Efficacy of Transdermal Clonidine for Headache Prophylaxis and Reduction of Narcotic Use in Migraine Patients

A Randomized Crossover Trial

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Thirty patients completed a double-blind, randomized crossover study utilizing transdermal clonidine and an identical-appearing placebo. Crossover occurred at 6 weeks, with a total study time of 12 weeks. Subjects were asked to record daily in a special diary (1) the presence or absence of headache, (2) duration of headache, (3) severity of headache, and (4) use of pain medication for headache relief. The severity of the headaches was rated from 1 (very mild) to 5 (very severe). Although the subjects reported a decrease in frequency, duration, and intensity of headaches while using the medicated patch, these differences did not reach statistical significance. Nineteen patients subjectively preferred the medicated patch, while five preferred the placebo ($P<.01$). During use of the medicated patch, a significant reduction ($P = .039$) occurred in use of class II narcotics. Three doses of these substances were used by the patients when treated with clonidine, while 34 doses were taken during placebo use. These findings suggest that clonidine might have a role in reduction of parenteral narcotic use in acute pain syndromes.

Clonidine has recently been shown to have therapeutic value in a number of clinical situations other than its original indication for hypertension. Clonidine was found to be effective in control of symptoms related to withdrawal from substances such as narcotics, ethanol, and nicotine.[1–5] Menopausal symptoms have also been found to be ameliorated by clonidine.[6]

European studies have largely shown clonidine to be effective in the prophylactic treatment of migraine headaches.[7–9] Although clonidine has gained acceptance as a migraine prophylatic agent in Europe, it has failed to become established in this country as a drug of choice for this illness. The primary reason for the lack of enthusiasm by American physicians for the use of clonidine in migraine prophylaxis is the failure of studies performed in this country to corroborate the findings of the European investigations.[10,11] Despite the lack of corroboration by American studies, clonidine remains an agent recommended as a potential prophylatic agent by several respected American sources.[12–14]

Clonidine is now available in the form of a transdermal patch that results in a constant plasma level.[15] Because troughs in drug levels are avoided, this form of clonidine delivery might enhance the prophylactic treatment of migraine headaches and, since the patch is changed on a weekly basis, might also improve patient compliance. The use of transdermal clonidine for migraine prophylaxis has not yet been studied. This report describes a double-blind, placebo-controlled crossover trial of transdermal clonidine for the prophylaxis of migraine. Specific variables studied included headache frequency, duration, and intensity. In addition, the effect of transdermal clonidine upon the use of medication for acute pain relief was investigated.

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METHODS

Selection of Patients

The study population consisted of patients presenting to one of three outpatient clinics operated by the Southern Illinois University School of Medicine, Department of Family Practice. Patients were enrolled in the study between June 1987 and January 1988. Study participants included patients of the respective clinics previously diagnosed as having migraines as well as patients referred into the study by community physicians. Sixty-nine patients were screened for study participation, of which 43 met study criteria and agreed to enroll in the investigation.

To participate in the study, patients were required to meet the following criteria: (1) age of 18 years or more, (2) diagnosis of migraine headaches in accord with the standard criteria established by the Ad Hoc Committee on the Classification of Headache (episodic, severe, throbbing headaches lasting several hours and usually associated with anorexia and nausea),[16] (3) at least one attack of migraine headache during the month preceding the study, (4) a history of such attacks on a recurrent basis for at least 6 months, (5) initial onset of the headaches prior to the age of 40 years, and (6) no current use of other recognized prophylactic medications for any reason. (These medications included tricyclic antidepressants, β-blockers, calcium channel blockers, and nonsteroidal anti-inflammatory drugs.)

Research Design

The efficacy of transdermal clonidine was compared with that of placebo using a randomized crossover design described in detail by Tfelt-Hanson and Olesen.[17] The patients were assigned to receive either a 6-week supply of Catapres TTS-2 patches* (A) or placebo patches of identical appearance (B) on an alternating basis upon entering into the study. The Catapres TTS-2 patch delivers clonidine at a serum level equal to the average level produced by 0.1 mg of clonidine taken orally twice daily, a commonly prescribed migraine prophylactic dose.[12–14] The patches were changed weekly. After the initial 6 weeks of therapy, the patients received a 6-week supply of the other patches to complete the crossover. The subjects were thus involved in the study for a total of 12 weeks. Of the 30 patients who completed the study, 16 received the clonidine patch initially and 14 received the placebo patch initially.

*Catapres TTS-2 (clonidine) patches were manufactured by Boehringer-Ingelheim Pharmaceuticals, Inc, Ridgefield, Connecticut.

Patient compliance with the study protocol was accessed by discussion with the patient during the return visit at 6 weeks and at the end of the study. Compliance was also evident upon review of the migraine diary for daily entry regarding presence or absence of a headache (the use of the migraine diary is discussed below).

