on standing) during any of the phases were excluded from the study. Those patients who have achieved BP control (SpDBP< 90 mmHg) were admitted to phase III.

During phase III (sixteen weeks maintenance), patients were maintained on the same Nicardipine dosage as in the last visit during phase II and were then evaluated every four weeks.

c. Measurements

i. Blood Pressure and Heart Rate

The patients' blood pressure (BP) was determined non-invasively by an automatic BP measuring device (EME auto monitor model 3100/3200). Patients were evaluated at least two hours after the morning dose at each review visit. Measurement were made on the same arm and by the same observer, where possible, throughout the study. Systolic and diastolic BP were recorded at rest in both the supine and the upright (standing) positions. Supine BP was

represented by the average of at least 3 consecutive BP recordings taken approximately 1 minute apart while the patient had rested quietly for at least five minutes.

Subsequently, three repeated measurements were taken approximately one minute apart in the standing position after three to five minutes. Measurements of heart rates were made concurrently and the average of the three readings recorded.

ii. **Body weights**

Body weights were measured with the patient in light-weight clothing and without shoes.

iii. **Laboratory investigations**

Laboratory investigations were done by the Pathology Department of UKM and the General Hospital Kuala Lumpur (GHKL) and included renal profile, hepatic profile and haematological profile.

iv. **Fasting lipid profile**

The fasting lipid profile was done in a special laboratory set up in the Pathology Department of the Medical Faculty of UKM. The high density lipoprotein was analysed by precipitation technique using phosphotungstic acid and magnesium ions as described by Virella et al 1977[5]. The fasting serum cholesterol and triglyceride were analysed enzymatically by using triglyceride and cholesterol enzymatic kits by Boehringer Mannheim. The coefficient of variation for the intra-assay and inter-assay approximation in the laboratory were 6.8% and 4.5% for cholesterol; 8.4% and 5.6% for triglyceride and 7.7% and 7.8% for HDL-cholesterol.

v. **Statistics**

All the data were analysed using the paired t-test and all values given are in mean ± standard deviation.

Results

Thirty one patients who satisfied the entry criteria were enrolled in the study. Two patients dropped out of the study at the end of four weeks of treatment because of intolerable headaches while another patient could not achieve the desirable diastolic blood pressure of ≤ 90 mmHg. These three patients were therefore considered as treatment failures and were not included in the statistical analysis.

Table I shows the characteristics of the twenty-eight patients who completed the study.

Table I
Patients characteristics at baseline (n = 28)

Male : Female	16 : 12
Race (M:C:I)	21 : 5 : 2
Age (range)	49.1 ± 6.4 (40 – 63) years
Weight (kg)	68.7 ± 11.5 kg
Supine BP	149 ± 8/98 ± 4 mmHg
Serum Creatinine	98 ± 22 umol/L
SGOT	30 ± 18 IU/L

Values = Mean ± sd.
M = Malay
C = Chinese
I = Indian

a. **Dose requirements**

The dose requirement in these patients is shown in the histogram in Fig 1. Twenty five percent (7/28) of the patients required 10mg tds, 46%(13/28) required 20mg bd, 18% (5/28) required 20mg tds and 11% (3/28) required 30mg tds dose.

