Clinical note

Case report: Long-standing CRPS relieved by a cephalosporin antibiotic

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Abstract

We describe a young woman who had suffered from treatment refractory Complex Regional Pain Syndrome (CRPS) for 6 years before receiving antibiotic treatment with cefadroxil (a cephalosporin derivative) for a minor infection. Cefadroxil reduced the patient’s pain and motor dysfunction (dystonia and impaired voluntary movement) within days, the pain and motor disorder returned when cefadroxil was discontinued, and both again abated when cefadroxil was re-instituted. The patient has now had symptom relief for over 3 years on continuing cefadroxil therapy. We discuss this case in the context of previous reports of antibiotic treatment relieving neuropathic pain in experimental animals.

Case report

The patient is a young right-handed woman who developed CRPS in the left upper extremity when she was 24 years old. The injury occurred in February 2004 while her arm was elevated and stretched as she pulled a sweater over her head. She reports feeling a slightly painful “popping” sensation at the time of injury and points to the posterior shoulder region as its location.

A report of an electrodiagnostic examination performed in May 2004 stated “She can only abduct the left arm from the side of her body to about 50\(^0\). There is virtually no ability to elevate the left arm above the horizontal plane. The left hand remains visibly edematous. The median, radial and ulnar sensory nerve action potentials were studied bilaterally and no abnormalities were seen. However, there was some relative reduction in the sensory nerve action potential amplitudes on the left side. The median and ulnar
nerve motor conduction velocities were studied bilaterally and no abnormalities were seen. The distal right and left ulnar F-wave latencies were comparable in value. EMG of the left biceps and left abductor pollicis brevis was normal. “

Her first examination in our clinic was 10 months after the precipitating injury. Her history revealed the following. She was previously well aside from routine tonsillectomy and appendectomy. She reported that pain and weakness in the left extremity were evident the morning after the injury and that within a few days her entire arm and hand had became painful and allodynic to touch, bluish-purplish in color, and that the whole arm and the left breast were swollen. She described the pain as “burning” and “pulling”, continuous but fluctuating, and with an average intensity of 8.5 on a 0-10 numerical rating scale (NRS). The tactile allodynia was severe, with contact from clothing unbearable and pain being felt when a breeze blew across the skin. She reported that her pain was worsened by cold, but it is not certain that this reflected cutaneous cold-allodynia. She stressed that the pain and alldynia interfered with her sleep to the point that her work and daily activities were badly compromised. The patient reported that the fingernails of the affected hand grew abnormally quickly and were brittle. The patient reported that her hand and arm was unresponsive to motor commands and that she could lift her arm only slightly and that the attempt required great effort and induced a coarse tremor. She complained of occasional spontaneous convulsive arm movements.

Examination revealed minor atrophy of the left arm muscles, skin discoloration, tremor, and tactile allodynia on the hand and forearm. The left hand was slightly warmer than the right. The hair on the dorsal hand and forearm was darker and coarser than on the other side. She held the arm in a flexed position next to her body for protection. The
hand was in a stiff claw-like posture and she could not move her fingers or thumb. (Over the following three years, this progressed to a posture with all fingers flexed and the thumb locked in adduction and trapping the index finger – see Fig. 1A). Subsequent investigations included blood test for autoimmune disease, venogram, brain, cervical, thoracic, and brachial plexus MRI, brachial plexus and lumbar CT scan, and lumbar puncture: none of these was informative. Psychological evaluation in February 2005 revealed no evidence of depression but significant anxiety with regard to her future (work, health, sleep). She had had episodes of panic attack and agoraphobia. Her daily activities were dominated by her preoccupation with pain and the loss of use of her arm. Subsequent evaluation by medical specialists in neurology, psychiatry, neurosurgery, and anesthesia confirmed the diagnosis of CRPS. The patient refused an offer to have a spinal stimulator installed.

The following treatments were tried without success: stellate ganglion blocks, intra-articular shoulder injections, three suprascapular nerve root blocks, extensive physiotherapy including mirror box therapy, TENS, and a hand brace. Individual psychotherapy was conducted with the aim of reducing anxiety and improving coping skills. She attended a group therapy self-management program. Medication trials included NSAIDs, tricyclic antidepressants, gabapentin, pregabalin, venlafaxine, opioids (codeine, oxycodone, and methadone), topiramate, calcitonin, and intravenous lidocaine, none of which afforded her any useful relief. Her pain and disability were pronounced and she struggled to cope. After participating in a clinical trial of smoked cannabis [15], she continued to use cannabis because it helped with sleep and reduced her tremor and convulsive arm movements (without any effect on the pain).
In March 2010 she was started on cefadroxil 500mg PO b.i.d. for an infection under the lateral fold of the fingernail on digit IV of her left (CRPS) hand. Starting within 1-2 days she noted a gradual reduction in dystonia (reduced clenching of the fingers and thumb, and improved voluntary movement of her arm) and a lessening of her fatigue ("more energy"). Over the next several days her motor function continued to improve and she noted a reduction in the intensity of her pain and allodynia. Pain, allodynia, and motor symptoms returned within 12 h after she completed her 10 day course of antibiotic treatment.

