Epidural Clonidine Treatment for Refractory Reflex Sympathetic Dystrophy

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Background: Intraspinally administered α₂-adrenergic agonists may relieve pain in sympathetically maintained pain (SMP) syndromes, such as reflex sympathetic dystrophy (RSD), by spinal, peripheral, and central nervous system actions. This study examined analgesic efficacy and side effects of epidurally administered clonidine in patients with severe, refractory RSD.

Methods: Twenty-six patients with severe chronic pain consistent with RSD were studied in a randomized, blinded, placebo-controlled design. Cervical or lumbar epidural catheters were inserted for patients with upper or lower extremity RSD, respectively, and patients received, in random order on three consecutive days, epidural injection of clonidine, 300 or 700 μg, or placebo. Pain (by visual analog score [VAS] and McGill Pain Questionnaire), sedation, blood pressure, and heart rate were monitored at specified intervals for 6 h after injection. Patients who responded to clonidine, but not placebo, then entered a trial of open-label, continuous epidural infusion of clonidine (10–50 μg/h).

Results: Clonidine, but not placebo, caused pain relief, sedation, and decreased blood pressure and heart rate after bolus epidural injection. The smaller clonidine dose (300 μg) produced pain relief and decreases in blood pressure and heart rate similar to those of the 700 μg dose, but with less sedation. Epidural clonidine was infused for a mean of 43 days in 19 patients at a mean rate of 32 μg/h for sustained analgesia.

Conclusions: Transdermal clonidine has been demonstrated to produce analgesia in the area surrounding its application site in patients with SMP. The current study indicates that extensive analgesia may be obtained by epidural administration. Sedation and hypotension may limit bolus epidural clonidine administration for RSD. The role for chronic epidural infusion of clonidine has not yet been established. (Key words: Anesthetic techniques; epidural. Pain, chronic: reflex sympathetic dystrophy; sympathetically maintained pain. Sympathetic nervous system, α₂-adrenergic agonists: clonidine.)

Patients with refractory reflex sympathetic dystrophy (RSD) experience severe pain and, often, progressive loss of function of the involved extremity. Many physical and emotional changes occur that often render the patient unable to function. Although many treatment modalities exist, including sympathetic nerve blocks, physical therapy, opioid and nonopioid medications, transcutaneous electrical nerve stimulation (TENS), and psychological interventions, these therapies are often inadequate for relieving symptoms or halting progression of the disease. Chronic opioid administration is not recommended in treatment of this disease, because the degree of tolerance and risk for addiction make long-term use of opioid agents undesirable in this patient population.¹

Intraspinally administered α₂-adrenergic agonists may diminish pain in patients with RSD by reducing sympathetic nervous system activity² or decreasing transmission of pain information at the level of the spinal cord.³ Epidurally administered clonidine produces analgesia in patients with chronic cancer pain⁴ and in those with acute postoperative pain.⁵ Unlike epidurally administered opioids, clonidine does not cause pruritus or respiratory depression. Lack of severe, or even moderate, respiratory depression, and avoidance of chronic opioid exposure, are important potential advantages of clonidine therapy in some patients with RSD who will be managed at home. With chronic opioid use, the risk of respiratory depression lessens, but tolerance often occurs, necessitating profound dose escalation. Other RSD patients will not be candidates for chronic opioid use; they either derive no analgesic benefit, cannot tol-

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erate side effects, or have addictive personalities that would represent a contraindication to their use.

The purpose of this study is to examine analgesia and side effects produced by epidurally administered clonidine in patients with severe, chronic RSD. In addition, feasibility of chronic continuous epidural clonidine infusion in these patients in an ambulatory setting is assessed.

Materials and Methods

After IRB approval, 26 patients with chronic RSD were enrolled. Reflex sympathetic dystrophy was diagnosed clinically by history of trauma or surgery with subsequent complaints of burning, throbbing, or aching pain and presence of sudomotor changes, vasomotor instability, or contractures (table 1). Initially, all patients were diagnosed with sympathetically maintained pain, supported by relief obtained with sympathetic block. At the time of admission to this protocol, all patients had developed a component of sympathetically independent pain. The benefit of sympathetic blocks had diminished in all patients. When indicated, further diagnostic tests were performed, including three-phase bone scans and ice-cold stress testing with laser Doppler. Patients with advanced renal insufficiency (serum creatinine > 3.5 mg/dl), atrioventricular block greater than first degree, concurrent use of α₂-adrenergic agonists or α-adrenergic antagonists, pregnancy, or hypersensitivity to clonidine were excluded. Patients taking tricyclic antidepressants did not alter their dosage of this medication during the study period. Clonidine was supplied under IND 25,169 to Dr. Eisenach by Fujisawa Pharmaceutical (Deerfield, IL) in vials containing 100 µg/ml clonidine hydrochloride in preservative free saline.