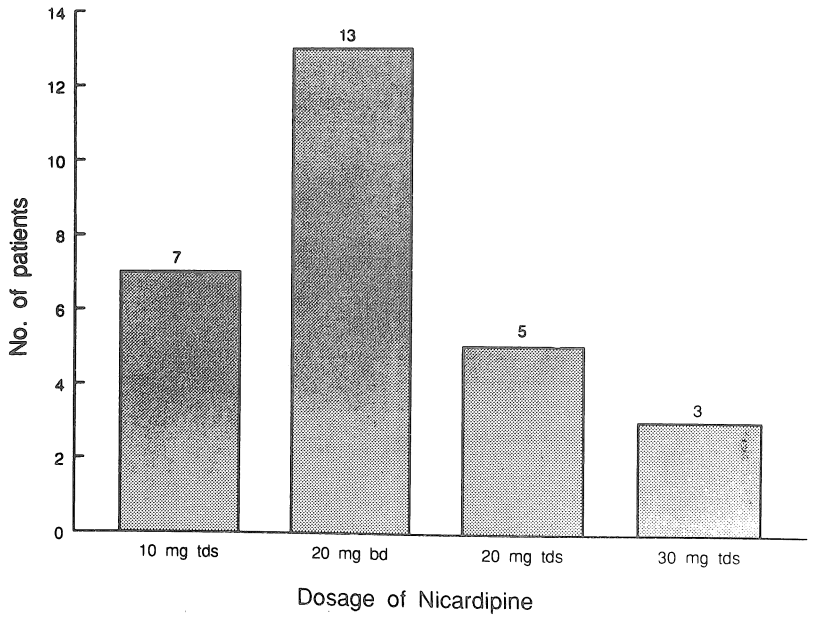

Fig. 1 : Nicardipine p.o. dosage distribution in the population studied

b. **Effect on Blood Pressure and Heart Rate**

Nicardipine treatment at doses varying from 30 mg to 90 mg daily in two or three divided doses allowed adequate control of blood pressures in both the supine and the standing positions throughout the sixteen weeks maintenance period (Fig 2). The SpDBP dropped from 98 ± 4 mmHg at baseline (end of placebo period) to 84 ± 4 mmHg at the end of sixteen weeks maintenance and the supine systolic from 149 ± 8 mmHg to 136 ± 12 mmHg. The standing diastolic blood pressure (Std. DBP) dropped from 103 ± 6 mmHg at baseline to 89 ± 6 mmHg at the end of 16 weeks maintenance and the standing systolic blood pressure (Std. SBP) from 150 ±9 mmHg to 136± 13 mmHg. The average reduction in the mean diastolic blood pressures (15%) being greater than the reduction in systolic blood pressure (9%).

Fig 3 depicts the mean blood pressures in patient-groups requiring different doses of Nicardipine. Mean heart rates after titration and after sixteen weeks maintenance therapy with Nicardipine did not vary significantly from the heart rates at the end of the placebo period (Fig 4).

c. **Effect on fasting serum lipid profile**

Table II shows the effects of optimal antihypertensive doses of Nicardipine on the lipid profile after twenty-four weeks treatment when compared to the values at the end of placebo phase, end of titration and at the end of sixteen weeks maintenance did not vary significantly. The fasting plasma total cholesterol, triglyceride, LDL cholesterol and HDL cholesterol at baseline were 6.08 ± 0.96 mmol/L, 1.55 ± 0.49 mmol/L, 4.06 ± 0.87 mmol/L and 1.29 ± 0.34 mmol/L respectively. The values after 16 weeks maintenance therapy with Nicardipine were 6.30 ± 1.00 mmol/L, 1.59 ± 0.59 mmol/L, 4.30 ± 0.99 mmol/L and 1.28 ± 0.31 mmol/L respectively. Therefore Nicardipine treatment for a total period of twenty-four weeks did not cause any significant changes in the fasting plasma total cholesterol, triglyceride, LDL and HDL cholesterol in these patients.

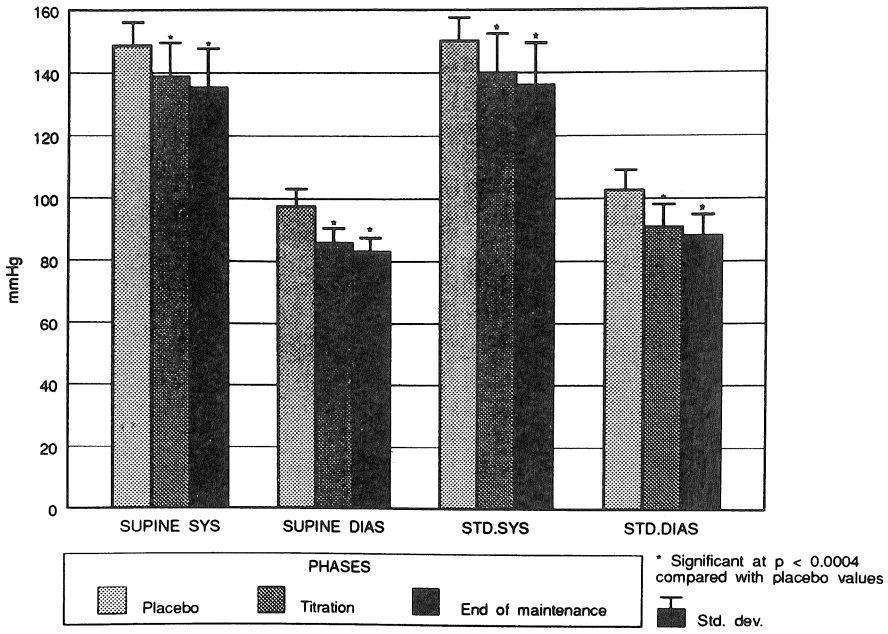

Fig. 2 : Blood pressure values at the end of placebo, end of titration and end of maintenance phases with Nicardipine

