ASSESSMENT OF THE EFFECTS OF NISOLDIPINE IN PATIENTS WITH MILD TO MODERATE HYPERTENSION

By

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SUMMARY

Objective: The primary objective of the study is to show that once daily nisoldipine is effective in the control of blood pressure in patients with mild to moderate hypertension. The secondary objectives of the trial are to evaluate safety and the change in treatment in patients taking once daily nisoldipine.

Subjects and Methods: A non-randomized, dose rising trial with a placebo run-in was done in which 20 consenting subjects (11 males and 9 females) with mild to moderate hypertension participated.

Results: Sixteen subjects (80% of total) made up of 9 males and 7 females had a satisfactory response defined as either a mean sitting trough-diastolic blood pressure (DBP) of below 90mmHg or a mean DBP that has decreased by 10mmHg or more from the baseline DBP after placebo run-in. Ten subjects responded at 10mg dose; 3 at 20mg; and 3 responded at 40mg dose. There was no significant mean change in heart rate in the subjects. There was also no significant drug induced adverse events.

Conclusion: This study demonstrated the efficacy, tolerability and safety of Syscor CC^{R} 10mg, 20mg and 40mg once daily in Nigerian patients with mild to moderate hypertension: Nisoldipine produced significant reduction in blood pressure within twelve weeks of active treatment.

Key Words: *Hypertension, Patients, Nisoldipine*

INTRODUCTION

An Expert Committee on Non-Communicable Diseases in Nigeria reported that Hypertension is the commonest non-communicable disease in Nigeria affecting about 4.33 million Nigerians aged 15 years and above, using the same criteria that we used for this study (Systolic Blood Pressure (SBP) ≥ 160mmHg and/or Diastolic Blood Pressure (DBP) ≥ 95mmHg)[1]. Over 20 million Nigerians would be affected using the recently recommended cut off (≥ 140/ 90mmHg) by the World Health Organization/International Society of Hypertension (WHO/ISH[2]). Hypertension and its complications are responsible for a significant percentage of admissions into the medical wards of tertiary health institutions in Nigeria[3].

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Apart from life-style modification, various antihypertensive drugs are used for therapy. Calcium channel blockers (CCB are among the most widely used class of anti-hypertensive drugs. Advantages of these drugs include convenient dosing, metabolic neutrality and minimal adverse effect on electrolytes and lipids. CCB of the dihydropyridine group have been found to be effective in treating hypertension in Nigerians[4]

Nisoldipine (Syscor CC®) is a second generation dihydropyridine type calcium antagonist which acts selectively on vascular smooth muscles[5, 6]. Studies have shown that nisoldipine is four to ten times more potent than Nifedipine as an inhibitor of vascular contraction, with virtually no effect on the myocardium or on cardiac conduction[5].

De Divitus et al have shown nisoldipine to be an effective anti hypertensive agent[7]. Other trials gave similar results[8]. An extended-release formulation of Nisoldipine, the coat-core (cc) tablet has been developed to produce sustained plasma levels of the drug for at least 24 hours after oral intake, thereby giving prolonged anti-hypertensive effect with reduced side effects and resultant improved patient compliance[9].

Studies have shown that immediate release (or intravenous bolus) formulations while giving rapid attainment of an effective plasma concentration do not appreciably decrease the blood pressure due to a marked increase in heart rate[10]. Same studies also show that major fluctuations in blood pressure during the dosing interval may persist for drugs and formulations that are short acting. Lasseter et al, using 24-hr ambulatory blood pressure monitoring, showed that Nisoldipine has a smooth onset of action with a consistent reduction in both systolic and diastolic blood pressure over the entire monitoring interval[11].

Coat core formulation of nisoldipine has been shown to give decreased incidence of side effects (headache, flushing, dizziness, palpitations, weakness, and peripheral oedema) common with immediate release (IR) formulations. This is due to its smoother pharmacokinetic profile over the IR formulations.

Frohlich et al [12] compared short acting and long acting dihydropyridine calcium antagonist formulations (Nifedipine) and found that while both had similar effects on mean blood pressure and total peripheral resistance, the long acting preparation produced significantly lower neurohumoral stimulation as adjudged by norepinephrine measurements. Rousseau et al [13] found no significant effect by Nisoldipine on norepinephrine, atrial natruretic peptide, arginine vasopressin, plasma renin activity and angiotensin converting enzyme inhibitor.

