Vilnius University Press

Contents lists available at Vilnius University Press

Acta Medica Lituanica
2023. Online ahead of print

ISSN 1392-0138 eISSN 2029-4174
DOI: https://doi.org/10.15388/Amed.2023.30.2.14

Narrative Literature Review of Potential Atrial Fibrillation Mechanism of Action Induced by Discontinuation of Benzodiazepines

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Abstract. ***Introduction.*** Benzodiazepines are commonly prescribed but often misused, leading to dependence and withdrawal symptoms. Increased worldwide prescriptions raise adverse effects and overdose concerns, especially for the elderly. Caution is needed in prescribing and considering alternative treatments to minimize risks.

Aim. Narrative literature review of potential atrial fibrillation mechanism of action induced by discontinuation of benzodiazepines.

Materials and methods. Database PubMed was searched using the combinations of keywords – "Benzodiazepine AND atrial fibrillation OR peripheral benzodiazepine receptors", "history of benzodiazepines", "benzodiazepines mechanism of action", "benzodiazepines indications", "benzodiazepines adverse effects" and "benzodiazepines withdrawal effects". Non-full-text and non-English scientific publications were removed. A total of 31 publication was included.

Discussion. Benzodiazepines (BZDs) were synthesized in 1955 and initially considered less toxic than barbiturates. They interact with GABA-A receptors, causing hyperpolarization and inhibitory effects in the central nervous system. BZDs are used to treat various clinical disorders, but long-term use can lead to adverse effects and withdrawal symptoms. There is evidence that genetic diversity can influence the response to BZDs through GABA receptors. The interaction between benzodiazepines and peripheral benzodiazepine receptors may influence calcium ion channels, affecting cardiac action potential and contractility, and discontinuation of these medications can potentially contribute to atrial fibrillation. Additionally, benzodiazepines may directly affect calcium channels, causing antiarrhythmic effects and vasodilation.

Conclusion. In summary, benzodiazepines, once considered safer sedatives, now raise concerns about misuse, dependence, and withdrawal symptoms. While there is a potential link between discontinuing benzodiazepines and atrial fibrillation through mechanisms involving peripheral benzodiazepine receptors and cardiac calcium channels, causality remains uncertain and multifaceted. Further research is needed to clarify these mechanisms, and healthcare providers should exercise caution in long-term benzodiazepine prescriptions while exploring alternative treatment strategies to mitigate risks.

Keywords: benzodiazepines, atrial fibrillation, peripheral benzodiazepine receptors.

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Received: 21/05/2023. **Revised:** 24/10/2023. **Accepted:** 24/10/2023

Potencialaus prieširdžių virpėjimo, sukelto nutraukus vartoti benzodiazepinus, atsiradimo mechanizmo literatūros apžvalga

Santrauka. ***Įvadas.*** Benzodiazepinai yra vieni iš dažniausiai skiriamų vaistų, tačiau dažnai netinkamai vartojami, dėl ko išsivysto priklausomybė, o nutraukus vartoti šiuos vaistus – atsiranda nutraukimo sindromo simptomai. Vis dažnesnis šių vaistų skyrimas kelia susirūpinimą dėl perdozavimo, ypač skiriant jų vyresniems pacientams. Siekiant sumažinti nepageidaujamų reiškinių atsiradimą vartojant šiuos vaistus, dėmesingiau turėtų būti išrašomi šie vaistai, kartu apsvarstoma alternatyvaus gydymo galimybė.

Tikslas. Mūsų tikslas buvo pateikti literatūros apžvalgą benzodiazepinų nutraukimo sukelto prieširdžių virpėjimo mechanizmo tema.

Medžiaga ir metodai. PubMed duomenų bazėje naudojant raktažodžių derinius „Benzodiazepine AND atrial fibrillation OR peripheral benzodiazepine receptors“, „history of benzodiazepines“, „benzodiazepines mechanism of action“, „benzodiazepines indications“, „benzodiazepines adverse effects“ ir „benzodiazepines withdrawal effects“ buvo atlikta mokslinių šaltinių paieška. Nepilno teksto ir ne anglų kalba publikacijos į apžvalgą nebuvo įtrauktos. Šia tema apžvelgta 31 publikacija.

Diskusija. Pirmą kartą benzodiazepinai buvo susintetinti 1955 m., tuo metu jie laikyti saugesniais preparatais nei barbitūratai. Šie vaistai centrinėje nervų sistemoje sąveikauja su GABA-A receptoriais, sukelia hiperpoliarizaciją ir slopinamąjį efektą. Benzodiazepinai yra vartojami įvairiems klinikiniams sutrikimams gydyti, tačiau ilgalaikis jų vartojimas gali sukelti nepageidaujamų reiškinių ir nutraukimo sindromą. Yra tyrimų, rodančių, kad benzodiazepinų veikimą per GABA receptorius gali lemti genetinė įvairovė. Sąveika tarp benzodiazepinų ir periferinių benzodiazepinų receptorių gali paveikti kalcio jonų kanalus, širdies veikimo potencialą ir susitraukimo dažnį, o šių vaistų nutraukimas gali prisidėti prie prieširdžių virpėjimo atsiradimo. Be to, benzodiazepinai gali tiesiogiai paveikti kalcio kanalus, sukeldami antiaritminį poveikį ir vazodilataciją.

