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## CLINICAL REPORT

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# Treatment of Complex Regional Pain Syndrome Type I With Oral Phenoxybenzamine: Rationale and Case Reports

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■ **Abstract:** The nonselective  $\alpha$ -adrenergic antagonist, phenoxybenzamine, has been used in the treatment of neuropathic pain syndromes, specifically, complex regional pain syndrome (CRPS) types I and II. This agent has also previously been used in intravenous regional peripheral blocks for treatment of CRPS I; however, an intravenous preparation of phenoxybenzamine is not currently available in the U.S.A. In this case series, systemic administration was more appropriate for three of the four patients, as their syndromes had spread beyond the initial area of surgery or trauma. We report an apparent clinical benefit in three of the four patients following oral administration. We postulate that this may be due to the noncompetitive (irreversible) blockade of  $\alpha_1$ - and  $\alpha_2$ -adrenergic receptors. We further hypothesize that this blockade could reduce stimulation of an increased population of adrenergic receptors in hyperalgesic skin, blunt the stimulation by norepinephrine of  $\alpha_2$ -adrenergic receptors on macrophages, and ultimately reduce the release of proinflammatory cytokines from cellular elements. ■

**Key Words:** complex regional pain syndrome type I, complex regional pain syndrome type II, pharmacologic action, sympathetic-blocking agents, therapeutics

### INTRODUCTION

Complex regional pain syndrome (CRPS) type I, previously termed reflex sympathetic dystrophy, and CRPS type II, also termed causalgia, are severe neuropathic pain syndromes.<sup>1,2</sup> The commonly held distinction between these two syndromes has been that there is clear evidence of neuronal damage in CRPS II, but that CRPS I is associated with soft tissue trauma, without nerve injury.<sup>3</sup> Recent studies suggest that there may not be a clear distinction between the syndromes, and that CRPS I may involve damage to small diameter nociceptive fibers.<sup>4,5</sup> However, the subject remains controversial.<sup>6</sup> The search for effective treatment of this broad range of disorders continues. There are previous reports on the use of oral phenoxybenzamine (PBZ) for the treatment of both type I and type II CRPS.<sup>7-9</sup> Despite the apparently favorable treatment responses in those studies, the drug is not widely recognized as a treatment alternative for these syndromes. PBZ is a noncompetitive (irreversible) antagonist of  $\alpha_1$ - and  $\alpha_2$ -adrenergic receptors.<sup>10</sup> In animal studies, full recovery of  $\alpha_1$ -adrenergic receptor response (blood pressure elevation with phenylephrine) took eight or more days after a single intravenous injection of PBZ;

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the return of response represents repletion of receptors.<sup>11</sup> The acute alleviation of symptoms in some CRPS patients through  $\alpha$ -adrenergic blockade has been used to identify a subset of patients with sympathetically maintained pain syndromes.<sup>12</sup>

We reported earlier on the successful treatment of several cases of CRPS type I of the upper extremity with intravenous regional blocks that contained both PBZ and lidocaine.<sup>13</sup> The inclusion of PBZ in the injected solution was considered to be a principal factor, as conventional Bier blocks are not associated with a reliable long-duration of pain relief in CRPS. The study was carried out under a Food and Drug Administration (FDA) Investigational New Drug Application, as there is no currently approved intravenous form of PBZ that is available in the U.S.A. We have since lost a supplier for the intravenous preparation and are currently only able to use, or refer patients to the use of, the oral preparation of the drug (DIBENZYLINE).

Because of the devastating effects of CRPS, and in view of the still limited and often unsuccessful options for its treatment, we have elected to present the results of treatment with oral PBZ in four patients, three of whom had apparently clear signs and symptoms of CRPS I, and who had been previously diagnosed with the syndrome by their treating physicians. A fourth patient did not present with a diagnosis or classical signs of CRPS, but received PBZ as a trial approach for her pain, after consultation between the patient and her treating physician. An intravenous regional block with PBZ would not have been an option in three of the cases, even if the intravenous form of the drug had been available, because the syndromes were no longer limited to an extremity. The spread of CRPS beyond the initial site of trauma or surgery is well-recognized.<sup>14,15</sup> We were directly involved in the treatment of one of the patients that received PBZ (case 1), but, in response to inquiries, we brought the treatment to the attention of the other patients, and thereby to their treating physicians. The patients treated outside of our institution kept us closely apprised of their treatments and outcome, and they have all reviewed and approved the summaries presented below.

