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Aspects regarding the pharmacological and toxicological effects of benzodiazepines

Daniela Cîrțînă[1], Crinela Șerban[2]

[1] "Constantin Brâncuși" University of Târgu-Jiu, Faculty of Medical and Behavioural Sciences, România
[2]"Ion Mincu" Technical College, Târgu-Jiu, România

E-mail: danielacirtina@gmail.com

Abstract. The importance of this study concerning the pharmacological and toxicological effects of benzodiazepines is based on the fact that in clinical practice the use and abuse of benzodiazepine tranquilizers is remarkable. Its use is fully justified in certain situations, as it represents a turning point in the treatment of anxiety and insomnia; however, it should not be abused, as benzodiazepines are capable of conditioning habituation, tolerance and physical addiction, although relatively rarely and only after prolonged use.

Keywords: *benzodiazepines, pharmacokinetics, adverse effects, overuse*

Introduction

Benzodiazepines, originally used as myorelaxants, were introduced into clinical practice as anxiolytic agents in the 1960s. The discovery of benzodiazepines made it possible to distinguish between sedatives and hypnotic tranquilizers, although the possibility of significant overlap in their pharmacological profiles in some areas of their activity is taken into account. Although benzodiazepines are first-line drugs in the treatment of anxiety and insomnia, their pharmacological effects include drowsiness, sedation, SNC depression in synergy with other compounds (especially alcohol) and dependence on continuous use. The effects range from anxiolytic to sleep-inducing (hypnotic), without excessively interfering with other brain functions.

These drugs have difficulty in distinguishing their anxiolytic and hypnotic properties by being all anxiolytic and all can alter sleep as long as effective doses are achieved. What distinguishes them, however, is that hypnotic benzodiazepines are potent drugs that can therefore alter sleep conditions at relatively low doses, whereas anxiolytic benzodiazepines are less potent, allowing a therapeutic window in which anxiolytic action is possible without significantly interfering with sleep [1,2].

Benzodiazepines that have a relaxing effect on skeletal muscles are used to treat muscle spasms around joints affected by an inflammatory or traumatic process, after sports injuries, incorrect sleeping position, stiff necks and other such painful changes and discomfort through restricted movement Benzodiazepines have strong anticonvulsant activity in both animals and humans. The anticonvulsant effect of benzodiazepines can be demonstrated.

These compounds are effective in the acute treatment of epileptic seizures, alcohol withdrawal and strychnine or tetanus toxin intoxication. The benzodiazepines most commonly used in these situations are diazepam, clonazepam and nitrazepam. Another important point to note is that benzodiazepines do not cause destruction or loss of memories recorded before administration, i.e. they do not cause retrograde amnesia. Instead, events that occur from taking the drug are susceptible to ”forgetting” (anterograde amnesia) [3].

The structure-activity relationship

Benzodiazepines are synthetic organic compounds obtained by condensation of a benzene nucleus with a diazepine nucleus.

The variations in therapeutic effect are given by the positions of the two nitrogen atoms of the diazepin heterocycle. All benzodiazepines regularly used in therapy are 1,4-benzodiazepines, with the exception of clobazam, and many contain a carboxamide group in the heterocyclic structure.

The term benzodiazepine refers to that portion of the structure composed of a benzene ring (the A ring) fused to a diazepine ring (the B ring) which has an "aryl" group (ring C) attached at the 5-position. For sedative-hypnotic activity a substitution at carbon 7 with a halogen or nitro group is required. The general chemical structure of benzodiazepines is shown in Figure 1.

The structure of triazolam and alprazolam includes the addition of a triazole ring at positions 1 and 2, which are occasionally referred to as triazolobenzodiazepines [4].

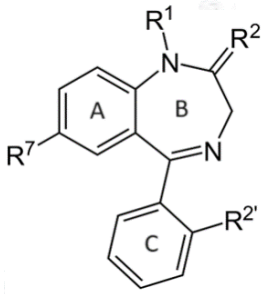

Figure 1. General chemical structure of benzodiazepines.

