Efficacy and Safety of Two-Year Therapy with Transdermal Clonidine for Essential Hypertension*

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We evaluated the safety and efficacy of transdermal clonidine (TC) in 23 patients with essential hypertension over a two-year period. Fourteen patients achieved control of blood pressure using TC alone. Six patients achieved control with a combination of TC and the diuretic chlorothalidone (CH). Three patients had control with CH alone or did not achieve control with either TC alone or TC plus CH and were dropped from the study. Of the 20 patients remaining in the study, six patients remained on TC or TC plus CH for the two-year study. Ten of the 20 patients quit the study because of skin reactions and four because of other side effects. No clinically significant changes were noted in serum or urinary laboratory parameters. Finally, TC was effective as long-term monotherapy for essential hypertension in only four of our patients. The major limitation is skin-related side effects.

The transdermal delivery of drugs is becoming more common with the success of nitroglycerin and scopolamine. Clonidine also has the ability to be readily absorbed through the skin, and blood levels can be therapeutic and relatively constant with the application of the patch once weekly. Transdermal clonidine (TC) is now commercially available as Catapres-TTS 1,2,3 which represents differing sizes (3.5-, 7.0-, and 10.5-cm patch diameter) designed to deliver 0.1, 0.2, and 0.3 mg of clonidine per day. This method of drug delivery has a potential advantage over the oral route regarding compliance in the very young, the elderly, or in those who are not able to reliably take oral medications because of physical or mental illness, thus reducing the danger of over- or under-medication. Clonidine may be considered as first-line therapy in this way and serve as an alternative to thiazide diuretics or β-blockers to avoid known side effects of those drugs.

It has not been clear whether this preparation could meet the goal of first-line therapy; as previous reports have been of short-duration therapy. The data presented here represent the findings of a two-year follow-up on patients with mild essential hypertension who were treated with TC.

METHODS

This study was a prospective study involving 23 patients who were treated with TC for mild to moderate hypertension over a two-year period. With informed consent, blood pressures and clinical laboratory tests after two weeks of transdermal placebo therapy were compared with those measured after 1, 12, 18, and 24 months of TC therapy. Clonidine was delivered by means of a transdermal patch applied to a hairless area on the upper torso once weekly. At the start of the study, the patients' ages ranged from 22 to 66 years with a mean age of 53 years and a standard deviation of ± 13 years. The requirements for entry into the study were a baseline diastolic blood pressure (DBP) between 90 and 104 mm Hg; no significant cardiovascular, renal, or hepatic disease; serum creatinine value less than 2.0 mg/dL; no skin disease of any type; no history of any allergies; and women could not be pregnant or nursing.

Systolic blood pressure (SBP) and DBP were recorded with a mercury sphygmomanometer after the patient had been seated for five minutes. The reported blood pressures are the average of three measurements. Mean arterial pressure (MAP) was calculated from the formula: MAP = DBP + (SBP - DBP)/3.

Patients were seen weekly during the titration period until they were stable. They were then seen monthly for two months, and finally every two months until the study was concluded. Control of blood pressure was defined as a DBP less than 90 mm Hg, a 5-mm Hg minimum drop in DBP for patients with a baseline DBP of 90 to 99 mm Hg, or a 10-mm Hg drop in DBP for patients with a baseline DBP of 100 to 104 mm Hg. If control was not achieved after one week of therapy, the next higher dose of TC was applied until control was achieved or until the maximum dose had been given.

If control was not achieved with the maximal dose of TC, then 25 mg of a diuretic, chlorothalidone (CH), alone was initiated. If control was achieved with this diuretic alone, the study was terminated for that particular subject, and the patient was considered a TC failure. If the patient was not controlled with CH alone, then TC was added to the CH in increasing dosages until control was achieved. If the DBP was controlled using both of these drugs, this regimen was continued until termination of the study, but the patient was considered a TC alone failure. If control was not achieved with CH and the maximum dose of TC, the patient was considered a treatment failure.