## CASE REPORTS

### Case 1

Female, age 27 years at start of PBZ treatment.

**Injury/Surgery.** The patient resides in England. Five years prior to the initiation of PBZ treatment in the

U.S.A., the patient had bunions removed from both feet. After the surgery, her feet turned a purple-blue color and felt extremely cool. Pain increased progressively over the ensuing months. A second bunion removal operation was performed 9 months later. Symptoms spread to other extremities and included weakness, joint pain, stiffness, and difficulty gripping objects. She developed sensitivity to bed coverings and clothing and experienced the sensation of a friction burn. Additional signs and symptoms included heaviness in her limbs, itching of her limbs, tremors in the extremities, asymmetry of skin temperature and color, and marked edema in her lower legs. Her skin quality was poor (she lost the texture of her skin that produced a fingerprint), and virtually all sense of smell and taste. She received a diagnosis of "reflex sympathetic dystrophy" from her English physicians. Courses of treatment with physical therapy, ankle blocks and acupuncture, and pain medications including a mixture of acetaminophen and dihydrocodeine tartrate (CO-DYDRAMOL), meloxicam, and amitriptyline did not lessen the symptoms. She was severely depressed when she came to the U.S.A. for treatment. She had been using a wheelchair intermittently at home, but was ambulating with one or two canes upon her arrival. She was prone to lose her balance upon standing, and rated her visual analog pain scale score (VAS) as 10/10.

**Treatment.** Phenoxybenzamine was started at 10 mg/day in the evening. (The patient continued to take meloxicam, 7.5 mg/day, and amitriptyline, 50 mg/day, while taking PBZ.) The next morning the patient felt dizzy and slightly nauseated; treatment was omitted for the second day, but was then tolerated well for the next 9 days before the patient returned to England. In the duration of her stay in the U.S.A., her pain diminished progressively. The edema in her lower limbs resolved completely, and she felt confident to walk without a cane. On the morning of her departure from the U.S.A., she was able to walk a distance of more than 1 mile, and rated her VAS pain at 5–6/10. A month after returning to England, she estimated her VAS pain at 4/10.

While in the U.S.A., the patient had taken the FDA-approved formulation of PBZ, ie, DIBENZYLINE. This formulation of PBZ is not available in England. After considerable difficulty, the patient was able to convince her healthcare provider to prescribe the formulation that is available in England, which is marketed as DIBENZYLINE. She developed an apparent allergy to this preparation; the basis for this was not pursued, but it

was determined that the European preparation contained several excipients, including titanium dioxide, indigotin, and edible gray ink, which are not present in the U.S. preparation. The patient decided to return periodically to the U.S.A. for treatment.

Over the next 5.5 years, the patient returned to the U.S.A. six times for treatment with PBZ; each period of treatment was approximately 6 weeks. At no time did the dose exceed 10 mg/day. As the patient could not transfer any of her health insurance to the U.S.A., all medical treatment fees were waived, although she did have the expense of PBZ prescriptions. (PBZ costs approximately 5 dollars [U.S.] per 10 mg capsule.) The dose during her last three visits to the U.S.A. was 10 mg every other day. In the period between visits, it has been 10 mg every third day, or less frequent at times to conserve medication. She monitored her own blood pressure while not in the U.S.A.; it was consistently normal. At the end of her last period of treatment in the U.S.A., she rated her VAS pain score as 3–4/10. Her senses of smell and taste have partially returned; she rates these at about 1/3 of normal. Her skin quality is improved; she now has a fingerprint. Her condition did regress somewhat in the periods between treatments in the U.S.A., when she was taking the drug less frequently, but did not return to the level of her initial condition. The patient is now fully ambulatory, active in her own art business, volunteer work, and social activities. As of this writing, the patient has been on PBZ for a period of 57 months.

