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Reflex Sympathetic Dystrophy Treated With Gabapentin

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The use of the recently released anticonvulsant, gabapentin (Neurontin), in the treatment of severe and refractory reflex sympathetic dystrophy (RSD) pain in six patients ranging in age from 42 to 68 years is reported. Satisfactory pain relief obtained in all six patients suggests that this medication is an effective treatment for RSD pain. In addition to pain control, early evidence of disease reversal in these patients is suggested. Patient 6 is the first documented case of successful treatment and cure of the RSD pain syndrome using gabapentin alone. Specifically, reduced hyperpathia, allodynia, hyperalgesia, and early reversal of skin and soft tissue manifestations were noted. Gabapentin was chosen because it has properties similar to other anticonvulsant drugs and because previous studies have shown that it is well tolerated and appears to have a benign efficacy-to-toxicity ratio. It was considered an acceptable and compassionate therapeutic choice because previous medical and surgical approaches had been ineffective for these patients, who represent the first case series documenting the use of gabapentin for pain management. Presently, the mechanism of pain relief in these patients is unknown. In this article, the pathophysiology of RSD is discussed, and a mechanism by which gabapentin provides pain relief is proposed. In view of encouraging results in these and other RSD patients, further scientific investigation is needed to delineate the role of gabapentin in the treatment of reflex sympathetic dystrophy.

REFLEX SYMPATHETIC dystrophy (RSD) and causalgia are generic terms that describe signs and symptoms that follow injury to bone, soft tissue, and nerve. It is a syndrome characterized by severe burning pain, hyperpathia, allodynia, vasomotor and sudomotor changes, edema, stiffness, and discoloration; if left untreated, it may progress to fixed trophic changes.[1] It typically occurs in an extremity and can result from trauma,[2,3] inflammatory disorders, myocardial infarction, cerebral infarction, osteoarthritis, degenerative joint disease, frostbite, burns, drugs (particularly phenobarbital),[4,5] malignancy, and paraneoplastic syndromes.[6] No known cause is identified in approximately 35% of the cases of RSD.

The burning pain, which may begin within minutes or hours after the injury, is often inordinately intense and completely out of proportion to the original injury. Certain aspects of the syndrome had been previously described,[7-9] but the breadth of the syndrome was not recognized until 1864 when Mitchell and colleagues[10] described their experiences with Civil War wounded. Since most of the burning pain that Mitchell described resulted from nerve trauma, he labeled the condition "causalgia."[10] Characteristically, the initial pain may be confined to a peripheral nerve or specific vascular distribution, but if not treated promptly or effectively, the syndrome will grow beyond the original area of injury, sometimes even spreading to involve the opposite extremity. The syndrome is arbitrarily divided into three stages, but since the condition represents a spectrum, few patients exhibit all the signs and symptoms in the same order.[11]

The acute stage begins at the time of injury, lasts for several weeks to months, and is characterized by aching and burning pain restricted to a vascular, nerve, or root territory. Redness, edema, and decreased range of motion may also be seen in this stage.

The dystrophic stage begins approximately 3 months after the injury and is characterized by pain extending outside of the original vascular area or dermatome of injury. There may be increased joint thickness, tenderness, and stiffness, and the hyperpathia and swelling is more pronounced. Some muscle wasting and osteoporosis may be seen by the dystrophic stage.

The atrophic stage represents end-stage RSD. It usually develops after 6 months of RSD. Pain is usually intense but may be less severe than in the previous stages. The skin is customarily cyanotic, pale, and cool. Conspicuous irreversible trophic changes are evident in the skin and subcutaneous tissues. The skin has a smooth, glossy appearance, with loss of the usual skin folds and wrinkles. The joints are typically thick and tender, and joint motion is more restricted. In this stage, muscle wasting and osteoporosis are more evident. Swelling and hyperpathia may be more pronounced.

The mechanism of the development of RSD symptoms is not known, but many of them correlate with sympathetic nervous system activity. In fact, improvement after sympathetic blockade is common. For this reason, most RSD management strategies consist of procedures that will block central or peripheral sympathetic activity to decrease pain intensity and reverse some of the tissue changes of reflex sympathetic dystrophy.