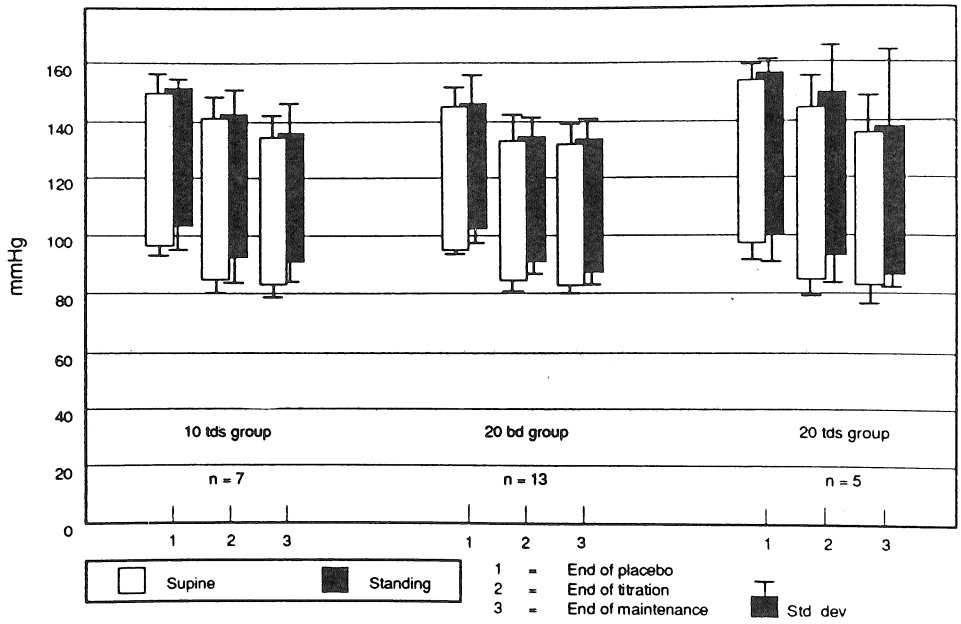

Fig. 3 : Blood pressure values in three groups of patients requiring 10mg tds, 20mg bd and 20mg tds respectively

d. Effect on serum biochemistry

There were no significant alterations in renal, liver and hematological parameters measured at the end of placebo and at the end of twenty-four weeks of treatment with Nicardipine.

