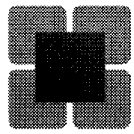

# Patient acceptance of transdermal clonidine

## A retrospective review of 25 patients

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■ The clinical records of 25 ambulatory patients who received clonidine (Catapres-TTS) for periods of one to 19 months were reviewed to determine the effectiveness and long-term patient tolerance of this transdermal antihypertensive medication. In 11 patients with mild to moderate hypertension in whom Catapres-TTS was initiated as monotherapy or added to an oral diuretic, significant blood pressure reduction was observed during the initial four weeks of therapy. In 14 patients who had more severe hypertension and who were receiving multiple antihypertensive agents, Catapres-TTS did not result in significantly reduced blood pressure. Daily home blood pressure measurements in five patients showed no day-to-day variations in blood pressure during the seven days each patch was worn. Catapres-TTS was discontinued in 11 patients because of localized contact dermatitis (six patients), patient dissatisfaction (three patients), and physician's decision (two patients). In three patients, localized contact dermatitis developed only after continuous use for periods of four to 13 months. Other adverse effects such as drowsiness and dry mouth were less apparent than with comparable doses of oral clonidine, and did not necessitate discontinuation of therapy in any patient. Black patients appear to tolerate Catapres-TTS better than whites. Catapres-TTS appears to be effective in patients with mild to moderate hypertension and may be a useful alternative to oral clonidine in patients experiencing drowsiness or dry mouth with the oral preparation.

□ INDEX TERM: CLONIDINE □ CLEVE CLIN J MED 1988; 55:21–26

CATAPRES-TTS (clonidine) is a transdermal system designed to provide continuous systemic delivery of clonidine at a constant rate for seven days. It is the first, and currently the only, approved antihypertensive agent for transdermal administration. The system is a thin multilayered adhesive patch available in three dosage sizes. The 3.5, 7.0, and 10.5 $cm^2$ systems deliver 0.1, 0.2, and 0.3 mg of clonidine per day, respectively, each providing a relatively constant release of drug over seven days.

Catapres-TTS is effective in treating mild to moderate arterial hypertension and maintains relatively constant plasma levels of clonidine. In contrast to twice-daily oral administration of similar doses, Catapres-TTS has been associated with fewer adverse effects,[1–4] the most common being transient localized contact dermatitis, usually associated with pruritus and erythema. Previous reports have generally addressed the issues of safety and patient tolerance to Catapres-TTS, in studies

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**TABLE 1**
CHARACTERISTICS OF PATIENTS*

| | Group 1 (n = 11) | Group 2 (n = 10) | Group 3 (n = 4) |
|---|---|---|---|
| Age | 62±3.9 | 58±4.1 | 56±8.5 |
| Race | | | |
| White | 9 | 8 | 4 |
| Black | 2 | 2 | 0 |
| Etiology of hypertension | | | |
| Essential | 8 | 1 | 3 |
| Renal | 3 | 9 | 1 |
| Initial systolic blood pressure (mmHg) | 187±5.6 | 177±9.2 | 141±9.5 |
| Initial diastolic blood pressure (mmHg) | 97±2.8 | 96±4.3 | 85±2.8 |
| Clonidine dosage (mg)† | 0.19±0.03 | 0.17±0.02 | 0.15±0.02 |

*Values are expressed as mean ±SEM.
†Mean dosage during the first four weeks of observation.

lasting several weeks to several months.[5–8]

We reviewed the clinical records of patients treated with Catapres-TTS at the Cleveland Clinic between 1985 and 1987, in an effort to determine the clinical effectiveness and patient acceptance of this transdermal delivery system.

## METHODS

### Patient selection

Between November 1985 and August 1987, treatment with Catapres-TTS was initiated in 28 outpatients. Three patients with incomplete clinical records were excluded from analysis, leaving 25 patients suitable for evaluation (*Table 1*). Of these 25 patients, 12 had a diagnosis of mild or moderate essential hypertension, five had hypertension associated with angiographically documented renal artery disease, and eight had hypertension associated with renal parenchymal disease, including five with end-stage renal disease who were being maintained on hemodialysis. Patients ranged in age from 32 to 78 years; average, 60 years. There were 12 men and 13 women, and all but four patients were white.