### Case 2

Female, age 40 years at start of PBZ treatment.

**Injury/Surgery.** The patient resides in England. Thirteen months prior to the initiation of PBZ treatment, the patient had bunions removed from her feet. She was diagnosed with CRPS, which developed initially in her left foot, but progressively spread, as she perceived it, to her entire body. During the first 6 months of her illness, there was marked swelling of her foot and changes in skin temperature, followed by muscle wasting and bone demineralization (from X-ray examination). She also noted that her shoe size had decreased. In addition to severe pain (VAS 10/10), she had coarse and fine muscle spasms, allodynia (she could not tolerate bed coverings), and migraine headaches. The spasms almost precluded sleep. Her skin in the affected areas became dark in color, and her toe nails developed deep dark grooves, which required cosmetic coverage. She required two

canes to ambulate. Prior to treatment with PBZ, the patient received three intravenous regional blocks in her lower limb with guanethidine. The blocks produced only transient relief of symptoms.

**Treatment.** Phenoxybenzamine with the European formulation (DIBENYLIN) was taken at 10 mg/day. (She continued to take paroxetine, 20 mg/day, while taking PBZ; the drug had been prescribed for depression related to her illness and subsequent loss of her employment.) She took PBZ at this dose for 12 days, but then discontinued use intermittently or reduced the dose to 5 mg/day because of nasal congestion. She found that she could tolerate the medication better with the use of a nasal saline spray to relieve the congestion. The patient had a marked relief of symptoms starting after the first 3 days of PBZ at 10 mg/day. Notably, she could sleep with bed coverings, her migraine headaches disappeared, she could walk without the use of a cane, and her muscle spasticity was greatly reduced. Two months after starting PBZ treatment, she rated her VAS as 2/10, although it would be higher on days when the air temperature was cold.

The patient gradually tapered her dose, and approximately 2 years after starting PBZ, she was taking 10 mg every third day. Her symptoms were well-controlled and she considered that they were reduced overall by 90% since initiation of treatment. As of this writing, the patient has taken PBZ for 60 months. Her former CRPS symptoms continue to be largely well-controlled with 10 mg of PBZ every third day. She has noted that about midway between PBZ doses, her VAS score is approximately 3/10, and may approach 7/10 shortly before the next dose. Her skin color and toe nails are essentially normal now, and there has been no further decrease in her shoe size. She recently received a diagnosis of fibromyalgia of her facial muscles, for which she receives periodic injections of *botulinum* toxin.

### Case 3

Female, age 37 years at start of PBZ treatment.

**Injury/Surgery.** Six years before initiation of PBZ treatment, the patient injured her left hand in a sleighing accident. She was diagnosed with “reflex sympathetic dystrophy,” which was at first limited to her injured hand, but the pain spread progressively to the left side of her body, including her left leg; she had to drag that leg in order to ambulate. Her left arm and leg were edematous, cold, and abnormal in skin color; the skin had a

shiny appearance. She also had severe chronic headaches and great difficulty in sleeping. She had received extensive prior treatment with narcotics, notably, oxycodone (OxyContin) orally, and morphine by a spinal pump. She rated her VAS pain score as 8–9/10 at the start of PBZ treatment.

**Treatment.** Phenoxybenzamine was started at 10 mg/day. She took no other medication in conjunction with PBZ. After 12 days on PBZ, the patient reported that her symptoms were much improved. Her headaches were essentially nonexistent and she could sleep through the night, and walk with much greater ease; she rated pain on a VAS as 5/10. A report from the patient after 3.5 months of treatment at 10 mg/day of PBZ indicated that she walked then with only a slight limp in her left leg, she could go up and down stairs without a cane, and had returned to doing household activities that had not been possible before. Also, the skin in the affected areas no longer had a shiny appearance. Although she indicated that her VAS pain score was 5/10, it was no longer as debilitating to her. For a few days, her doctor had prescribed a trial with PBZ at 20 mg/day, but she could not tolerate the dizziness that it caused, and returned to 10 mg/day. Eleven months after the start of treatment, she was still taking PBZ at 10 mg/day, had returned to working 20 hours per week, and rated VAS as 3–4/10. The edema on her affected limbs had resolved completely over the course of treatment. Fourteen months after continuous treatment with PBZ, the patient had surgery for an unrelated problem. The PBZ treatment was interrupted at that time and, in the absence of any return of CRPS symptoms, treatment was not restarted. In the most recent contact with the patient, more than 3 years after the discontinuation of PBZ, the patient has not had the need to resume treatment.