The primary objective of this study is to show that once daily nisoldipine is effective in the control of blood pressure in patients with mild to moderate hypertension. The secondary objectives of the trial are to evaluate safety and tolerability to treatment in patients taking once daily nisoldipine.

SUBJECTS AND METHODS

Study Design: This is a non randomized, rising dose trial with a placebo run in period to evaluate the efficacy, safety and tolerability of Nisoldipine once daily dosing in patients with mild to moderate hypertension. The trial included a two weeks placebo lead-in period followed by twelve weeks treatment with Syscor CC^R (Nisoldipine).

All the patients received 10mg Syscor CC^R for two weeks. If BP was not controlled, the dose of Syscor CC^R was increased to 20mg for a further two weeks. If still not controlled the Syscor CC^R dose was further increased to a maximum of 40mg.

Patients were advised to take Syscor CC^R once daily between the hours of 7.00am and 10am except on the days of visit when drugs were taken after clinical evaluation to allow for trough measurements.

Inclusion Criteria:

i) Patients aged 18 to 70 years inclusive willing to give informed consent prior to initiation of trial.

ii) Patients with mild to moderate high blood pressure (HBP) as described by diastolic blood pressure (DBP) criteria of the WHO/ISH Stage 1 (DBP 95 to 104mmHg) and stage 2 (DBP 105 to 119mmHg).

iii) At the end of the placebo run-in phase (visit 3, end of week 3). The trough diastolic blood pressure (where trough is defined 23 to 25 hours after the previous morning dose of trial medication but before the next dose) must be within 95 to 119mmHg inclusive. All office BP measurements during the trial were assessed using standard mercury sphygmomanometer.

iv) All antihypertensives must be terminated before entering the placebo run in phase of the trial. The run in phase would last for two weeks, consistent with acceptable clinical practice.

Exclusion Criteria

i) Patients with secondary hypertension of any aetiology and orthostatic hypertension.

ii) Patients with severe (Grade 3) hypertension at visit 1

iii) Patients who have sinus bradycardia (<45bpm) or resting heart rate >100bpm during the placebo run in phase.

iv) Patients who have had stroke or myocardial infarction in the previous 6 months or have clinical symptoms suggesting impending stroke.

v) Clinically significant cardiac pathology (e.g. congestive heart failure, cardiogenic shock, non controlled arrhythmias, acute myocarditis or pericarditis, significant valvular or congenital heart disease, severe unstable angina pectoris or second or third degree atrio-ventricular heart block.

vi) Pregnant women, nursing women or women of child-bearing age who are not on chemical or mechanical contraception.

vii) Cimetidine, phenytoin or any class 1 anti-arrhythmic (e.g. Disopyramide) intake during the 3-week before the start or during the trial.

viii) Significant gastrointestinal disease likely to interfere with complete absorption of drugs (e.g. major bowel resection and inflammatory bowel disease).

ix) Patients with a history of allergy or intolerance to nisoldipine or other dihydropyridines.

x) Patients who are expected to comply poorly with treatment (i.e. those with < 85% overall compliance during placebo run in period) or who are suspected of drug or alcohol abuse.

xi) Patients on antihypertensives that cannot be withdrawn safely before starting the trial.

xii) Patients who have participated in an investigational drug trial within the past 30 days.

xiii) Patients with a mid arm circumference > 41cm in either arm.

Restrictions

i) Patients were not allowed to smoke or consume alcohol during the morning of visits 1 to 9 before seated office blood pressure measurements and collection of blood samples.

ii) Patients were not allowed to consume grapefruit within 6 – 8 hours of taking the daily dose of Nisoldipine (Syscor CC^{R}).

Ethical Clearance for the study was obtained from the University of Nigeria Teaching Hospital Ethical Committee.

The following assessments were carried out at the appropriate visit. Detailed medical history was taken from each patient so as to establish laid down inclusion and exclusion criteria during visit 1. History of concomitant medications and diagnosis was obtained.

Complete physical examination was performed at visit 1 and at visits 6 and 9 (or on premature withdrawal). Office blood pressure and heart rate (radial pulse) taken at every visit (23 to 25hours) after previous morning dose. Blood pressure was taken by the previous trial personnel and on the same arm for each patient in the sitting and standing position with an appropriate blood pressure cuff size. Phase V (i.e. disappearance of Korotkoff sound) was used in determining diastolic blood pressure.

