Systemic Alpha-adrenergic Blockade with Phentolamine: A Diagnostic Test for Sympathetically Maintained Pain

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The diagnosis of sympathetically maintained pain (SMP) is typically established by assessment of pain relief following local anesthetic blockade of the sympathetic ganglia that innervate the painful body part. To determine if systemic alpha-adrenergic blockade with phentolamine can be used to diagnose SMP, we compared the effects on pain of local anesthetic sympathetic ganglion blocks (LASB) and phentolamine blocks (PhB) in 20 patients with chronic pain and hyperalgesia that were suspected to be sympathetically maintained. The blocks were done in random order on separate days. Patients rated the intensity of ongoing and stimulus-evoked pain every 5 min before, during, and after the LASB and PhB. Patients and the investigator assessing pain levels were blinded to the time of intravenous administration of phentolamine (total dose 25–35 mg). The pain relief achieved by LASB and PhB correlated closely (r = 0.84), and there was no significant difference in the maximum pain relief achieved with the two blocks (t = 0.19, P > 0.8). Nine patients experienced a greater than 50% relief of pain and hyperalgesia from both LASB and PhB and were considered to have a clinically significant component of SMP. We conclude that alpha-adrenergic blockade with intravenous phentolamine is a sensitive alternative test to identify patients with SMP. (Key words: Anesthetic techniques: sympathetic ganglion block. Antagonists, alpha adrenergic receptor blockers: phentolamine. Pain: reflex sympathetic dystrophy. Sympathetic nervous system: Alpha-adrenergic receptors.)

Certain patients with chronic pain are distinguished by pain that is dependent on sympathetic innervation of the affected area.1–5 The pain, in most cases, results from skeletal, soft tissue, or nerve injury. Terms such as reflex sympathetic dystrophy, Sudeck’s atrophy, and causalgia all have been used to refer to these patients.6 However, the link between pain and sympathetic function often is not precisely identified in patients with these diagnoses. Therefore, we prefer the term “sympathetically maintained pain” (SMP), introduced by Roberts, to refer to that aspect of pain that is dependent on sympathetic efferent activity in the painful part.7 The term SMP also helps to differentiate this group of patients with chronic pain from those whose pain is independent of the sympathetic nervous system.8,9

The diagnosis of SMP may be established by assessment of the results of a local anesthetic block of the sympathetic ganglia that innervate the painful part.10,11 Because of the technical expertise required in the performance of these local anesthetic sympathetic ganglion blocks (LASB) and the potential complications associated with the LASB, alternate tests for the diagnosis of SMP have been studied. For example, intravenous (iv) regional sympathetic blockade with guanethidine has been used for the diagnosis and treatment of SMP.11

Several lines of evidence suggest that alpha-adrenergic receptors play a critical role in SMP. 1) Drugs that either deplete norepinephrine from the sympathetic nerve terminals (e.g., regional guanethidine)12–14 or block activation of sympathetic terminals (e.g., LASB) promptly relieve pain. 2) Oral administration of the alpha-adrenergic antagonists phenoxybenzamine and prazosin decreases pain in SMP disorders.15,16 3) In SMP patients temporarily relieved of their causalgia, hyperalgesia is rekindled by local iontophoresis of norepinephrine into the originally painful area.17 4) Local administration of epinephrine to experimentally produced neuromas in animals, a model for nerve injury-induced pain, evokes neural activity, as does electrical stimulation of the sympathetic chain.18–21 This effect is blocked by systemic administration of the alpha-adrenergic antagonist phentolamine.19

Since the studies discussed above indicate that the alpha-adrenergic receptor plays a vital role in SMP, it should be possible to diagnose SMP with the use of a short-acting alpha-adrenergic blocking agent such as phentolamine.22,23 We demonstrate here that this technique effectively relieves pain and hyperalgesia in patients with SMP and provides a well-tolerated, safe means of diagnosing SMP.