#### Case 4

Female, age 54 years at start of PBZ treatment.

**Injury/Surgery.** Twenty months prior to the initiation of PBZ treatment, the patient had a neuroma removed from her right foot. Approximately 6 months after the surgery, the pain had spread to her left foot, involving the toe joints and the backs of her heels, and with slight edema at times. The pain was quite severe at times, and about one year after the surgery she resorted to the use of a wheelchair for a period of several weeks. However, she was never diagnosed with neuropathic (CRPS) pain. Treatments before PBZ included cortisone injections,

gabapentin (up to 1200 mg/day), physical therapy, acupuncture, and the use of orthotic support, with no apparent benefit.

**Treatment.** Phenoxybenzamine was started at 10 mg/day. (The patient reported little or no use of any analgesic drugs in conjunction with PBZ.); after 1 week, the dose was increased to 20 mg/day. The dose was eventually increased to 30 mg/day, but as the patient observed no improvement in her symptoms, PBZ was stopped after a total of 6 weeks of treatment. Following a new evaluation, the patient's symptoms were considered to have a significant psychogenic component. Psychotherapy helped to identify stressors that contributed to her symptoms.

#### DISCUSSION

An apparently favorable therapeutic response was obtained with PBZ treatment in three of the four patients (cases 1 through 3). These patients all had classical signs and symptoms consistent with criteria for CRPS, as defined by the International Association for the Study of Pain.<sup>1,16</sup> They all had an initiating traumatic or surgical event. They all demonstrated hyperesthesia/allodynia, edema, weakness, varying degrees of spasticity and movement impairment, changes in skin temperature, color and appearance and integrity, and changes in nail quality and appearance. Also, there did not appear to be an alternative diagnosis that was more appropriate for their signs and symptoms. They had received diagnoses of “reflex sympathetic dystrophy” from their healthcare practitioners before starting PBZ, and all have described their improved physical conditions following PBZ treatment as being “life-changing.” Patient number 4 had never received a diagnosis of CRPS, but sought out recommendations for her pain condition. Although we explained that her condition was not typical for CRPS I, she and her physician decided on a therapeutic trial of PBZ. It is of interest that she did not receive any apparent benefit from the treatment, even with an extraordinary dose compared to the other patients. Her experience lends emphasis to the importance of the reliance on diagnostic criteria to guide treatment of this syndrome.

None of the patients in this case series had been tested a priori for the presence of sympathetically maintained pain. However, there may be a reasonable scientific rationale for the use of PBZ in the treatment of CRPS, particularly if the pain component is suspected of being initiated or maintained by the sympathetic nervous

system, either peripherally<sup>17-19</sup> or centrally.<sup>20</sup> As PBZ is an irreversible (noncompetitive) antagonist of  $\alpha$ -adrenergic receptors, it would be expected to produce a long-lasting blockade of adrenergic input that is mediated through activation of  $\alpha_1$ - or  $\alpha_2$ -adrenergic receptors.

