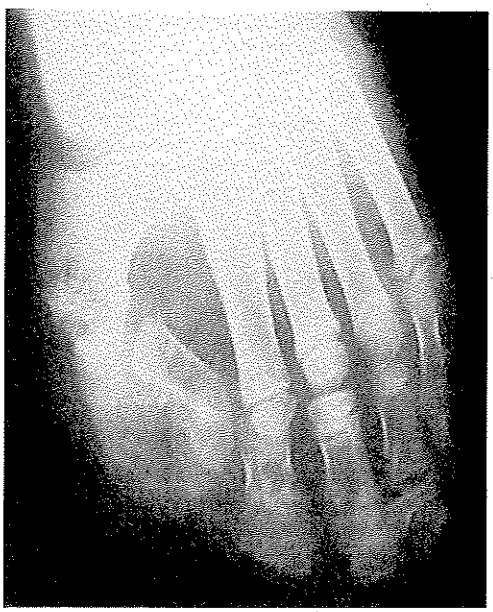

Figure 4. Weightbearing dorsoplantar radiograph reveals the short first metatarsal, with medial deviation and duplication of the proximal phalanx, and fusion of the distal phalanges of the third and fourth toes.

The purpose of this article was to present an isolated case of Apert syndrome, concentrating on the associated deformities of the feet. The patient presented here displayed a type III foot, according to the classification system described by Blauth and von Torne,[7] with separation of the fifth toe only on the plantar surface. The patient also displayed a type II foot, as categorized by Upton,[5] with duplication of the proximal phalanx. Interphalangeal joint fusion of the toes has been commonly reported, but the fusion of phalanges of contiguous toes, as was found in this patient, is a less frequent finding.[8, 12]

Surgical treatment of deformities of the foot in patients with Apert syndrome is indicated only to relieve pain and to remedy difficulties with fitting and using footwear when all conservative methods of treatment have failed.[7] However, surgical treatment may provide a more permanent solution than orthotic treatment, especially in younger patients. Although syndactyly of the digits contributes to the deformities, it does not require treatment.

The specific surgical treatment of the foot for patients with Apert syndrome has been described for deformities of the metatarsal and the great toe. It consists of osteotomy of the proximal phalanx, resection of the intermetatarsal bony bridge, and basal metatarsal osteotomy and placement of the bone in its normal position.[7, 8, 10-12]

ANDRÉS CARRANZA-BENCANO, MD
JOSÉ ANTONIO GÓMEZ-ARROYO, MD
JOSÉ JUAN FERNÁNDEZ-TORRES, MD
FERNANDO MOYA CORRAL, MD
"Virgen del Rocío" University Hospital
c/o Santa Clara 16, 1, D
41002, Seville, Spain

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Use of a Clonidine Patch in the Treatment of Ischemic Ulcerations of the Foot

To the Editor:

Clonidine is indicated for the treatment of hypertension and may be used alone or in combination with other antihypertensive medications. Clonidine is a centrally acting α_2-agonist.

Clonidine was originally marketed as a nasal decongestant in 1962. At that time, clonidine was also

found to cause hypotension, sedation, and bradycardia. Taking advantage of its side effects, researchers began to use it to treat hypertension in the 1970s and also for Tourette's syndrome beginning in the 1980s. Recently it has been used for behavioral symptoms of attention-deficit hyperactivity disorder, hyperarousal syndromes associated with post-traumatic stress disorder, and aggression.[1]

Clonidine is available in patch form as the Catapres-TTS Transdermal Therapeutic System (Boehringer Ingelheim Pharmaceuticals, Ridgefield, Connecticut). Catapres-TTS is available in three strengths: 1, 2, and 3, which correspond to a clonidine content of 2.5 mg, 5.0 mg, and 7.5 mg, respectively. These patches deliver daily doses of 0.1 mg, 0.2 mg, and 0.3 mg, respectively. Catapres-TTS patches are available in boxes of four packets. Each packet consists of a patch on a plastic sheet and a round adhesive cover.[2]

Clonidine stimulates the α_2-adrenergic receptors in the brain stem. This causes a reduced sympathetic outflow from the central nervous system along with a decrease in peripheral resistance, renal vascular resistance, heart rate, and blood pressure. Renal blood flow and glomerular filtration rate remain largely unchanged. Normal postural reflexes remain intact; therefore, orthostatic hypotension is infrequently encountered.[2]

Catapres-TTS was developed to release clonidine at an approximately constant rate for 7 days. During long-term therapy, cardiac output tends to return to pretherapy levels while peripheral resistance remains low.