Išvada. Apibendrinant galima teigti, kad anksčiau saugesniais raminamaisiais vaistais laikyti benzodiazepinai dabar kelia susirūpinimą dėl netinkamo vartojimo, priklausomybės ir vartojimo nutraukimo simptomų. Nors yra galimas benzodiazepinų vartojimo nutraukimo ir prieširdžių virpėjimo atsiradimo mechanizmo ryšys, veikiant periferinius benzodiazepinų receptorius ir širdies kalcio kanalus, tačiau priežastinis ryšys lieka neaiškus ir daugialypis. Siekiant patvirtinti šiuos mechanizmus yra būtini tolesni tyrimai, o gydytojai, skirdami benzodiazepinus ilgalaikiam vartojimui, turi būti atsargūs, kartu apsvarstyti alternatyvius gydymo metodus, kad būtų mažiau benzodiazepinų vartojimo ir nutraukimo sukeliamų reiškinių.

Raktažodžiai: benzodiazepinai; prieširdžių virpėjimas; periferiniai benzodiazepinų receptoriai

Introduction

Benzodiazepines are commonly prescribed drugs in psychiatry and are primarily indicated for conditions such as anxiety, sleep induction, muscle relaxation, convulsions, and alcohol withdrawal [1, 2, 3]. However, these medications are often misused and continued after prescription time has elapsed. This may lead to withdrawal and discontinuation symptoms. Even though many guidelines suggest prescription with caution, many physicians prescribe benzodiazepines for months or years, putting the patient at risk of becoming dependent on the medicine [2, 3]. The number of prescriptions worldwide is continually increasing, raising concerns about overdose risk [1, 2, 3]. Expanding consumption of benzodiazepines is especially dangerous for the elderly as it increases the risk of combining medications as they tend to have comorbidities, trauma incidence, and hospitalization, leading to increased healthcare costs [3, 4].

Aim

Narrative literature review of potential atrial fibrillation (AF) mechanism of action induced by discontinuation of benzodiazepines.

Materials and methods

Database PubMed was searched using the combinations of keywords – "Benzodiazepine AND atrial fibrillation OR peripheral benzodiazepine receptors", "history of benzodiazepines", "benzodiazepines mechanism of action", "benzodiazepines indications", "benzodiazepines adverse effects" and "benzodiazepines withdrawal effects". Non-full-text and non-English scientific publications were removed. A total of 31 publication was included.

Limitations

Atrial fibrillation may be precipitated by a myriad of underlying comorbidities and contributing factors that cannot be definitively excluded, therefore discontinuation of benzodiazepines as certain cause of atrial fibrillation cannot be confirmed.

Discussion

History of benzodiazepines

Benzodiazepines (BZDs) were synthesized in 1955 by chemist Leo Sternbach, who at that time worked in Hoffmann-La Roche. Initially, these drugs seemed less toxic, and the likelihood of dependency was less likely to be caused. Unlike barbiturates, benzodiazepines did not inhibit respiration. They were initially enthusiastically received by medical professionals, and their popularity and patient demand grew significantly. By the mid-to-late 1970s, benzodiazepines were at the top of all "most commonly prescribed" lists. It took researchers 15 years to establish a link between benzodiazepines and their effects on gamma-aminobutyric acid (GABA). However, in the 1980s, concerns arose due to doctors' enthusiasm and tendency to prescribe these drugs, raising the risk of abuse and dependence [5].

Mechanism of action

GABA is the most abundant neurotransmitter in the central nervous system, with the highest concentrations found in the cortex and limbic system [5].

GABA has an inhibitory effect that reduces the excitability of neurons. There are three types of GABA receptors: A, B, and C, but benzodiazepines primarily interact with GABA-A receptors. The GABA-A receptor complex consists of 5 transmembrane glycoprotein subunits. Each receptor complex has two GABA, but only 1 BZD binding site. The binding site of these drugs is in a special pocket at the intersection of the alpha and gamma subunits. BZD binds to the pocket, causing conformational changes in the chloride channel of the GABA-A receptor. These changes result in hyperpolarization in the cell, leading to GABA-induced inhibitory effects on the entire central nervous system [5, 6, 7].

According to the alpha subunit isoforms and clinical effects that differ for each type, benzodiazepine receptors are classified into several types. The BZ1 receptor has an alpha-1 isoform and is responsible for the drug's sedative effects, anterograde amnesia, and some of the anticonvulsant effects of diazepam [5].

BZ2 receptors contain the alpha 2 isoform and are responsible for the anxiolytic and myorelaxant effects of benzodiazepines. Different benzodiazepines may interact with different BZ receptors and may have diverse affinities for specific receptors, resulting in various effects on the central nervous system [5].

