Conversion from 2.5 mg to 1.25 mg Indapamide in Patients with Mild to Moderate Hypertension

Barton Levine, MD; William Lee, MD; Gary Boyd, MD; Steven Chrysant, MD; Jack Dawson, MD; Timothy Gardner, MD; Gregory Hill, MD; James Vergis, MD; Joseph Codispoti, MD; Arthur Stokes, MD; and Charles McNally, MD

Los Angeles, California; Lansdale, Bristol, and Collegeville, Pennsylvania; Birmingham, Alabama; Oklahoma City, Oklahoma; Atlanta, Georgia; and Spokane, Washington

Background. Indapamide is an effective antihypertensive drug with diuretic and vasodilating activities. The common starting dose has been 2.5 mg to 5 mg. A lower dose formulation (1.25 mg) is now available. The safety and efficacy of switching patients from indapamide 2.5 mg to indapamide 1.25 mg was evaluated in this randomized, double-blind, multicenter clinical trial.

Methods. Three hundred seventy-eight adult patients with mild to moderate essential hypertension were enrolled in a washout period, during which patients received single-blind placebo for 4 weeks. All 378 patients qualified for the study and received open-label treatment with indapamide 2.5 mg for 8 weeks. Of the 378 patients, 265 responded to indapamide 2.5 mg and were randomized to receive double-blind treatment with either indapamide 1.25 mg (n=132) or 2.5 mg (n=133) for 8 weeks. Overall, 245 of the 378 patients who were initially enrolled completed the study. The primary efficacy variable was the number of patients in each treatment group who maintained a supine diastolic blood pressure of ≤90 mm Hg (treatment success) by the end of the double-blind period (week 16).

Results. Treatment with indapamide 1.25 mg once daily was as efficacious as the 2.5-mg once-daily dose. No significant difference was observed for the percentage of patients who achieved treatment success between the patients switched from indapamide 2.5 to 1.25 mg (74%) and the control group maintained on indapamide 2.5 mg (70%). The incidence of drug-related adverse events during the double-blind period was similar between the two treatment groups. The mean change from pretreatment baseline to endpoint in serum potassium was −0.2 mEq/L (−0.2 mmol/L) in the indapamide 1.25 mg treatment group, compared with −0.4 mEq/L (−0.4 mmol/L) in the indapamide 2.5 mg treatment group.

Conclusions. Indapamide 1.25 mg given once daily for 8 weeks was as effective as 2.5 mg once daily in reducing systolic and diastolic blood pressure in patients with mild to moderate hypertension.

Key words. Indapamide; drug therapy; hypertension; antihypertensive agents; diuretics. (*J Fam Pract 1995; 41:75-80*)

Indapamide, the first of a class of oral antihypertensive and diuretic agents, the indolines, is indicated for the treatment of mild to moderate essential hypertension or fluid retention associated with congestive heart failure. Indapamide decreases peripheral vascular resistance with little or no effect on lipid levels, cardiac output, rate, rhythm, or intravascular volume.[1] The lowest available dose for indapamide when the drug was introduced was 2.5 mg once daily with an increase to 5.0 mg once daily if the response to 2.5 mg was not satisfactory.[2]

Most adverse effects associated with indapamide 2.5 mg and 5.0 mg have been shown to be mild and transient. Adverse laboratory changes include clinical hypokalemia in 3% of patients receiving indapamide 2.5 mg, and in 7% of patients receiving indapamide 5.0 mg. Because of this dose relationship with potassium loss, as well as with other

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From the VA Medical Center, Los Angeles, California (B.L.); North Penn Hospital, Lansdale (W.L.), Lower Bucks Hospital, Bristol (J.V.), and Rhône-Poulenc Rorer Pharmaceuticals, Inc, Collegeville (J.C., A.S., C.M.), Pennsylvania; Southern Drug Research (G.B.) and SORRA Research Center (G.H.), Birmingham, Alabama; Oklahoma Cardiovascular & Hypertension Center, Oklahoma City (S.C.); Atlanta Medical Associates, Atlanta, Georgia (J.D.); and Pacific Coast Clinical Coordinators, Spokane, Washington (T.G.). Requests for reprints should be addressed to Barton Levine, MD, VA Medical Center, W111L Bldg 500, Room 6023, Los Angeles, CA 90073.