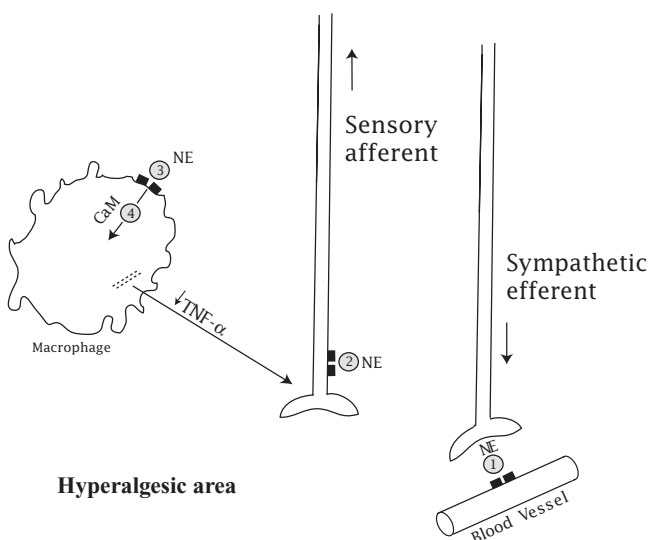
One site of action where this might be of therapeutic importance is the blockade of  $\alpha_1$ -adrenergic receptors mediating vasoconstriction in an affected limb (Figure 1, site 1). The cold skin surface that is characteristic of the late chronic stage of CRPS I may be attributed to a supersensitivity to catecholamines in the affected area.<sup>21</sup> This is also consistent with the increased density of  $\alpha_1$ -adrenergic receptors that have been demonstrated in hyperalgesic skin in CRPS.<sup>22</sup> There is a growing consensus that the supersensitivity follows from a decreased efferent sympathetic activity in the late stages of CRPS.<sup>2,12,23</sup>

A second locus at which an  $\alpha$ -adrenergic antagonist might reduce the severity of CRPS I symptoms is through blockade of the adrenergic receptors that have been found to populate afferent nerve endings, and which mediate a catecholamine-induced stimulation of A $\delta$  and C fibers<sup>2,12,17,22,24</sup> (Figure 1, site 2). Blockade of

these receptors may be responsible for the fact that patients 1 through 3 experienced relief of symptoms within a few days of the initiation of PBZ treatment; this, in turn, may have facilitated movement maneuvers that contributed to clinical improvement. The prompt relief of symptoms may be analogous to the immediate, transient decrease in pain in the diagnostic test for sympathetically maintained pain using intravenous phentolamine, a competitive, reversible inhibitor of  $\alpha$ -adrenergic receptors.<sup>25</sup> However, as noted above, PBZ produces a long-lasting blockade of  $\alpha$ -adrenergic receptors by its noncompetitive, irreversible action.<sup>10</sup>

Additionally, PBZ may have a potential role in suppressing the contribution of proinflammatory cytokines in the CRPS syndrome. Substance P, interleukins 1 $\beta$  and 6, and tumor necrosis factor alpha (TNF- $\alpha$ ) have been implicated as mediators that result in increased sensitivity of afferent neurons.<sup>2,12,26,27</sup> PBZ has been demonstrated to suppress the release of TNF- $\alpha$  in endotoxin-treated mice.<sup>28,29</sup> And, TNF production by macrophages appears to be augmented by  $\alpha_2$ -adrenergic agonists;<sup>30,31</sup> this could represent another potential target for PBZ blockade (Figure 1, site 3). Finally, another potential target relates to the fact that TNF production by macrophages is under calmodulin control,<sup>32</sup> and PBZ is a potent inhibitor of calmodulin<sup>28,33,34</sup> (Figure 1, site 4). The possible suppression of TNF production by PBZ is of particular interest in view of the fact that another inhibitor of TNF elaboration, thalidomide, is known to have therapeutic efficacy in CRPS.<sup>35-37</sup>

A comment is warranted regarding an apparent paradox in the use of an adrenergic receptor antagonist in a syndrome that appears to be associated, at least in its later stages, with decreased efferent sympathetic nerve activity.<sup>2,12,23</sup> A favorable early response to PBZ may result from adrenergic receptor blockade in areas of skin or deeper structures that have become supersensitive to catecholamines, as outlined above. It is possible that escalations in the dose of PBZ may become counterproductive by further reducing sympathetic efferent effects, thereby maintaining or worsening the pathology. This proposal is highly speculative but, if valid, may help to explain the fact that the potential value of PBZ in CRPS is not recognized at this time; also, higher doses would be associated with increased side effects that would lead to discontinuation of treatment. In this connection, it is of interest that patients 1, 2, and 3 demonstrated early favorable responses on relatively low doses of PBZ (10 mg/day), and patients 1 and 2 have been maintained on 10 mg