Indications

According to the World Health Organization (WHO), BZDs are used as a part of the treatment for several clinical disorders, including panic attacks, various types of epileptic attacks, seizure disorders, depression, anxiety, insomnia, excitation, aggression, phobias, inducing amnesia, alcohol withdrawal, and catatonia [8, 9, 10, 11]. Nevertheless, these medications are recommended to be used for a short period of time – two to four weeks or if treatment with other drugs is unsuccessful [11].

Adverse effects

By taking benzodiazepines or mixing them with alcohol or other substances that affect the central nervous system, people can commit crimes due to the disinhibition effect and aggressiveness. In addition, individuals may experience impaired judgment or cognitive impairment because of amnesia induced by benzodiazepines. Furthermore, long-term use of these medications can dampen or diminish the experience of pain or pleasure [10, 11, 12, 13].

Withdrawal effects

Symptoms typically occur after 2–3 days of discontinuing short-acting benzodiazepines or after 5–10 days of discontinuing long-acting medications [14, 15]. The condition known as Postacute Withdrawal Syndrome (PAWS) can occur when symptoms persist for several weeks or even months after the discontinuation of benzodiazepines, and the severity of the symptoms can vary [30]. Most benzodiazepine withdrawal symptoms are due to increased brain excitability [14, 15, 17]. All symptoms can be divided into three main groups – psychological, physical, and sensory symptoms. The most common psychological symptoms are anxiety, depression, sleep disturbances, decreased concentration, and confusion [14-18]. Physical and sensory symptoms include muscle spasms, pain, sweating, tremors, paresthesia, hypersensitivity or hyposensitivity to environmental changes, arrhythmias, and palpitations [14-18]. Seizures are possible in rare cases [15].

Potential mechanism of action for atrial fibrillation after discontinuation of benzodiazepines

Rare side effects while using BZDs or when medications are withdrawn may be due to the genetic diversity of individuals and can influence the binding affinity and response to benzodiazepines through GABA receptors. [19].

Peripheral benzodiazepine receptors (PBRs) are found in a variety of tissues, such as the kidney, adrenal gland, brain, and heart, where these receptors bind to calcium ion channels [20, 21, 23, 24]. These receptors were first discovered in 1970 by Braestrup and Squires as benzodiazepine binding sites, but it was later found that these receptors differ from binding sites in the central nervous system [20, 23]. Most PBRs are present in the outer membrane of mitochondria and are therefore often referred to simply as mitochondrial receptors (mBzR), but PBRs can be found in other structures such as the nucleus or plasma membrane. PBR is a protein composed of more than 150 amino acids that form a protein complex with a voltage-gated ion channel on the outer and adenine nucleotide translocators on the inner membrane [20].

There is growing evidence that mBzR may be responsible for the activity of certain vital functions and may have a protective function for various cells, such as cardioprotective function in the heart. These receptors in the heart have also been shown to be responsible for apoptotic cell death, changes in mitochondrial membrane potential, permeability, and intracellular calcium excess [20].

Ligands synthesized specifically for these receptors, namely BZDs, affect cardiac chronotropy and inotropy. The possible interaction between mitochondrial receptors and voltage-gated calcium

channels may lead to a change in cardiac action potential time and altered cardiac contractility [20-22, 24].

One study which researched canines and humans injected with 4'-Cl-DZP (an mBzR antagonist) at various sites and observed the effects on the positron emission tomography system. It was found that the rate and strength of atrial contraction were reduced when the medication was injected into the sinus node [20, 21].

The negative effect on inotropy and chronotropy while taking benzodiazepines are thought to be due to a change in the conformational calcium channels when these drugs bind to peripheral benzodiazepine receptors, and discontinuation of these drugs may result in paradoxical positive inotropic effects leading to atrial fibrillation [21-23, 25].

In addition, benzodiazepines may also directly affect calcium channels when micromolar concentrations interact with these receptors, thereby causing an antiarrhythmic effect and vasodilatation [23, 26].

Conclusions

In conclusion, benzodiazepines have a complex history marked by their initial promise as safer sedatives but later concerns regarding misuse, dependence, and withdrawal symptoms. This narrative review explored the potential link between discontinuing BZDs and AF. While causality remains uncertain, PBRs found in various tissues, including the heart, may play a role in cardiac function. Disruption of these receptors, possibly due to BZDs discontinuation, could alter cardiac action potential, contractility, and calcium channel conformation, potentially leading to arrhythmias like AF. BZDs themselves may also directly affect cardiac calcium channels, resulting in antiarrhythmic effects and vasodilation at specific concentrations. These complex mechanisms highlight the need for caution in prescribing these medications for extended durations and monitoring patients for cardiovascular symptoms. However, attributing AF solely to benzodiazepine discontinuation is challenging due to the multifaceted nature of this arrhythmia. Further research is essential to clarify the exact mechanisms and risk factors associated with benzodiazepine-related AF. Healthcare providers should consider alternative treatments and strategies to mitigate dependence and withdrawal risks when prescribing BZDs for extended periods.

Conflict of interest

The authors have stated that there are no conflicts of interest.

Funding

No funding is to be reported.

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