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potential side effects, the use of the lowest possible efficacious dose is of paramount importance.

A 1.25-mg dose formulation of indapamide is now available. This study examines the safety and efficacy of switching patients from indapamide 2.5 mg to the lower dose of 1.25 mg in the general hypertensive population. For patients currently receiving the 2.5-mg dose of indapamide, a switch to the 1.25-mg dose may be beneficial with respect to side effects, particularly if it can be shown that there is no loss of blood pressure control.

Methods

Patients

Three hundred seventy-eight adult patients with mild to moderate essential hypertension, defined as supine diastolic blood pressure between 95 mm Hg and 114 mm Hg, inclusive, were screened for enrollment into this study. The following patients were excluded from enrollment in the study: patients who had any clinically significant disease, including a disease state causing secondary hypertension; congestive heart failure; history of electrolyte imbalances; grade III retinopathy; significant renal impairment; a history of stroke within 1 year; cardiac surgery within 2 years; myocardial infarction within 2 years; severe hypertension; any arrhythmia requiring drug treatment; diabetes treated with insulin. Also excluded were patients with any clinically significant laboratory abnormality; patients whose serum potassium was <3.4 or >5.4 mEq/L (<3.4 or >5.4 mmol/L); female patients with a positive pregnancy test immediately before study entry or lactating women of childbearing potential; and patients requiring the use of another hypertensive agent. It was predetermined that patients for whom additional hypertensive treatment became necessary during the study period would be dropped from the study. All patients who participated in the study provided informed consent.

The demographic characteristics of patients randomized to receive double-blind treatment with indapamide 1.25 mg or 2.5 mg are shown in Table 1.

Design

This study was conducted at 19 sites. Patients who met the entry criteria entered a washout period (the first phase of the study) during which they received single-blind placebo for 4 weeks, and a diagnosis of mild to moderate uncomplicated hypertension was confirmed (supine diastolic blood pressure between 95 mm Hg and 114 mm Hg, inclusive).

Table 1. Characteristics of Patients in the Two Indapamide Treatment Groups

Characteristic	Treatment Group: Patients Switched from 2.5 mg to 1.25 mg Indapamide (n=131*)	Treatment Group: Patients Maintained on 2.5 mg Indapamide (n=133)
Mean age, y (range)	55.8 (26–76)	54.2 (25–75)
Mean weight, lb (range)	181.3 (112–257)	180.3 (88–253)
Sex, %		
Male	47	50
Female	52	50
Race/ethnicity, %		
White	60	61
Black	17	15
Hispanic	23	20
Asian	0	2
Other	0.8	3
Mean baseline SDBP, mm Hg	98.3 (n=126†)	98.5 (n=129†)

**Demographic information for one patient was unavailable for all characteristics except weight.*
†Patients from one center were not included in the mean baseline supine diastolic blood pressure calculation.
SDBP denotes supine diastolic blood pressure.
NOTE: Percentages may not total 100 because of missing data or rounding.

Patients were then entered into the second phase of the study, during which they received open-label indapamide 2.5 mg for 8 weeks. At each of the open-label visits, three supine systolic and diastolic blood pressure readings were obtained approximately 3 to 5 minutes apart, and two standing systolic and diastolic blood pressure readings were obtained, one immediately after standing, followed by a second reading obtained after 2 minutes of standing. These readings were obtained in the nondominant arm and, whenever possible, by the same individual in each center using the same blood pressure measuring device throughout the study. The average of the blood pressure readings for each position was recorded and used in the data analysis. Heart rate and body weight measurements also were obtained, and adverse events, test medication, and concomitant medication were recorded.

At weeks 2 and 4 only, fasting clinical laboratory values, measured by a common central laboratory, were obtained for glucose, electrolytes, blood urea nitrogen (BUN), and creatinine. At week 8, an electrocardiogram (ECG) was taken, and blood samples for hematology, biochemistry, lipid profile, and urinalysis were obtained. Potassium supplements were allowed during the open-label period. If a patient's potassium level decreased to <3.0 mEq/L (<3.0 mmol/L) at any time during the

open-label period, the patient was dropped from the study.