Materials and Methods

Patients in whom the diagnosis of SMP was under consideration based on clinical criteria (chronic pain and hyperalgesia to mechanical and/or cooling stimuli) were enrolled in this study. The study protocol was approved by the Institutional Clinical Investigation Committee, and informed consent was obtained from each patient. In each of 20 patients, two tests for SMP were performed. One

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test consisted of a LASB of the appropriate sympathetic ganglion (cervicothoracic or lumbar sympathetic ganglion). The other test, a phenolamine block (PhB), consisted of iv administration of phenolamine mesylate (Regitine®) to block alpha-adrenergic receptors. The tests were done on separate days, 1–40 days apart (median = 7 days). The sequence of the two sympathetic blocks was randomized such that half of the patients received the LASB first and the other half received the PhB first. Exclusion criteria for the study included current anticoagulant therapy, pregnancy or its possibility, or a history of ischemic heart disease, cardiac arrhythmias or peptic ulcer disease. However, none of the patients presenting to our clinic had to be excluded based on the above criteria.

**Patients**

All 20 patients in this study presented with pain and hyperalgesia to mechanical and cooling stimuli in an extremity. At the time of initial evaluation, the patients ranged in age from 20 to 57 yr (mean = 40 yr) and had had severe, disabling, ongoing pain for 6–120 months (mean = 37 months). In 10 patients, an upper extremity was affected, whereas in the other 10 patients the symptoms were localized to a lower extremity. In 7 patients, the affected extremity was at least 1°C colder than the unaffected extremity. All patients had a previous history of traumatic or surgical injury, and in 10 patients the injury involved one or more peripheral nerves.

**Pain Measurements**

Patients were asked to mark the intensity of their ongoing (stimulus-independent) pain on a 100-mm visual analog scale (VAS) on which 0 represented “no pain” and 100 the “most intense pain imaginable.” The VAS has been validated for both clinical and experimental pain by previous studies. Pain induced by brushing (soft hair brush), pressure (blunt, thermally neutral brass probe, pressure = 1.6 g/mm², area = 150 mm²), or cooling (application of a drop of acetone or a 0°C brass probe) stimuli were rated by the subject on a 0–10 verbal scale. Ongoing pain and stimulus-evoked pain were measured every 5 min before, during, and after the sympathetic blocks. Baseline pain measurements were made for at least 15 min prior to the sympathetic blocks. To determine the duration of pain relief following PhB, pain ratings were obtained at hourly intervals for several hours in four patients who had a greater than 50% relief of pain after phenolamine administration.

**Local Anesthetic Sympathetic Blocks (LASB)**

Sympathetic ganglion blocks were performed with 0.25% bupivacaine hydrochloride solutions. Lumbar sympathetic ganglion blocks (20 ml) were performed under fluoroscopic guidance by a single-needle technique. The needle was placed at the anterolateral border of the body of the second or third lumbar vertebra. The anterior paratracheal approach was used for the cervicothoracic (stellate) sympathetic ganglion blocks with 10 ml of the local anesthetic. The adequacy of the sympathetic block was monitored with cutaneous temperature measurements on the finger tips or toes of the blocked and unblocked extremities. After each block, sensory testing was done for evidence of somatic nerve blockade. No patients had any evidence of somatic blockade.

**Phentolamine Block (PhB)**

The alpha-adrenergic blocker phentolamine was administered in the following manner. An iv catheter was inserted in an unaffected extremity. For example, if pain was in the hand, the iv catheter was inserted into a lower extremity vein. To minimize the hypotensive effects of phentolamine, an initial bolus of 300–400 ml lactated Ringer’s solution was infused prior to the drug administration and was followed by a basal infusion of 2 ml·kg⁻¹·h⁻¹. Patients were kept supine throughout the procedure. The ECG was continuously monitored and blood pressure was recorded every 3–5 min with an automated blood pressure cuff. Skin temperature was recorded bilaterally at 1-min intervals on the fingertips or toes.

Two investigators were present during the block (Fig. 1). One investigator monitored the patient’s hemody-
dramatic status and skin temperature and administered the drugs through the peripheral iv line. The second investigator obtained ratings of ongoing (stimulus-independent) and stimulus-evoked pain as discussed above. Both the patient and the second investigator were blinded to the time of the iv drug administration.

