Topical Clonidine for Orofacial Pain: A Pilot Study

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An open-label trial of clonidine, an α_2-adrenergic agonist, was prescribed for patients with a clinical diagnosis of oral neuropathic pain or neuralgia involving the oral cavity. Clonidine (0.2 mg/g) was prepared in a cream base and applied four times daily to the site of pain. Seventeen patients were assessed: 10 were diagnosed with neuropathic pain, and 7 with neuralgia. Two of the 17 patients had complaints overlapping both neuropathic and neuralgic pain. In the patients with neuropathic pain, an overall mean reduction in severity of burning of 36% (on a 10-point visual analogue scale) was reported. Half of these patients reported clinical improvement; however, no patients reported complete resolution of symptoms. Of the patients with characteristics of neuralgia, 57% improved; and in those who reported improvement, a mean reduction of approximately 54% was reported. In the 4 patients with neuralgia who responded, a 94% reduction in pain was reported, with complete resolution of pain in 2 patients. This open-label clinical trial suggests that topical clonidine may be effective in the management of some patients with oral neuralgia–like pain, but may have a more limited effect in those patients with oral neuropathic pain. Besides type of pain, no other variables predicted which of the patients would achieve pain reduction with topical clonidine. Although confirmation of clinical efficacy requires double-blind clinical studies, this initial trial suggests that further study is warranted.

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Diagnosis of neuralgia and neuropathic pain is made from patient history and examination.[1] Current therapy of persisting neuralgia and neuropathic pain is conducted by selection of an appropriate pharmacologic agent based on the clinical diagnosis and by clinical trial. Since individual responses to agents and doses are highly variable, an adequate trial for each agent is required to evaluate the effect of pharmacologic treatment. Anticonvulsant drugs are the first-line medical treatment for neuralgia. Tricyclic antidepressants are first-line agents for neuropathic pain, although other drugs (including anticonvulsants, local anesthetic antiarrhythmics, clonidine, opioids, and certain topical agents such as capsaicin[2,3]) may offer pain relief in some patient populations.[1] Ongoing developments in understanding the neurobiology of pain are providing guidance in the search for new approaches to the management of pain.

Clonidine, which is an α_2-adrenergic agonist originally developed as an antihypertensive, has been shown to modify nociception in animal and in human studies.[4–32] While these effects have

been reported in the majority of studies, they have not been observed in all studies.[33] The effects of clonidine in reducing pain reaction to mechanical stimuli and temperature tests are mediated by the α_2-adrenoceptors, causing presynaptic inhibition of nociceptive input, postsynaptic inhibition of nociception, facilitation of central pain modulation, and/or central suppression of sympathetic transmitter release.[4,26,28,30,34–37]

Clonidine has been used in human trials assessing neuropathic pain, cancer pain, and postsurgical pain, and in the majority of these studies it has shown effectiveness in pain reduction.[13–22] Systemic administration of clonidine in animal studies supports the use of α_2-adrenergic drugs in the management of chronic pain.[27,32,35] Prevention of hyperalgesia, autonomies, and increased central nervous system–evoked potentials have all been documented when both α_2-adrenergic agonists and β-blockers were administered at the time of nerve injury.[27,39] Several studies have combined an α_2-adrenergic with an opioid and demonstrated either enhanced pain relief or pain relief comparable to that of lower doses of opioids when compared to the use of opioids alone.[39–44]

In contrast, a few studies of clonidine have not demonstrated effects on pain.[45,46] In some studies,[43] although not all studies,[25,47,48] α_2-adrenergic agonists have been shown to be superior to morphine in certain neuropathic pains. Other studies have shown that while α_2-adrenergic medications can affect pain behavior associated with neuropathic pain in animals, concomitant use of morphine was also able to reduce the development of this pain.[48] The bulk of the literature demonstrates that clonidine produces analgesia, and it may be used in combination with opioids to provide better analgesia with fewer side effects from either agent.[44]

