CASE REPORT

Treatment of pediatric chronic pain with tramadol hydrochloride: Siblings with Ehlers-Danlos syndrome – Hypermobility type

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OBJECTIVE: To evaluate the effectiveness of tramadol hydrochloride for the treatment of chronic pain refractory to previous treatment in two pediatric patients.

METHODS: Tramadol hydrochloride was administered (50 mg/day to 150 mg/day) to two siblings with Ehlers-Danlos syndrome – Hypermobility type refractory to previous pharmacological treatments, and changes in pain intensity and physical activity were assessed.

RESULTS: Pain intensity decreased and physical activity improved within days of starting therapy. Positive results have been maintained for 30 months.

CONCLUSIONS: Tramadol hydrochloride was a safe and effective treatment for relieving chronic pain in two pediatric patients suffering from the hypermobility type of Ehlers-Danlos syndrome. No morbidity or side effects were noted during the 30-month follow-up.

Key Words: Chronic pain; Ehlers-Danlos syndrome; Pediatrics; Tramadol

EHLELS-DANLOS SYNDROME

Ehlers-Danlos syndrome (EDS) refers to a group of heritable systemic disorders of connective tissue manifesting joint hypermobility, skin extensibility and tissue fragility. The early onset of chronic pain in childhood or adolescence is a common problem for the participants in the study.

OBJECTIF : Évaluer l’efficacité de l’hydrochlorure de tramadol pour le traitement de la douleur chronique réfractaire à un traitement antérieur chez deux patients pédiatriques.

MÉTHODOLOGIE : De l’hydrochlorure de tramadol a été administré (entre 50 mg/jour et 150 mg/jour) à deux membres d’une fratrie atteints du syndrome d’Ehlers-Danlos avec hypermobilité, réfractaires à des traitements pharmacologiques antérieurs, et les modifications à l’intensité de la douleur et à l’activité physique ont été évaluées.

RÉSULTATS : L’intensité de la douleur a diminué et l’activité physique ont augmenté dans les jours suivant le début du traitement. Les résultats positifs se sont maintenus pendant 30 mois.

CONCLUSION : L’hydrochlorure de tramadol était un traitement sûr et efficace pour soulager la douleur chronique de deux patients pédiatriques atteints du syndrome d’Ehlers-Danlos avec hypermobilité. Aucune morbidité et aucun effet secondaire n’ont été remarqués pendant le suivi de 30 mois.

Le traitement de la douleur pédiatrique chronique par hydrochlorure de tramadol : Les membres d’une fratrie atteints du syndrome d’Ehlers-Danlos avec hypermobilité


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TRAMADOL HYDROCHLORIDE
Tramadol hydrochloride is an aminocephoxanole derivative that displays a weak affinity for the mu opioid receptor and an extremely weak affinity for the delta and kappa opioid receptors (6). It produces an analgesic effect through central actions, and its efficacy lies between codeine and morphine. A re-evaluation of its pharmacology in the 1980s revealed a nonopiod component to its mechanism of action. Two tramadol hydrochloride enantiomers are present: the opioid and serotoninergic activities are associated with the (+) enantiomer, and the noradrenaline modulation effects are associated with the (−) enantiomer. Tramadol hydrochloride is of particular interest because it has relatively few of the side effects seen with nonsteroidal anti-inflammatory drugs (NSAIDs) and other opioids of comparable efficacy. Tramadol hydrochloride has a low potential for respiratory depression, abuse and psychological dependence. Since its clinical introduction in the 1980s in Europe, considerable experience has been gained across a large spectrum of pain states.

CASE PRESENTATIONS
Patient 1 (AC) was born in 1994, and was six years old when he was first seen at the chronic pain clinic at The Hospital for Sick Children in Toronto, Ontario. He had been diagnosed with EDS – Hypermobility type during the previous year. The joints involved with dislocation included his fingers, toes, ankle, knees, elbow and shoulder. He experienced approximately 20 joint dislocations per day. His pain was constant, and his pain intensity was rated as 5 (numerical zero to 10 scale). The pain disturbed his sleep nightly. He had become wheelchair bound and suffered from increased pain when walking. The patient, who weighed 25 kg, took acetaminophen 400 mg four times daily, which he felt helped with the pain. AC had a host of allergies, including codeine (produced hives), hydrocodeone bitartrate (produced hives), ibuprofen (produced pharyngeal edema) and sulfonamides. Comorbid conditions included gastroesophageal reflux, for which he took lansoprazone, and asthma, for which he took salbutamol and sodium cromoglycate. Anaphylaxis from latex exposure was also documented. A recent, brief trial of rofecoxib resulted in an allergic reaction (rash). Furthermore, his mother had confirmed EDS.

In May of 2001, AC was started on tramadol hydrochloride at a dose of 50 mg twice daily. Initial follow-up was at one week by phone, followed by a visit to the clinic at one month. Subsequent clinical follow-up was set at three-month intervals, and is currently every six months. A mid-day dose of 50 mg was added in January 2002, dispensed as required. At the patient’s most recent follow-up in November of 2003, his weight had increased to 43 kg. Due to increased complaints of pain secondary to trauma post-falling, his dose was increased to 50 mg four times daily.