### Treatment regimens

For evaluation, patients were divided into three treatment groups (*Table 1*). Group 1 included 11 patients, six of whom were receiving no other antihypertensive drugs at the time Catapres-TTS was initiated as monotherapy, and five whose blood pressure was not controlled by an oral diuretic. In these latter five patients, dosage of the diuretic was not changed during the initial four-week period of observation. Group 2 consisted of 10 patients being treated with a two- or three-drug regimen consisting of a diuretic, a vasodilator, and/or an adrenergic inhibiting agent other than clonidine. These 10 patients were not at goal blood pressure (diastolic blood pressure ≤ 90 mmHg) and Catapres-TTS was added to their regimen in an effort to improve blood pressure control. Group 3 included four patients whose blood pressure was controlled on a two- or three-drug regimen. Catapres-TTS was added to the regimen in an effort to reduce the dosages of oral clonidine or vasodilator being administered. In the majority of patients (*Table 2*), therapy was initiated with Catapres-TTS #1 or TTS #2. In two patients, both in Group 1, therapy was initiated with Catapres-TTS #3 and TTS #4 (two TTS #2 patches), respectively.

Patients were evaluated for periods of one to 19 months; average duration of follow-up was eight

**TABLE 2**
CATAPRES-TTS DOSE DURING THE FIRST FOUR WEEKS OF TREATMENT

| | TTS-1 | TTS-2 | TTS-3 | TTS-4* |
|---|---|---|---|---|
| Group 1 (n = 11) | 4 | 5 | 1 | 1 |
| Group 2 (n = 10) | 3 | 7 | 0 | 0 |
| Group 3 (n = 4) | 2 | 2 | 0 | 0 |
| TOTAL | 9 | 14 | 1 | 1 |

*Catapres-TTS #4 (Catapres-TTS #2 x 2)

**TABLE 3**
SUPINE BLOOD PRESSURE AT BASELINE AND FOUR WEEKS OF THERAPY

| | Group 1 (n = 11) | Group 2 (n = 10) | Group 3 (n = 4) |
|---|---|---|---|
| Systolic blood pressure (mmHg) | | | |
| Baseline | 187 | 177 | 141 |
| Treatment | 161 | 158 | 138 |
| Change | -26* | -19 | -3 |
| Diastolic blood pressure (mmgH) | | | |
| Baseline | 97 | 96 | 85 |
| Treatment | 86 | 88 | 83 |
| Change | -11* | -8 | -2 |

*$P<0.01$

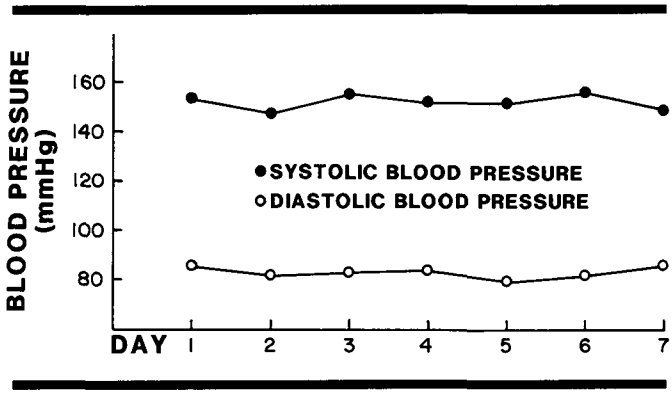


**FIGURE 1. Seven-day variability of blood pressure in five patients.**

months. At each clinic visit, blood pressure was measured with a mercury sphygmomanometer after the patient was in the supine position for five minutes and after two minutes of quiet standing. Two sets of blood pressure determinations were made in each position and were averaged to give the mean blood pressure determination in each position for the visit. For statistical analysis, comparison of blood pressure values at baseline and four weeks of therapy was performed by paired *t* test (*Table 3*).

## RESULTS

### Response after four weeks of therapy

The blood pressure response to Catapres-TTS was evaluated by comparing the blood pressure readings at baseline with those obtained after four weeks of treatment. During this initial period of observation, no changes were made in the dosages of concurrent medications nor were changes made in the initial dose of Catapres-TTS administered. As noted in *Table 3*, reductions of supine systolic and diastolic blood pressures, respectively, in Group 1 patients were statistically significant at four weeks ($P<0.01$, $P<0.01$). Reductions observed in systolic and diastolic pressures in Group 2 and Group 3 patients were not statistically significant after four weeks of treatment.

### Consistency of blood pressure control during 7-day patch administration

In five patients, twice-daily measurements of blood pressure at home were accomplished by means of conventional cuff sphygmomanometers. Measurements were obtained for days one through seven of patch administration. In three patients, a two-week period of observation was available (two patches). All blood pressure readings in the five patients were averaged day by day for days one through seven of patch administration (*Figure 1*).