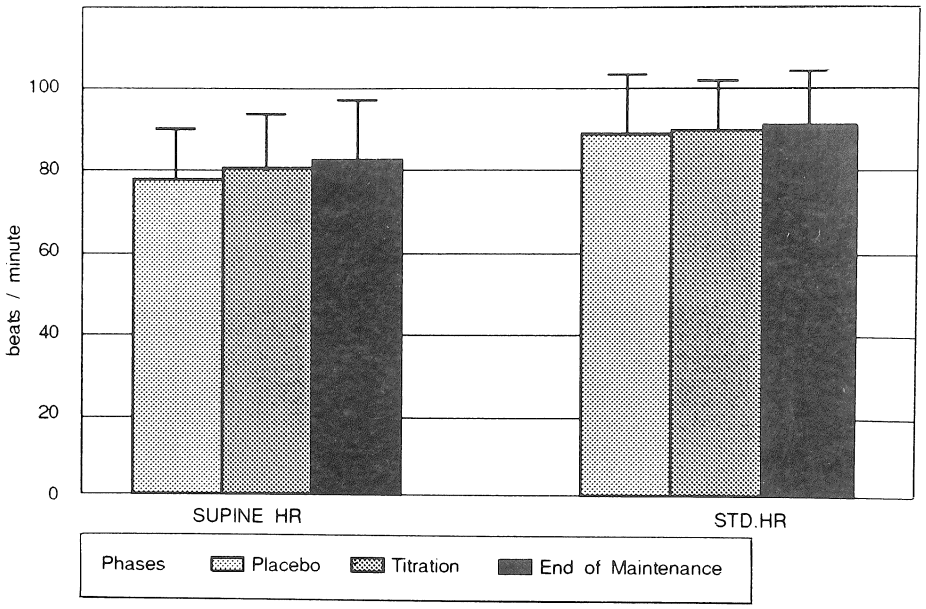

Fig. 4 : Heart rate values at the end of placebo, titration and maintenance with Nicardipine

Table II
The mean body weights and lipid profiles during the various treatment phases (n = 21)

	Placebo	Week 16	End of Study
Weight (kg)	67.9 ± 11.10	67.0 ± 9.86	63.6 ± 17.04
Total Cholesterol (mmol/L)	6.08 ± 0.96	6.19 ± 0.99	6.30 ± 1.00
Triglyceride (mmol/L)	1.55 ± 0.49	1.56 ± 0.54	1.59 ± 0.59
LDL (mmol/L)	4.06 ± 0.87	4.25 ± 0.88	4.30 ± 0.99
HDL (mmol/L)	1.29 ± 0.34	1.24 ± 0.29	1.28 ± 0.31

Note: Only values of patients with complete sets of lipid profile at all three stages were used for statistical analysis.

e. Side effects

Table III displays the evolution of side-effects during this study. No serious side-effects were encountered during the entire duration of the study. Headaches and palpitations occurred in four of thirty-one patients at the beginning of the study. These complaints became less noticeable in the two patients who continued the study. Two patients exhibited mild ankle oedema, after sixteen weeks of treatment. This mild ankle oedema did not seem to worry the patients and was only detected by the attending doctors.

Table III
Incidence of side-effects

	during placebo n = 31	week 2 n = 31	week 4 n = 29	week 16 n = 28	week 24 n = 28
Headache	1	4*	2	0	0
Fatigue	1	0	0	0	0
Palpitation	1	4*	2	0	0
Insomnia	0	1	0	0	0
Pedal oedema (mild)	0	0	0	2	1
Decreased libido	0	0	0	0	0

**includes 2 patients who discontinued at week 4 due to side-effects*

Discussion

Calcium channel blockers have recently and in a very short period of time became widely accepted in the management of patients with ischaemic heart disease and hypertension. Nicardipine is a dihydropyridine calcium channel blocker which has been shown in several studies to be a safe and effective antihypertensive agent[6,7].

Dosage requirements in this group of mild to moderate hypertensive Malaysian patients varied from 30mg to 90mg daily in two or three divided doses. The median dose requirement was 20mg twice daily. In the USA and Europe, the dose recommendations for Nicardipine range from 30mg to 120mg three times daily. Nicardipine produced a statistically significant reduction in the systolic and diastolic blood pressures both in the supine and standing postures when compared with the placebo treatment. There is no significant difference between the blood pressure and heart rate values at the end of the maintenance phase compared to the end of titration (start of maintenance phase), thus the decrease in blood pressure was maintained throughout the maintenance phase with no diminution in the effectiveness of Nicardipine. Heart rates during Nicardipine treatment were not significantly different from pre-treatment values at all doses and at the different treatment periods.

Based on its short half-life (t1/2) of four to five hours[8]. Nicardipine has been recommended to be given three times daily. However, in selected patients, several studies have shown that Nicardipine given twice daily were able to control the BP throughout the day[9].

Nicardipine treatment for twenty-four weeks did not cause any important changes in serum levels of sodium, potassium, uric acid or glucose. De Moustier et al[10] have shown that Nicardipine does not alter fasting and postprandial blood glucose concentrations, fasting plasma insulin level or glycosylated haemoglobin A1 after sixty to one hundred and twenty days treatment with doses ranging from 60 - 90 mg daily.

