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Quetiapine adverse reactions – case report
Działania niepożądane kwetiapiny – opis przypadku

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Summary

Background. Quetiapine is an atypical antipsychotic drug indicated in the treatment of schizophrenia, bipolar disorder and as adjunctive therapy in major depression. The off-label use of this drug is the treatment of anxiety disorders, dementia, autism, treatment-resistant obsessive-compulsive disorder, delirium and insomnia. ***Material and methods.*** We present a case report of a 41-year-old woman with insomnia who was administered with quetiapine 50 mg, which caused daytime sleepiness and dizziness. ***Results.*** Quetiapine was discontinued and the treatment with mirtazapine and psychiatric consultation were initiated. ***Conclusions.*** The described case confirms the risk of adverse effects resulting from the therapy with quetiapine. This drug, due to its high affinity to histamine and α1-adrenergic receptors, has a sedative and hypnotic effect, which is the reason why it is frequently used in the treatment of sleep disorders beyond its primary purpose. As quetiapine is indicated for the treatment of a wide range of conditions (different dosing schedules for each indication), its safety profile should be based on the individual diagnosis and dose administered. *(Farm Współ 2020; 13: 167-171)*

Keywords: quetiapine, insomnia

Streszczenie

Wstęp. Kwetiapina jest atypowym lekiem przeciwpsychotycznym wskazanym w leczeniu schizofrenii, choroby afektywnej dwubiegunowej oraz jako leczenie wspomagające ciężkiej depresji. Pozarejestracyjne stosowanie tego leku (ang. *off – label* use) to leczenie zaburzeń lękowych, demencji, autyzmu, opornych na leczenie zaburzeń obsesyjno-kompulsyjnych, majaczenia i bezsenności. ***Materiał i metody.*** Przedstawiamy przypadek 41-letniej kobiety, u której zastosowanie kwetiapiny w dawce dobowej 50 mg z powodu bezsenności spowodowało senność w ciągu dnia i zawroty głowy. ***Wyniki.*** Zaprzestano stosowania kwetiapiny i wdrożono leczenie mirtazapiną i konsultację psychiatryczną. ***Wnioski.*** Opisany przypadek potwierdza ryzyko wystąpienia działań niepożądanych leku wynikających z jego mechanizmu działania. Kwetiapina ze względu na wysokie powinowactwo do receptorów histaminowych oraz α1-adrenergicznych wykazuje działanie uspokajające i nasenne, przez co jest często wykorzystywana w terapii zaburzeń snu poza jej pierwotnym przeznaczeniem. Ponieważ kwetiapina wskazana jest w leczeniu wielu chorób (dla każdego wskazania schemat dawkowania jest inny), profil jej bezpieczeństwa powinien być określony w oparciu o indywidualne rozpoznanie i stosowaną u pacjenta dawkę. *(Farm Współ 2020; 13: 167-171)*

Słowa kluczowe: kwetiapina, bezsenność

Introduction

Insomnia is one of the most common disorders affecting the patient's health and quality of life. There are many ways to cope with this ailment, for example over-the-counter preparations, such as melatonin, lemon balm, valerian, and combination preparations containing various herbal extracts. However, some patients require pharmacological treatment. Here, the following groups of drugs are applied: hypnotics, antihistamines, antidepressants, antipsychotics and sedatives from the benzodiazepine group. Although FDA-approved GABAergic benzodiazepines and Z-drugs (zolpidem, zopiclone, and zaleplon) have a strong evidence base, they are characterized by multiple adverse effects, such as cognitive impairment, rebound insomnia upon discontinuation, increased risk of falls and car accidents,