Pharmacodynamics

A large number of substances in this category are used in medical practice for their sedative, tranquilizing and/or hypnotic effects. This is why they are grouped into a single class called sedative hypnotic and tranquilizing drugs. Although some of them predominantly produce a particular effect, it has been observed that the three effects overlap and are predominantly one, depending on the dose of drug administered. Thus, at low doses, hypnotics have a sedative effect and, at low doses, sedatives have a tranquilising effect. In high doses, tranquilisers have a sedative and sometimes even hypnotic effect.

Along with these effects, which vary depending on the dose and are difficult to identify only visually on the body, BZD also produce other effects of lower intensity but which must be considered. BZDs increase the threshold of seizure resistance by having anticonvulsant effects. They also have a myorelaxant action on striated muscles and have the property of causing superficial general anaesthesia. Because of their anaesthetic effects, they are used in pre-anaesthesia, in endoscopic procedures and in anaesthesia after post-traumatic shock.

Among the side effects of BZD, there are enzyme-inducing and even self-inducing effects with mild manifestations. These effects become dangerous only if therapeutic doses are exceeded or if the medication is used for long periods of time. BZD does not strongly influence respiratory functions and does not alter the rhythm and physiological quantities of hormonal secretions when administered in therapeutic doses [4,5].

Pharmacokinetics of benzodiazepines

BZDs are slowly absorbed from the digestive tract and are biotransformed in the liver. Following biotransformation, some are directly decomposed into inactive metabolites with a short period of action and others are decomposed into active intermediate metabolites which increase their period of action. BZDs are eliminated via the kidney and bile and have a relatively long half-life (over 20 hours).

The mechanism of action of benzodiazepines is their binding to specific membrane receptors under the action of GABA mediators. Under the influence of these mediators, benzodiazepines favour the opening of transmembrane channels for chloride ions and their penetration into nerve cells. Increased intracellular chloride concentration reduces cell excitability.

Benzodiazepine receptors are found throughout the SNC. They are of two types:

a. benzodiazepine receptors type 1, involved in reducing anxiety;

b. benzodiazepine receptors type 2, involved in inducing sedation and ataxia.

The association of BZD with each other is not recommended because they act on the same receptors. Thus, competition for receptor binding would occur, which would require increased doses with side effects of accumulation and increased risk of toxicity [6,7].

Pharmacotoxicology and adverse effects

At the beginning of treatment with BZD undesirable effects may occur such as weakness, headache, nausea, dizziness, vomiting, taste changes, diarrhoea and ataxia. In some cases, they increase appetite leading to weight gain. Abrupt discontinuation of long-term treatment with BZD (several weeks) leads to the appearance and onset of the rebound effect. This varies in duration and intensity depending on the type of drug administered. It is possible to avoid this unpleasant phenomenon if treatment is stopped with discernment over time and with a gradual reduction in dosage.

The association of BZD with some central depressants, such as alcohol, potentiates their depressant effect on the SNC. In such situations, serious accidents may result, due to decreased psychomotor performance and attention, with profound and lasting impairment of daily activities, depressed respiratory and cardiac functions. Sometimes such associations can have lethal effects. Combination with other SNC depressant drugs is strictly forbidden. Side effects of BZD include enzyme induction and even self-induction with mild manifestations. These effects become dangerous only if therapeutic doses are exceeded or if the medication is used for long periods of time [8].

BZD tranquilizers (anxiolytics) are drugs that reduce states of mental tension, anxiety, psychomotor reactions and other symptoms such as emotionality, asthenia, insomnia, palpitations and functional digestive disorders. Anxiolytics have the ability to install a state of calm without affecting sensory functions, intellectual capacity and without inducing drowsiness. At therapeutic doses, they do not produce obvious psychomotor depression or sleepiness and do not affect sensory functions. They are used in the treatment of neuroses, psychotic agitation, disorders with psychoactive implications and in pre-anesthesia. Taken for a long time, they cause tolerance and dependence. Overdosing leads to drowsiness and coordination disorders. BZD sedatives administered in therapeutic doses induce a state of motor and sensory-sensory calmness and mild drowsiness. BZD hypnotics induce a deep restful and refreshing sleep. They shorten the sleep onset period, increase total sleep time and reduce the number of awakenings and their duration during the night.

