

# Use of Oxcarbazepine to Treat a Pediatric Patient With Resistant Complex Regional Pain Syndrome

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**Abstract:** We describe a 12-year-old patient with severe, protracted complex regional pain syndrome type I. His pain did not respond to gabapentin, amitriptyline, physical therapy, opioids, or nonsteroidal drugs. Sympathetic or regional block was not attempted because of persistent bacteremia and severe local sepsis. His pain responded dramatically to the addition of oxcarbazepine, with rapid improvement in his symptoms and functional status. We suggest that oxcarbazepine might be a useful adjunct in the treatment of gabapentin-resistant complex regional pain syndrome type I in children and should be considered.

**Perspective:** Oxcarbazepine's antinociceptive effect is mediated via sodium channel inhibition in neuropathic models and by inhibition of substance P and prostaglandins in anti-inflammatory models. The efficacy of oxcarbazepine in this patient might be attributable to these mechanisms or possibly to synergism with either gabapentin or the anti-inflammatory effects produced by amitriptyline.

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**Key words:** Child, CRPS, oxcarbazepine, gabapentin.

Complex regional pain syndrome type I (CRPS-I) occurs in both adults and children, although with different characteristics. Pediatric CRPS differs from adult CRPS in that it is 6 times more common in the lower limb compared with the upper limb, has a 7:1 female:male ratio, and frequently resolves completely.<sup>3</sup> Active physical therapy with restoration of limb function is the mainstay of therapy in children, and effective pain control might be necessary to facilitate treatment. Cognitive-behavioral therapy and attention to individual and family psychological issues are important aspects of management.<sup>20,21,25</sup>

We describe a pediatric patient with severe, protracted CRPS-I caused by tibial osteomyelitis. Despite aggressive treatment, his condition was complicated by septic arthritis of the hip, soft tissue infection, and femoral and sciatic neuritis. The pain failed to respond to gabapentin, amitriptyline, large doses of opioids, and physical therapy. His symptoms resolved rapidly after the initiation of oxcarbazepine therapy. We are not aware of any reports describing the successful treatment of gabapentin-resistant CRPS-I with oxcarbazepine in children.

## Case Report

A 12-year-old boy who weighed 72 kg presented to an outside hospital with a 5-day history of fever, left knee pain, loose stool, vomiting, and rash. He was treated for suspected Kawasaki disease with intravenous immunoglobulin and high-dose aspirin. His fever persisted, and his knee pain got worse. His blood culture grew oxacillin-sensitive *Staphylococcus aureus*, and he was transferred to the pediatric intensive care unit at our institution for management of hypotension and sepsis. After fluid resuscitation, a magnetic resonance imaging scan of his left leg showed proximal tibial osteomyelitis. Surgical incision and drainage of his tibia showed necrotic material without any frank pus.

The patient remained febrile, and 4 days later he developed pain of a different intensity and quality in his left thigh, leg, and foot that was superimposed on his dull leg pain. This pain was intermittent, of a burning nature, and radiated down his leg into his foot and big toe. It lasted approximately 30 seconds to 1 minute and would cause him to suddenly clutch his leg and cry out loudly several times a day. He was extremely anxious and afraid of these painful episodes. Physical examination showed edema of his left foot with tactile allodynia and mechanical hyperesthesia over his big toe and the medial plantar surface of his foot, corresponding to territory served by the superficial peroneal and medial plantar nerves. He also had pain with flexion and extension of his foot and big toe, accompanied by a decreased range of motion. The Pediatric Acute Pain Service was consulted, and the diagnosis of CRPS-I was made.

Before the onset of his CRPS-related pain, he was being treated with intravenous morphine sulfate and oral oxycodone as needed. Treatment focusing on his CRPS pain

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included methadone (10 mg 3 times daily), gabapentin (600 mg 3 times daily), amitriptyline (25 mg at night), and a 5% lidocaine patch applied to his left foot and big toe. The lidocaine patch provided some relief but was discontinued at the patient's request because of his discomfort associated with placement and removal of the patch. Physical therapy was initiated to assist with desensitization and to increase his range of motion, but it was limited by anxiety, pain, and multiple surgical debridements.

Four days after the onset of his CRPS pain, he developed progressive left hip pain exacerbated by weight bearing, which was accompanied by a decreased range of motion of his hip joint. During the next 5 weeks he developed fluid in the left hip joint, osteomyelitis of the femoral head with avascular necrosis, pelvic and quadriceps myositis with the formation of a small abscess, and femoral and sciatic neuritis. Treatment included open incision and drainage of his septic hip joint, consultation with the pediatric infectious disease team, and multiple courses of intravenous antibiotics. Despite these interventions, he remained febrile, and his pain persisted.

The patient's analgesic regimen was adjusted in stepwise fashion during the next 5 weeks in an attempt to achieve control of his symptoms. Breakthrough pain was treated with oxycodone, morphine sulfate, hydromorphone, and intravenous ketorolac. Despite ongoing treatment with gabapentin (1200 mg 3 times a day), amitriptyline (75 mg at night), and opioids (methadone 130 mg/day orally and hydromorphone via patient-controlled analgesia), his symptoms did not subside. His pain improved slightly with a combination of ketorolac and lorazepam, but this was not consistent.