Epidural, intrathecal administration of α_2-adrenergic agonists and other agents have also been studied in the management of neuropathic pain.[31,34,37,42,48–53] Use of either intrathecal or epidural clonidine alone results in pain reduction, and in combination with opioids results in enhanced antinociception.[49,52,53] Neuropathic pain is thought to be mediated by low-threshold mechanoreceptors, which are sympathetically dependent and sensitive to both α_2-agonists and N-methyl-D-aspartate (NMDA) antagonists.[34] Intrathecal clonidine may act to diminish sympathetic outflow, whereas agents that block the NMDA receptor (eg, MK-801) are thought to be associated with other spinal systems related to pain transmission and appear to have different mechanisms of action that may account for the synergy observed.[34]

Clonidine has been shown to be safe, nonhabituating, and to have clinical effect in pain management when administered epidurally, intramuscularly, intrathecally, or topically in transdermal patches.[4,44] The principle dose-related side effects of systemic clonidine are decreased systolic pressure, decreased heart rate, sedation, and dry mouth.

Davis et al[10] showed that topical clonidine reduced mechanical and cold hyperalgesia in patients with sympathetically maintained pain in certain areas. Application of clonidine has been studied using a transdermal patch as a means of topical application in sympathetically maintained pain,[54] and in patients with diabetic neuropathy.[4,56] In a study of 41 patients with diabetic neuropathy, pain intensity differed little during the first phase of clonidine and placebo. However, 12 "responders" who were placed into a second crossover phase had 20% less pain with clonidine than with placebo ($P = .015$).[55] A post-hoc analysis suggested that patients who described their pain as sharp and shooting had a greater likelihood of responding to clonidine.[55] In another study of patients with diabetic neuropathy, a subset of patients also responded to transdermal clonidine; however, the authors were unable to identify patient characteristics that predicted response to the topical therapy.[4]

The potential of topical therapies for the management of orofacial pain is of interest. The mucosal barrier may allow more rapid absorption than skin, which may allow topical therapies to significantly affect nociception. Because clonidine has previously been shown to affect chronic pain states following transdermal application, a phase I/II pilot study was initiated using clonidine applied in a topical cream form to intraoral mucosal sites of chronic orofacial pain. The purpose was to assess the responses of each patient to topical clonidine in an open clinical study in order to determine if a double-blind placebo-controlled trial is warranted. The results of this trial are described in this paper.

Materials and Methods

The MEDLINE database was searched from January 1992 to May 1996 using the following search strategy: clonidine and pain, facial pain, neuralgia, facial neuralgia, and trigeminal neuralgia.

Patients with chronic orofacial pain referred for diagnosis and management were included in this open clinical trial. A complete history and examination of the head and neck were performed. The examination included cranial nerve examination,

Table 1 Patient Characteristics and Response to Topical Clonidine

			Pretreatment					Posttreatment		
Patient no.	Age	Sex	Pain description	Duration (mo)	Diagnosis	Site of pain	Severity pretreatment	Severity posttreatment	Overall improvement (%)	Follow-up (mo)
1	84	F	Sharp trigger	60	Neuralgia	Tongue/cheek	8	2	75	4
4	46	F	Sharp trigger	12	Neuralgia	Right cheek	9	9	0	1
7	71	M	Sharp trigger	12	Neuralgia	Left cheek	8	0	100	3
8	63	M	Sharp trigger	3	Neuralgia	Right lip anterior	9	0	100	11
13	63	M	Sharp trigger	4	Neuralgia	Right maxilla	8	8	0	2
16	67	F	Ache sharp	72	Neuropathy/neuralgia	Right lower molar/ right cheek	7	7	0	1
17	72	F	Sharp trigger	15	Neuropathy/neuralgia	Right cheek	8	2	80	5
2	41	F	Steady ache	20	Neuropathy	Anterior maxilla	3	3	0	1
3	81	F	Steady ache	74	Neuropathy	Left maxillary ridge	9	5	40	2
5	76	F	Steady ache	37	Neuropathy	Anterior maxilla	5	5	0	4
6	33	M	Ache sharp	132	Neuropathy	Right mandible	5	5	0	1
9	50	F	Steady ache	19	Neuropathy	Left posterior maxilla	7	1	80	3
10	51	F	Steady ache	65	Neuropathy	Left posterior mandible	6	2	75	1
11	61	M	Steady ache	60	Neuropathy	Left anterior maxilla	4	4	0	2
12	66	F	Steady ache	15	Neuropathy	Right tongue	5	5	0	1
14	48	F	Numb tingling	14	Neuropathy	Right lower lip	6	1	90	7
15	56	F	Ache burning	10	Neuropathy	Tongue	6	5	10	6