After baseline hemodynamic and pain measurements, at intervals varying from 8 to 36 min (mean = 21 min) after the first pain scores were obtained, one or more boluses of 3–5 ml normal saline were administered through the peripheral iv line as a placebo. Phentolamine was then injected iv at 3–8-min intervals in increasing doses ranging from 1 to 10 mg (e.g., 1, 2, 4, 8, 10, 10) up to a total of 25 (n = 9) or 35 (n = 9) mg. Two patients received only saline (see "Placebo Responses" below). Since one of the observed side effects of phentolamine administration in the initial series of patients (n = 8) was tachycardia (table 1; see Results), subsequent patients (n = 12) were pretreated with 1–2 mg propranolol iv, 5–10 min prior to the phentolamine administration.

STATISTICAL TESTS

The maximum pain relief resulting from LASB and PhB was compared using a linear regression analysis, and the Pearson correlation coefficient was calculated. A paired t test was used to determine if the magnitude of pain relief from the two tests was different. For the comparison of a new method to a more established "gold standard" where both the new and the established methods may be associated with substantial errors, an alternate method of analysis has been proposed. The difference between the magnitude of pain relief achieved with the LASB and PhB also was compared using the method described by Altman and Bland. A Pearson correlation coefficient was done to determine if there was a relationship between the mean pain relief and the difference in pain relief by the two methods. To determine if propranolol pretreatment altered the pain relief achieved with phentolamine, an analysis of covariance was used to compare the maximum pain relief achieved with the two blocks in patients with or without propranolol pretreatment. The maximum changes in heart rate and systolic and diastolic blood pressure after phentolamine administration were compared to control measurements prior to drug administration using Student's paired t test. In all cases, P < 0.05 was considered significant. All means are stated as mean ± the standard error of the mean (SEM).

Results

PLACEBO RESPONSES

We sought to distinguish effects of sympathetic blockade from placebo responses. There was no saline control injection for the LASB, since patients would not tolerate needles left in place long enough to evaluate the effects of placebo injections prior to injection of local anesthetics. As mentioned above, intravenous saline was administered for a variable period prior to the delivery of phentolamine. This provided an opportunity to determine whether there was a placebo response. Two patients had nearly complete relief of pain and hyperalgesia (80–100%) during the saline injection period prior to the administration of propranolol. These two patients were excluded from further analysis.

EFFECTS OF SYMPATHETIC BLOCKADE ON PAIN AND HYPERALGESIA

An example of the time course of pain relief after a PhB is shown in figure 2. This patient had pain and hyperalgesia on the anterior and lateral aspect of the knee.
after arthroscopy. Ratings of stimulus-independent pain did not change after the administration of normal saline. The first four boluses of phenolamine (total dose = 15 mg) were associated with a gradual decrease in pain of about 60%. Finally, after two additional injections, each of 10 mg, over 80% of the patient's pain and hyperalgesia was relieved. The patient's pain remained at this level for about 2 h, although the reported plasma half-life of phenolamine is 19 min.31 Pain gradually returned to near-baseline levels over the course of about 7 h. A series of LASBs failed to afford long-term relief, and the patient subsequently underwent a surgical lumbar sympathectomy. The patient had complete pain relief from this procedure and continues to be pain-free 24 months postoperatively.

In figure 3A, the maximum relief of ongoing pain with phenolamine is plotted as a function of the maximum relief with the local anesthetic block for all 18 patients who received both the PhB and the LASB. Maximum pain relief was calculated from the difference between the control and the lowest postblock rating and is expressed as a percentage of the control pain rating. The average of two consecutive pain ratings immediately prior to the phenolamine or local anesthetic administration was considered to be the control pain rating. The average of two consecutive lowest pain ratings after the end of the drug administration was accepted as the lowest postblock rating. The range of pain relief for both procedures extended from zero to total relief. There was a high correlation of the maximum pain relief resulting from the LASB and the PhB (r = 0.84). There was no significant difference in the pain relief achieved with the LASB and the PhB (paired t test, t = 0.19; n = 18, P > 0.8). The slope of the regression line (0.95) is not significantly different from 1 (t = 0.37, n = 18, degrees of freedom [df] = 16).

The difference in maximum pain relief achieved in each patient with the PhB and the LASB (PhB — LASB) is plotted against the mean pain relief resulting from the two blocks ((PhB + LASB)/2) in the same patient (fig. 3B). The mean difference, i.e., the bias, was −1% pain relief, and the standard deviation of the differences was 18%. There was no correlation between the mean pain relief and the difference in pain relief from PhB and LASB (r = 0.17, P > 0.5), indicating that the pain relief achieved with the two tests was similar throughout the range of the tests, i.e., 0–100%.