**Figure 1.** Depiction of possible sites of action of phenoxybenzamine in the suppression of neuropathic pain. (site 1) Blockade of norepinephrine (NE) effects on  $\alpha_1$ -adrenergic receptors on blood vessels, thereby promoting vasodilation; (site 2) blockade of adrenergic receptors that populate afferent sensory fibers; (site 3) blockade of  $\alpha_2$ -adrenergic receptors, on the surface of macrophages, which appear to mediate release of proinflammatory cytokines, including tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ); (site 4) inhibition of calmodulin (CaM), which is involved in the cytokine-release process (schematically based on figure 4 of Jänig and Baron<sup>12</sup>).



every third day for many months. Efficacy at this dosing rate is consistent with the long biological half life of the drug.<sup>11</sup> We speculate that, at this dose level, the possibly favorable effects of PBZ on the suppression of sensitization (perhaps in relation to cytokine diminution) balance the risks from sympathetic efferent blockade.

Certain adverse effects of PBZ may be anticipated on the basis of its blockade of  $\alpha$ -adrenergic receptors. Thus, the more common side effects are postural hypotension, reflex tachycardia, nasal congestion, miosis, and sexual problems in males (inhibition of ejaculation). Less common effects include confusion, drowsiness, dryness of mouth, fatigue, headache, and gastrointestinal irritation.<sup>38,39</sup> These effects are all dose-related, and should respond to an adjustment in dose. Caution may be warranted if PBZ is used in conjunction with other drugs that produce sedative or hypotensive effects, and in patients with medical conditions that may predispose to an adverse hemodynamic reaction, including cerebrovascular or cardiovascular disease. Acutely, the patient experiencing hypotension should remain recumbent, with elevation of legs; and, fluid resuscitation may be considered. The pressor response to sympathomimetic agents is antagonized by PBZ.<sup>38,39</sup> A pharmacodynamic tolerance appears to develop to at least some of the side effects with the continued use of the drug.<sup>39</sup>

Te<sup>40</sup> has discussed the concerns about the fact that animal testing of PBZ at doses that are considerably greater than human recommendations produced gastrointestinal tumors in rats, and mutagenic activity in certain in vitro tests. However, it was also noted that there have been no reports of drug-related tumors in more than 50 years of clinical use of PBZ. Although evidence of tumorigenic effects in animals should not be discounted, and risk/benefits considerations must be factored, such a finding with PBZ is not unprecedented. For example, the 3-hydroxy-3-methylglutaryl-coenzyme reductase inhibitors, atorvastatin, lovastatin, rosuvastatin, and simvastatin are all carcinogenic in animals at above-clinical doses, but have no recognized human risks, in that regard.<sup>38</sup> Also, PBZ has not been given a “black box” warning, as in the case of the antibiotic, metronidazole, which is known to be carcinogenic in rats and mice, but not in humans.

In summary, we were prompted to report our small case series because of accumulating evidence that may suggest a mechanistic basis for a possible therapeutic value of PBZ in the treatment of CRPS, and because its

possible value in CRPS may be underappreciated. It is obvious that our report suffers from the small number of patients that were followed, and no conclusions can be drawn about the efficacy of PBZ for CRPS. However, positive features are that the drug is readily available, and it has been used chronically in our series and other trials.<sup>7,9,40</sup> For example, PBZ is an accepted treatment for benign prostatic hypertrophy, although it is not labeled for that use.<sup>39</sup> In view of its comparatively mild and predictable side effects, which are clearly attributable to  $\alpha$ -adrenergic blockade (dizziness, nasal congestion, etc.), PBZ may represent an option in a refractory case of CRPS, before resorting to a more toxic alternative, such as thalidomide.

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