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CASE REPORT

UNCORRECTED PROOF

Gabapentinoids and lactation: Review of the literature

Gabapentinoidler ve laktasyon: Literatürü gözden geçirme

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Summary

Gabapentin and pregabalin, which belong to the gabapentinoid drug family, are widely used, especially in neuropathic pain treatment, due to their effectiveness in pain management. Although many of the comorbidities and symptoms that limit the use of gabapentinoids are clearly described in the literature, there is limited data on their use during lactation. A 33-year-old female patient was admitted to our clinic with neuropathic pain and muscle weakness in her left lower extremity following spinal anesthesia for a cesarean section. We aimed to present the gabapentin treatment of a breastfeeding patient with persistent neuropathic pain in light of a literature review.

Keywords: Gabapentin; lactation; neuropathic pain; pregabalin.

Özet

Gabapentinoid grubuna ait olan gabapentin ve pregabalin ilaçları, ağrı tedavisinde gösterdikleri etkinlikler nedeniyle, özellikle nöropatik ağrı tedavisinde günümüzde yaygın olarak kullanılmaktadır. Gabapentinoid kullanımını kısıtlayan ek hastalıklar ve semptomlar çoğunlukla literatürde net olarak tanımlanmış olmakla birlikte, bu ilaçların emzirme dönemindeki kullanımına ilişkin çok az veri bulunmaktadır. Kliniğimize 33 yaşında bir kadın hasta, sezaryen operasyonu sırasında uygulanan spinal anestezi esnasında başlayan, sol alt ekstremitede nöropatik nitelikte ağrı ve kas gücü kaybı şikayetiyle başvurmuştur. Emzirme dönemindeki ve nöropatik ağrısı devam eden hastamıza uygulanan gabapentin tedavisini, literatür bilgileri eşliğinde sunmayı amaçladık.

Anahtar sözcükler: Gabapentin; laktasyon; nöropatik ağrı; pregabalin.

Introduction

Gabapentin and pregabalin, which are part of the gabapentinoid group of drugs, were initially developed as anticonvulsant medications. However, due to their effectiveness in pain management, they are now widely used, especially for the treatment of neuropathic pain.[1]

Gabapentinoids exhibit their effects by binding to the α2δ-1 subunit of voltage-dependent calcium channels, inhibiting calcium influx. This action reduces presynaptic excitatory transmitter release and spinal sensitization. Gabapentinoids also activate the descending noradrenergic pain inhibitory system linked to spinal α2 adrenoceptors. Gabapentinoid treatment can indirectly affect neuroimmune mediators, such as proinflammatory cytokines. These drugs have been found effective against neuropathic pain in both high-dose acute and repeated applications.[2]

For gabapentin, the only pain-related indication approved by the United States Food and Drug Administration (FDA) is postherpetic neuralgia. The FDA-approved indications for pregabalin related to pain are limited to postherpetic neuralgia, diabetic neuropathy or neuropathic pain associated with spinal cord injury, and fibromyalgia. Despite these limited indications, gabapentin and pregabalin are prescribed off-label for various other pain syndromes based on clinical observations and studies.[1]

Many of the comorbidities and symptoms that limit the use of gabapentinoids are clearly defined in the literature. In addition, there is very little data in the literature on lactation related to new anticonvulsant drugs, including gabapentin and pregabalin. Manufacturers state that these drugs pass into breast milk and the effect on newborns is unknown. Gabapentin manufacturers recommend cautious use during lac-

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tation only when the benefits clearly outweigh the risks.[3] Moreover, pregabalin manufacturers do not recommend the use of pregabalin during lactation.[4]

We aimed to present our case of a patient who used gabapentinoid treatment during lactation for neuropathic pain and neurological deficits following spinal anesthesia for cesarean section (C/S), along with a review of the literature on the compatibility of gabapentinoid treatment with lactation and its effects on infants.