The addition of propranolol did not augment the pain relief achieved with phenolamine. Nine patients experienced a greater than 50% pain relief during the LASB and were considered to have a clinically significant component of SMP. The maximum pain relief achieved, with or without propranolol pretreatment, in these nine patients was similar (86 ± 5%, n = 3 vs. 74 ± 8%, n = 6, respectively). In addition, the correlation of pain relief achieved with the LASB and the PhB was similar in all patients, whether or not they received propranolol pretreatment (analysis of covariance, F = 0.03, df = 1, P > 0.8).

Phentolamine was equally effective in reducing ongoing and stimulus-evoked pain. In six patients who achieved a greater than 50% pain relief during the PhB, the relief of ongoing and stimulus-evoked pain during PhB were compared. The magnitude of relief of ongoing pain (83 ± 3%) was similar to the relief of pain induced by brush or pressure stimuli (82 ± 9%, n = 6). Similarly, in eight patients who achieved less than 50% relief of ongoing pain (9 ± 3%) during the PhB, there was minimal change in their stimulus-evoked pain (15 ± 12%) as well.

**TIME COURSE OF RELIEF OF PAIN AND HYPERALGESIA**

After phentolamine administration, the time of maximum relief of stimulus-evoked pain closely approximated the time at which there was maximum relief of stimulus-independent pain (see fig. 2). The maximum pain relief was achieved 20–30 min after the last dose of phentol-
amine was administered. In four of the nine SMP patients, the duration of pain relief after PhB was followed for several hours. The duration of pain relief varied from 3 to 10 h (fig. 4). In three of the four above-mentioned SMP patients, the duration of pain relief after LASB also was followed for 4–8 h. All three patients had less than 20% of their initial pain reappear during the observation period.

CUTANEOUS TEMPERATURE CHANGES DURING SYMPATHETIC BLOCKADE

An increase in cutaneous temperature of 5.1 ± 1.2°C (n = 8) and 7.1 ± 1.5°C (n = 8) was observed in the affected extremity after stellate or lumbar sympathetic ganglionic blockade, respectively. In contrast, the change in cutaneous temperature after PhB was variable. The mean increase in skin temperature after phenolamine administration was 1.8 ± 0.7°C (mean ± standard error of the mean [SEM]). There was no significant correlation between temperature change and percent maximum pain relief after the phenolamine (r = 0.03) or local anesthetic blocks (r = 0.38).

DOSE OF PHENTOLAMINE AND CARDIOVASCULAR EFFECTS

To avoid profound hypotension and tachycardia, we chose a cumulative dose of phenolamine that did not result in a greater than 30% decrease in systolic and diastolic blood pressure or an increase in heart rate exceeding 140 beats per min. The total dose ranged from 25 to 35 mg and was administered over a 20–50-min period.

The maximum changes in heart rate and systolic and diastolic blood pressure produced by phenolamine in patients with or without propranolol pretreatment are shown in table 1. The systolic blood pressure was not significantly changed, whereas the diastolic blood pressure was decreased by approximately 20% in both the propranolol-treated and the untreated groups (P < 0.05). The increase in heart rate after phenolamine administration was significantly less in patients pretreated with propranolol (P < 0.05). The changes in blood pressure associated with the use of phenolamine for the diagnosis of SMP were short-lived, unlike the pain relief that lasted for hours, and all patients were able to assume an upright position within a half hour after the end of the test.

SIDE EFFECTS OF PHENTOLAMINE ADMINISTRATION

Side effects associated with the phenolamine administration were minimal. The principal side effects observed were nasal stuffiness (n = 10), headache (n = 3), and dizziness (n = 2). The dose of phenolamine after which patients first reported nasal stuffiness ranged from 7 to 25 mg (13 ± 2.5 mg, mean ± SEM) after the initiation of phenolamine. An average of 65% of the maximum decrease in pain ratings were reported prior to the onset of nasal stuffiness in the patients who achieved greater than 50% pain relief with the PhB. All patients preferred the PhB over the LASB, mainly because it was less painful.