To allow for the attainment of adequate serum levels and for the adequate washout of clonidine, the first and seventh weeks of the study were not included in comparisons between the A and B patches. The code identifying clonidine as the A patch and the placebo as the B patch was broken after the final patient concluded the study and analysis was performed.

Measurement of Outcome Variables

The effectiveness of the clonidine patch was determined by means of a migraine diary. The diary was a daily record in which the patient recorded (1) the presence or absence of headache each day, (2) duration of the headache, (3) severity of the headache, and (4) use of pain medications for headache relief. The severity of the headaches was rated from 1 (very mild) to 5 (very severe). The patients were asked to avoid the use of over-the-counter, nonsteroidal preparations while in the study because of potential prophylactic characteristics of these medications. Study participants were encouraged to take only those over-the-counter medications containing acetaminophen or narcotic preparations as prescribed by their physicians. The patients were asked to record in their diary the name of any medications taken and the amount used for each acute headache.

Upon completion of the study the diaries were analyzed to compare the effectiveness of the placebo with the clonidine patch in reduction of frequency, duration, and severity of migraines. In addition, comparisons were made of the quantity of acute pain medicine used during the period studied. Finally, the patients were asked whether either patch was more helpful in relieving their symptomology. Split-plot analysis of variance for a crossover design was used to compare differences in headache frequency, intensity, and duration as well as in comparisons of medication use. Differences in preference for the medication or placebo patch was accessed by means of a Z test for proportions.

RESULTS

Forty-three patients were entered into this study, of which 30 successfully completed the entire 12 weeks and properly maintained their migraine diary. Of the 13 patients who

TABLE 1. HEADACHE FREQUENCY, INTENSITY, AND DURATION

	Clonidine	Placebo	*P* Value
Average number of headaches per patient	10.0	11.2	.2441
Average duration (hours)	7.0	8.9	.0954
Average intensity (1 = very mild; 5 = very severe)	2.4	2.5	.2719

Note: Periods of comparison were five weeks

dropped out of the study, the majority did so because of difficulty complying with the required daily entry into the migraine diary. In addition, three patients dropped out as a result of feeling "overtired" while using the clonidine patch. One patient was eliminated from the study because she became pregnant during the course of the investigation. Finally, one subject was eliminated from the study because he placed himself on an elimination diet, which caused marked improvement in his migraines and which made interpretation of the effect of clonidine on his headaches impossible.

In general, both patches were well tolerated by study participants. The side effects were, as expected, similar to those described in the package insert for Catapres TTS-2. As previously mentioned, three patients elected to discontinue the study due to lethargy while using the medicated patch. Another patient complained of feeling "overtired" but elected to continue in the study. Six patients experienced irritation under the medicated patch, which improved with transfer of the patch to a different site. This side effect seemed to occur predominantly in fair-skinned individuals. Several patients mentioned some degree of dry mouth, but none withdrew from the study for this reason.

All study participants were normotensive at the time of entry into the study, and no problems with hypotension were encountered. (The authors have subsequently experienced one case of orthostatic hypotension in a patient with borderline [100/60 mm Hg] low blood pressure prior to using the clonidine patch.) Of the 19 patients who felt that their headaches were helped by the medicated patch, 18 elected to continue the patch after the study was completed.

Of the 30 subjects who successfully completed the study, 6 were male and 24 were female. The age range of this population was from 20 to 57 years. The study population included 2 black and 28 white patients. Since this was a crossover study, these subjects served as their own controls.

When patients used the medicated patch, they reported a slight decrease in frequency, duration, and severity of their migraine headaches as compared with placebo (Table 1). None of these differences was statistically significant, however. When asked which patch, if either, gave them the greatest relief from their headaches, 19 patients (63.3%) felt that patch A (clonidine) was the most helpful, while 5 (16.7%) believed that patch B (placebo) gave them the greatest relief of their symptoms. Six subjects reported that neither patch was more effective than the other. The difference in these proportions is statistically significant ($P<.01$).