To further investigate her response to cefadroxil, we performed an unblinded trial of alternating periods of one week on-drug and one week off-drug at the dose that she had used previously. The trial began on July 13, 2010 with the patient keeping a pain diary in which she recorded daily average pain-at-rest on a 0-10 NRS (where 0 = no pain, and 10 = worse pain imaginable). She also made daily entries of the average severity of her motor dysfunction using a 0-10 scale that she devised. Cefadroxil was resumed and six days later the trial began (Fig. 2). For the first six days on drug her pain ranged from 3.5-4.0, while her motor dysfunction was steady at a score of 4.0. When drug was withdrawn, her pain and motor dysfunction worsened quickly (starting within 1 day), with her pain score climbing to 8.0 and her motor score to 7.5. Re-instating drug resulted in improved pain scores and motor scores within 2-3 days. Discontinuing drug for a second time again resulted in a rapid (1 day) worsening of pain and motor scores. Re-instating drug for a second time again resulted in marked symptom improvement within a period of 2-3 days.

At the conclusion of this trial and after consulting infectious disease specialists
and discussing the risks of prolonged antibiotic exposure, the decision was made to continue cefadroxil at 500 mg b.i.d. Subsequent, efforts to use intermittent dosing (one week on, one week off) saw continuing rapid worsening of symptoms during the off week. Reducing the dose to 250 mg b.i.d. resulted in symptoms returning. She has remained on cefadroxil 500 mg b.i.d. ever since with regular follow-up examinations every four months.

While on cefadroxil, the patient reports loose stools, difficulty initiating sleep, and mild irritability. She describes her sleep problem as serious and ascribes it to the feeling of “having more energy”. She now takes an over-the-counter probiotic supplement (Bio-K+; Bio-K Plus International Inc., Laval, QC, Canada) which corrects her bowel function. She continues to use cannabis to help her sleep (her cannabis use is under the aegis of the Canadian Marihuana for Medical Purposes Regulations). An informal trial of oral nabilone as a sleep aide was unsuccessful.

When last seen (November 2013; 3 yr 8 mo after starting cefadroxil) she rated her pain-at-rest as 0/10 but said that the pain increases to 3/10 with prolonged use of her arm/hand. She had nearly normal function of the left arm and she noted that her left biceps had returned to near normal size; however, her left forearm muscles were still atrophied. The nails were normal, skin color was normal, and the hair on the dorsal hand and forearm was normal or very nearly so. The hand (Fig. 1B) was greatly improved, although not fully functional. The fingers were unclenched but now distorted by disuse contractures. The thumb was mobile. The intrinsic muscles of the hand were atrophied. She continues to take cefadroxil 500 mg twice daily and has had no serious adverse effects from therapy. She is active and doing yoga. She left her previous job and started
her own business. She sleeps well with continued use of cannabis before bedtime. She states that while she was initially dominated by her condition, she “doesn’t think about it any more”. When asked what she thought the most significant results of cefadroxil therapy had been, she noted the elimination of tactile allodynia and the relief from her motor dysfunction.

Discussion

The patient’s diagnosis of CRPS is based on the Budapest clinical criteria [4]. The onset with an out-stretched arm and the nerve conduction studies suggest that the precipitating event was a brachial plexus stretch injury, in which case the diagnosis would be CRPS Type II. An alternative diagnosis of acute onset brachial plexus neuritis (Parsonage-Turner syndrome) can not be excluded but seems unlikely given the tight link between symptom onset and a precipitating event that could have caused a brachial plexus stretch injury. Moreover, the long duration (over six years) of her condition and the pronounced involvement of the lower extremity are atypical for Parsonage-Turner syndrome [17].

The patient received ceftriaxone in an open-label trial and her responses to treatment are thus subject to the usual uncertainties regarding interpretation. However, the rapid onset of pain relief and motor improvement, the rapid worsening of symptoms upon drug discontinuation, and the rapid re-instatement of symptom relief when treatment was resumed strongly suggest that the symptom relief was due to cefadroxil. The patient had several years of experience with smoked cannabis as a bedtime sleep aide and continued to use cannabis during the drug trial. However, she had never noticed any effect of cannabis on her pain and allodynia. It thus seems unlikely that cannabis had any
role in the analgesic effect.