Discussion

These data indicate that, in patients who present with chronic pain and cutaneous hyperalgesia, there is a close correlation between the pain relief achieved by LASB and the systemic alpha-adrenergic block with phenolamine. The ease of performance and patient preference indicate that the use of intravenous phenolamine may be a preferred test for the diagnosis of SMP.

Several disadvantages apply to the use of LASB and iv regional sympathetic blocks. 1) LASB is subject to false negative results if the local anesthetic fails to anesthetize adequately the sympathetic ganglia. 2) LASB is subject to false positive results on three accounts. The anesthetic may reach the somatic afferent fibers in the nearby nerve roots and produce pain relief because of concurrent somatic blockade. In addition, blockade of certain afferent fibers that course with the sympathetic efferent fibers may result in pain relief.32 Finally, the local anesthetic may have systemic effects. 3) LASB involves precise localization of the needle prior to injection, and so fluoroscopy often is needed. 4) A number of complications have been reported with LASB, including pneumothorax, phrenic nerve block causing diaphragmatic paralysis, cardiac arrhythmias, injury to the kidney, hemorrhage, and inadvertent intravascular or epidural injections.33 In addition,
patients often do not tolerate the LASB well and find the insertion of a needle in the neck or back uncomfortable. 5) Certain patients tolerate poorly the application of the tourniquet required with iv regional blocks. 6) In iv regional sympathetic blocks, guanethidine is often co-injected with local anesthetics since the release of norepinephrine by guanethidine is usually associated with an exacerbation of pain. As a result, the diagnosis is often confounded by the effects of the local anesthetic. 7) With iv regional blocks, the guanethidine may escape into the systemic circulation with resultant systemic hemodynamic effects. 8) The iv regional block is more difficult to perform in the lower extremity because of greater mass and circumference of the limb. 9) It is difficult to evaluate placebo responses with both LASB and iv regional sympathetic blocks.

Pharmacologic sympathetic blockade using adrenergic receptor antagonists such as phentolamine has distinct advantages over the conventional forms of sympathetic blockade. In addition to ease of performance and better patient acceptance, PhB offers the advantage that false positive results, including placebo effects, can be avoided. Though the placebo effects associated with sympathetic blocks have not been quantified, they are important in the context of diagnosis and management of chronic pain. With the PhB, a significant observation period can be used prior to the administration of the drug, and the patient can be blinded to the time of drug administration. A recent report suggests that phentolamine also can be used safely in children with reflex sympathetic dystrophy. In this group of patients, the response to phentolamine administration was a useful predictor for success of therapy with iv regional guanethidine.

Except for the two patients who had demonstrable placebo effects, it is unlikely that the observed effects of phentolamine could be secondary to experimenter bias or placebo effects. Half of the patients received the PhB prior to the LASB. The investigators were therefore not biased by previous results of LASB in these patients. The maximum pain relief achieved with the LASB and the PhB was similar in these patients. Although patients experienced nasal stuffiness after the phentolamine administration, the onset of pain relief preceded the symptoms of nasal stuffiness in all the patients.

Dose–response curves for phentolamine were not obtained, and it may be argued that comparable efficacy could have been achieved with smaller doses. However, the doses used here were well tolerated without notable side effects, such that there was no compelling need to decrease the dose. Conversely, it could be argued that a larger dose of phentolamine should have been used, particularly in view of the observation that temperature increases were not always observed. If the extent of pain relief by appropriate LASB is considered the maximal possible effect in each patient, PhB was on the average equally effective. Thus, the dosages used in this study are likely to be near the high end of the linear part of the dose–response curve.

It is a common observation that sympatholytic treatment may confer long-term therapeutic benefit. This has been reported for sympathetic ganglion blocks, guanethidine blocks, and oral phenoxybenzamine treatment. All patients in this study received only one PhB, and no patient had long-term benefit from the block. However, it is worth evaluating if a series of PhBs will result in long-term therapeutic benefit in SMP patients.

We did not observe a significant correlation between change in cutaneous temperature and percent maximum pain relief after PhB. This finding is consistent with our earlier observation that alterations in vasomotor tone alone do not result in pain relief. When pain relief and cutaneous temperature changes after LASB, PhB, or passive warming of the extremity with radiant heat were compared, no correlations were observed. Thus, the mechanism of pain relief during sympathetic blockade seems to be independent of cutaneous vasodilatation or skin temperature changes.