TABLE 2. COMPARISON OF TOTAL MEAN MEDICATION USE, BY CLONIDINE AND PLACEBO GROUPS

Medication Type	Clonidine (N = 30) No. (%)	Placebo (N = 30) No. (%)	*P* Value
Class II narcotics*	3 (0.10)	34 (1.13)	.0387
Class III† and class IV‡ narcotics	338 (11.3)	376 (12.5)	.7684
Over-the-counter medications	430 (14.3)	505 (16.8)	.5067

**Class II narcotics are described as carrying high potential for abuse by Drug Enforcement Agency*
†Class III narcotics are described as carrying some potential for abuse by the Drug Enforcement Agency
‡Class IV narcotics are described as carrying low potential for abuse by the Drug Enforcement Agency

Medication use for acute pain was reduced during use of the clonidine patch. A significant reduction in use of class II narcotics (the most potent narcotics available for purposes other than investigational) was noted in patients while using the clonidine transdermal patch (Table 2). Two patients in the clonidine group received a total of three doses of class II narcotics (one received two doses and one received one dose). Nine patients in the placebo group received a total of 34 doses of class II substances (1 received 12 doses, 3 received 5 doses, 2 received 2 doses, and 3 received 1 dose). The differences in the proportions of patients receiving class II substances (30% for the placebo, 6.7% for the clonidine group, $P = .025$) and the mean number of doses of class II substances (1.13 for the placebo group, 0.01 for the clonidine group, $P = .039$) were both statistically significant. The class II medications used by these patients included oral meperidine hydrochloride and oxycodone hydrochloride as well as parenteral meperidine hydrochloride, meperidine hydrochloride with hydroxyzene pamoate, and morphine sulfate. Two oral and one parenteral doses of class II substances were taken by patients receiving clonidine while 5 oral and 29 parenteral doses were taken by patients receiving the placebo.

No statistically significant differences were noted between the medicated and placebo patches in regard to the

average number of doses taken of nonprescription medication as well as class III and class IV substances. Finally, no significant order effect was found in beginning the study with either patch in regard to subject preference for the clonidine patch or in reduction of class II narcotic use.

DISCUSSION

This study demonstrated markedly decreased use of class II narcotics by patients receiving transdermal clonidine as compared with those receiving placebo. Patients also reported a subjective perception of overall improvement when using clonidine. The small, statistically insignificant differences in mean number, duration, and severity of headache all favored clonidine over placebo as well. These findings suggest that while transdermal clonidine may not be an overly efficacious agent for the prophylaxis of migraine headaches, it may have a role for this indication in the reduction of narcotic use by these patients.

The possible mechanism by which clonidine caused a decreased utilization of narcotic analgesia may be related not to clonidine's vasoconstrictor activity for which it was originally suggested as a migraine prophylactic agent, but rather to its central action of inhibiting sympathetic outflow. Clonidine has previously been found to decrease the discomfort of narcotic and alcohol withdrawal related to increased sympathetic outflow.[1,2,18–20] The authors suspect that clonidine might also have an impact on the sympathetic outflow resulting from acute pain and thus lessen the associated symptoms, if not the actual intensity of the pain. Thus, patients may be just as aware of their headaches with respect to pain intensity, but they may suffer less of the secondary discomfort associated with increased sympathetic outflow that is due to acute pain (ie, tachycardia and diaphoresis). It is possible that these associated symptoms contribute to the patient's decision to actively address his or her discomfort with a trip to the hospital or office for an injection. It is also possible that clonidine may have a role in the reduction of parenteral narcotic use for a variety of other acute pain syndromes.

Obviously, the patients involved in this investigation were extremely well motivated toward improving their situation, as shown by their completion of the requirements of the study. One would not necessarily expect clonidine to reduce narcotic use in patients motivated by the secondary gains of euphoria, which can result from the use of these medications. For patients who seek to reduce their use of potent narcotic agents for acute painful conditions, however, clonidine may offer a means to accomplish this objective. Further studies to examine the utility of clonidine in the reduction of parenteral narcotic use for other painful conditions are suggested.

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Commentary

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This study by Dr. Bredfeldt and colleagues addresses two problems important to family physicians—the prevention of chronic headaches and the use of narcotic analgesics. Ten million patients in the United States visit their physicians annually because of chronic headaches,[1,2] and overuse of pain medication in these patients is widespread. In 1981, 57.7 million prescriptions were written for codeine and combination narcotic analgesics.[3]

The study used transdermal clonidine to ensure steady absorption of a drug with a reported antimigraine effect. Results failed to show a significant reduction of headache, but there was a significant reduction in parenteral use of narcotics.

The role of clonidine in migraine has been the subject of much debate since 1969, when Wilkinson first reported a prophylactic action in headache.[4] Some subsequent studies have supported her findings[5] and others[6] have not. The effectiveness of clonidine in suppressing narcotic withdrawal symptoms is well documented and not in dispute. Testing drugs for their prophylactic effect in migraine is notoriously difficult, as are most studies attempting to measure therapeutic effect against complex constellations of subjective symptoms.