After obtaining written informed consent, an epidural catheter was inserted via the C7–T1 or L2–3 interspace in patients with upper or lower extremity RSD, respectively, and advanced 3–5 cm into the epidural space. Catheter tip location was verified by bilateral sensory block to lidocaine or by injection of radio contrast material under fluoroscopy.

Patients then received, on subsequent days and in random order, epidural injection of normal saline, 300 µg clonidine, and 700 µg clonidine, in a 10-ml volume through the epidural space. Catheter tip location was verified by bilateral sensory block to lidocaine or by injection of radio contrast material under fluoroscopy.

Patients then received, on subsequent days and in random order, epidural injection of normal saline, 300 µg clonidine, and 700 µg clonidine, in a 10-ml volume through the epidural space. Catheter tip location was verified by bilateral sensory block to lidocaine or by injection of radio contrast material under fluoroscopy.

Table 1. Patient Pain Characteristics

<table>
<thead>
<tr>
<th>Pain Characteristic</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom complex</td>
<td></td>
</tr>
<tr>
<td>Burning pain</td>
<td>19</td>
</tr>
<tr>
<td>Hyperalgesia</td>
<td>22</td>
</tr>
<tr>
<td>Edema</td>
<td>16</td>
</tr>
<tr>
<td>Trophic changes</td>
<td>7</td>
</tr>
<tr>
<td>Joint contractions</td>
<td>2</td>
</tr>
<tr>
<td>Temperature (&gt;1°C difference between extremities)</td>
<td>10</td>
</tr>
<tr>
<td>Bone scan positive</td>
<td>8</td>
</tr>
<tr>
<td>Bone scan negative</td>
<td>1</td>
</tr>
<tr>
<td>Pain location</td>
<td></td>
</tr>
<tr>
<td>Upper extremities (n = 16)</td>
<td></td>
</tr>
<tr>
<td>Hand</td>
<td>14</td>
</tr>
<tr>
<td>Forearm</td>
<td>14</td>
</tr>
<tr>
<td>Arm</td>
<td>6</td>
</tr>
<tr>
<td>Shoulder</td>
<td>5</td>
</tr>
<tr>
<td>Lower extremities (n = 10)</td>
<td></td>
</tr>
<tr>
<td>Foot</td>
<td>9</td>
</tr>
<tr>
<td>Leg</td>
<td>7</td>
</tr>
<tr>
<td>Thigh</td>
<td>2</td>
</tr>
<tr>
<td>Ankle</td>
<td>8</td>
</tr>
<tr>
<td>Pain duration (months)</td>
<td></td>
</tr>
<tr>
<td>Mean = 45.7 ± 36</td>
<td></td>
</tr>
<tr>
<td>Median = 31.5 months</td>
<td></td>
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</tbody>
</table>

completed a McGill Pain Questionnaire before and 360 min after each injection. Effects of treatment on alldynia or thermal hyperalgesia were not specifically tested. Sedation was assessed on a five-point scale (0 = wide awake; 1 = drowsy; 2 = dozing intermittently; 3 = sleeping but arousable; and 4 = unarousable) at the same times as the VAS pain scores. Blood pressure and heart rate were determined noninvasively and recorded before injection, every 5 min for 60 min after injection, then at 2, 3, 4, and 6 h after injection.

At the completion of the three injection days, the code was broken and patient response examined. Patients who did not respond to placebo, but did respond to clonidine, and who wished to continue received a continuous epidural infusion of clonidine at 20 µg/h. Clonidine infusion rate was titrated between 10 and 50 µg/h at weekly intervals, as determined by degree of pain relief and sedation or hypotension. Patient satisfaction and limb function were not systematically examined during this uncontrolled portion of the study.

Unless otherwise stated, data are presented as mean ± SEM. Effect of drug on hemodynamic variables, sedation, and VAS pain was determined by a univariate ANOVA for repeated measures. Because of missing data for several of the McGill Pain Questionnaire variables

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(PRI Total, PRI Sensory, PRI Affective, and PRI Miscellaneous), maximum likelihood estimates were obtained using BMDP5V and analyzed using Wald tests. Post hoc analysis of significant interactions were conducted by paired t tests using Bonferroni corrections. P < 0.05 was considered significant.

