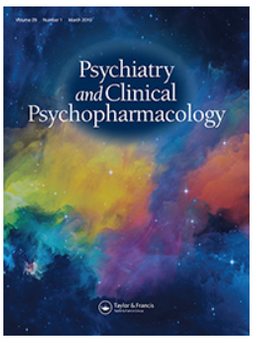

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CASE REPORT

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The impact of high doses of pregabalin on pregnancy – case report

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ABSTRACT

Pregabalin is a medication which is classified as a close analogue of gamma-aminobutyric acid. It has been modified to be a lipophilic analogue to enhance diffusion across the blood–brain barrier. Pregabalin was approved for the treatment of neuropathic pain associated with diabetic peripheral neuropathy, spinal cord injury, postherpetic neuralgia, and fibromyalgia, and as an adjunctive therapy for partial-onset seizures. In recent years, this medicament has also been used in the treatment of generalized and social anxiety disorder, bipolar disorder, chronic pain, and insomnia. The United States Food and Drug Administration categorized pregabalin to the pregnancy category C. The authors present the case of a 27-year-old female with mixed anxiety and depressive disorder who overused pregabalin (3000 mg per day) and was four months pregnant. The patient reported mood reduction and problems with falling asleep. The patient had a negative response to treatment. On the fourth day of hospitalization, she left the department at her own request. Five months later, she was admitted to the Maternity Ward with the beginning of delivery in the 36th week of pregnancy. During the entire pregnancy, the woman took pregabalin in the maximum dose of 3000 mg per day and smoked cigarettes. The child weighed 3450 g, measured 54 cm and was born with congenital pneumonia. One year after her first hospitalization, the patient came to the Detoxification Department with withdrawal syndrome, including anxiety, tremors, diarrhoea, abdominal pain, and sleeping problems. This time, in addition to her overuse of pregabalin (3000 mg per day), she became addicted to tramadol (750 mg per day). We concluded that pregabalin is not seriously toxic to the patient and foetus. It should be noted that pregabalin may have potential addictive effects.

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KEYWORDS
Pregabalin; overuse; pregnancy; addiction; women; teratogenic effect

Introduction

Pregabalin is a medication which is classified as a GABA analogue and gabapentinoid. It is a close analogue of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) [1,2]. It has been modified to be a lipophilic analogue to enhance diffusion across the blood-brain barrier. In animal models, it has been demonstrated that pregabalin in central nervous system tissues binds to presynaptic voltage-gated calcium channels at the alpha-2-delta subunit. Consequently, the alpha-2-delta subunit decreases the depolarization-induced influx of calcium into neurons which reduces the release of excitatory neurotransmitters, which are probably associated with analgesic and anticonvulsant effects. Pregabalin is rapidly absorbed following oral administration, with peak plasma concentrations occurring between 0.7 and 1.3 h. Pregabalin oral bioavailability is approximately 90% and is independent of dose and frequency of administration. Its elimination half-life is approximately 6 h and steady state is achieved within 1–2 days of repeated administration. [1–4].

The United States Food and Drug Administration (FDA) approved pregabalin for the treatment of neuropathic pain associated with diabetic peripheral neuropathy, spinal cord injury, postherpetic neuralgia and fibromyalgia, and as an adjunctive therapy for partial-onset seizures [5,6]. In recent years, the application of pregabalin has been extended to such disease entities as generalized and social anxiety disorder, bipolar disorder, chronic pain, and insomnia [5,6].

Reproductive toxicity, such as skeletal malformations, neural tube defects, and other abnormalities, have been reported by animal studies [5,6]. However, data on pregabalin use during human pregnancy are limited. A significant increase in the risk of major congenital disabilities after exposure to pregabalin in the first trimester was reported by a recent prospective study [7]. The teratogenic effect could be triggered by the L-amino acid transporter (LAT) present in the intestine, brain, and placenta [8]. Lower rates of live birth and higher rates of central nervous system (CNS) malformations were found in the pregabalin group than in the control group [7]. Patorno et al.

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did not report the teratogenic effects of pregabalin, although they could not exclude a modest increase in risk [9]. Studies do not recommend pregabalin use during pregnancy or when breastfeeding [10]. Currently, there are increasing reports about potential abuse liabilities and overdose fatalities in association with pregabalin [11]. The FDA had categorized pregabalin in the pregnancy category C, which means that there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks [12].