Usually, their use causes undesirable side effects such as drowsiness and drowsiness on awakening and residual sedation, which are accompanied by decreased psychomotor performance during the day. Hypnotics are not recommended for transient insomnia such as jet lag in people with disturbed biorhythms (who sleep during the day), insomnia caused by pain or anxiety. These manifestations are best treated symptomatically. It is therefore recommended to use hypnotic BZD in the treatment of persistent or chronic insomnia [6-8].

Long term administration disrupts the physiological sleep pattern and causes a state of post-hypnotic sedation. Thus, it is necessary to use with caution in people with professions requiring increased alertness or in those driving vehicles. Sudden treatment interruption leads to the onset of a

rebound effect, which can be intense for short-acting substances and reduced for long-acting substances, allowing the body to adapt to the absence of the drug [7,8].

BZD have a rebalancing and psychic stabilizing role, contributing to:

a. decreasing stress sensitivity;
b. balancing emotional conditions;
c. increasing self-control;
d. decrease aggression and impulsive relationships during the day.

Benzodiazepine's use and overuse

Many countries in Europe, including Romania, are facing an opioid crisis. Emergency services staff are seeing more overdoses as well as deaths caused by these drugs. Usually these cases involve children, teenagers or young adults exploring the world of drugs. However, an often unrecognised group are older adults taking a combination of an opioid and benzodiazepine (BZD). These drug combinations are prescribed by a doctor to treat symptoms such as pain, but also lead to increased overdoses as well as deaths in the older population. Since 2000, opioid overdose deaths have quadrupled overall, but for people aged 55 and over, the increase has been much greater. Accumulated experiences involving physical and emotional trauma, loss of loved ones, lifestyle changes and disabilities can lead to anxiety and depression. These challenges make it necessary to treat physical and emotional pain using several types of medication. In addition to prescribing an opioid to treat chronic pain in older adults, a growing practice is to add a BZD to the pain management regimen, which is often done in rapidly increasing doses due to tolerance. In an article by MacReady, it notes, " prescription rates nearly doubled between 2001 and 2013, going from 9% to 17%. Between 1996 and 2013, BZD prescriptions increased by 67% and, unfortunately, the number of deaths associated with BZD overdoses increased from 1135 to nearly 9000." Safety issues regarding psychotropic drug use in older adults are of great concern due to comorbidities, pharmacokinetic changes and pharmacodynamic properties of drugs related to aging processes [9-11].

Benzodiazepine abuse has also been reported among athletes. The use drugs to enhance performance has become a fairly widespread phenomenon in sport, both for professionals and amateurs. There are various reasons why athletes might be guided to use certain substances (some of which are banned). Their use in an attempt to improve their sports performance, although often in the absence of real scientific evidence of their effectiveness, or to achieve good quality sleep in order to recover quickly after intense exercise. Recent case reports of high levels of benzodiazepine use among athletes have highlighted the lack of scientific evidence in this area of research. In general, long-term benzodiazepine use is avoided because of the risk of side effects and the potential to develop addiction. Even though levels of benzodiazepine use and abuse are increasing in Europe, scientific research seems to surprisingly overlook this problem [12,13].

New benzodiazepines

According to the European Drug Report (2019), EMCDDA has monitored 28 new benzodiazepines, of which 23 have been detected for the first time in Europe in the last 5 years. In 2017, almost 3 500 new benzodiazepine seizures were reported to the EU early warning system. Most seizures consisted of tablets, amounting to more than 2.4 million units - a strong increase from the around half a million tablets reported in 2016. This increase can be attributed to significant seizures of etizolam - a substance first reported to the EU's early warning system in 2011 - made in one country. In addition, approximately 27 kg of powder, 1.4 litres of liquid and 2 400 patches containing new benzodiazepines were reported to have been seized in 2017.