At the final open-label visit, the patient had to demonstrate an average supine diastolic blood pressure of <90 mm Hg with the high and low values of the three readings not varying by more than 7 mm Hg in order to qualify for the third phase (double-blind) of the study. All potassium supplementation was to be discontinued at this time and reevaluated after 2 weeks of double-blind treatment.

During the third phase of the study, patients were randomized to receive double-blind treatment with indapamide either 1.25 mg or 2.5 mg for 8 weeks. During this period, patients were seen every 2 weeks, at which time blood pressure (using the routine described earlier), heart rate, and body weight were measured. Adverse events, study medication, and concomitant medication were recorded at each double-blind visit. At weeks 10 and 14, fasting clinical laboratory values were obtained for glucose, electrolytes, BUN, and creatinine. At the final visit (week 16), patients had a complete physical examination, including vital signs and weight, a 12-lead ECG, and fasting clinical laboratory tests (hematology, biochemistry, lipid profile, and urinalysis).

Statistical Analysis

Efficacy analyses were carried out on all of the treated patient population. The primary efficacy variable was the number of patients on each regimen who maintained a supine diastolic blood pressure of ≤90 mm Hg by the end of the double-blind treatment period. Secondary efficacy variables were the mean changes from baseline in diastolic (supine and standing) and systolic (supine) blood pressure. For the primary efficacy variable, comparisons between regimens were made using the Cochran-Mantel-Haenszel test, stratified by center. For the secondary efficacy variables, treatment comparisons were made using a two-way analysis of variance model with effects for center, treatment, and center-by-treatment interaction. Under the assumption that at least 70% of the patients treated with indapamide would maintain a supine diastolic blood pressure of ≤90 mm Hg by the end of double-blind treatment, a sample size of 93 patients per treatment arm would provide 90% power to detect a treatment difference of 20% in responder rate. With respect to the secondary efficacy criterion, the sample size in this study provided 84.3% power to detect a difference of 2.125 mm Hg between the treatment groups,[3] assuming a within-group variance of 29.81 mm Hg, as estimated from the data in this study.

The incidence rates of adverse events by body system were compared for treatment regimen differences using Fisher's exact test. For adverse events that occurred with an incidence rate of at least 5% in either treatment group, similar comparisons were made for all adverse events and for adverse events considered related to the study medication. Treatment comparisons with regard to incidence rates of hypokalemia were also carried out using Fisher's exact test. Descriptive statistics were used to summarize mean changes from baseline in laboratory values.

Results

Patient Disposition

Of the 378 patients who enrolled, 245 completed the study. Of the 133 patients who were prematurely discontinued, 113 were not randomized. Of the remaining 20 patients, 6 were lost to follow-up, 4 were withdrawn owing to protocol violations, 4 were withdrawn because of clinical or laboratory adverse experiences, 2 withdrew consent, 1 withdrew as a result of ineffective therapy, and 3 were withdrawn for other reasons. A flow diagram of patient disposition by study period is presented in the Figure.

Efficacy

In the primary analysis, 74% (85/115) of patients in the indapamide 2.5→1.25 mg group had a decrease in supine diastolic blood pressure to ≤90 mm Hg (treatment success) by week 16, compared with 70% (83/119) of patients in the indapamide 2.5→2.5 mg group. This difference was not statistically significant. At the last observation during the study (endpoint), similar results were observed: 73% (96/131) of the patients in the 2.5→1.25 mg group achieved treatment success, compared with 67% (89/132) of patients in the indapamide 2.5→2.5 mg group. This difference was not statistically significant. Of note, 245 patients were classified as completers by the investigator; however, 11 of these patients had their week 16 visit outside the visit window (ie, ±1 week from protocol schedule), and therefore are not included in the efficacy analysis for this timepoint.