Gabapentin (Neurontin[a]), an anticonvulsant introduced in February 1994, has been recognized as an effective, adjunctive therapy with other antiepileptic drugs for partial seizures with or without secondary generalization. It is approved for patients with epilepsy over the age of 12 years.[12-14] Gabapentin is available in 100-, 300-, or 400-mg capsules and can be taken with or without food. The effective dose range is 300 to 600mg three times per day. The usual starting dose is one 300-mg capsule taken on day 1, two 300-mg capsules on day 2, and three 300-mg capsules on day 3.[15]

Common side effects of gabapentin include somnolence, dizziness, ataxia, and fatigue. Gabapentin, a structural analogue of γ-aminobutyric acid (GABA), was synthesized as a GABA-mimetic drug that could cross the blood-brain barrier[16] however, its pharmacodynamic mechanism is different from other substances that interact with GABA synapses, such as valproic acid, phenobarbital, benzodiazepines, and vigabatrin. Its binding occurs in the outer layers of the neocortex and the hippocampus, but the receptor and its biochemical function remain undiscovered. Gabapentin does not bind to benzodiazepine.

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glutamate, glycine, $GABA_A$, $GABA_B$, and *N*-methyl aspartate receptors and may have a novel binding site in the nervous system.[17] The drug is absorbed orally without interference by food and reaches peak serum concentrations after 2 to 3 hours. Gabapentin is not bound to plasma proteins and is eliminated only by renal excretion in its original form. It is not metabolized by the liver and does not induce hepatic oxidase enzymes. Because of the absence of hepatic metabolism and lack of protein binding, there are almost no interactions between gabapentin and other drugs. Antacids reduce the bioavailability of the drug up to 24%, which may require an appropriate increase in the dose of gabapentin. Although cimetidine induces a slight decrease in renal excretion, it is not expected to be of clinical significance.[16]

CASE REPORTS

Case 1

A 52-year-old woman developed right arm reflex sympathetic dystrophy after she fell down on November 21, 1991. When she grabbed the railing she wrenched her shoulder and right arm. Subsequently, she experienced gradual onset of burning pain and swelling in her right hand, arm, and shoulder. Six months later, after evaluation by 6 different physicians, RSD was diagnosed. In the ensuing months, 5 stellate ganglion blocks were completed, each resulting in an ipsilateral Horner's syndrome, vasomotor dilatation, and normalization of skin color in the involved extremity. The patient, however, experienced only temporary pain relief. Previous treatments had also included a transcutaneous electrical-nerve stimulation (TENS) unit, physical therapy, peripheral nerve anesthetic blocks, mild to moderate opioid analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), and occupational therapy that resulted in transient improvement only. When seen in our clinic in January 1993, she complained of burning pain in the right hand and wrist, extending to her shoulder. She also experienced cramping and paresthesias of the right arm and hand associated with numbness and throbbing of the fingers. On a verbal pain scale she rated her pain at 8/10 to 10/10 in severity. The pain was made worse by light touch, rubbing, anxiety, fatigue, strong emotions, raising her arm, or driving her car. Besides RSD, her medical history was significant for multiple medication allergies and a secondarily generalized seizure disorder.

Examination revealed a swollen right forearm and hand that was red and exquisitely painful. Her fingers were swollen and finger movement was limited because of flexion deformities. Her skin had a waxy sheen and she withdrew from even the lightest touch by her examiner. The remainder of the examination was significant for findings consistent with rotator cuff tear of the left shoulder. A triple phase bone scan showed symmetric bilateral increased uptake involving the joints of the hands and wrists. The pattern of uptake was consistent with the clinical diagnosis of RSD.

RSD developed in her left arm and hand in September 1993 and the patient experienced major depression. She eventually agreed to treatment with gabapentin, and received the initial 300-mg capsule on May 20, 1994, at 5PM. Within 2 hours, she had complete relief of pain. She experienced euphoria, mild disorientation, dizziness, and drowsiness. After her second 300-mg gabapentin capsule, she developed a slight headache and a "tight hat band" sensation. She experienced leg cramps and diarrhea after the third dose. (The leg cramps responded to baclofen, but have since resolved.) By day 3 of treatment, the diarrhea was gone and her mood had improved; she awakened with a feeling of increased energy. On day 4, she developed pruritus which was mostly relieved by diphenhydramine HCl. On day 10 of gabapentin therapy, she held her grand nephew for the first time. By day 15, she reported only slight burning in the right upper extremity, increased finger movement, and improved handwriting. Occupational therapy sessions subsequently were less painful, and her therapist (who was unaware of the gabapentin therapy) observed that after a year of treatment, the patient was finally showing improved range of motion. Follow-up examinations showed complete disappearance of allodynia, and hyperesthesia in her right hand. Approximately one month after she began gabapentin therapy, the skin color and texture of her right hand was normal, she had regained use of her middle finger (which previously had been immobilized by the RSD), and she had a strong (5−/5), pain-free grasp.