Patient 2 (JC) was born in 1996 and is the brother of AC. He was 3.5 years old when first seen at the chronic pain clinic. He was diagnosed with EDS – Hypermobility type in the year before being seen in our clinic. The joints involved with dislocation included his ankles, knees, shoulder and wrist. He experienced approximately 12 joint dislocations per day. His pain was constant, and pain intensity varied from 8 to 10 (numerical zero to 10 scale). His sleep was disrupted nightly by pain. JC was an active boy who limited his activity when in pain. In the month before coming to the chronic pain clinic, his complaints of joint pain had increased. The patient, who weighed 15 kg, received 240 mg of acetaminophen every 4 h during waking hours. He had documented asthma, for which he took beclomethasone dipropionate and salbutamol puffers. He had a number of recorded environmental allergies. The control of pain at the patient’s initial assessment appeared satisfactory with the use of acetaminophen. This regimen of pain management was maintained until the age of six years, when an alternative pain management strategy was required because of increasing pain, deterioration in sleep and deteriorating performance at school. Comorbid conditions included asthma, which was treated with fluticasone propionate, salmeterol xinafoate and montelukast, and gastroesophageal reflux disease, which was treated with pantoprazole sodium. There was definite concern that JC may have had similar medication allergies (eg, to NSAIDs) as his brother.

In November 2002, JC discontinued acetaminophen and was started on tramadol hydrochloride 5 mg twice daily. Initial follow-up was at one week by phone, followed by a visit to the clinic at two months. At his follow-up in January 2003, JC remained on the same dosage. After JC’s most recent follow-up in November 2003, at which his weight was 26 kg, he remained on the same dosage of 25 mg twice daily.

FINDINGS
AC was maintained on tramadol hydrochloride 50 mg three or four times daily for 30 months, and has consistently decreased his pain scores from a 5 to a 1 or 2 (numerical zero to 10 scale). AC has experienced a sustained and dramatic improvement in school attendance and performance, improved sleep, and the ability to increasingly participate in the activities of daily living (such as walking). Due to the decrease in pain, AC has begun to participate in sports. To quote a written assessment by the mother of AC, “An hour after the first time he took tramadol hydrochloride, he stated that he didn’t hurt anywhere. This was something he hadn’t experienced in a long time. That night when I tucked him into bed, he hugged me and said that he didn’t remember the last time he had no pain all day.”

JC was maintained on a constant dose of tramadol hydrochloride 25 mg twice daily for 12 months, and has consistently decreased his pain from an 8 to 10, to a 5 (numerical zero to 10 scale). Tramadol hydrochloride lessened his pain to the extent that he was able to consistently attend school, and his concentration and performance at school has improved. He is now sleeping consistently at night. To quote a written assessment by the mother of JC, “The first night he had tramadol hydrochloride, he slept through the night and woke happy and rested. He reported that he was pain free. His need for afternoon naps decreased. Some days he states that he only needs one dose of tramadol hydrochloride because he is not hurting. He does not seem to be distracted by pain most of the time. His medication requirements for gastroesophageal reflux disease symptoms have decreased. His pain has been very well...
managed almost all the time with tramadol hydrochloride without any side effects.”

DISCUSSION

In the chronic pain program at The Hospital for Sick Children, a multimodal and multidisciplinary approach is employed to care for children with chronic pain conditions. Many aspects of this care, including psychiatry, physiotherapy and occupational therapy, have been provided to treat these children, but these measures have ultimately failed to adequately control their pain.

Tramadol hydrochloride has many indications for use in both acute and chronic pain states, including cancer (7-9). Its use for acute pain in pediatric surgery has been well-documented, and its safety and efficacy for children over 12 months of age has been shown (10). Rose et al (11) have also shown tramadol hydrochloride to be safe and effective for the treatment of pain of seven to 30 days in duration in children. Sacheti et al (1) have referred to its possible use in patients with EDS, but until now, there have been no reports of the use of tramadol hydrochloride in EDS or for the pediatric patient with chronic pain.

The two pediatric patients in the present study had EDS – Hypermobility type and experienced chronic daily pain due to multiple daily joint dislocations. These patients could not be prescribed any of the conventional narcotics or NSAIDs due to multiple drug allergies; this point is of note because both of the patients had failed pain control at six years of age with over-the-counter analgesics.

A trial of tramadol hydrochloride was one of the few alternatives left in the care of these children. Tramadol hydrochloride has a good safety profile with a low potential for respiratory depression, abuse and psychological dependence. With the potential of long-term employment of this medication in these young patients, safety was paramount in our thoughts. Tramadol hydrochloride is not yet released to the market in Canada, but was made available to our study by a special drug access program. Tramadol hydrochloride has revolutionized the lives of AC and JC – they are now essentially pain free, attending school daily and achieving improved academic records. They are also becoming freely involved with sports activities – a joy they were previously not able to participate in. There have been no side effects from use of tramadol hydrochloride in 30 months of continuous use with AC and 12 months of continuous use with JC.

CONCLUSION

The authors recommend the use of tramadol hydrochloride in pediatric patients with EDS – Hypermobility type. In similar chronic pain presentations in the pediatric patient in which there are no contraindications to the prescription of tramadol hydrochloride, we also recommend its use. Well-designed, placebo-controlled studies are required to further evaluate the safety and efficacy of tramadol hydrochloride for pediatric chronic pain states.

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REFERENCES