With respect to the secondary efficacy analyses, both indapamide regimens produced comparable decreases from baseline in mean supine diastolic and systolic blood pressures throughout the study period. Patients in the indapamide 2.5→1.25 mg treatment group experienced a mean decrease in supine diastolic blood pressure of 11.5 mm Hg (from 98.3 to 86.6 mm Hg) by week 16, compared with a decrease of 10.4 mm Hg (from 98.5 to 88.0 mm Hg) for patients who received indapamide 2.5→2.5 mg. This difference was not statistically significant. The mean decrease in supine systolic blood pressure by week

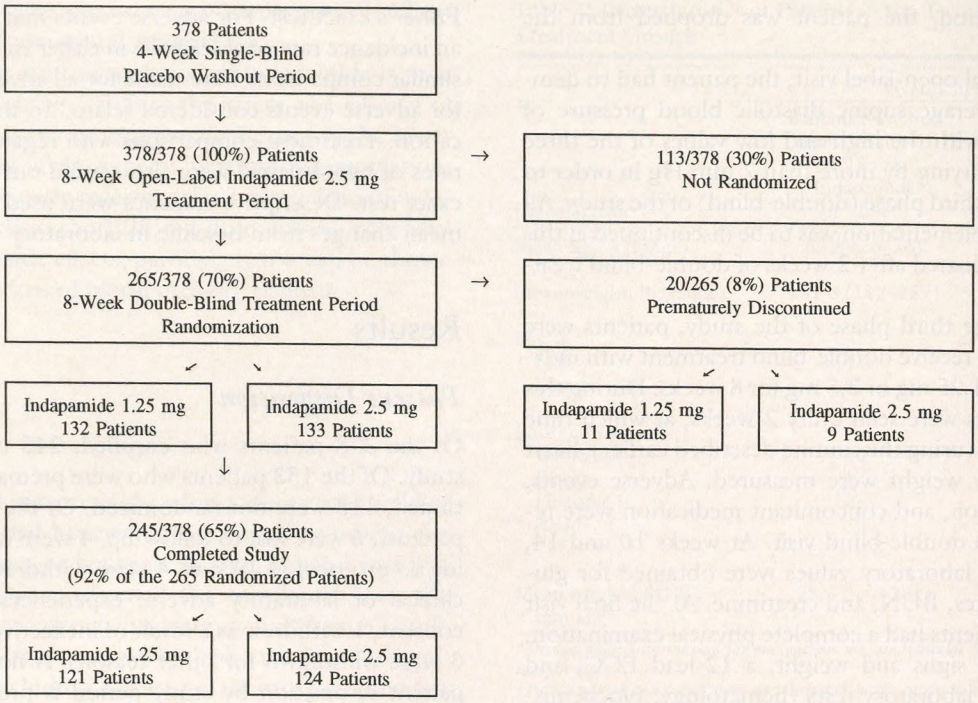

Figure. A flow diagram of the various stages of patient allocation during the study.

16 was 12.2 mm Hg for patients in the indapamide 2.5→1.25 mg group, compared with a mean decrease of 13.7 mm Hg produced in the indapamide 2.5→2.5 mg group. The secondary efficacy analyses excluded patients from one center because of a statistically significant treatment-by-center interaction.

Safety

Adverse events were tabulated for all patients combined during the open-label period and separately for each treatment group during the double-blind period. Patients were instructed by the investigator to immediately report the occurrence of any adverse event, which was defined as any undesirable event associated with the use of study medication, regardless of whether it was considered drug-related. Adverse events included side effect, injury, toxicity, and sensitivity reaction, or any clinical or laboratory change that did not commonly occur in that individual. During the 8-week open-label period, the most frequently reported adverse events overall were flulike symptoms (8.7%), headache (8.2%), and asthenia (3.7%). During the 8-week double-blind period, the incidence rates for all adverse events were similar between the two treatment groups. The most frequently reported adverse events were flulike symptoms and dizziness (Table 2). In addition, incidence rates of drug-related adverse events were similar between the two regimens. The most frequently reported drug-related adverse events in the indapamide 2.5→1.25 mg and indapamide 2.5→2.5 mg treatment groups were dizziness (1.5% and 0.8%, respectively) and asthenia (1.5% and none, respectively). No drug-related adverse event occurred at an incidence rate of ≥2% for either regimen.