Systemic phentolamine, as used in this study, is associated with minimal side effects. Tachycardia resulting from phentolamine may be a direct "sympathomimetic" effect on the heart or a reflex response to peripheral vasodilatation. The tachycardia may be minimized by the use of iv propranolol prior to the phentolamine administration. Although vasodilator therapy with phentolamine was found to be beneficial in the treatment of severe heart failure, its use in patients with cardiac disease has been associated with troubling adverse effects. Tachycardia and positive inotropic effects can worsen angina. These adverse side effects can be explained by phentolamine's potent effects not only at postsynaptic vascular alpha1 receptors, but also at presynaptic alpha2 autoreceptors. The blockade of alpha2 receptors causes an increased neuronal release of norepinephrine, which leads to enhanced stimulation of the beta-adrenergic receptors in the heart, resulting in positive inotropic and chronotropic effects. Though these side effects of phentolamine can be blocked effectively with beta-blockers, we advise that phentolamine be used with caution in patients with ischemic heart disease.

It may be debated whether the site of action of the phentolamine administered systemically is central or peripheral. Phentolamine is a reversible competitive antagonist that acts at both alpha1- and alpha2-adrenergic receptor sites. Moreover, the drug appears to be capable of crossing the blood–brain barrier. Studies indicate that the adrenergic receptor that is involved in the modulation of the nociceptive input at the level of the spinal
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cord is of the alpha2-adrenergic receptor subtype.\textsuperscript{43,44} Local application in the intrathecal space of adrenergic agonists such as epinephrine results in analgesia. Thus, the effect of alpha-adrenergic receptor blocking agents acting at the level of the spinal cord would be a reversal of the analgesic effects of adrenergic agents. In contrast, phentolamine decreased the pain and hyperalgesia in patients with SMP. Therefore, it is likely that phentolamine is acting at a peripheral alpha-adrenergic site.

Studies have demonstrated an interaction between cardiovascular and pain regulatory systems in experimental animals.\textsuperscript{45,46} Elevation of either arterial or venous blood pressure by alpha-adrenergic agents such as phenylephrine was associated with antinociception in the tail-flick test, an effect mediated by sinoaortic baroreceptors.\textsuperscript{†} Alpha-adrenergic blockade with phentolamine prevented both the pressor and the antinociceptive effects of phenylephrine.\textsuperscript{47} Thus, the decrease in pain observed in patients with SMP after phentolamine administration probably cannot be explained by an effect of the drug on the cardiovascular system.

Regional injection of phentolamine, using a Bier block technique, in a manner similar to the use of guanethidine, might be considered an option in the diagnosis of SMP. This route undoubtedly would allow the use of a smaller dose of phentolamine. However, we observed in earlier studies that the hyperalgesia in patients with neuropathic pain is signalled by large myelinated fibers and is relieved, though transiently, by an ischemic tourniquet.\textsuperscript{48} Thus, it would be difficult to differentiate if the relief of pain after a Bier block technique with phentolamine was secondary to alpha-adrenergic blockade or secondary to conduction blockade of myelinated fibers. In addition, in preliminary studies, it was noted that patients found the process of exsanguination of the limb and the application of a tourniquet itself painful. The advantage of the Bier block technique is that it allows larger doses of a given drug to be delivered to the affected area in cases where untoward side effects from systemic delivery compromises the amount of drug that can be delivered to the affected region. Because systemic phentolamine was well-tolerated by patients in this study, further use of regional techniques was abandoned.

In conclusion, SMP appears to be a condition wherein pain is related to activation of peripheral alpha-adrenergic receptors. Therefore, a logical choice for the diagnosis of this condition is the administration of an alpha-adrenergic antagonist. This study demonstrates that iv phentolamine achieves pain relief similar to that obtained by a more conventional technique, local anesthetic block of the sympathetic ganglion. Phentolamine administration is less invasive, has fewer potential side effects, is preferred by patients, and can enhance the ability to diagnose conditions wherein the pain is dependent on activation of alpha-adrenergic receptors.

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