For laboratory evaluations, urine and blood samples were taken in visit 2 and any other visit if deemed necessary by the investigator. Urinalysis was done for glucose, protein, and microscopical examination for red cells, white cells and casts. Full blood count, serum urea, creatinine, electrolytes and cholesterol were checked. These were repeated after the treatment phase (Visit 9). Other investigations done included an electrocardiogram and chest x-ray done on visit 2.

The primary efficacy variable was predetermined to be the change in baseline mean diastolic blood pressure (DBP after placebo run-in period) to a DBP of below 90mmHg or a mean DBP that has decreased by 10mmHg or more from baseline DBP after placebo in. The secondary efficacy parameter was a change in mean systolic blood pressure to less than 160mmHg.

Safety assessments consisted of monitoring and recording all adverse effects, the monitoring of haematology, blood chemistry and urine values (at onset and termination of treatment), regular measurement of vital signs and performance of physical examination.

At each visit when trial medication is dispensed to the patient, a tear off label was attached to the appropriate case report form (CRF). This label is used to verify that the patient has received correct medication. All returned unused trial medication were counted by the trial centre personnel and recorded on CRF to assure patient compliance with the regimen and detect non-compliance.

RESULTS

Twenty-three intent to treat patients were recruited for the study. All satisfied the inclusion criteria and gave written consent. Three of the subjects dropped out of the study before visit 9. Of the twenty who completed the study, 11 were males and 9 were females. The patients were aged 48.00 $\pm$ 10.62 years with an age range of 26 to 68 years. After 4 weeks of treatment with Syscor CC ^{R} 10mg 60% of the patients had a mean sitting DBP of <90mmHg or a decrease from baseline DBP of greater or equal to 10mmHg.

Table 2 shows the mean systolic and diastolic pressures and Syscor dose at visits 3, 4, 5 and 9.

By the end of visit 9, six of the patients had had their doses increased to 40mg; 3 of these responded to therapy. Four of the patients had their doses increased to 20mg by the end of the study.

At the end of active treatment, sixteen of the patients (80%) responded to treatment with Syscor CC^{R}.

Table 3 shows the summary of pulse rate, blood pressure and body mass index of patients at visits 3 and 9. There was a statistically significant difference in mean systolic blood pressure in visit 3 (153.08 $\pm$ 18.20mmHg) and visit 9 (135.30 $\pm$ 12.80mmHg). There was also a statistically significant change in mean diastolic blood pressure (100.30 $\pm$ 5.23mmHg) and visit 9 (86.75 $\pm$ 7.85mmHg).

There were no statistically significant changes in BMI and pulse rate. None of the subjects in this study reported any adverse events and tablet compliance was total for all subjects.

DISCUSSION

The efficacy of Syscor CC^{R} (Nisoldipine administered at doses 10mg, 20mg and 40mg) was determined in the study by the reduction in mean diastolic blood pressure (DBP) from the level at the end of placebo run in period from100.30 $\pm$ 5.23mmHg to 86.75 $\pm$ 7.85mmHg at the end of the trial

period. There was a mean reduction in DBP of 13.55 ± 1.73mmHg.

Mean systolic blood pressure (SBP) was also reduced by 17.78mmHg. The value is greater than that obtained by Lasseter et al[14, 15] in their study of patients with essential hypertension. Trough mean reductions in the above named study were 8.9mmHg and 9.9mmHg for DBP and SBP respectively. The values in this study were also less than those obtained by Weiss and Schimtz [16] in their study of 6 patients with mild to moderate hypertension. The differences can probably be attributed to differences in sample size. Frishman et al in their study noted that immediate release formulations had different pharmacokinetics from the coat core formulations[17].

The result obtained in our study is similar to that obtained in the South African study of 206 patients[18]. There was a statistically significant difference in mean systolic and diastolic blood pressure in that study as there was in our study.

In this study 60% of the patients responded within 4 weeks of treatment with Syscor CC^R 10mg, 20mg and 40mg indicating a fairly reasonable early response to treatment.

In this study there were no statistically significant difference in heart rate (as measured by pulse rate) and body mass indices. This rules out reflex tachycardia found in some short-acting calcium channel blockers[19].

In keeping with previous reports attesting to the metabolic neutrality of calcium antagonists, no significant alterations in serum cholesterol, or electrolytes were reported in the subjects[20, 21, and 22].