Case Report

A 33-year-old female patient presented to our clinic with neuropathic pain and muscle weakness in her left lower extremity. Her symptoms started during spinal anesthesia for a cesarean section (C/S) one month prior, continuing with sensations of electric shocks, burning, and pain in the left lower extremity. During C/S, no other anesthetic or analgesic procedures were performed apart from spinal anesthesia. Postoperative follow-ups revealed increased pain and motor deficits in the left lower extremity. Lumbar magnetic resonance imaging (MRI) showed a left parasantral protrusion at the L5-S1 disk space, compressing the dural sac. At this level, bilateral neural foramina and other levels of dural sac, radixes, and neural foramina were reported normal. Based on these findings, the patient, evaluated by neurosurgeons, neurologists, and physical medicine and rehabilitation physicians at another center, was started on treatment for neuropathic pain with vitamin B12, methylprednisolone 16 mg/day, and gabapentin 1200 mg/day, and was enrolled in a rehabilitation program.

The patient, who showed improvement in symptoms with medical treatment and a rehabilitation program, was observed to transition from walking with a walker to using Canadian crutches in the physical examination at our clinic. No urinary or fecal incontinence was reported. Muscle strength examination assessed ankle dorsiflexion and big toe dorsiflexion as 0/5, and ankle plantar flexion as 4/5. Sensory examination revealed hypoesthesia in the L4, L5, and S1 dermatome areas. Deep tendon reflexes were normoactive in the patellar tendon and hypoactive in the Achilles tendon. No pathological reflexes were detected.

Electromyography (EMG) and nerve conduction study (NCS) of the patient indicated, "On the left, there are signs of total or near-total axonal degeneration in the L4-S1 spinal nerves, also affecting sensory ganglions. Involvement is total in muscles innervated by the fibular nerve and advanced partial in muscles innervated by the posterior tibial and sciatic nerves."

The patient, with no significant history apart from an uncomplicated C/S, continued to experience pain (visual analog scale score of 8) despite the current treatment. Considering her ongoing lactation, the gabapentin dosage was adjusted to a total of 1500 mg/day in divided doses of 600, 300, and 600 mg/day. Continuation of the rehabilitation program was planned.

Following the adjustment of her pharmacological treatment, the patient was scheduled for regular follow-ups for symptom control, planning of interventional algology procedures, and EMG/NCS monitoring.

Discussion

Pregabalin, an anticonvulsant, has numerous clinical indications including partial seizures, fibromyalgia, and neuropathic pain.[5,6] Due to its small molecular weight (approximately 159), minimal metabolism, lack of binding to plasma proteins, and a moderately long elimination half-life (6 hours), pregabalin consistently passes into breast milk.[5,7] In a study conducted by Peter A. Lockwood et al.,[8] ten breastfeeding women at an average of 35.6 weeks postpartum (20–43 weeks) were administered 150 mg of pregabalin every 12 hours, four times. Breast milk samples were collected five times within 24 hours before and after the last dose. The average steady-state concentration in breast milk was found to be 76% of that in maternal plasma. The steady-state concentration of pregabalin in breast milk was 2.05 mcg/ml, and the peak concentration was 2.47mcg/ml. Based on these data, the estimated average dose of pregabalin in infants, assuming an intake of 150 ml/kg/day of milk, was found to be 0.31 mg/kg/day. This dose corresponds to 7% of the maternal dose by weight.

According to animal studies, there is a potential risk of tumor formation in offspring exposed to pregabalin through breast milk. Current clinical study data do not provide a clear conclusion about the poten-

tial risk of tumor formation with pregabalin. Due to the potential risk of tumor formation, breastfeeding during treatment is not recommended.[9]

As pregabalin is a freely water-soluble agent, it is expected that the highest concentrations of the agent will be found in the foremilk.[7] Common side effects observed in adults include dizziness, somnolence, dry mouth, edema, blurred vision, weight gain, attention disruption, and loss of concentration. Infants should also be monitored for these effects during pregabalin use in the breastfeeding period.