abuse, and dependence liability. As a consequence the application of off-label drugs and novel drugs that do not target the GABAergic system is increasing [1]. Quetiapine (a dibenzothiazepine derivative) is an atypical antipsychotic drug approved by FDA (Food and Drug Administration) for the treatment of schizophrenia, acute manic, depressive, or mixed episodes of bipolar I disorder and adjunctive treatment of major depressive disorder. Apart from that, this drug has also been administered for the off-label treatment of dementia, autism, anxiety disorders, refractory obsessive-compulsive disorder, delirium and, importantly, insomnia. The use of quetiapine in the treatment of insomnia is based on its sedative action [2]. This drug is known to act as an antagonist of serotonin, dopamine, histamine, and adrenergic receptors. Remarkable affinity for antagonism at histamine H1-receptors (comparable to diphenhydramine, amitriptyline, mirtazapine, and doxepin) and a moderate affinity for serotonin type 2A (5-HT2A) receptors presumably underlie quetiapine's sedative properties [3]. After oral administration, quetiapine fumarate is rapidly absorbed, reaching peak plasma concentrations within 1.5 hours and is bound to serum proteins in 83%. Quetiapine's mean terminal elimination half-life is 6 hours and it is mainly eliminated through hepatic metabolism, specifically CYP3A4. Sex does not affect quetiapine pharmacokinetics, but in patients aged 65 and older, clearance is reduced by 40% [1]. With regard to the potential adverse effects of quetiapine, i.a., orthostatic hypotension, hyperlipidemia, hyperglycemia, the treatment with this drug is only recommended in patients with comorbid insomnia and in cases when patients may benefit from both the primary action of the drug and the sedating effect [2]. Only in Canada between 2005 and 2012 prescriptions of quetiapine for insomnia increased by 300%. According to the National Health and Nutrition Examination Survey data, between 1999-2010 quetiapine was the fourth most common drug prescribed for sleep disturbances (11% of all patients using an insomnia medication were taking quetiapine) [4]. Despite the occurrence of adverse reactions and poorly documented efficacy in the treatment of insomnia, the administration of quetiapine has become widespread considering sleeping disorders.

Case report

A 41-year old woman reported to general practitioner due to insomnia lasting several days. The interview excluded comorbidities and previous sleep problems. Therefore, this physiological response was associated with the stressful situation in the patient's life. Before visiting the doctor, the patient used a plant preparation containing: melatonin, *Melissa officinalis*, *Passiflora edulis*, *Humulus lupulus*, magnesium and vitamin B6. Subjective lack of efficacy of the preparation and previous paradoxical reactions following the use of estazolam and zolpidem (during hospitalization) resulted in the choice of 50 mg quetiapine as a hypnotic drug. The first administration was associated with daytime sleepiness and dizziness, preventing normal functioning. These reactions reappeared with subsequent doses of drugs. After a week of therapy, the patient reported to the family doctor. The drug was discontinued. A single dose of 15 or 30 mg of mirtazapine and psychiatric consultation were recommended.

Discussion

Insomnia is the most common sleep disorder and one of the most common mental disorders and is defined as dissatisfaction with sleep either qualitatively or quantitatively. This complex ailment is associated with distress or daytime function impairment and can be identified with difficulty falling asleep, difficulty maintaining sleep (frequent awakenings or problems returning to sleep after awakenings), and early awakening with the inability to fall asleep again, despite an adequate opportunity for sleep [5]. To diagnose insomnia, symptoms must be present for at least a month. As staded by the International Classification of Sleep Disorders, 3rd Edition (ICSD-3), due to the duration of symptoms, insomnia occurs at least 3 nights per week despite adequate opportunity to sleep and can be distinguished into short term (if present for less than 3 months) and acute (present for at least 3 months) [6]. Short-term insomnia is not considered as a disease state, but a physiological reaction in situations of sudden stress, somatic diseases, crossing time zones, shift work and others, occurring in healthy people. As reported by many epidemiologic studies, the prevalence of insomnia has been estimated at 5% to even 50% in the general population. Regarding Poland, this condition affects about 24-29% of the population. More than 30% of adults report at least one symptom of insomnia. When daytime consequences, like excessive daytime sleepiness, are taken into consideration, the rate drops to 10%–15% [1,7]. It has been found that sleep difficulties are more common in women than in men, increase with