In 2021, the proportion of overdose deaths involving benzodiazepines increased in several countries and was present in more than half of the cases in Denmark (120), Austria (119), Portugal (43), Luxembourg (4) and Finland (127).

In the European Drugs Report 2022, data on the number and categories of new psychoactive substances notified for the first time through the EU Early Warning System, 2011-2021, included 33 new benzodiazepines in addition to other categories of opioid substances.

There are also concerns about an increasing cross-linking between the market's illegal drugs and new psychoactive substances. Among the examples are the production of fake drugs, such as oxycodone tablets that have been shown to contain potent benzimidazole-based opioids, and fake Xanax and diazepam tablets containing novel benzodiazepines. As a result of these developments, users may be unknowingly exposed to high-potency substances, which can increase the risk of fatal or non-fatal overdose events [13-15].

Interactions between new benzodiazepines and opioids

The European Drugs Report 2023 draws attention to the lack of toxicological information on benzodiazepines, which makes it difficult to understand their role in opioid-induced deaths. It also reports on the increasing number of new and uncontrolled benzodiazepines available in Europe, the extent of their use being difficult to establish due to limited data. What is certain is that these substances can have important health consequences, particularly when taken in combination with other drugs. BZDs are often very cheap and can be used especially by young people in combination with alcohol, which sometimes leads to potentially serious health reactions, aberrant behaviour and an increased risk of death from opioid overdose. Qualitative and descriptive results indicate that combining benzodiazepines with alcohol increases the intoxicating effects of both substances. Recent data (2022) indicate an increasing proportion of overdose deaths involving benzodiazepines, particularly in countries such as Estonia, where mixtures containing both the new synthetic opioid metonitazen and bromazolam, a new benzodiazepine, have been seized. Mixtures containing the new opioids protonitazen and metonitazen and the animal sedative and analgesic xylazine have also been reported by Estonian police.

Current monitoring approaches makebzdp it difficult to assess the extent of benzodiazepine use, although there are signs that benzodiazepines can have important health consequences, particularly when taken in combination with other drugs. In countries such as Canada and the United States, mixtures containing the new benzodiazepines and sedatives, known as ”benzo-dop” and ”tranq-dope”, have been reported and have been linked to increased overdose deaths [14,15].

Conclusions

Benzodiazepines are used to treat health problems including sleep disorders, anxiety, management of alcohol withdrawal. They act on a process in the brain with a tranquilising effect. The association of benzodiazepines with alcohol can be lethal. BZDs pose health risks, so benzodiazepines may increase the risk of dementia, brain damage, promote certain cancers or even cause premature death when used long-term. Benzodiazepine addiction may be more common among people suffering from anxiety, sleep disorders or temper problems. Often, people diagnosed with anxiety or sleep disorders will find the drug helpful and will gradually increase doses to maintain or enhance its effects. This is how addiction occurs, by taking higher and higher doses. The therapeutic efficacy of benzodiazepines in reducing anxiety, inducing sleep and relieving symptoms in panic attacks has been proven in numerous placebo-controlled studies and is undisputed. Their anxiolytic and hypnotic effect is very high, which is why they are used a lot, especially in psychiatry. The use and overuse of drugs leads to physical and psychological damage, damaging the individual and affecting the community, by definition repeated drug use leads to addiction. Although data are limited, it is emerging that, at least in some countries, benzodiazepines are implicated in a large number of opioid drug-induced deaths. Benzodiazepines have the potential to be addictive and should therefore be used with caution. Benzodiazepine addiction can occur when these drugs are used long-term or in high doses. Interruption symptoms may be experienced when someone tries to stop or suddenly reduce the dose. These symptoms can include anxiety, insomnia, tremors, sweating, confusion and even seizures in severe cases. To avoid addiction and other complications related to benzodiazepine use, it is important that these drugs are prescribed and taken as directed by a doctor and used as short term as possible. It is also important to avoid their use in combination with other substances that may potentiate their effects, such as alcohol or other drugs with central nervous system depressant potential.

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