Nicardipine treatment for 24 weeks did not produce any significant effects on the fasting lipid profile. On the other hand, in vivo studies using laboratory animals suggested that calcium channel blockers

including Nicardipine possess antiatherogenic properties[11,12]. Nicardipine has been shown to decrease plasma levels of cholesterol when administered for sixteen weeks, and that HDL cholesterol tend to be increased over the same period[13]. However, long term large scale clinical trials must be carried out to confirm these findings. Leonetti et al[14] reported a low incidence of drug-related withdrawals when using Nicardipine in treating mild to moderate hypertension. The increase of adverse effects among the elderly hypertensive patients was found in the treated population as a whole (5.4%) and the nature of adverse effects was similar to that in the younger patients.

In another study on the long term effects of Nicardipine in treatment of essential hypertension, the majority of withdrawals for adverse events occurred early in the study[9]. The most frequently reported side effects were flushing, headache, ankle oedema and palpitations.

Conclusion

Nicardipine 30mg to 90mg daily in two to three divided doses were effective in controlling 96.5% (28/29) of mild to moderate hypertensive patients. Tolerance to its hypotensive effects did not develop during the sixteen weeks maintenance therapy. Side effects were mild and transient.

Nicardipine did not alter the fasting serum total cholesterol, triglycerides, LDL-and HDL-cholesterol level with twenty-four weeks treatment.

Acknowledgements

We wish to thank Messrs Unam Corporation (M) Sdn Bhd and specially Mr Gaven Woon for all assistance in supplying us with technical material during the study. Special thanks are due also to S/N Kumari A, Ms Ooi Suan Bee for their excellent assistance in the clinics, Ms Vijaya for her computer assistance in analysing the data and Ms Rosnah Abdul Manaf for typing the manuscript. This study was jointly sponsored by Grant IRPA 3-07-03-010 and Unam Corporation (M) Sdn Bhd.

References

1. Kaplan NM. Calcium entry blockers in the treatment of hypertension. JAMA 1989; 262: 817 - 23.

2. Silke B, Frais MA, Verma SP, Reynolds G, Taylor SH & Jackson NC. A review of the haemodynamic effects of Nicardipine in ischaemic heart disease. Br J Clin Pharmac 1986;22:203S - 13S.

3. Feely J, Cullen M & Collins W. Metabolic and endocrine consequences of calcium channel blockade. Br J Clin Pharmac 1986; 22: 231S - 6S.

4. Asplund J. Nicardipine hydrochloride in essential hypertension - a control study. Br J Clin Pharmac 1985: 20: 120S - 4S.

5. Virella MFL, Stones P, Ellis S & Wells JAC. Cholesterol determination in high density lipoproteins separated by three different methods. Clin Chem 1977; 23: 882 - 4.

6. Castle CH & Wolbach RA. Long term systemic arterial blood pressure control with Nicardipine. Am J Cardiol 1989; 64: 35H - 41H.

7. Littler WA. Nicardipine in the elderly hypertensives: A review of experience in the United Kingdom. Am Heart J 1989; 117: 262.

8. Graham DJM, Dow RJ, Hall DJ, Alexander OF, Mroszczak EJ & Freedman D. The metabolism and pharmacokinetics of Nicardipine hydrochloride in man. Br J Clin Pharmacol 1985; 20 (supp 1) : 23S - 8S.

9. Murray TS, Langan J, Coxhead PF & Levinson N. Long term effects of Nicardipine in the treatment of essential hypertension. Br J Clin Pharmac 1986; 22: 249S - 57S.

10. De Moustier BF & Paoli V. The influence of Nicardipine in type 2 diabetic patients with slight hypertension. J Cardiovasc Pharmacol 1990; 16 (suppl 2) : S26 - S33.

11. Ouchi Y & Orimo M. The role of calcium antagonists in the treatment of atherosclerosis and hypertension. J Cardiovasc Pharmacol 1990; 16 (suppl 2) : S1 - S4.

12. Willis AL, Nagel B, Churchill V, Whyte MA, Smith DL, Mahmud I & Puppione DL. Antiatherosclerotic effects of Nicardipine and Nifedipine in cholesterol-fed rabbits. Arteriosclerosis 1985; 5: 250 - 5.

13. Ishikawa H et al. Alteration of serum lipid levels after Nicardipine administration. Kiso-to-Rinsyo 1985; 19: 939 - 43.

14. Leonetti G & Chianca R. The effects of Nicardipine in elderly hypertensive patients. J Cardiovasc Pharmacol 1989; 16 (Suppl 2): S5 - S8.