palpation of the cervical and masticatory muscles and the temporomandibular joint (TMJ), assessment of the range of jaw movement and joint sounds, an oral and dental examination, and appropriate radiographs. Patients without evidence of head and neck and dental pathosis were included in the trial. Six patients were assessed by nuclear bone scanning (99 MDP-technetium) with SPECT analysis as an additional aid to rule out pathosis. These patients had chronic pain despite prior treatment; no changes in systemic medications were made during the trial period. Patients were classified as presenting with neuralgia or neuropathic pain according to criteria of the International Association for the Study of Pain.[56] Trigeminal neuralgia is defined as sudden, usually unilateral, severe, brief, stabbing, recurring pains in the distribution of one or more branches of the fifth cranial nerve. Neuropathic pain is defined as constant or intermittent burning, aching, or lancinating pains caused by generalized or focal diseases of peripheral nerves.

Patients were given clonidine in a cream (Glaxo) base at a concentration of 0.2 mg/g Glaxo base. Patients were instructed to apply the clonidine cream with their fingers four times daily to the site of the pain. They were reviewed 4 weeks later, and follow-up was continued as long as possible.

Prior to treatment, pain levels were assessed using a 0-to-10–point visual analogue scale (VAS) with anchors of "no pain" (0) and "worst pain ever" (10). The VAS was completed at follow-up. Patients were also asked to assess their overall pain levels by percentage change in pain experienced. Compliance was assessed based upon the patient history, which was collected by phone after two or three visits and at the follow-up clinical visit.

The effect of clonidine in neuralgia versus neuropathic pain was assessed using the nonparametric Kruskal and Wallis test.[57]

Results

Patient demographics and the results of this trial are shown in Table 1. Seventeen patients (12 women and 5 men) were prescribed clonidine cream. Seven patients were classified as having neuralgia and 10 as having neuropathic pain: in 2 of these 10 patients, characteristics of both neuropathy and neuralgia were noted. Patients who had neuralgia-like pain were combined for analysis purposes.

The seven patients with neuralgia consisted of three men and four women, who had a mean age of 66 years (range 46 to 84 years) and a mean duration of pain prior to the clinical trial of 25 months. The mean pretreatment VAS pain rating was 8.1 (range 7 to 9) for neuralgia; the mean posttreatment VAS pain rating was reduced to 4 (range 0 to 9). Four of the seven patients reported improvement, including two who reported resolution of pain. Of the four patients with neuralgia who reported improvement with clonidine, three continued with topical applica-

tions following completion of the trial (since all three experienced recurrence of their pain when clonidine application was stopped), and one patient was able to stop using clonidine without recurrence of pain during the follow-up period.

The 10 patients with neuropathic pain consisted of 2 men and 8 women who had a mean age of 56 years. The mean duration of pretreatment pain was 45 months and a mean VAS rating of 5.6 (range 3 to 9). Following the topical trial of clonidine, a mean posttreatment VAS rating of 3.6 (range 1 to 5) was reported. While half of the 10 patients reported improvement, none had complete resolution of pain. Three patients continued use of clonidine following completion of the drug trial, since all three experienced pain recurrence upon cessation of clonidine.

No significant differences in response of neuralgia-like pain compared to neuropathic pain were seen. A high correlation was seen when changes on VAS scores were compared to patients' overall assessment of improvement ($\rho = .975$, $P < .001$).

In all 17 patients, no side effects were identified by history, although taste complaints were noted by five patients. Two patients stopped using the medication because of lack of effectiveness, and three patients reported difficulty applying the cream to the site of pain in the mouth and discontinued its use.