Sudden cessation of clonidine has in some cases resulted in nervousness, agitation, headache, and confusion accompanied or followed by a rapid rise in blood pressure and elevated catecholamine concentrations in the plasma. The likelihood of these reactions to discontinuation of clonidine therapy appears to be greater after administration of higher dosages or continuation of other β-blocker treatment.[2] Special caution, therefore, is recommended in such situations.

Clonidine may potentiate the depressive effects of alcohol, barbiturates, or other sedating drugs on the central nervous system. Owing to the potential for additive effects, such as bradycardia and atrioventricular block, caution is advised in patients receiving clonidine along with agents known to affect sinus node function or atrioventricular nodal conduction. Transdermal therapeutic systems may induce localized miliaria, microbial growth, and allergic contact dermatitis.[3]

Most adverse systemic effects during clonidine therapy are mild and tend to decrease with continued therapy. Reported systemic effects include dry mouth, drowsiness, fatigue, headache, lethargy, sedation, insomnia, dizziness, impotence or other sexual dysfunction, dry throat, constipation, nausea, change in taste, and nervousness. However, in a 3-month trial, 51 of 101 patients had localized skin reactions that included erythema, pruritus, or both. Allergic contact sensitization was also seen in five patients.[2] These reactions, however, subsided with subsequent treatments.

A study conducted in 1997 found that Catapres-TTS lowers both systolic and diastolic blood pressure within the first 24 hours of application. The antihypertensive effect persists at the end of the first week, as well as after 14 days. Clonidine seems to act as an antihypertensive agent rather than a hypotensive drug, as it normalizes blood pressure without lowering it below physiologic levels.[4]

Catapres-TTS has been shown to reduce the cardiovascular impact of hypertension in patients with diabetes mellitus. Clonidine significantly reduced systolic (153 *versus* 163 mm Hg) and diastolic (88 *versus* 98 mm Hg) blood pressure, left ventricular mass (94 *versus* 99 g/m^2), and fasting blood glucose levels. Urinary albumin excretion was also noted to decrease with the use of Catapres-TTS.[5]

Bathing appears to have a negligible effect on plasma concentration levels of clonidine. However, the plasma clonidine concentration was found to be greater in patients during the summer months than during the winter. It is theorized that the passage of an agent across the skin might be enhanced by greater hydration of the stratum corneum due to sweating.[6] Increased blood flow through the dermal vessels as well as higher relative humidity levels could also contribute to the higher plasma clonidine levels seen during the hot summer months.

Podiatric Applications

Podiatric applications include the administration of Catapres-TTS on the lower extremity as a means of increasing perfusion in vascularly compromised regions. The administration of clonidine results in a decreased sympathetic outflow from the central nervous system. This in turn produces a vasodilation response in the peripheral vessels, thereby decreasing peripheral resistance. The authors theorize that this results in an increase in oxygenation and blood tissue perfusion to previously ischemic areas. Distal lower-extremity ulcerations are often the consequence of chronic ischemic disease that cannot be treated with bypass surgery, such as frostbite, Mönckeberg's sclerosis, Buerger's disease, and Raynaud's phenomenon. In other circumstances, the patient may not be a candidate for a bypass of the diseased vessel. Catapres-

TTS thus offers the physician a viable alternative treatment.