There was no significant effect on the BMI of the subjects before and after treatment although this would have been more relevant if a control group was included in this study.

Conclusion

This study has demonstrated the efficacy, tolerability and safety of Syscor CC^R 10mg, 20mg and 40mg once daily in Nigerian patient with mild to moderate hypertension with significant reduction in blood pressure occurring within twelve weeks of active treatment.

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TABLE 1: VISIT SCHEDULE

VISIT NUMBER	1	2	3	4	5	6	7	8	9
WEEK NUMBER	0	1	3	5	7	9	11	13	15
INFORMED CONSENT	x								
MEDICAL HISTORY	x								
Confirm General trial eligibility	x	x							
Physical examination	x					X			x
Weight	x	x	x	x	x	X	x	x	X
Mid arm Circumference	x								
Taper Current antihypertensives	x	x							
Biochemistry		x							x
Haematology		x							x
Urinalysis		x							x
Pregnancy Test		x							
Chest x-ray		x							
ECG		x							x
Sitting trough (23-25hrs post dose BP)	x	x	x	x	x	x	x	x	x
Standing BP		x	x	x	x	x	x	x	x
Heart rate (radial pulse)		x	x	x	x	x	x	x	x
Assess response to treatment					x	x	x	x	x
Enquire about current medication	x	x	x	x	x	x	x	x	x
Instruct patient when to take trial medication		x	x	x	x	x	x	x	x
Dispense trial medication		x	x	x	x	x	x	x	x
Adverse events		x	x	x	x	x	x	x	x
Tablet compliance			x	x	x	x	x	x	x

TABLE 2: MEAN SYSTOLIC PRESURE, DIASTOLIC PRESSURE AND SYCSCOR CC[R] DOSAGE

S/NO	VISIT 3			VISIT 4			VISIT 5			VISIT 9		
	Dosage mg	SBP mmHg	DBP mmHg	Dosage mg	SBP mmHg	DBP mmHg	Dosage mg	SBP mmHg	DBP mmHg	Dosage mg	SBP mmHg	DBP mmHg
1.	10	140	95	10	100	70	10	120	90	10	130	88
2.	10	130	100	10	120	100	10	115	87	10	128	90
3.	10	146	98	20	147	110	40	160	100	40	148	90
4.	10	158.6	98.8	20	148	96.7	40	141.7	96.7	40	142	82
5.	10	140	95	20	123	84	20	118.6	69.3	20	118	80
6.	10	168	104	10	153	100	20	138	90	40[+]	130	87
7.	10	178	95	10	148	85	10	144	80	10	150	90
8.	10	190	114	20	190	120	40	190	118	40	133	88
9.	10	183	103	20	164	104	20	178	104	40	170	110
10.	10	146	103	10	130	90	10	130	88	10	130	90
11.	10	137	97	10	130	90	10	131	90	10	137	80
12.	10	160	100	10	130	90	10	123	78	10	130	80
13.	10	165	110	10	140	90	10	140	87	10	140	80
14.	10	170	100	10	143	90	10	120	80	10	120	80
15.	10	130	95	10	113	80	10	130	83	10	120	80
16.	10	140	100	10	130	90	10	135	85	10	120	80
17.	10	130	100	10	120	90	10	140	90	20**	130	90
18.	10	160	103	20	173	117	20	150	100	20	140	100
19.	10	140	95	10	140	90	20	127	87	20	140	80
20.	10	150	100	20	140	100	20	150	110	40	150	90

Dosage is that given to the patient at the end of the indicated visit
[+]Dose changed at visit 6
[**]Dose changed at visit 8

TABLE 3: SUMMARY OF PULSE RATE, BP AND BMI AT VISITS 3 AND 9

Parameter	Visit 3	Visit 9	P value
1. BMI (Kg/m^2)	23.58 ± 4.59	23.67 ± 4.65	$^{+}P > 0.05$
2. Pulse rate (no/min)	74.95 ± 10.16	74.65 ± 8.45	$^{+}P > 0.05$
3. Systolic blood pressure mmHg	153.08 ± 18.20	135.30 ± 12.80	$^{*}P < 0.05$
4. Diastolic blood pressure mmHg	100.30 ± 5.23	86.75 ± 7.85	$^{*}P < 0.05$

*Significant
+Not Significant

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