Discussion

In a previously reported open-label clinical trial of capsaicin cream (a "substance P depleter" used for treatment of oral neurologic or neuropathic pain), it was found that patients with characteristics of burning, aching pain responded better to capsaicin than those patients with lancinating, sharp pain.[2] This finding contrasts with the results of the present trial with clonidine, in which patients with lancinating, sharp pain qualities with periodicity and with trigger sites appeared to respond better to the topical application of an α_2-adrenergic agonist than those patients with symptoms more characteristic of neuropathic pain.[2,3] Similarly, it has been reported that patients with diabetic neuropathy associated with lancinating pain responded more frequently to transdermal clonidine[55] than patients without this lancinating quality. The differing mechanism of action of α_2-agonists, compared to a substance P depleter such as capsaicin, suggests their greatest effect would probably be on neuralgia-like pain rather than the burning, aching pain of neuropathy.[4,34,37]

Topical clonidine ointment (prepared in a hydrocarbon gel base 60 μg/g) has also been used for treatment of sympathetically maintained pain.[58] Of six patients who had relief by sympathetic blockade, two experienced relief by topical application as well. In that study, the effect of topical applications of clonidine was attributed to local effect, since plasma concentrations of clonidine were much lower than the concentration observed to reduce blood pressure.

Another study, which used topical clonidine transdermal patches in varying concentrations (0.1, 0.2, or 0.3 mg/day) in patients with diabetic neuropathy, found that pain relief was obtained only in a minority of patients.[4] In that study, the clinical features of burning, dull, aching, throbbing, tingling, pressure, sharp, or lancinating did not distinguish "responders" from those who did not respond to topical clonidine.[4] This outcome is in contrast to the current trial, where differences were found between patients with sharp, lancinating pain versus patients with aching, burning pain. Similarly, we could not distinguish any other differences between "responders" and "nonresponders."

We found a high correlation between patients' overall assessments of improvement following treatment and pre- and posttreatment VAS ($P < .001$).

The principle disadvantages of systemic clonidine include a limited duration of action and the effects associated with sedation hemodynamic and respiratory depression. However, repeated topical application may provide continuing effect and carry with it little risk of the side effects noted with systemic dosing. Other α_2-agonists with greater duration of action (eg, guanfacine,[31] tizanidine[43]) are currently being studied for future use in epidural and intrathecal administration, and may also be candidates for future trials of topical application in chronic pain.

The α_2-adrenergic agonists may have an additional role when used in combination with other analgesics. Clonidine and morphine were found to exhibit an additive effect against low-intensity pain with negligible potential for development of tolerance in a rat model of low-intensity tonic pain.[25] A double-blind crossover study of tizanidine conducted in 10 patients with refractory trigeminal neuralgia resulted in 8 of 10 patients reporting fewer painful episodes; however, symptoms recurred after 1 to 3 months in the majority of patients who continued the medication.[32] The limited duration of effect was thought to be a result of low-threshold mechanoreceptor neurons, which were not affected by the medication.[32] The α_2-adrenergic agonists may be useful as adjuvant agents in lowering dose levels of other analgesic agents through their mechanism of blocking nociceptive afferent transmission, rather than as the principle analgesic agent.

Because a variety of mechanisms may generate neuropathic pain, conventional clinical trial methods may fail to identify some potentially useful drugs, since a drug affecting just a single mechanism may work in too few patients to yield a statistically significant result.[55] The potential for topical agents alone or in combination with systemic agents to modify pain is of increasing interest. Combinations of agents with different mechanisms of action have the potential to decrease the side effects of each medication while increasing the effectiveness of pain reduction.

Since estimates of placebo effects of up to 50% in persisting pain states have been discussed,[2] review of the results reported in this open-label trial would not be complete without discussion of the placebo effect. This may be particularly important in the patients with neuropathy, where an overall reduction of only 30% was seen, and only a 59% reduction in those patients who did respond to medication. In contrast, it should be noted that, in the neuralgia group, pain reduction efficacy was noted with an overall reduction of 55% and a 94% mean reduction of pain in four of the seven patients who did respond to medication. We did not detect statistically significant differences in response of patients with neuralgia versus those with neuropathic pain, likely due to the wide range of effect and the small numbers of subjects studied.

However, it appears that some patients with neuralgia with intraoral triggers may respond to topical application of clonidine. If response is seen with topical clonidine, the use of systemic medications or other forms of therapy may not be needed. The obvious benefits include avoidance of systemic medications and thus the potential side-effects of systemic treatment. Furthermore, even when topical use of drugs such as clonidine is not effective alone in the management of neuralgia-like pain, there still exists the potential for topical application to allow a lower dose than when systemic medications are used alone.