One patient in the indapamide 2.5→1.25 mg treatment group was prematurely discontinued from the study because of an abnormal ECG, which occurred during double-blind treatment. This patient had a myocardial infarct that was considered by the investigator to be a

Table 2. Adverse Events Reported by at Least Three Percent of Patients in Either Indapamide Treatment Regimen During the Double-Blind Treatment Period

	Treatment Group	
Adverse Event	% Patients Switched from 2.5 mg to 1.25 mg Indapamide (n=132)	% Patients Maintained on 2.5 mg Indapamide (n=133)
Flulike symptoms	7.6	8.3
Headache	3.8	0.0
Pain	0.0	3.0
Dizziness	3.8	3.0
Pharyngitis	2.3	3.8
Sinusitis	0.8	3.8

Table 3. Mean Changes in Selected Laboratory Values from Phase II Baseline (Week 0) to the Last Observation of the Indapamide Study

Laboratory Values	Indapamide 2.5 mg to 1.25 mg (n=116–131*)	Indapamide 2.5 mg to 2.5 mg (n=119–132*)	P Value†
Mean change (SD) from baseline			
Glucose, mg/dL	+3.5 (21.4)	+8.6 (20.5)	NS
Potassium, mEq/L	−0.2 (0.44)	−0.4 (0.49)	.02
Triglycerides, mg/dL	+4.8 (88.3)	+19.2 (66.4)	NS
Cholesterol, mg/dL	−1.3 (24.5)	+4.1 (23.1)	NS
HDL cholesterol, mg/dL	−1.2 (6.63)	+0.8 (6.85)	.02
LDL cholesterol, mg/dL	−1.1 (22.0)	+0.6 (20.3)	NS
Uric acid, mg/dL	+0.1 (0.74)	+0.5 (0.93)	.002

**Values were recorded only for patients with data.*
†Treatment comparisons were based on two-sided t tests.
SD denotes standard deviation; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

serious adverse event, but unrelated to the study drug. The patient was noted to have recovered.

Table 3 shows the mean changes in selected laboratory values from open-label baseline to the last observation of double-blind therapy. Mean changes ± standard deviation (SD) in laboratory values were noted for glucose (+8.6±20.5 mg/dL [+0.5±1.1 mmol/L]), potassium (−0.4±0.49 mEq/L [−0.4±0.49 mmol/L]), uric acid (+0.5±0.93 mg/dL [+30±55 μmol/L), and triglycerides (+19.2±66.4 mg/dL [+0.22±0.75 mmol/L) in the indapamide 2.5→2.5 mg group. Mean changes (±SD) from baseline in the indapamide 2.5→1.25 mg group were +3.5±21.4 mg/dL (+0.19±1.19 mmol/L), for glucose; −0.2±0.44 mEq/L (−0.2±0.44 mmol/L) for potassium; +0.1±0.74 mg/dL (+6±44 mmol/L) for uric acid; and +4.8±88.3 mg/dL (+0.05±0.10 mmol/L) for triglycerides. Thus, there was no evidence of a difference between the two treatment regimens for the changes in metabolic values.

During the open-label period, 21% of the patients (77/367) had at least one occurrence of hypokalemia, defined as a potassium level <3.5 mEq/L (<3.5 mmol/L). During this phase of the study, 63 patients required some form of potassium supplementation. When analyzed only for the 8-week double-blind period, there was no mean change in potassium for the 2.5→2.5 mg group. However, the 2.5→1.25 mg group showed a mean increase in potassium of +0.1 mEq/L (+0.1 mmol/L). Eight patients in the indapamide 2.5→1.25 mg treatment group and 13 patients in the indapamide 2.5→2.5 mg treatment group became hypokalemic only during the double-blind period. During the double-blind phase of the study, 20% (26/133) of the patients in the 2.5→2.5 mg group and 13% (17/132) of the patients in the 2.5→1.25 mg group had at least one occurrence of hypokalemia. Of these, nine patients in the 2.5→2.5 mg group and seven patients in the 2.5→1.25 mg group returned to normal without potassium supplementation by their last visit. Thus, only 13% (17/133) of patients in the 2.5→2.5 mg group and 8% (10/132) of patients in the 2.5→1.25 mg group were still hypokalemic by the end of the double-blind period or became normokalemic only with the aid of potassium supplementation. Only one patient in the 2.5→1.25 mg group and two patients in the 2.5→2.5 mg group had a potassium level of <3.0 mEq/L (<3.0 mmol/L) during the double-blind period. In total, 12 patients in the 2.5→2.5 mg group and six patients in the 2.5→1.25 mg group required potassium supplementation during the double-blind period.