age, and the risk of insomnia is higher in shift workers, and people who are divorced, widowed, separated and with low socioeconomic status [7]. People struggling with such problems usually reach for non-prescription sleep promoting preparations or ask for a doctor's intervention. Then, they are usually subjected to symptomatic treatment with one of the hypnotics registered for the treatment of insomnia (non-benzodiazepine hypnotics and benzodiazepine derivatives). Sedative antidepressant drugs (trazodone, doxepin, mirtazapine) and, in certain clinical situations, low dose psychotic drugs from the phenothiazine group (such as promazine, perazine, levomepromazine, chloroprotixene or second-generation antipsychotic sediments such as olanzapine and quetiapine) are also used [1]. For the treatment of insomnia in clinical practice, the most commonly used antipsychotic medications are quetiapine 25-250 mg and olanzapine 2.5-20 mg [8]. Quetiapine, developed for the treatment of psychiatric disorders, gained huge interest in the treatment of sleeping disorders, because of its antagonism of the H1- and 5-HT2A receptors, known to cause the sedative effect. In in 2012, sleep disturbances placed in the top 4 diagnoses associated with quetiapine, together with mood, psychotic, and anxiety disorders. This drug become so prevalent, that between 2005 and 2012, there was a 300% increase in the number of dispensed prescriptions (1.04 million in 2005 to 4.17 million in 2012) ordered by general practitioners. Considering psychiatrists, the number of prescriptions increased by 141.6% (0.87 million in 2005 to 2.11 million in 2012). Preferential increase in the use of quetiapine over other antipsychotic drugs has been noted, emphasizing, that the increased use is in majority a result of off-label prescribing by family doctors [9]. It raises a lot of controversy, because the number of studies, data, and thus, evidence to prove the effectiveness and safety of using quetiapine in the treatment of insomnia is insufficient. Rigorous double-blind, randomized, placebo-controlled trials demonstrating the efficacy of any antipsychotic medication for the treatment of insomnia are lacking. Only few small studies of quetiapine have been conducted considering niche populations and the data would not be generalizable to the general population. There were only few clinical trials investigating the application of quetiapine for the treatment of insomnia in the absence of comorbid conditions, but the number of patients participating in these researches was rather small. The reports indicated, that quetiapine improved wake time after sleep onset in a trial of 20 patients during early recovery from alcohol dependence [10]. One double-blind, randomized, placebo-controlled trial of quetiapine 25 mg was conducted in a group of 13 patients with primary insomnia. It occurred that the drug improved total sleep time and reduced sleep latency but not reaching statistical significance and in addition had few adverse effects (day time drowsiness, dry lips and tongue) [11]. Another trial (open-label) revealed that quetiapine 25–75 mg/day was effective at reducing symptoms of insomnia, increasing total sleep time and reducing PSQI (Pittsburgh Sleep Quality Index) [12]. There was also a randomised, double-blind, cross-over, placebo-controlled trial with a sample of 19 healthy, non-smoking male participants, in which the influence of 50 mg quetiapine on both normal sleep and sleep disturbed by acoustic stress as a model for transient insomnia was assessed. It turned out that quetiapine caused daytime sleepiness and lessened sustained attention [13]. The other open-label studies generally resulted in positive outcomes, although they were performed in a wide range of patient populations, including patients with treatment-resistant depression, bipolar disorder, Parkinson's disease, breast cancer with tamoxifen-induced insomnia, and insomnia induced by detoxification from substance abuse [1].

Adverse drug reactions (ADRs) and safety of quetiapine

The data from small, short-term trials and reviews related to adverse effects of quetiapine for insomnia, indicated tolerance to this drug. The studies of Wiegand et al. and Tassniyom et al. bring information, that in the absence of comorbidities, quetiapine was generally well tolerated at a dosage of 25-75 mg nightly for the period of two to six weeks [11,12]. On the other hand, some reviews warn that low-dose quetiapine (less than 300 mg per day) may contribute to the occurrence of ADRs [2]. According to the European Medicines Agency (EMA), there were 209,571 ADR reports relating to quetiapine from 2005 to 2016. The number of reports increased consistently year per year. 8,112 of those reports were related to misuse/abuse/dependence/withdrawal issues (corresponding to 884 patients) which was 8.64% of all ADRs recorded. Over 87% of patients were in the 18- to 64-year age range, whereas 2.1% were in the 9- to 18-year age range. Most frequently occuring adverse reactions to quetiapine were classified as "drug abuse" counting 52.21%, "drug