Although the Catapres-TTS patch is available in formulations that deliver 0.1 mg, 0.2 mg, or 0.3 mg of clonidine per day, only the 0.1-mg system is used for lower-extremity applications. This low dose reduces the risks of possible systemic side effects that may result from stronger concentrations of the drug.

The Catapres-TTS patch therapy is used in cooperation with the patient's primary-care physician owing to the systemic effects of the drug. The patient applies the 0.1-mg patch once a week. Its placement depends on the location of the ulceration. When the ulceration is located on the rearfoot or midfoot, the patch is applied just proximal to the lesion. If the ulceration is located on a digit, the patch is applied at the proximal aspect of the affected digit. The patch is changed weekly, and the patient is permitted to get it wet. The authors stress that this treatment acts as an adjunct therapy and does not replace local wound care and supportive therapies.

Patients treated with Catapres-TTS by the authors were selected on the basis of their nonresponse or minimal response to local wound therapy and recommendations from vascular surgeons that bypass surgery would be ineffective. Patients were also chosen on the basis of their history of compliance with therapeutic regimens. Because this medication has potentially serious side effects, compliance and follow-up visits are important. Blood pressure readings were taken at each visit to ensure that no significant pressure problems developed during treatment. If it is necessary to discontinue the medication, the patient must be closely monitored, as sudden cessation can lead to serious systemic problems. As mentioned earlier, the use of clonidine patches to treat ischemic foot ulcerations should be avoided in patients taking medications that affect sinus node function or atrioventricular nodal conduction. It should also be avoided or closely monitored in patients who are taking sedatives or barbiturates.

The authors have used this therapeutic modality in 30 patients who were not considered candidates for surgery. Of these 30 patients, 18 had ischemic digital ulcerations. In 13 of these patients, healing of the ulcerations occurred with local wound care in conjunction with use of the 0.1-mg clonidine patch, while 4 patients underwent digital amputations and 1 had a transmetatarsal amputation. The remaining 12 patients had ulcerations on the midfoot or rearfoot. Of these, 8 went on to heal, while 2 had transmetatarsal amputations and 2 had below-the-knee amputations. In treating these 30 patients, the authors encountered minimal adverse reactions to the use of this medication, in part because the lowest concentration of clonidine available was used. Two patients experienced mild pruritus around the patch; one experienced headaches; and three experienced dry mouth. None of these reactions were severe enough to require discontinuation of the medication. However, patients need to receive thorough instructions on the proper application of the patch and its potential for side effects. The patch was applied for a period ranging from 10 weeks to 5 months, depending on the treating physician and the success or lack of success of the treatments rendered.

Conclusion

The authors have found that Catapres-TTS can be successfully used to increase local blood flow to vascularly compromised areas and may act as an adjunct in the treatment of ischemic ulcerations. Catapres-TTS does not replace current treatment modalities; rather, it serves to complement current wound-healing methodologies. When Catapres-TTS is used, a team approach by the internist and the podiatric physician is needed to monitor any possible systemic effects of the drug. A study should be conducted to fully evaluate the effect of Catapres-TTS on ischemic ulcers, but the authors believe that their findings are valuable and should prompt discussion. Catapres-TTS may offer the physician another alternative in the treatment of ischemic ulcerations of the lower extremity.

KEVIN J. O'CONNOR, DPM
JOHN F. GRADY, DPM
Department of Veterans Affairs
Chicago Healthcare System, Westside Division
Chicago, IL
Foot & Ankle Associates
4650 Southwest Hwy
Oak Lawn, IL 60453

CAROL J. MOORE, DPM
JIM LICANDRO, DPM
Department of Veterans Affairs
Chicago Healthcare System, Westside Division
Chicago, IL

LORI A. BRENNER, DPM
Foot & Ankle Associates
Oak Lawn, IL

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Acral-Lentiginous Melanoma

To the Editor:

Cutaneous malignant melanoma is a devastating disease with a potentially lethal course. There are five types of cutaneous malignant melanoma: superficial spreading, lentigo maligna, nodular, acral-lentiginous, and amelanotic.[1-3] A cutaneous malignant melanoma develops in one of two ways: a mole undergoes a malignant transformation, or a group of pigment cells in normal skin becomes malignant.[4] Clinical warning signs are often referred to by the letters A, B, C, and D: A represents asymmetry of the lesion; B, border irregularity; C, color variation; and D, diameter greater than 6 mm (approximately the diameter of a pencil eraser).[1]

Numerous studies demonstrate a high incidence of cutaneous malignant melanoma in the lower extremity.[1,3,5] Cosman et al[6] reported the lower extremity to be the most frequently affected site in cases of cutaneous malignant melanoma, accounting for 26.1% to 39.6% of all reviewed cases. In contrast to nonmelanoma skin cancers, in which 85% of lesions appear on the head and neck, malignant melanoma appears primarily in the trunk in men and the lower extremity in women.[1] Clark et al[7] reported that malignant melanoma on the thigh and lower leg is three times more common in women than in men.

Early recognition and surgical excision to prevent tumor spread are paramount for patient survival. There are three local classification systems designed to help determine the severity of a lesion. The Clark classification system is based on the level of tissue invasion.[1,7,8] The Breslow[9] and Day[10,11] classification systems are based on the depth (in millimeters) of tissue invasion. Clark and colleagues[7,8] defined five levels of microinvasion by melanoma: in level I, the tumor invades the epidermis; in level II, the tumor penetrates the papillary dermis; in level III, the tumor extends through the papillary dermis; in level IV, the tumor extends to the reticular dermis; and in level V, the tumor invades the subcutaneous tissue. The 10-year survival rates of 1,130 patients reported by the New York University Melanoma Clinical Cooperative Group (NYUMCCG) for levels I through V were 96%, 96%, 90%, 67%, and 26%, respectively.[1]

The Breslow[9] classification measures tumor thickness, in millimeters, from the top of the granular layer to the deepest penetration of the melanoma. There are three thickness levels: less than 0.75 mm, 0.75 mm to 1.50 mm, and greater than 1.50 mm. Day et al,[10,11] using a multivariate mathematical technique, reported four statistically significant thickness ranges: less than or equal to 0.85 mm, 0.86 to 1.69 mm, 1.7 to 3.59 mm, and 3.60 mm or greater. NYUMCCG 10-year survival rates based on tissue thickness were 98%, 89%, 67%, and 43%, respectively.[1] Day et al[11] also reported that nearly all patients with melanoma of the hands and feet died of the disease if the primary tumor was more than 2.75 mm thick.

The NYUMCCG classified cutaneous malignant melanoma into three stages: stage I, localized; stage II, nodal involvement; and stage III, disseminated disease.[12] Acral-lentiginous melanoma, which occurs on the palms, soles, and subungual area, accounts for 4% to 8% of cases of cutaneous malignant melanoma.[1] Keyhani[13] reported on 228 cases occurring in the foot and 55 occurring in the hand; of melanomas of the foot, 45.4% were subungual and 50% affected the sole. Clark et al[7] reported a high frequency of pedal melanoma in blacks, with the heel, sole, and nail bed being the most commonly affected sites. Initially, melanoma of the sole appears as a brownish-black pigmented stain, which may or may not be related to a preexisting nevus.[14]

Acral-lentiginous melanoma has a very short *in situ* growth phase.[3] It usually has irregular borders and pigmentation on presentation. Nodular forms can supervene and rapidly metastasize. Cutaneous ulceration may occur with early invasion of neoplastic cells into the vessels and lymphatics of the dermis.[15]

At the palms, soles, and subungual areas, histologic examination of acral-lentiginous melanoma reveals lentiginous, or freckled, patterns at the dermal-epidermal junction. The epidermis is hyperplastic with rete ridge accentuations.[15] Acral-lentiginous melanoma has three tumor growth phases: the lentiginous phase, the radial phase or dysplastic precursor phase, and the vertical or nodular phase. The lentiginous phase is characterized by atypical melanocytic cells.[3]