Results

Patient demographic data are presented in Table 2. All patients had history and physical examinations consistent with RSD, and all had undergone multiple therapies. Of the 26 patients, 16 had upper extremity involvement and 10 had lower extremity involvement. Diagnostic sympathetic nerve blocks had been performed on all patients. In all cases, sympathetic blocks initially caused analgesia, but later became ineffective. With failure of sympathetic local anesthetic blocks and other conventional therapies to relieve pain, more aggressive and interventional treatments had been used, with only transient success (Table 2). Pain before experimental treatment was severe, as determined by VAS score (7.8 ± 0.4) and McGill Pain Questionnaire descriptors (PRI Total 37.1 ± 3.4; PRI Sensory 21.5 ± 1.8; PRI Affective 5.4 ± 0.8; and PRI Miscellaneous 7.1 ± 0.9).

Epidural clonidine (both doses) reduced VAS pain scores by a similar amount within 20 min of injection, lasting throughout the 6-h period, but placebo had no effect (Figure 1). Epidural clonidine also reduced pain as measured by the McGill Pain Questionnaire (Table 3). For the MPQ PRI Total significant main effects for dose ($\chi^2(2) = 50.73, P < 0.001$) and time ($\chi^2(1) = 34.81, P < 0.001$) and a significant Dose × Time interaction ($\chi^2(2) = 34.64, P < 0.001$) were obtained. These results are indicative of a general reduction in qualitative aspects of pain self-report after drug administration and between-dose differences in the degree of this reduction. Inasmuch as the PRI Total scores were not significantly different before drug administration, the significant Dose effect provides confirmation for the strength of the interaction effect. Post hoc analyses indicated that both 300- and 700-µg doses of clonidine effected pain reductions (t = 3.03 and 3.64, respectively), but the placebo did not. Those with upper extremity RSD did not differ from those with lower extremity RSD in pain assessments before drug or in their response to clonidine.

Results indicating a significant overall reduction in pain self-report (e.g., a significant main effect of time) were likewise obtained for PRI Sensory ($\chi^2(1) = 13.43, P < 0.001$), PRI Affective ($\chi^2(1) = 7.16, P < 0.001$), and PRI Miscellaneous ($\chi^2(1) = 5.70, P < 0.05$) sub-
scale scores from the MPQ. Thus, overall, patients tended to report reliable reductions in qualitative aspects of their pain experience after drug administration. The more important issue pertained to whether these reductions were nonspecific or differed between drug levels.

For the MPQ PRI Sensory scale, a significant Dose × Time interaction ($X^2(2) = 7.73, P < 0.05$) indicated that the drug dose significantly affected the patient report of sensory aspects of pain. The reduction in the sensory dimension of pain was significant for both the 300-µg (t = 3.40, P < 0.01) and the 700-µg dose (t = 3.46, P < 0.01), but not for placebo (t = 0.65).

The Dose × Time interaction for the PRI Affective subscale ($X^2(2) = 3.03, P = 0.22$) was not significant, although these scores were significantly decreased by both the 700-µg (t = 3.56, P < 0.01) and the 300-µg dose of clonidine (t = 2.47, P < 0.05), but not by placebo (t = 0.67). Thus, although the Affective component of patients’ pain experience diminished significantly after administration of each level of clonidine, this reduction was not significantly different from the change that occurred after placebo administration.

Similarly, the Dose × Time interaction for PRI Miscellaneous items was not statistically significant ($X^2(2) = 4.69, P < 0.1$). These scores were significantly reduced by 700 µg of clonidine (t = 3.41, P < 0.01), but the reduction after the 300-µg dose failed to reach designated levels of statistical significance (t = 2.04, P = 0.052). Also, the change after placebo was not significant (t = 0.99).

Epidural clonidine (both doses) reduced blood pressure and heart rate by similar amounts, beginning within 15 min of injection and lasting 3 h, but placebo had no effect (fig. 2). Placebo produced no sedation, but clonidine produced sedation that was more marked after the 700-µg dose (fig. 3). Patients with upper extremity RSD did not differ from those with lower extremity RSD in clonidine-induced changes in blood pressure, heart rate, or sedation.

Clonidine was administered by continuous epidural infusion in 19 patients (12 with upper extremity involvement and 7 with lower extremity involvement) after the conclusion of the bolus study. Clonidine was infused for 43 ± 8 days (range 7–225 days) with a mean rate of 32 ± 6 µg/h (range 14–50 µg/h). Visual analog pain scores, recorded in all but 2 of the 19 patients at a minimum of weekly intervals, averaged 5.1 ± 0.6 during clonidine infusion, compared with 7.9 ± 0.4 before clonidine therapy (P < 0.05 by Student’s paired t test on these 17 patients). Side effects observed during this period were dizziness (five patients), nausea (five patients), mouth sores (four patients), dry mouth (three patients), and penile blisters (one patient). The cutaneous lesions did not appear herpetic in nature. Side effects were generally transient, and did not result in discontinuation of therapy in any patient. Incidence of side effects did not differ between patients with upper extremity RSD and those with lower extremity RSD.