The baseline studies consisted of a history and physical examination performed by one of the physician investigators, an electrocardiogram (ECG), and laboratory determinations. The laboratory studies consisted of a complete blood cell count (CBC), electrolyte values, cholesterol levels, triglyceride, albumin, alkaline phosphatase, aspartate aminotransferase, bilirubin, urea nitrogen, calcium,
globulins, glucose, lactic dehydrogenase, phosphorous, total protein, uric acid values, urinalysis, and creatinine clearance. These tests were done by a standard hospital clinical laboratory. Special urine studies consisted of urine sodium and urine potassium measured by ion selective electrodes (Nova, Newton, MA); urine calcium and urine magnesium measured by the DuPont ACA method; urinary osmolality measured by freezing point depression (Fiske, Uxbridge, MA); and urine prostaglandin E sub 2 measured by radioimmunosassay as described previously.

Statistical analysis was performed with the aid of the Hewlett Packard STAT PAC and a personal computer using Lotus 123. Analysis of variance and chi-square test were used to analyze study results. All tabular results are reported as the mean ± SEM. A 95 percent confidence interval (p<0.05) was considered statistically significant.

Results

The course of treatment for each patient is shown in Figure 1. Twenty-three patients were initially entered into the study. At the end of the dose-titration period, 14 patients (61 percent) had achieved blood pressure control on TC alone. An additional six patients (26 percent) were controlled with a combination of TC and CH. Three patients failed to achieve control criteria and were dropped from the study per protocol: two patients (9 percent) were controlled with CH alone; the blood pressure of one patient (4 percent) was not controlled with TC alone, CH alone, or TC and CH therapy. Twenty of the initial 23 patients (86 percent) achieved blood pressure control with TC alone or TC and CH therapy. These patients were monitored over a two-year period as described previously. During the first month following initial blood pressure control, six patients (30 percent) dropped out of the study because of side effects from the TC therapy. After 12 months of therapy, nine patients (45 percent) remained in the study, and a total of 11 patients (55 percent) had been dropped from the study because of side effects. At the end of the two-year study, six patients (30 percent) remained on TC or TC and CH therapy. A total of 14 patients (70 percent) had dropped out of the study secondary to side effects. Four patients (18 percent) out of the initial 23 patients in the study were treated successfully for two years on TC monotherapy.

In the 11 patients meeting control criteria with TC alone therapy and remaining in the study one month after achieving control, DBP was reduced from 99±2 at baseline to 81±1 mm Hg at the time they met control criteria (p<0.01). One month after achieving control, the DBP had increased to 92±2 mm Hg (p<0.05). In the eight patients remaining in the study after 12 months of TC alone therapy, DBP was reduced from 100±1 at baseline to 87±4 mm Hg (p<0.05). In the four patients remaining in the study after two years of TC alone therapy, blood pressure was reduced from 99±1 to 84±3 mm Hg (p<0.05). The SBP was reduced from 144±3 at baseline to 124±4 mm Hg at the time the patient met control criteria (p<0.01). One month after achieving control, the SBP had increased to 137±6 mm Hg (p<0.01). The SBP was not significantly different from baseline at any other time in the study. Average blood pressures of the patients remaining in the study at baseline, 1, 12, and 24 months and the average blood pressure of the four patients who remained on TC alone for the entire 24 months are shown in Figure 2.

Patients who dropped out of the study because of side effects are summarized in Table 1. Fourteen of
the 20 patients (70 percent) achieving control on TC therapy dropped out of the study secondary to side effects. Ten patients (50 percent) dropped out because of severe skin reactions. Four patients (20 percent) dropped out because of non-skin-related complaints. Of the various side effects reported that did not merit dropping the patient from the study, by far the most common were fatigue and dry mouth. Also reported were headache, fluid retention, dry eyes, light-headedness, nausea, vomiting, constipation, leg cramps, dizziness, back pain, urinary frequency, anorexia, irritability, insomnia, blurred vision, numb fingers, non-cardiac chest pain, and impotence.

Impotence occurred in three patients (15 percent). One patient continued on in the study with persistence of the symptom; one patient had a reversal after discontinuation of the drug; and one patient did not have a reversal but quit the study secondary to a severe skin reaction that developed later.

