

Letters

An Effective Treatment of Severe Complex Regional Pain Syndrome Type 1 in a Child Using High Doses of Intrathecal Ziconotide

To the Editor:

Ziconotide (Prialt, Elan Pharmaceuticals Inc., San Diego, CA) is a calcium channel blocker approved by the U.S. Food and Drug Administration for treatment of chronic pain by the intrathecal (IT) route. Although ziconotide has been used for a considerable time in clinical practice, there are only a few reports on its effectiveness and associated side effects. Three published double-blind and placebo-controlled trials demonstrated significant improvement in control of refractory pains and warned of the numerous potential side effects from infusion of IT ziconotide.¹⁻³ There are no reports on effectiveness and side effects of IT ziconotide treatment in a pediatric patient population. Here, we present a difficult case of a now 17-year-old female with long-standing, severe Complex Regional Pain Syndrome (CRPS) type 1, already in trophic phase and with persistent, severe allodynia, who had full resolution of allodynia, improvement of functional capacity, and diminished pain scores when IT infusion of ziconotide was optimized.

Case

A 13-year-old female was first referred with right lower extremity pain following an ankle sprain two months earlier. The pain was described as burning, sharp, shooting, stabbing, throbbing, and was rated 5 on a pain visual analog scale (VAS). Initial examination revealed coldness with allodynia over the lower leg and a foot that was swollen with dry skin and

scaling. Thermographic imaging with a cold pressor test reflected delayed extremity re-warming, and positive response to lumbar sympathetic block confirmed a provisional diagnosis of CRPS type 1, with sympathetically maintained pain. Following short-lasting pain relief from three repeated blocks, she underwent an implant of a tunneled epidural catheter (TEC) and a 10-week infusion of bupivacaine 0.05% and fentanyl 2 µg/ml. This led to improvement in her lower extremity function. The patient was also commenced on terazosin 1 mg twice a day. Upon removal of the TEC, the patient remained asymptomatic and had good leg function.

Four months later, she reinjured the ipsilateral ankle during gym exercises. Pain was rated 4 on the VAS, and there was mild swelling around the lateral malleolus and tenderness with slight palpation. Motor strength had decreased. The patient was placed on a membrane stabilizer, and two weeks later, had even more marked allodynia and hyperalgesia, with decreased range of motion. She was then commenced on baclofen and the decision was made to undertake an extended trial of spinal cord stimulation (SCS). Following placement of SCS, the patient's symptoms were resolving. She was weight bearing and no swelling was apparent in the foot. The allodynia and discoloration were absent. Four weeks later, the spinal cord stimulator was turned off, and after two months, the temporary SCS lead was removed.

Two months later, the patient complained again of a burning dysesthesia, with limited range of motion in the affected ankle. No color or temperature changes were evident. The plan was to restart terazosin and tizanidine with continuing therapy. A few months later, because of continuing and worsening symptoms, a permanent SCS was placed. The patient did well until 10 months later, when



Fig. 1. (A) and (B) CRPS affected foot before and after titration of intrathecal ziconotide. See detailed description in the text.

she reinjured her ankle while riding a mountain bike. She developed a severe exacerbation of her previous symptoms. During the succeeding months, the allodynia extended to the hip. The patient wore no clothing covering the entire leg. The foot assumed an equinus position. She was nonambulatory and developed an exfoliative dermatitis with scaling and desquamation of skin, and cracking of the dermis over the foot, ankle, and lower leg. Although good topographical paresthesias from SCS were felt in the foot and entire leg, she had minimal pain relief. However, when the system was turned off, there was an increase in the burning dysesthesia and deep aching pain. The neurostimulation seemed to have no influence whatsoever on the allodynia and hyperalgesia.

About six months later, an IT catheter was placed for a single shot bupivacaine injection.

The patient was able to move her foot and toes, and had a marked reduction in allodynia and hyperalgesia. With the continuous IT infusion of bupivacaine and sufentanil (unable to tolerate other IT opioids), there was some pain relief, with little influence, however, on the allodynia and hyperalgesia. In addition, some reduction in the patient's symptoms was apparent and VAS pain score was 8.