Because of the pilot nature of this study, no conclusions can be drawn; however, on the basis of the current results, double-blind placebo-controlled trials of α_2-agonist agents in the management of facial pain of probable neurologic origin appear to be warranted.

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Resumen

Clonidina Tópica para el Dolor Orofacial: Estudio Piloto

En este estudio se recetó clonidina (con su rótulo de identificación al descubierto), un agonista adrenérgico-a2, para pacientes cuyo diagnóstico clínico era dolor neuropático oral o neuralgia que envolvía la cavidad oral. Se preparó clonidina (0,2 mg/g) en una crema base y fue aplicada cuatro veces diariamente en el sitio del dolor. Se evaluaron 17 pacientes: 10 fueron diagnosticados con dolor neuropático, y 7 con neuralgia. Dos de los 17 pacientes tenían quejas que ocasionaban la superposición del dolor neuropático y del neurálgico. En los pacientes con dolor neuropático, se observó una reducción media total en la severidad del ardor, de un 36% (sobre una escala análoga visual de 10 puntos). La mitad de estos pacientes reportaron una mejoría clínica, sin embargo, ningún paciente reportó una resolución completa de los síntomas. En los pacientes con problemas de neuralgia, el 57% mejoró; y en aquellos que reportaron una mejoría, una reducción media de un 54% aproximadamente fue reportada. En los cuatro pacientes con neuralgia que respondieron, se reportó una reducción del 94% en cuanto al dolor; dos pacientes reportaron la resolución completa de su dolor. Este estudio (que tenía el rótulo de la droga utilizada al descubierto), indica que la clonidina tópica puede ser efectiva en el manejo de algunos pacientes con dolor oral tipo neuralgia, pero puede tener un efecto más limitado en aquellos pacientes con dolor neuropático oral. Además del tipo de dolor, ninguna otra variable pudo predecir cuales pacientes experimentarían una reducción en su dolor con la clonidina tópica. Aunque la confirmación de la eficacia clínica requiere la utilización de estudios clínicos al doble diego, este estudio inicial indica que son necesarios más estudios.

Zusammenfassung

Lokales Clonidin bei orofazialen Schmerzen: eine Pilotstudie

Ein "open-label" Versuch mit Clonidin, einem α_2-adrenergen Agonisten, wurde Patienten mit einer klinischen Diagnose eines oralen neuropathischen Schmerzes oder einer Neuralgie, welche die Mundhöhle einschliesst, verschrieben. Clonidin (0,2 mg/g) wurde in einer Cremebasis hergerichtet und viermal täglich auf die Schmerzstelle verabreicht. Siebzehn Patienten wurden beurteilt: 10 wurden mit neuropathischen Schmerzen diagnostiziert und 7 mit Neuralgie. Zwei der 17 Patienten hatten Beschwerden, welche beide neuropathischen und neuralgischen Schmerzen überschnitten. Bei den Patienten mit neuropathischen Schmerzen wurde eine durchschnittliche Gesamtreduktion von 36% für die Stärke des Brennens (auf einer 10-Punkte Visual-Analog-Scale) angegeben. Die Hälfte dieser Patienten berichteten über eine klinische Verbesserung; dagegen gab kein Patient eine vollständige Auflösung der Symptome an. Von den Patienten mit Charakteristika einer Neuralgie zeigten 57% eine Verbesserung; bei diesen, die eine Verbesserung angaben, ergab sich eine durchschnittliche Reduktion von 54%. Bei den vier Patienten mit einer Neuralgie, die antworteten, wurde eine Schmerzreduktion von 94% angegeben, mit einer vollständigen Schmerzauflösung bei zwei Patienten. Dieser "open-level" klinische Versuch lässt vermuten, dass lokales Clonidin bei manchen Patienten mit oralen neuralgieartigen Schmerzen wirksam sein kann, aber bei den Patienten mit oralen neuropathischen Schmerzen eine begrenztere Wirkung haben mag. Abgesehen vom Schmerztyp sagten keine anderen Variablen voraus, welche der Patienten eine Schmerzreduktion mit lokalem Clonidin erreichen können. Obwohl die Bestätigung der klinischen Wirksamkeit doppel-blinde klinische Studien erfordert, legt dieser Anfangsversuch nahe, dass weitere Studien berechtigt sind.