Infections occurred in 6 of the 19 patients during continuous clonidine infusion. Four patients with temporary (nylon) epidural catheters developed catheter-related infections 12, 18, 22, and 24 days after catheter insertion. Two patients had superficial cellulitis infections treated with oral antibiotics. One patient had a superficial abscess requiring incision and drainage and oral antibiotics. The fourth patient developed a febrile illness, and Staphylococcus epidermidis was cultured from her CSF. She recovered uneventfully with intravenous and oral antibiotics. Superficial infections occurred in two patients with externalized catheters at 4.5 and 7.5 months after catheter insertion, respectively, requiring catheter removal and treatment with oral antibiotics.
in patients with SMP. Transdermal application of clonidine relieves pain without signs of local anesthesia in patients with SMP, presumably by reducing norepinephrine release from sympathetic nerve endings.

Discussion

These data demonstrate acute efficacy and indicate chronic efficacy from epidurally administered clonidine in patients with chronic RSD and severe pain. There are several possible mechanisms by which clonidine may relieve SMP in these patients, according to the pathophysiologic theory of Roberts (fig. 4).7

First, clonidine may stimulate prejunctional α2-adrenoceptors in the periphery to reduce norepinephrine release. Several lines of evidence indicate that there is a hypersensitivity to norepinephrine in nerve endings of the affected extremity in SMP. Subcutaneous injection of dilute solutions of norepinephrine or the specific α1-adrenergic agonist, phenylephrine, cause pain in the affected limb of patients with SMP, but not in volunteers, and intravenous injection of the α-adrenergic antagonist, phentolamine, produces pain relief in patients with SMP. Transdermal application of clonidine relieves pain without signs of local anesthesia in patients with SMP, presumably by reducing norepinephrine release from sympathetic nerve endings.

Fig. 3. Median sedation scores in patients receiving epidural bolus injection of saline (●), 300 µg clonidine (●), or 700 µg clonidine (▲). All groups differ by Kruskal-Wallis analysis of variance (P < 0.001).

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Although it is conceivable that analgesia from epidurally administered clonidine in the current study may be partly caused by peripheral actions, it is unlikely that this is the major mechanism, because transdermally administered clonidine, in dosages similar to those in the current study and probably yielding similar plasma concentrations, only causes analgesia in a small area surrounding the patch, not in the entire limb.\textsuperscript{10}

Clonidine could relieve pain in patients with SMP by reducing sympathetic nervous system outflow.\textsuperscript{2} Clonidine's antihypertensive efficacy after systemic administration is caused primarily by actions on \(\alpha_2\)-adrenergic and imidazoline receptors in the brainstem to decrease sympathetic nervous system activity. One would expect, if this is clonidine's major mechanism of action, that transdermally administered clonidine, which achieves its antihypertensive effect by central redistribution, would relieve pain throughout the extremity, not just locally, in patients with SMP. Nonetheless, the current study cannot exclude an action by central redistribution, and a study comparing epidural and oral clonidine administration in the treatment of RSD is underway.

Clonidine also reduces sympathetic outflow by direct actions on preganglionic sympathetic neurons in the spinal cord,\textsuperscript{12} and may afford pain relief in patients with RSD by this mechanism. However, whether clonidine produces regional sympatholysis after intraspinal administration is controversial. Clonidine reduces blood pressure more when injected intrathecally at the thoracic than at the lower lumbar dermatomes in sheep\textsuperscript{13} and humans,\textsuperscript{14} arguing for an action on preganglionic sympathetic neurons that are concentrated at the thoracic and upper lumbar levels. In contrast, lumbar epidural clonidine injection in humans produces analgesia in the foot, but not the hand, but produces a similar blockade of sympathetic response to cold stimulation in both the foot and the hand,\textsuperscript{15} arguing for general sympatholysis after epidural injection. The current study did not determine the degree of reduced sympathetic activity or its distribution after epidural clonidine administration.