dependence" – 26.43%, and "substance abuse" – 7.6% [14]. The Danish Medicines Agency database was searched for all quetiapine ADRs involving individuals (<18 years) between 1997-2015. About 15 adverse drug events related to quetiapine in children and adolescents were identified. The main reported adverse drug events were endocrine (hyperprolactinemia and hyperthyroidism), cardiac (tachycardia and QT prolongation), neurological (seizures and cerebral hemorrhage), and psychiatric (hallucinations) [15]. Concerning older patients, El-Saifi et al. analyzed quetiapine ADE reports from the period from 2000 and 2014, obtained from the Australian Therapeutic Goods Administration's (TGA) Database of Adverse Event Notifications (DAEN). The most commonly reported quetiapine-related ADRs in this population were nervous system disorders (extrapyramidal symptoms and neuroleptic malignant syndrome, somnolence, drowsiness, dizziness and headache) – 23.7%, psychiatric disorders – 12.6%, general disorders – 8.9%, and gastrointestinal and skin disorders – 6.8% each [16]. The confirmation is presented case report of a woman taking low-dose quetiapine (50 mg) for sleeping problems, who experienced ADRs in the form of somnolence and dizziness. Considering the use of quetiapine as indicated, in schizophrenia trials, somnolence was reported in 24.7% of patients, in a bipolar depression clinical trial, somnolence was reported in 51.8% of patients and in 50.3% of patients in a clinical trial for bipolar mania Quetiapine has been also confirmed to decrease thyroid hormone levels in a dose-related manner (free thyroxine of approximately 20% at the higher end of the therapeutic dose range). Usually patients required drug discontinuation or initiation of thyroid replacement therapy [17]. Quetiapine is also correlated with some metabolic risks, including hyperglycemia, diabetes, hyperlipidemia, and frequently weight gain. Quetiapine (≤ 200 mg nightly) for insomnia has been shown to cause significant increases in weight and body mass index [2]. Other nonmetabolic ADRs that have been associated with low-dose quetiapine are restless legs syndrome and periodic limb movements in sleep [17].

Interaction

There is no extensive evaluation of the risks of using quetiapine in combination with other drugs. As Quetiapine metabolism is mediated by the CYP3A4, potentially multiple pharmacokinetic interaction may take place with a variety of drugs, including antibiotics, analgesics, antiarrhythmics, anticonvulsants, antihistamines, antiparkinsonian, pump inhibitors, steroids, and triptans. Caution should be used when quetiapine is applied in combination with other drugs acting on CNS, especially antidepressants (most typically reported are citalopram, trazodone, and sertraline), benzodiazepines, and opiates/opioids. Additionally, the high plasma concentrations of free testosterone in male patients is supposed to contribute to increased activity of CYP3A4, which can be associated with faster quetiapine biotransformation, and thus a possible tendency to increase its dosage. Concomitant administration of quetiapine with strong hepatic enzymes inducers significantly reduces its plasma concentration, which may affect the efficacy of treatment with quetiapine. In patients receiving a hepatic enzyme inducer, initiation of quetapine treatment should only be considered if the physician suspects that the benefits of quetiapine outweigh the risks of discontinuation of the hepatic enzyme inducer. Quetiapine potentiates the cognitive and motor effects of alcohol in subjects with selected psychotic disorders, thus alcohol should be limited while taking this drug. Caution is advised when quetiapine is co-administered with drugs that may cause electrolyte disturbances or prolong the QTc interval [14,17].

Conclusion

Quetiapine is indicated for the treatment of a broad spectrum of conditions using different dosing schedules for each indication. The off-label administration of quetiapine in the treatment of sleeping disturbances is prevalent. This drug possesses sedative and hypnotic properties and may indeed improve the situation of patients suffering from insomnia and other sleep disorders. However, the decision to prescribe this medication in the case of such conditions should be carefully considered taking into account its safety profile, that should be based on the individual diagnosis and dose administered. It is crucial to compliance with these precautions, as safety and efficacy of quetiapine for the treatment of insomnia is not supported by data from robust studies, there are broad adverse-effect profiles, and it is not easy to decide, whether the benefits of using quetiapine to improve the quality of sleep outweigh potential risks.

Conflict of interest
None

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