Oxcarbazepine (75 mg twice a day) was then added to his regimen. The dose was titrated up to 150 mg twice a day (4.1 mg/kg/day), with a dramatic decrease in the frequency and intensity of his pain and improvement of allodynia and hyperesthesia within 4 days of initiation of therapy. He was able to tolerate the lidocaine patch, take a more active role in his physical therapy, and place his foot on the ground with little discomfort. His pain continued to improve, and his infective process gradually resolved during the next month. He was discharged to inpatient rehabilitation on gabapentin, oxcarbazepine, amitriptyline, citalopram, and a methadone taper schedule. He remained on intravenous antibiotics for another month while undergoing rehabilitation.

Two weeks after his discharge from rehabilitation he was seen in our pain clinic and was able to walk and wear shoes with only minimal discomfort in his left foot. Physical examination of his feet did not reveal any edema, allodynia, or hyperesthesia. He was weaned from all his medications during the next few months and remained free of symptoms a year later.

## Discussion

Anticonvulsant drugs are commonly used to treat neuropathic pain. They might inhibit various biochemical targets invoked by neural injury such as sodium channel up-regulation and proliferation, calcium channel acti-

vation, inhibitory neurotransmitters, and glutamate-induced excitation.<sup>1,10,13</sup>

Gabapentin is effective in treating pain caused by postherpetic neuralgia and painful diabetic neuropathy; it can also be effective in treating other neuropathic pain syndromes.<sup>2,17</sup> Its exact mechanism of action is unknown, but it has been shown to inhibit high-voltage-activated calcium conductance.<sup>23</sup>

Oxcarbazepine is an anticonvulsant that is effective in trigeminal neuralgia and neuropathic pain.<sup>5,7,11,12,18,24</sup> Oxcarbazepine decreases abnormal high-frequency nerve discharges seen in animal models of peripheral neuropathy.<sup>12</sup> Oxcarbazepine might act at multiple target sites to control neuropathic pain, because it has been shown to inhibit voltage-sensitive sodium channels as well as high-voltage-activated calcium channels.<sup>15,22</sup> Recent open-label trials suggested that oxcarbazepine is effective in treating painful diabetic neuropathy, painful neuropathy, and CRPS refractory to gabapentin in adults.<sup>5,18,24</sup>

Our patient had severe, refractory CRPS-I with a persistent infectious process, and he did not respond to opioids, gabapentin, amitriptyline, nonsteroidal anti-inflammatory drugs, and physical therapy. Physical therapy proved to be difficult to implement in our patient, because his severe pain and extreme anxiety limited his ability to cooperate with treatment.

We were reluctant to use a regional anesthetic technique for pain control because of his extensive and persistent sepsis. Evidence for the role of local anesthetic sympathetic blockade for the treatment of CRPS is based mainly on case series. A systematic review of the literature revealed that less than one third of patients obtained full pain relief, and the lack of control groups might have overestimated the treatment response.<sup>8</sup> In addition, a blinded meta-analysis of randomized clinical trials for the treatment of CRPS showed that the quality-weighted summary effect size of sympathetic suppressors or of intravenous regional anesthesia was not significant.<sup>16</sup> A recent novel approach with a combination of continuous peripheral nerve block for 96 hours and intravenous regional anesthesia with buflomedil showed 100% success in treating 13 children with recurrent CRPS-1. No recurrence of pain was observed during the 2-month follow-up period.<sup>9</sup>

It is worthy of note that Sherry et al<sup>19</sup> have reported high rates of recovery of limb function by using a regimen of intensive directed exercises, hydrotherapy, desensitization, and psychological counseling, but no medications or nerve blocks.

We do not know whether the dramatic response to oxcarbazepine is attributable solely to its therapeutic effect, or whether it is in fact due to synergism with gabapentin or amitriptyline. Tricyclic antidepressants and the carboxamides (carbamazepine and oxcarbazepine) are structurally related and share the ability to modify inflammatory response by inhibition of mediators such as substance P and prostaglandin E<sub>2</sub>; therefore, an anti-inflammatory mechanism of action of oxcarbazepine is also plausible.<sup>6,14,26</sup> Spontaneous resolution of the infectious process and accompanying neuritis could have contributed to the de-

crease in his pain after the addition of oxcarbazepine; however, the rapid improvement in pain and functional status suggests that oxcarbazepine was instrumental in achieving pain control and facilitating rehabilitation.

In summary, oxcarbazepine might be a useful alternative for the treatment of CRPS-I in children who do not

respond to gabapentin. Oxcarbazepine has been shown to be safe and efficacious for children with seizure disorders.<sup>4</sup> Additional prospective studies are necessary to establish safety and tolerability in children with CRPS and to compare its efficacy to gabapentin as a first-line agent in the treatment of CRPS in children.

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