We hypothesize that epidural clonidine injection relieved pain in these patients by inhibition of neurotransmission in the spinal cord dorsal horn. \(\alpha_2\)-Adrenergic agonists can inhibit nociceptive neurotransmission by both pre- and postsynaptic mechanisms in the spinal cord,\textsuperscript{3} and intraspinally administered \(\alpha_2\)-adrenergic agonists produce regional analgesia in animals\textsuperscript{16} and humans.\textsuperscript{15} Intraspinally administered clonidine reduces autotomy in a rodent model of neuropathic pain\textsuperscript{17} and provides analgesia in cancer patients with neuropathic pain.\textsuperscript{4} That clonidine is effective in these types of pain, which are typically thought to be resistant to opioids,\textsuperscript{18} indicates a rationale for clonidine use in SMP, which is also thought to be poorly opioid sensitive. Indeed, sensitivity of pain in these patients with RSD to clonidine is similar to that in patients after surgery.\textsuperscript{10-21}

Patients' responses on the McGill Pain Questionnaire indicated that clonidine produced reductions in broad qualitative aspects of their pain experience. These changes were most reliably evident in reduction in the sensory component of pain. There also was evidence that both doses of clonidine reduced the affective dimension of patients' pain, although this change was not significantly different from placebo. Although the 700-\(\mu\)g dose of clonidine effected slightly greater reductions in pain self-report than those produced by the 300-\(\mu\)g dose, in no instance were these differences significant. Finally, the responses reflecting the greatest change in the qualitative aspects of pain were represented by descriptors in subclass 2 (mean change of \(-0.02, -0.82,\) and \(-0.76\) for placebo and 300- and 700-\(\mu\)g clonidine doses, respectively), subclass 3 (mean change of \(-0.24, -0.97,\) and \(-1.05\) for placebo), subclass 8 (mean change of \(0.80, -0.65,\) and \(-0.56\), and subclass 20 (mean change of \(-0.09, -0.41,\) and \(-0.81\)).

These subclasses have been labelled as reflecting perceptions of spatial, punctate pressure, brightness, and miscellaneous qualities of pain experience.

Bolus epidural clonidine injection produced side effects (sedation and decreased blood pressure) in this study similar to those observed in other patient populations.\textsuperscript{5} Clonidine decreases blood pressure more after intrathecal injection at thoracic than cervical dermatomes in sheep,\textsuperscript{13} probably reflecting the lack of preganglionic sympathetic neurons in the cervical spinal cord. For this reason, and to maximize clonidine concentrations at cervical dermatomes supplying the upper extremity, we injected clonidine in the cervical epidural space in this study in patients with upper extremity involvement with RSD. That cervical epidural clonidine injection did not affect blood pressure or heart rate more than lumbar injection is consistent with these findings, and indicates that these side effects are not the result of cephalad distribution of drug in cerebrospinal fluid.

\(\alpha_2\)-Adrenergic agonists' sedative-hypnotic effect is caused by actions primarily in the locus coeruleus in the brainstem.\textsuperscript{22} Sedation may, therefore, be more in-
tense with intraspinal injection closer to brainstem sites. However, intensity and duration of sedation in patients with cervical catheters was similar to that in patients with lumbar catheters. This may reflect similar degrees of systemic absorption and central distribution after injection at these two sites, and minimal dispersion along the neuraxis after epidural administration. The latter concept is supported by analgesia in the lower, but not upper, extremity after lumbar intraspinal clonidine injection in animals and humans.

The role of continuous epidural clonidine infusion in the treatment of patients with chronic RSD is uncertain. Visual analog pain scores were decreased compared with baseline in patients receiving chronic epidural clonidine infusions in this study. However, placebo control was not included in this portion of the study, and assessment of extremitiy function was not performed. Both pain relief and improved function should be demonstrated before such invasive long-term therapy can be recommended in this patient group.

Of particular concern in this group of patients is the high incidence of infections with chronic epidural treatment. Nearly 25% of patients with “temporary” epidural catheters developed infections between 12 and 24 days of catheter insertion. Although all patients in this study recovered uneventfully from their catheter-related infections, it appears imprudent to leave temporary catheters in this patient population for infusion durations greater than 2 weeks. Alternatively, it is conceivable that patients with RSD are more prone to these infectious complications than those without RSD.

In summary, epidural clonidine, 300 and 700 μg, decreases pain, blood pressure, and heart rate and produces sedation in patients with chronic, intractable RSD. Clonidine most likely relieves pain in these patients by inhibitory actions in the spinal cord dorsal horn, although central, spinal, and peripheral sites of sympatholysis by clonidine may also contribute. Chronic epidural clonidine infusion appears to provide sustained analgesia, but the role for such invasive therapy in symptomatic treatment and functional recovery in RSD remains to be assessed.

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References

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