With informed consent, five patients who suffered a skin reaction were tested with the drug in a neutral base (petrolatum), and all five patients developed a skin rash at the site. This implies that the problem is with the drug itself and not the vehicle. One of these patients underwent a skin punch biopsy which showed a superficial, perivascular dermatitis with focal spon-

Table 1—Patients Who Dropped Out of Study*

<table>
<thead>
<tr>
<th>Controlled on TC Alone</th>
<th>Controlled on TC and CH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Remain</strong></td>
<td><strong>Drop-Skin</strong></td>
</tr>
<tr>
<td>End of titration</td>
<td>14 (61%)</td>
</tr>
<tr>
<td>1 month from</td>
<td>11 (55%)</td>
</tr>
<tr>
<td>achieving control</td>
<td>8 (40%)</td>
</tr>
<tr>
<td>12 months from</td>
<td>6 (30%)</td>
</tr>
<tr>
<td>achieving control</td>
<td>4 (20%)</td>
</tr>
<tr>
<td>18 months from</td>
<td>4 (20%)</td>
</tr>
<tr>
<td>achieving control</td>
<td>24 months from</td>
</tr>
<tr>
<td>achieving control</td>
<td>...</td>
</tr>
</tbody>
</table>

*Drop-skin, dropped out because of skin reactions; Drop-NSR, dropped out because of non-skin-related side effects.

Table 2—Cross-Tabulation Analysis of Complaints During Clinic Visits Among Those Successfully Treated and Those Who Dropped Out of Study

<table>
<thead>
<tr>
<th>Complaints</th>
<th>Skin</th>
<th>Non-Skin</th>
<th>Total</th>
<th>No. of Visits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Successful group</td>
<td>22 (13%)</td>
<td>60 (36%)</td>
<td>82 (49%)</td>
<td>166</td>
</tr>
<tr>
<td>Failure group</td>
<td>15 (15%)</td>
<td>37 (37%)</td>
<td>52 (32%)</td>
<td>101</td>
</tr>
<tr>
<td>Total</td>
<td>37 (14%)</td>
<td>97 (36%)</td>
<td>134 (50%)</td>
<td>267</td>
</tr>
</tbody>
</table>

giotic dermatitis. These findings, while nonspecific, are consistent with allergic, contact dermatitis. Two of these five patients consented to an oral challenge with clonidine with equipment and personnel readily available for resuscitation. There was no local or systemic reaction to orally administered clonidine in either patient.

To determine if patients who dropped out of the study registered more complaints during clinic visits than those successfully treated with the transdermal patch, a cross-tabulation analysis of complaints was performed at 12 months. The results are shown in Table 2. There was no statistical difference in percentage of complaints by chi-square analysis between patients who completed the study and patients who dropped out of the study due to side effects. The former group registered a non-skin-related complaint on 60 of 166 clinic contacts (36.1 percent), while the latter group had a non-skin-related complaint on 37 of 101 visits (36.6 percent). The first group offered a skin-related complaint on 22 of 166 visits (13.3 percent), and the second group had a skin-related complaint on 15 of 101 visits (14.9 percent). All patients in the study complained of a non-skin-related symptom on 97 of 267 visits (36.3 percent) compared with 36.1 and 36.6 percent for the individual groups. All patients in the study registered a skin-related complaint on 37 of 267 visits (13.9 percent) compared with 13.3 and 14.9 percent for the individual groups.

During the study, all blood and urine chemistry
measured within accepted clinical normal ranges. However, several parameters displayed statistically significant decreases at some point during the study for the four patients on TC alone therapy. Serum sodium was decreased from 144 ± 1.0 mM/L at baseline to 142 ± 0.5 mM/L at one month and to 140 ± 0.3 mM/L at 12 months (p < 0.05). GLOB was decreased from 3.1 ± 0.08 to 2.7 ± 0.14 mg/dL (p < 0.05). GLOB was decreased from 3.1 ± 0.08 to 2.7 ± 0.14 mg/dL (p < 0.05) between baseline and 12 months.

**DISCUSSION**

Ten of the 20 patients (50 percent) controlled with TC therapy had serious skin reactions, necessitating discontinuation of the drug. The study was initiated in the summer months, and the population tested consisted of fair-skinned Midwesterners. Four reactions occurred within two weeks of using the drug while two reactions took place after two months. The other four reactions took place later in the study.

There were no other serious adverse effects of the drug. Severe rebound hypertension with the patches was not seen in our patients but has been recently reported in elderly patients. It takes from 48 to 72 h to reach therapeutic blood levels so this would not seem likely to be helpful for the rebound hypertension that can develop after stopping orally given clonidine. Other agents (nifedipine) or the sublingual form of captopril may be more useful in these acute hypertensive situations.