During the first week of therapy, the euphoria and disorientation gradually diminished; nevertheless, the patient's mood improvement was almost as consequential as her pain relief. She began dressing neatly, wearing make-up and dieting, and she started an exercise program. Family and friends were now able to touch and hug her without inducing pain. Finally, she began a support group for other RSD patients.

Case 2

A 42-year-old woman was referred for evaluation and treatment of RSD of her left arm after she fell and dislocated her elbow on November 14, 1992. The arm was placed in a cast, but she experienced severe pain in her left hand and arm, which was swollen and red when the cast was removed on December 12, 1992. A repeat x-ray showed continued partial elbow dislocation with a small chip fracture. In February 1993, she was told that she had RSD; she was unable to care for her disabled child, or to drive or to curl her hair. Past treatments consisted of ibuprofen 400 mg four times daily, an elbow and hand brace, and a TENS unit. Her medical history was significant for glaucoma and decreased visual acuity.

Upon presentation, her left shoulder, arm, and hand pain was described as 8-9/10 on a verbal pain scale of severity. The shoulder pain was piercing and burning, and the elbow pain was stabbing in nature. She also described a subjective sensation of cold and burning in her hand and arm. Finger pain was accompanied by tightness and numbness. Rubbing, vibration, light touch, straining, or cold temperatures aggravated the pain.

Her left upper extremity was cold to touch and the mottled skin had a bluish hue. The hand and fingers had a white, glossy sheen and there were flexion contractures. Elbow extension was painful and limited to 70°. Her grasp was 3+/5, finger abduction was markedly restricted, and wrist dorsiflexion was 4/5 but was limited by pain. Allodynia and hyperpathia were present in the left arm and hand. Additionally, it was noted that she had sensory loss to pin prick and temperature in the ring and little finger of the left hand

Initial management of the RSD included stellate ganglion blocks, which provided significant reduction of her pain and temporary reversal of her other symptoms. Peripheral anesthetic nerve blocks gradually reduced her hand pain and physical therapy maintained limited extremity mobility.

After appropriate discussion, the patient consented to a trial of gabapentin therapy. After taking only one 300-mg gabapentin capsule in late May 1994, the patient reported that her pain intensity dropped to a tolerable 1-2/10 severity on a verbal pain scale. With her second capsule, she noted increased throbbing and enhanced warmth in her left arm and hand. Associated with this warmth was a change in skin color and resolution of the mottled appearance that had been present in her left upper extremity for years. Additionally, she noted a moderate reduction in arm swelling and reported increased finger range of motion and touch sensation. Initial side effects included diarrhea, euphoria, giddiness, dizziness, mild disorientation, and leg cramps. The diarrhea ceased after 24 hours and the euphoria, giddiness, and disorientation resolved after the first week of therapy. Reduced extremity pain was accompanied by an increase in temperature from 34°C to a maximum of 37°C. This patient twice had dramatic worsening of her pain—once when she missed two doses of gabapentin and once when ciproheptadine, a serotonin antagonist that was used to treat her migraine headaches, resulted in a temporary loss of pain control.

Case 3

A 57-year-old woman medical transcriptionist developed severe pain in the right foot in July 1991. To understand what was being said on tapes that she transcribed, she rewound them repeatedly, using her right foot. Her pain syndrome was diagnosed as posterior tibial nerve entrapment and pain was relieved only temporarily by a surgical procedure. X-rays of her foot and magnetic resonance imaging (MRI) of the back obtained in 1993 were negative. Following chiropractic therapy in January 1994 (to correct a leg length discrepancy), the patient also developed severe right back, groin, and hip pain. On presentation, she complained of constant, severe pain (8-10/10) in the right foot. The right knee pain was described as "suffocating." Her back pain was dull and stabbing; the pain increased with leg movement or ambulation.

At initial evaluation she was taking no medications, but past treatments had included NSAIDs. Additionally, she had received 4 anesthetic nerve blocks at a major pain center. The staging questionnaire established that she was in the atrophic stage of RSD. Otherwise, she was in excellent health, without any known medical problems.

Examination showed evidence of previous third-degree burns of the right anteromedial leg. The skin on the right foot was smooth and her toenails were coarse. She demonstrated allodynia, hyperesthesia, hyperalgesia, and hyperpathia of the right foot. She could not extend her knee completely and palpation of the medial aspect of the knee and the lumbar spine area caused pain. Straight leg raising was negative. The neurological examination was otherwise within normal limits. A triple phase bone scan showed bilateral diffusely increased uptake of the radiotracer in the joints of the left forefoot and hindfoot as well as along the calcaneal surface consistent with RSD.