After about six months, ziconotide was added to the infusion of bupivacaine and sufentanil at 0.5 $\mu\text{g}/\text{day}$. The dose was gradually increased. At 3 $\mu\text{g}/\text{cc}$ of ziconotide, she described her pain as 7 on the VAS and increased her activities, although she was still wheelchair-bound. At 6 μg per day, the edema of the leg and foot were reduced but the skin remained scaly, dystrophic, and fissured, and extreme allodynia was present (Fig. 1). At 14 μg per day, pain level decreased to a rating of 6 and desquamating skin was receding toward the foot. The right foot and ankle were swollen, but there were times when the edema disappeared altogether. One month later, at 18 $\mu\text{g}/\text{day}$ of ziconotide, most of the patient's skin scales had disappeared and the foot was appearing pink. Movements of the hindfoot and forefoot were noted, and the patient was able to sleep in the bed under the cover (VAS of 5 and now on crutches). While still unable to bear weight, the allodynia was almost absent. Two months later, at 24 $\mu\text{g}/\text{day}$ of ziconotide, she was ambulating with little or no allodynia or hyperalgesia (Fig. 1). She rated her pain at 4 on the VAS. The appearance of the leg was almost normal and she had full plantar flexion and partial dorsiflexion, and had no eversion and inversion.

Comment

Although possibly effective,^{2,3} the IT effectiveness of ziconotide in CRPS type 1 has not been studied. We report here a case of severe CRPS type 1, in the trophic phase that was characterized by severe allodynia and hyperalgesia and a profound loss of range of motion in the patient's lower extremity, which improved significantly during gradual titration of ziconotide. The patient reported profound pain relief, suppression of her severe allodynia, and improved range of motion on 24 μg of ziconotide per day. Although previously reported upper limits of ziconotide titration

were 19 μg per day¹ and 21.6 μg per day³, we could not observe any significant side effects during a slow titration of ziconotide. Higher doses yielded additional pain relief and suppression of allodynia. Although there was no objective measurement of the patient's functional capacity, improvement of her function was observed by her parents and attending physician. Just the fact that she went from wheelchair to crutches, and then to almost normal activities without assistance, evidenced a dramatic improvement of her function.

There were no changes made to her other IT medications and no other interventions were applied during ziconotide titration. This suggests that pain relief and improvement in her function was solely related to the titration of ziconotide. This observation suggests that ziconotide may be an effective therapy for advanced CRPS type 1 and that it can be used in the pediatric patient population. It appears that slow titration of ziconotide may still bring benefits in suppression of allodynia and pain relief, even at doses of 24 $\mu\text{g}/\text{day}$, without producing obvious side effects.

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Paraneoplastic Liver Dysfunction in Prostate Cancer

To the Editor:

Paraneoplastic liver dysfunction is an uncommon phenomenon. It is most commonly described with renal cell carcinoma.^{1–3} It has also been reported with soft tissue sarcoma.⁴ A case of metastatic prostate cancer with symptomatic liver dysfunction of no obvious cause is described.

Case

A 64-year-old man was investigated for scrotal pain, lower backache, and raised serum levels of prostatic specific antigen (PSA) in December 2004. Clinical examination was unremarkable. Laboratory tests at the initial evaluation revealed the following: normal complete blood count, blood urea nitrogen, serum creatinine and serum electrolytes; serum PSA: 643.8 $\mu\text{g}/\text{L}$ (normal <4.5); serum total bilirubin: 9 $\mu\text{mol}/\text{L}$ (normal: 0–17); serum alanine transferase (ALT): 22 U/L (normal: 5–40); serum gamma-glutamyl transpeptidase (g-GT): 33 IU/L (normal: 11–50); and serum alkaline phosphatase: 86 U/L (normal: 30–120). A radioisotope bone scan showed widespread bone metastases, and the prostate biopsy demonstrated adenocarcinoma of the prostate, with a Gleason score of 4 + 3.

As he was undergoing assessment, he became jaundiced and developed pruritus in the second week of January 2005. Liver function tests became deranged just before goserelin, a gonadorelin analog, and cyproterone (later stopped after two weeks) were started (Table 1). There was no past history of jaundice, excess alcohol use, blood transfusion, or recent travel abroad. Ultrasound of abdomen showed no liver metastases, common bile duct obstruction or intrahepatic biliary dilatation. A few days before diagnosis, he had been taking ibuprofen, which was later changed to a diclofenac-misoprostol combination for pain in the hip. It was stopped four weeks (mid-February) after liver abnormality was first detected.

Serum levels of PSA dropped to 291.2 $\mu\text{g}/\text{L}$ two months later. However, liver dysfunction