Clinical trials in migraine are further complicated by the fluctuating nature of the condition. Records in our Headache Center over a 10-year period show that spontaneous remissions and recurrences of migraine are not uncommon. Another built-in problem that plagues headache research is diagnosis. In this study patients were selected from three different clinics using criteria laid down in 1962 by the Ad Hoc Committee on Classification of Headache.[7] This classification, which set the standards for two decades, increasingly has been found wanting by researchers because of its inadequacy in dealing with the many events and phenomena associated with chronic headache. Last year, the International Headache Association drew up a new, more detailed classification based on more rigorous diagnostic criteria.[8] In all, 129 different chronic headache conditions were categorized including 14 different types of migraine. The new classification will help eliminate some of the confusion in headache diagnosis and make future research more precise. For the practitioner, the new classification only emphasizes the problem of dealing with a patient with an undifferentiated headache.

The study deserves praise for bringing attention to the drug problem in patients with chronic headache. In seeking relief for recurring headaches, overmedication can easily result, as can happen with ergotamine preparations, the mainstay symptomatic treatment for acute attacks of migraine. Effective and toxic dose levels of ergotamine are not far apart, and early ergotism may be easily overlooked because its symptoms, nausea, vomiting and headache, closely mimic migraine. Ergotamine overuse fuels the need for more pain relief and "status migrainosus,"[9] or daily headache, results. Mathew and colleagues[10] report a similar syndrome in headache patients caused by narcotic analgesics, and Kudrow[11] showed that even nonnarcotic analgesics, if overused, paradoxically can also aggravate headache. Mathew and associates[10] also point out that daily pain medication appears to nullify the beneficial effects of any prophylactic medication that is being simultaneously used.

Whenever treatment with overused analgesics is abruptly ended, withdrawal symptoms, including exacerbation of headache, are likely. Some stoic patients can tolerate abrupt termination, an approach advocated by Mathew et al. They claim that a gratifying rapid decrease in headache occurs in a few days. Patients will require intensive support during this period, and treatment with clonidine (0.2 mg two or three times daily) and other agents to reduce withdrawal symptoms are usually necessary.

Saper[12] has developed a hospital inpatient program that, in addition to detoxification, provides a range of nondrug therapies including dietary control, psychotherapy, rehabilitation, and patient education. Our experience with such a program at Cincinnati has been very encouraging.

The cause of migraine is obscure, a cure remains elusive, and as pointed out by Critchley,[13] its history is one of discarded theories. Two new concepts, however, are worth mentioning, as they challenge two firmly held beliefs and are the cause of much current lively controversy.

A vascular basis for migraine has been firmly entrenched since Willis first proposed this model in the 17th century,[14] and there are still many modern-day proponents.[15] The well-known work on ergotamine by Graham and Wolff[16] in the 1930s seemed to place the matter beyond doubt. According to their theory, migraine consists of a preheadache cerebrovascular constriction phase causing ischemia and the aura, followed by vasodilatation and headache, which ergotamine, with its vasoconstrictive action, counteracted.

Oleson's careful cerebral blood flow studies in the early 1980s showed that migraine may not be initiated by vasoconstriction and cerebral ischemia.[17] Further doubt has arisen, as cortical ischemia resulting from vasoconstriction, thought to produce the visual aura of scotoma, cannot physiologically explain the round expanding loss of visual field in this condition. As the vascular basis of migraine weakens, a neurogenic one is taking its place. Leao,[18] in 1944, described a progressively widening circle of cortical depression caused by a variety of noxious stimuli, which could provide the mechanism of the scotoma. The concept of a neurogenic basis for migraine is gaining ground. There are many migraine trigger factors with direct links to the cortex, for example, flickering light, sounds of certain pitch, and aromas, as well as psychic factors, stress, fatigue, and sleep disturbance. A localized, reduced blood flow follows the cortical depression, suggesting that vasoconstriction in migraine may be a secondary phenomenon, not the initiating event. Efforts are now being made by Welch[19] and others to develop a single, unifying theory of migraine combining neurologic and vascular theories.

Another long-held belief being challenged is that migraine and muscle tension headache are separate entities. Although typical and pure forms exist, there are many transitional forms. In any one individual, headache not only changes over time quantitatively but also may change qualitatively, that is, migraine with aura may become migraine without aura, and either may be replaced by episodic tension-type headache. Headache patients cannot be classified, only their headaches can.[20] There is now growing belief that migraine and tension-type headache are physiologically related entities reflecting peripheral expressions of a simple central disturbance of neuroreceptor function in the brain stem, limbic, and hypothalamic regions.[21]

Since the first migraine symposium[22] was held in 1967, research in this field and its literature have expanded enormously. The American Association for the Study of Headache, The Migraine Trust in England, and the International Headache Society all promote study in this area and regularly provide educational programs for physicians. It is most important that family medicine, with its broad holistic approach, becomes increasingly involved in the study of headache, with more contributions coming from departments of family medicine such as that presented above.

Let us make sure that our discipline is kept fully aware of the rapid developments in this field. Migraine is best treated by well-informed family physicians ready to provide long-term care for this large group of patients.

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