The transdermal delivery route was well-received by the patients. Only one patient had difficulty with the patch adhering to the skin, and this patient was a frequent swimmer. The overlay patch was adequate for keeping the patch in place, since the rest of the patients did not experience any difficulty in this regard.

Our success rate with TC is less than that of other investigators; one group reported a 60 percent success rate over three months, and another group reported an 88 percent success rate when used with a diuretic. Most reports have been of short-duration therapy, and we initially had a comparable success rate of 61 percent after one month of monotherapy and a combined success rate of 87 percent for TC alone and TC plus diuretic therapy. However, at the end of the two-year study period, the success rate had fallen to 18 percent for TC monotherapy and an overall success rate of 26 percent for TC alone and TC plus diuretic therapy.

One may consider TC when compliance or confusion is a problem, such as in the very young or very old. Because of our success rate for short-term therapy, one could consider using TC when patients are unable to take oral medications owing to acute gastrointestinal disease or before surgery. One could also use TC as short-term therapy in pregnant patients before delivery when the blood pressure may be difficult to control and oral medications may not be tolerated. Clonidine may be an alternative for the elderly, especially if diuretics or β-blockers are not tolerated, since side effects can be particularly bothersome in the geriatric age group. The thiazides and β-blockers can have adverse effects in elderly patients, especially those with cardiovascular, cerebrovascular, peripheral vascular, diabetic, orthostatic, or hyperlipidemic diseases. Diuretics in full dosages in the elderly with significant cardiac disease may decrease preload and, thus, cardiac output. Other potential problems with the thiazides are increased glucose tolerance, orthostatic hypotension, and an adverse effect for those at risk for strokes. The β-blockers may have increased adverse effects in the elderly with left ventricular failure, peripheral vascular disease with vasoconstriction, and bronchoconstriction.

It is becoming more apparent that treating mild hypertension, whether it be diastolic/systolic or isolated systolic, is a desirable goal because of the increased morbidity and mortality when left untreated, even in the elderly. There are three large studies to support this concept. For this reason and because of the potential problems with thiazides and β-blockers as described before, there has been a suggestion that some of the central-acting agents (methyldopa, reserpine, and clonidine) may be better tolerated as step 2 agents in place of the β-blockers and especially so for isolated systolic hypertension in the elderly. Our experience, however, did not show any long-term control of SBP. The SBP was controlled initially, and then there was loss of control over the next month, and this remained statistically unchanged from baseline when measured at 12, 18, and 24 months. The DBP did go out of control temporarily at one month after achieving control, but then was statistically different at 12, 18, and 24 months from baseline.

Orally administered clonidine also has been used safely in patients who have undergone renal transplantation. However, clonidine itself has been reported to decrease cardiac output and cardiac index and thus may cause an adverse hemodynamic effect. Two laboratory values were statistically changed from baseline values at some point in the study (serum sodium and globulin), but these were not clinically significant.

In conclusion, we consider TC to be safe and efficacious as short-term monotherapy for treating mild to moderate essential hypertension. Fourteen of 23 patients (61 percent) were successful in achieving control with clonidine alone. Six patients (26 percent) were controlled with clonidine and the diuretic. Initial control of both SBP and DBP was attained, but within the next month both rose to levels statistically unchanged from baseline. Therefore, only the DBP was
statistically changed from baseline in those who were able to tolerate the medication without undue side effects. Ten of the 20 patients (50 percent) controlled with TC therapy dropped out due to severe skin reactions and four patients (20 percent) did so secondary to non-skin-related side effects. Thus, 14 of 20 (70 percent) discontinued the TC due to intolerable side effects. At the end of two years, four of the original 23 patients (18 percent) remained on TC monotherapy, so it seems likely that this will be effective as long-term monotherapy for mild to moderate hypertension.

Transdermal clonidine is more expensive than the oral form and considerably more expensive than diuretic diuretics; the average wholesale cost of the largest-sized patch in our area was eight times that of hydrochlorothiazide. Since only two of the patients who achieved control did so with the lowest strength TC preparation, we would recommend using only the two larger dosages. Unfortunately, the larger the size, the more the expense.

In those who do not develop skin reactions, it is a safe and efficacious agent for short-term therapy. Patient satisfaction in those cases will probably make it useful in certain clinical settings despite greater expense.

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