Discussion

In this study, patients were switched from indapamide 2.5 mg daily to 1.25 mg daily in an attempt to see whether improvement in metabolic function could be achieved without compromising indapamide's effectiveness in reducing blood pressure. Many of the laboratory changes caused by beta-blockers (eg, increased triglycerides and decreased high-density lipoproteins)[4] and thiazide diuretics (eg, hypokalemia, hypomagnesemia, hyperuricemia, and adverse effects on glucose tolerance and lipid metabolism)[4] are not seen or are less severe with indapamide. Chronic indapamide therapy has not been reported to

cause significant effects on glucose tolerance or lipid metabolism associated with thiazide diuretics.

The Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure has recommended that antihypertensive therapy be initiated in smaller doses.[4] The results of other studies using lower doses of hydrochlorothiazide have shown a reduced blood pressure lowering effect.[5,6] Results from one study showed that daily treatment with low-dose hydrochlorothiazide (12.5 mg) given in combination with a beta-blocker (nadolol 80 mg) was ineffective in reducing blood pressure.[6] This has not been the case in this study. Supine systolic and diastolic blood pressures were maintained equally for both indapamide treatment regimens. In terms of response rate, defined as supine diastolic blood pressure ≤90 mm Hg, there was no significant difference between the 1.25-mg and 2.5-mg treatment groups. Eight patients in the indapamide 2.5→1.25 mg treatment group and 13 patients in the indapamide 2.5→2.5 mg treatment group became hypokalemic only during the 8-week double-blind period. In addition, the incidence of hypokalemia was halved as the dose was halved. During the double-blind period, 26 patients in the 2.5→2.5 mg group and 17 patients in the 2.5→1.25 mg group had at least one occurrence of hypokalemia. Other evidence of decreased hypokalemia in the 2.5→1.25 mg group includes the total number of patients who required potassium supplementation at some time during double-blind therapy (12 of the 2.5→2.5 mg group vs 6 of the 2.5→1.25 mg group) and the actual mean increase of +0.1 mEq/L (+0.1 mmol/L) in serum potassium during the 8 weeks of administration of the 2.5→1.25 mg dose. Furthermore, the mean decrease in serum potassium from the beginning of the open-label period to the end of the double-blind period was −0.4 mEq/L (−0.4 mmol/L) for the patients who remained on the 2.5 mg regimen, and only −0.2 mEq/L (−0.2 mmol/L) for those who switched to 1.25 mg at the beginning of the double-blind period.

Indapamide demonstrated a lipid-neutral effect: no unexpected changes or clinically meaningful changes were observed in total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides. In addition, no unexpected or clinically meaningful changes were observed for glucose or uric acid. No definitive conclusions could be drawn from this study regarding the relationship between hypokalemia and the development of alterations in glucose and lipids.

For patients with arrhythmias or underlying ischemic disease, this potassium-sparing effect could conceivably be clinically relevant.[7,8] Other patient populations that could benefit from this improved electrolyte profile are those with recent myocardial infarctions or patients on digitalis therapy.[9,10] The 1.25-mg dosage may be particularly well suited to elderly patients, who are more sensitive to volume depletion and frequently have impaired cardiovascular reflexes that render them more susceptible to hypotension, arrhythmias, or generalized adverse systemic responses.[11] These factors, combined with the reduced effect on the metabolic values, render the 1.25-mg regimen ideal either for initiation of antihypertensive therapy or for reducing dosage to 1.25 mg from a higher indapamide dose.

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