Gabapentin, another drug in the anticonvulsant class, is used for partial seizures, neuropathic pain, and postherpetic neuralgia. Consistent with its low molecular weight (171) and low binding to proteins, gabapentin has been reported to pass into breast milk.[5] In one study, gabapentin levels in the milk of a mother taking 1800 mg/day were found to be 11.1, 11.3, and 11 mg/L at 2, 4, and 8 hours following a 600 mg dose. The milk/plasma ratio of gabapentin was 0.86, with a relative infant dose calculated at 2.3%. No gabapentin-related side effects were reported in the infant.[10]

In another study involving five mothers and infants, where gabapentin was used at 900–3200 mg/day, the average milk/plasma ratio was determined as 1 (0.7–1.3) during the postpartum period of 2 weeks to 3 months. Gabapentin was detected at measurable concentrations in two of three infants measured in the 2nd–3rd week (1.3 and 1.5 μM), while in one infant, it was below detectable levels. These levels were reported to be significantly lower than the normal plasma levels in the mother (11–45 μM). Assuming milk consumption of 150 ml/kg/day, the infant dose was calculated as 0.2–1.3 mg/kg/day, which corresponds to 1.3–3.8% of the maternal dose by weight. In one infant, the plasma level was 1.9 μM at the end of the third month of breastfeeding. The study indicated that the detectable gabapentin levels in infant plasma were low, and no side effects were observed.[11]

Although the long-term consequences of exposure to gabapentin through breast milk are limited, meta-analysis studies have not demonstrated a link between gabapentin and cognitive or psychomotor developmental delays. If gabapentin or pregabalin is to be used in breastfeeding mothers, the infant should be carefully monitored for gastrointestinal side effects, changes in appetite, adequate weight gain, sleepiness, and normal developmental parameters.[12] In our case where we started gabapentin, we informed the mother about potential side effects in the infant and recommended close monitoring in this regard.

Considering all these data, the gabapentin levels in infant plasma following lactational exposure appear to be low enough not to cause side effects in the infant. However, the effects of gabapentin on the infant and milk production are unknown. When using pregabalin or gabapentin during lactation, the developmental effects of breastfeeding and the clinical needs of the mother should be considered. The potential side effects of the drug on the infant and the maternal condition should be evaluated.

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References

1. Goodman CW, Brett AS. A clinical overview of off-label use of gabapentinoid drugs. JAMA Intern Med 2019;179:695–701. [CrossRef]
2. Kremer M, Salvat E, Muller A, Yalcin I, Barrot M. Antidepressants and gabapentinoids in neuropathic pain: Mechanistic insights. Neuroscience 2016;338:183–206. [CrossRef]
3. Electronic Medicines Compendium. Neurontin 100mg Hard Capsules —Summary of Product Characteristics Pfizer Limited. Available at: www.medicines.org.uk. Accessed Mar 13, 2018.
4. Electronic Medicines Compendium. Lyrica Capsules—Summary of Product Characteristics, Pfizer Limited. 2015. Available at: www.medicines.org.uk. Accessed Mar 13, 2018.
5. Pharmaceutical Press, Brayfield A. Martindale: The complete drug reference. London. Available at: http://www.medicinescomplete.com/. Accessed Mar 13, 2018.
6. Pharmaceutical Press. British National Formulary. London. Available at: https://www.pharmaceuticalpress.com/products/british-national-formulary/. Accessed Mar 13, 2018.
7. Briggs GG, Freeman RK. Drugs in pregnancy and lactation: A reference guide to fetal and neonatal risk. 10th ed. Philadelphia: Lippincott Williams and Wilkins; 2014.
8. Lockwood PA, Pauer L, Scavone JM, Allard M, Mendes da Costa L, Alebic-Kolbah T, et al. The pharmacokinetics of pregabalin in breast milk, plasma, and urine of healthy postpartum women. J Hum Lact 2016;32:NP1–8. [CrossRef]
9. Sauberan JB. FDA Pregnancy and lactation labeling rule, Considerations for population lactation section 8.2. Avail-

able at: https:www.fda.gov/media/97055/download. Accessed Nov 24, 2023.

10. Kristensen JH, Ilett KF, Hackett LP, Kohan R. Gabapentin and breastfeeding: A case report. J Hum Lact 2006;22:426–8.
11. Ohman I, Vitols S, Tomson T. Pharmacokinetics of gabapentin during delivery, in the neonatal period, and lactation: Does a fetal accumulation occur during pregnancy? Epilepsia 2005;46:1621–4. [CrossRef]
12. Specialist Pharmacy Service. Gabapentin and pregabalin—are they safe whilst breastfeeding? Prepared by UK Medicines Information (UKMi) pharmacists for NHS healthcare professionals Before using this Q&A. Available at: www.sps.nhs.uk/articles/about-ukmi-medicines-qas/. Accessed Mar 16, 2018.