Case presentation

A 27-year-old female was admitted to the Department of Psychiatry due to complaints of mixed anxiety and depressive disorder (MAD; F41.8). She was referred from another hospital due to the overuse in doses beyond the therapeutic range of pregabalin (3000 mg per day) from five months. Moreover she was in the fourth month of pregnancy. It was her fourth pregnancy. The previous pregnancies had run without complications, ending with childbirth on time. The patient reported mood reduction and problems with falling asleep. She confirmed cigarette smoking (10 per day) and denied any alcohol consumption. On the admission to the department, the patient had normal orientation and visible anxiety. She had a stifled affect. The patient denied the presence of hallucinations and delusions; she did not speak. She denied also the presence of suicidal thoughts. The physical examination was normal. A neurological examination did not detect focal CNS lesions. Laboratory tests, including electrolytes, blood counts, and liver enzymes demonstrated no deviations from the norm. During the hospitalization, the patient lay idle in a bed all day. From the beginning, the patient was negative for treatment. On the fourth day of hospitalization, she left the department at her own request before the treatment was finished.

Five months later, she was admitted to the Maternity Ward with the beginning of delivery in the 36th week of pregnancy. The medical interview results showed that during the entire pregnancy the woman took pregabalin in the maximum dose of 3000 mg per day. She also smoked cigarettes. Childbirth took place in the natural way. She was treated by one dose of dexamethasone. The amniotic fluid was green and the newborn was wrapped in the umbilical cord. From the newborn card, it follows that the newborn female received an Apgar score of 8 points at the 1st, 3rd, and 5th minutes of life. The child weighed 3450 g and measured 54 cm. The infant was diagnosed with congenital pneumonia during examination. The chest radiograph showed pulmonary consolidations in the right lobe. An antibiotic was administrated.

The patient's mental condition was unaligned. Depressive symptoms were dominant. A gynecologist ordered a psychiatric consultation. Unfortunately, before that could happen, the patient left the department with the baby at her own request.

Almost one year after hospitalization in the Department of Psychiatry, our patient came to the Detoxification Ward for the Treatment of Drug Dependent Patients with withdrawal syndrome. The patient reported anxiety, tremors, diarrhoea, abdominal pain and sleeping problems. At that time, in addition to the overuse of pregabalin (3000 mg per day), she was dependent on tramadol (750 mg per day), starting from three months before hospitalization. Similar to the previous stay in the psychiatric hospital, there were no deviations in the laboratory tests. Once again, the patient did not finish the therapy.

Discussion

To date on PubMed/Scopus, only one systematic review [13] has been conducted which included 106 studies evaluating the addiction risk of gabapentinoids, including pregabalin. The results have shown that pregabalin appeared to be more addictive than gabapentin [13]. The reports have demonstrated that the significant population at risk for addiction to gabapentinoids includes patients with present or past substance use disorders (SUD), mainly opioid and multi-drug users. These drug users also chose pregabalin. Moreover, overdoses of gabapentinoids appeared to be relatively safe but can be lethal in combination with other psychoactive drugs like opioids and sedatives (especially pregabalin) [13]. Our patient at first developed pregabalin abuse and then opioids addiction. In contrast, a randomized single-blind study presented that pregabalin can be useful in the treatment of opioid withdrawal syndrome. The authors suggested that treatment with pregabalin is effective and safe and patients tolerate it better, which leads to a higher detoxification completion rate [14].

Negative pregabalin impact on newborns was not significant. No serious cognitive malformations were documented. Similar observations were made by Patorno et al. [15], who performed a cohort study on a population that included 1,323,432 pregnancies. They assessed the risk of congenital malformations in babies born to women who took pregabalin during the pregnancy compared with women who did not take this drug. The results showed that of 477 infants exposed to pregabalin during the first trimester 5.9% had malformations compared to 3.3% in nonexposed infants [15]. Also, a developmental toxicity study with pregabalin in rats conducted by Morse et al. [16] showed that pregabalin was not teratogenic.

However, Mostacci et al. [8] showed that in pregnancies exposed to pregabalin, seven ended in spontaneous abortion and seven in terminations of pregnancy. Moreover, among the 16 newborns, 4 were born preterm and 2 were small for gestational age. Among the 13 newborns exposed to pregabalin during the first trimester, 1 had a major birth defect and was also small for gestational age [8].

We confirmed earlier studies that pregabalin has addictive properties [10].

Conclusions

We showed that pregabalin is not seriously toxic to the patient or the foetus. The possibility of its harmful effect on foetal development is not excluded. It should be noted that pregabalin may have potential addictive effects.

Disclosure statement

No potential conflict of interest was reported by the authors.

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