After consent was obtained, the patient began her first course of gabapentin therapy at 300 mg three times a day in May 1994. She reported pain relief in her right leg, but her foot was most improved. Subsequently, she quantified her pain relief as "good." Other than feeling groggy, the patient experienced few adverse effects from gabapentin therapy. This side effect has completely resolved.

Case 4

A 45-year-old woman was referred for treatment of RSD of both lower extremities. She was injured in June 1991 when she fell while climbing stairs. Burning pain began almost immediately and was accompanied by swelling and dark discoloration of her left leg. In the first three months after the injury, she experienced stiffness, limited mobility of the affected area, and severe burning and aching at the injury site. Later, she noted increased sensitivity to stimuli, accelerated nail growth, localized edema, muscle spasms, and vasospasm. As time passed, she noted muscle wasting, edema, and hair loss.

On presentation to our clinic she was experiencing intractable pain of the entire left limb. Her treatment included nortriptyline (Pamelor[b]) 25 mg at bedtime. By February 1994, despite a series of intravenous regional sympathetic blocks, she had increased sweating and pain in her right foot. Aerobics and water jogging were prescribed to slow the spread of the RSD, but these activities were routinely too painful to perform. She underwent autonomic testing to determine her potential response to lumbar sympathetic blocks, but she declined this therapy because of apprehension about needle injections. Adaptive behaviors initiated by the patient included tactile desensitization of her foot prior to putting on her sock. Additionally, she wore an oversized shoe and sock to reduce pain caused by their contact with her foot.

The pain in both knees, left foot, and ankle was described as burning, sharp, shooting, squeezing, and needlelike in quality and ranged from 5/10 to 9/10 in intensity on a verbal pain scale. Additionally, leg cramps routinely occurred throughout the night and she experienced burning back spasms. A triphasic bone scan obtained on October 14, 1991, showed diffuse uptake of the radiotracer in the joints of the left forefoot and hindfoot and along the posterior calcaneal surface.

Neurological examination of the left lower extremity was difficult because the patient's pain limited motor testing of her leg and foot. She exhibited a withdrawal response when the examiner attempted to touch her left leg. Her gait was antalgic; she had decreased range of motion of the left foot and ankle joints. The skin of her left leg showed dystrophic changes.

The patient gave her informed consent to pain therapy with gabapentin at a dose of 300 mg three times a day. The following week, she reported a 75% reduction of her pain intensity. Furthermore, she reported that her pain had dropped to 2-3/10 on a verbal pain scale after taking only 3 gabapentin capsules. Adverse effects of fatigue and drowsiness disappeared by the second day of therapy. Additionally, she had spontaneous resolution of back pain after starting gabapentin, but this was shortlived. A repeat bone scan obtained approximately 1 week after implementing gabapentin therapy showed diffuse increased uptake involving the joints of both feet. The patient continued to have excellent pain control while taking gabapentin therapy.

Case 5

This patient is a teacher who developed RSD of the right upper extremity after she fell on February 2, 1993. A comminuted Colles' fracture of her right wrist resulted in such severe pain that she would not allow the physician to touch her hand or wrist. External fixation of her wrist was completed in March with removal of the last of the pins on May 3, 1993. During the first 3 months, she experienced severe burning pain, aching, and stiffness at the injury site. Subsequently, she also noted increasing sensitivity to stimulus, more diffuse pain, accelerated hair and nail growth, localized edema, muscle spasm, and vasospasm in her right upper extremity. She reported pain in the right side of her neck, shoulder, rib cage, arm, forearm, and wrist. The shoulder verbal pain scale was 5/10 in severity and the wrist pain was rated at 10/10. She described a steel band–like sensation extending from her shoulder to her wrist when she moved her arm. Furthermore, she reported aggravation of her pain with vibration, fatigue, sudden movements, and lack of sleep. Additionally, 4 months before her initial evaluation, she had developed pain in the left hand.

Physical findings were consistent with the atrophic stage of RSD. Neurological examination showed weakness and limited motion of the interphalangeal joints of her right hand. She had mild atrophy and weakness of the right triceps muscle. Besides allodynia and hyperpathia, the patient demonstrated decreased pin prick and temperature sensation in the thumb and index finger of the left hand. Musculoskeletal examination of the right shoulder and neck showed trigger point tenderness and palpable