**TABLE 4**
REASONS FOR DISCONTINUATION OF CATAPRES-TTS

| Treatment Period | Reason | Number |
|---|---|---|
| ≤ 1 month | Patient dissatisfaction | 2 |
| 1–3 months | Skin reaction, | 3 |
| | patient dissatisfaction | 1 |
| 3–6 months | Skin reaction, | 2 |
| | physician decision | 1 |
| 6–12 months | Physician decision | 1 |
| > 12 months | Skin reaction | 1 |

### Response to long-term therapy

This retrospective review does not allow long-term evaluation of the efficacy of Catapres-TTS in blood pressure control. Eleven patients were withdrawn from the study between one month and 13 months of observation; the reasons for discontinuation are discussed below. In addition, changes in Catapres-TTS dosage as well as up-titration or down-titration of concomitant antihypertensive therapy do not enable conclusions to be drawn regarding the efficacy of Catapres-TTS during longer periods of observation.

### Reasons for discontinuation

During the period of observation, localized contact dermatitis developed due to Catapres-TTS in six of the 25 patients (24%); Catapres-TTS was discontinued in these six patients. In five, pruritus and erythema were evident, and in the other, a more severe localized reaction included papules and slight excoriation. Symptoms were not alleviated by the use of topical steroids applied around the patch or by not using the occlusive overlay. Consequently, therapy was discontinued after one to 13 months of treatment (*Table 4*). The two men and four women, all of whom were white, ranged in age from 37 to 78 years. Contact dermatitis did not develop in any of the four black patients included in the study over periods ranging from six to 19 months. Contact dermatitis was observed within one to three months of therapy in three patients and between three and six months in two patients. One patient had a skin reaction after 13 months of therapy, having tolerated Catapres-TTS well until that time.

In addition, Catapres-TTS was discontinued in two patients within the first four weeks of therapy because of patient dissatisfaction with this mode of therapy, and in another patient between one and three months of therapy due to reported inconvenience during showering.

Reported ineffectiveness of Catapres-TTS resulted in discontinuation as determined by the physician in one patient after six months of treatment, and therapy was stopped due to physician decision in one patient at the time of an elective hospitalization after 12 months of well-tolerated treatment.

Other adverse effects reported included drowsiness in four patients (16%) and dry mouth in two (8%) following the addition of Catapres-TTS to their therapeutic regimen. These adverse effects were acceptable to the patients and did not necessitate discontinuation of therapy. It is of interest that drowsiness and dry mouth appeared to be of less concern with Catapres-TTS in the patients who had experienced similar symptoms with oral clonidine therapy. No rebound hypertension was observed in any patient on cessation of Catapres-TTS during the periods observed in this study.

## DISCUSSION

The small patient group and the number of dropouts during the period of observation do not allow a definitive statement regarding blood pressure response to the addition of Catapres-TTS to treatment regimens except for the first four weeks of observation in Group 1 patients. In this group of 11 patients who were receiving no therapy or a small dose of diuretic, the addition of Catapres-TTS resulted in a significant reduction in systolic and diastolic blood pressure during the first four weeks of observation. Eight of the 11 patients in Group 1 had mild to moderate essential hypertension, which may help explain the initial responsiveness to Catapres-TTS.

Beyond four weeks, changes in dosages of medications, including Catapres-TTS, as well as administration of multiple antihypertensive medications in some patients, make it impossible to specify the effects of Catapres-TTS in treatment regimens.

During the first four weeks of therapy, the response to Catapres-TTS in Group 2 and Group 3 patients was not statistically significant, which might be expected in these patients, who had more severe hypertension and were already being treated with multiple-drug regimens. As noted in *Table 1*, 10 of the 14 patients in Groups 2 and 3 had secondary hypertension associated with either renovascular disease or renal parenchymal disease and were on therapy with two- or three-drug regimens prior to entry in the study, suggesting a more aggressive form of hypertension than Group 1 patients in whom mild to moderate essential hypertension predominated. Five patients with end-stage renal disease, chiefly secondary to diabetic nephropathy,[9] tolerated Catapres-TTS without significant adverse effects. In selected patients, the addition of Catapres-TTS enabled a reduction in oral clonidine therapy with a parallel reduction in adverse effects such as drowsiness or dry mouth, and in other selected patients allowed the reduction of other antihypertensive drug dosages.

The major cause of patient discontinuation of Catapres-TTS was localized contact dermatitis. Skin reactions have usually been observed to develop during early weeks of Catapres-TTS administration.[10] The reported incidence of localized contact dermatitis has ranged from 5% to 30% and may represent either irritant or allergic contact dermatitis.[11] Features usually observed include pruritus, erythema, and less frequently, induration and vesiculation beneath the transdermal patch.[11,12] Allergic contact dermatitis shares some features with irritant dermatitis but tends to be more severe, involving induration and, at times, vesiculation. Since patch testing was not performed in these patients, a clear distinction between irritant and allergic contact dermatitis is not possible. Nevertheless, the dermatitic reactions observed were sufficient to necessitate discontinuation of therapy.