To our knowledge, this is the first clinical report of neuropathic pain relief following treatment with cefadroxil or any other cephalosporin-like antibiotic. However, studies in laboratory animals have provided considerable evidence for an analgesic effect from the closely related cephalosporin derivative, ceftriaxone.

**Cefadroxil and ceftriaxone**

Cefadroxil (Duricef®, Actavis, Parsippany, NJ) is a first-generation cephalosporin derivative with activity against Gram positive bacteria and, to a lesser extent, Gram negative bacteria. Ceftriaxone (Rocephin®, Genentech, South San Francisco, CA) is a third-generation derivative of cephalosporin with improved activity against Gram negative organisms. Both have the cephalosporin core structure (7- aminocephalosporanic acid) but with different side chains that modify their susceptibility to bacterial degradative enzymes. As for all β-lactam antibiotics, the bactericidal mechanism of action is disruption of bacterial cell wall synthesis via inhibition of peptidoglycan cross-linking [12]. Both cefadroxil and ceftriaxone penetrate the CNS and both are presumably able to cross the perineurial barrier to gain access to peripheral nerve axons. Both will pass easily into the cell-rich region of dorsal root ganglia due to the fenestrated capillaries that are found in this part of the ganglia [10].

In rats, ceftriaxone has no effect on the pain threshold of normal animals but it reverses established neuropathic pain and prevents the pain if given in the period immediately after nerve injury [1, 5, 6, 9, 11]. Glutamate transporter 1 (GLT-1) is expressed by astrocytes and plays a key role in the clearance of glutamate released at
excitatory synapses. Nerve injury decreases the expression of (GLT-1) in the spinal cord dorsal horn and there is very strong evidence that the analgesic effect of ceftriaxone is due to a counter-acting up-regulation of dorsal horn GLT-1 expression [5, 6, 9, 11]. Up-regulation of GLT-1 expression is known to be a property of other cephalosporin derivatives, including cefadroxil, and of other β-lactam antibiotics (including penicillin and amoxicillin) [13]. In vitro assays suggest that there is at least a three-fold difference in potency amongst β-lactam antibiotics in their ability to up-regulate GLT-1 expression [13]; the reason for this is unknown.

Additional evidence from animal experiments suggests that ceftriaxone also has an analgesic effect in inflammatory pain conditions and that this effect is also due to up-regulation of GLT-1 expression [7, 8, 14, 16].

We are aware of only one clinical study of ceftriaxone's analgesic effect. Macaluso et al. [8] gave a single intravenous injection of ceftriaxone, cefazolin (a cephalosporin derivative that is reportedly without effect on GLT-1 expression), or saline to patients 1 h prior to carpal or cubital tunnel nerve decompression surgery and measured the mechanical pain threshold of the plantar surface of the appropriate digits before the injection and 4-6 h after surgery. Postoperatively, patients receiving ceftriaxone had a significant increase in the mechanical pain threshold, while there was no change in threshold in patients treated with saline or cefazolin. The interpretation of this finding is unclear. Firstly, there are no data to indicate whether these patients were suffering from neuropathic pain before or after surgery. Secondly, in the control groups there was no preoperative vs. postoperative change in threshold, indicating that the surgery did not produce inflammatory pain in the areas tested.
Repeated morphine administration produces hyperalgesia and this is blocked by ceftriaxone [2, 11]. Tolerance to the analgesic effect of cannabinoids is also blocked by ceftriaxone [3].

Conclusions
A randomized controlled trial of treatment with either cefadroxil or ceftriaxone in CRPS patients will be required to validate our observations. If our patient’s experience is a guide, then one would be able to judge whether there was a useful pain response within a week or two. It may be important to remember that our patient insists that motor dysfunction responded more rapidly to treatment than the pain; thus a clinical trial should monitor both pain and dystonia. A trial of antibiotic treatment should be safe in patients without allergy or kidney dysfunction but, of course, careful monitoring will be essential. Given the severity of unrelieved pain that is often present in CRPS patients, we believe that even a low incidence of responders would be an important outcome.

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References


Figure legends

Figure 1

Photographs of the affected hand taken in (A) March 2008 prior to antibiotic therapy, and
(B) in November 2013, after 3 years and 8 months of cefadroxil treatment.

Figure 2
Results of the open-label on-drug/off-drug trial. Red lines are the patient’s diary entries of NRS scores of daily average pain-at-rest; black lines are daily dairy scores on the patient’s 0-10 scale of motor dysfunction.
Summary

We report a patient with refractory CRPS who responded to the antibiotic cefadroxil, and consider that cephalosporin antibiotics may have analgesic properties in neuropathic pain.