It is important to note that localized contact dermatitis developed in two patients only after four and six months of continuous usage, and in one patient, who had tolerated Catapres-TTS well for a full year, a localized skin reaction developed after 13 months of treatment and required discontinuation of the therapy. The majority of reported reactions have been observed during the first 20 weeks of therapy,[12] although several patients did not develop contact dermatitis until their second year of treatment.[13]

Several fair-skinned patients did show areas of increased pigmentation at sites of prior patch application, but these were not necessarily associated with localized rash or pruritus.

It has been reported that patients with increased skin pigmentation appear to tolerate Catapres-TTS better than fair-skinned whites.[5] While there were only four black patients in this study group, all four tolerated Catapres-TTS well; skin reactions were observed only in the white treatment group.

Our experience has taught us that minor complaints of pruritus without significant skin eruption can often be

managed by simple measures such as the application of 0.5% to 1% hydrocortisone cream around the area covered by the patch. It may be helpful to use this preparation on the same areas after the patch has been removed to a new location for the next week of therapy. No clinical trials have addressed the role of local steroid application to retard or prevent contact dermatitis. It is possible that masking the local reaction early to allow continued usage may enhance the risk of later, more generalized eruptions. This issue needs to be addressed.

It may also be helpful to avoid or attempt to minimize the period of usage of the occlusive overlay during each week of therapy. The Catapres-TTS patch is waterproof and the primary purpose of the occlusive overlay is to assure skin adherence in patients who experience premature disengagement of the patch. We sometimes encourage patients to take sponge baths for the first two days of new patch application and then add the occlusive overlay if needed to resume normal showering. We may also advise patients to remove the occlusive overlay on Day 6 as opposed to Day 7 of treatment.

It is, of course, desirable that the patch location be changed each week to a new area, and we have preferred sites on the upper outer areas of the arms or on upper chest or upper back areas. No patient with a localized skin reaction that necessitated discontinuation of Catapres-TTS was rechallenged with this form of medication during their course of therapy. Several patients who had skin reactions were treated with oral clonidine subsequently or concurrently without evident exacerbations at prior sites of Catapres-TTS application.

When patient dissatisfaction resulted in discontinuation of Catapres-TTS (three patients), we changed to an alternate therapy, as insistence upon continuation is likely to result in noncompliance with the prescribed therapeutic regimen.

Fourteen patients remain on Catapres-TTS. Of six of the patients observed for less than six months, two have complained of dry mouth or drowsiness in association with the medication, but these complaints have not necessitated discontinuation of treatment. In eight patients, therapy has continued for six to 19 months, and only two individuals have persistently complained of mild drowsiness or dry mouth. Three of the four black patients in the study have tolerated Catapres-TTS well for periods of six, 18, and 19 months. Therapy was discontinued for one black patient after six months, by physician decision. Among the eight patients continuing therapy beyond six months, all are receiving concurrent therapy with at least a diuretic, and in four, with a calcium-channel blocker and/or an ACE inhibitor.

Hypersensitivity to clonidine or to other components of the adhesive patch was not observed in this study group. Localized skin reactions were limited to the areas of current patch administration. No recrudescent reactions were observed at areas of prior patch administration. While patient dissatisfaction or localized skin reactions generally led to discontinuation of therapy within the first six months, localized contact dermatitis may become apparent only after many months of treatment. Systemic adverse effects such as dry mouth or drowsiness tended to dissipate over time and were not a problem in the patients in whom therapy continued beyond six months.

## SUMMARY

Patient acceptance of Catapres-TTS was observed in 25 patients during periods of administration ranging from one to 19 months. Adverse skin reactions were the leading cause for discontinuation of Catapres-TTS, necessitating discontinuation of therapy in six patients. The appearance of localized contact dermatitis may be belated, having occurred after 4, 6, and 13 months of continuous treatment in three patients. Black patients appear to tolerate Catapres-TTS well, skin reactions having been observed only in the white patients included in this review. Adverse effects such as drowsiness and dry mouth are less commonly observed with the constant delivery of clonidine afforded by this transdermal delivery system. Longer periods of observation will be required in patients treated with Catapres-TTS to determine if adverse skin reactions will represent an increasingly significant problem affecting patient compliance and long-term therapy with this preparation.

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