REVIEW ARTICLE

Use of Benzodiazepines in Hypertension Treatment

Uso de benzodiazepinas en tratamiento de hipertensión

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ABSTRACT

Hypertension is a worldwide prevalent disease and one of the main cardiovascular risk factors. Today we live in a society dominated by stress, depression and anxiety, disorders generating a high sympathetic discharge which is damaging for the cardiovascular health. It is usual that as physician we meet patients who in the office and/or emergency departments present some degree of anxiety associated with elevated blood pressure, and in these cases, the treatment chosen to decrease blood pressure is frequently anxiolytics, specially benzodiazepines. As currently no guidelines support the use of anxiolytics for blood pressure management, we decided to carry out a bibliographic review to assess the evidences of their indication to treat hypertension.

Key words: Hypertension - Blood Pressure - Benzodiazepines

RESUMEN

La hipertensión arterial es una enfermedad de alta prevalencia mundial y es uno de los principales factores de riesgo cardiovascular. Hoy en día vivimos como sociedad en una época donde predomina el estrés, la depresión y la ansiedad: trastornos que generan una alta descarga simpática, lo cual resulta perjudicial para la salud cardiovascular. Es habitual que como médicos nos encontremos frente a pacientes que en consultorio y/o en salas de emergencias presentan algún grado de ansiedad asociado a registros elevados de presión arterial, y es frecuente que en estos casos el tratamiento elegido para la disminución de la presión arterial sean los ansiolíticos, y específicamente las benzodiazepinas. Actualmente no existen guías que avalen el uso de drogas ansiolíticas para el manejo de la hipertensión arterial, por lo que decidimos realizar una revisión bibliográfica para evaluar las evidencias sobre su indicación en el manejo de la hipertensión arterial.

Palabras clave: Hipertensión arterial - Presión sanguínea - Benzodiazepinas

INTRODUCTION

There is growing evidence on the relationship between anxiety disorders and cardiovascular disease (CVD) (1,2), but a positive association has also been shown between anxiety disorders and arterial hypertension (HTN). (3,4) Among CVD, HTN is a highly prevalent disorder affecting more than 1 in 3 adults in our country. (5) Despite the guidelines for the management of HTN developed by different Scientific Societies recommend hygienic-dietary measures and the use of antihypertensive agents as the main tools for its control, the use of benzodiazepines (BZD) associated with this condition is remarkably frequent.

There is evidence of an association between high blood pressure (BP) and conditions linked to anxiety, which would explain the more regular use of BZD in cases of severe HTN. (6,7)

Since anxiety-related disorders are common pathologies, with a global prevalence of 7.3% (8) and a very extended use of BZD, (9) we believe it is important to emphasize the correct use of these drugs in situations in which there is evidence for their use. The main reasons are that these drugs, due to their muscle relaxing and sedative effects, are associated with greater risk of falls and car accidents, and are often involved in overdose deaths. Regarding short-term amnesic effects, there is evidence of a mid-term and long-term impact in cognition, with a strong growing association with dementia, (10) though this last point should be evaluated in future investigations, as a meta-analysis published this year reports that the association observed with BZD did not persist after adjusting for confounders. (11)

Mechanism of benzodiazepine action

All the clinically used BZD facilitate the binding of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) at GABA A subtype receptors.

Although BZD have qualitatively similar clinical effects, there are important quantitative differences

Rev Argent Cardiol 2022;90:355-359. http://dx.doi.org/10.7775/rac.v90.i5.20558

Received: 05/26/2022 – *Accepted:* 08/18/2022

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in their pharmacodynamic spectrum and pharmacokinetic properties, which have determined diverse therapeutic indications. Different mechanisms of action contribute to the sedative-hypnotic, muscle relaxant, anxiolytic and anticonvulsant effects of BZD.

Practically all the BZD effects result from their action on the central nervous system (CNS), the most significant being sedation, hypnosis, reduction of anxiety, muscle relaxation, antegrade amnesia and anticonvulsant activity. Only two BZD effects are the result of peripheral actions: coronary vasodilation, observed after intravenous administration of therapeutic doses of certain BZD and neuromuscular blockade, only found at very high doses. As the BZD dose increases, sedation progresses to hypnosis and then stupor.

The physicochemical and pharmacokinetic properties of BZD greatly affect their clinical utility. They all have high lipid-water partition coefficients in the non-ionized form; however, the lipophilic activity varies >50 times according to the polarity and electronegativity of several substitutes.

All BZD are completely absorbed, except clorazepate, which is rapidly decarboxylated in the gastric juice to N-desmethyldiazepam (nordiazepam) and is then completely absorbed. Active drugs in the benzodiazepine receptor can be divided into four categories based on their half-life:

- Ultrashort-acting BZD
- Short-acting agents (half-life 6 hours), including triazolam, the nonbenzodiazepine zolpidem (half-life ~ 2 hours) and eszopiclone (half-life 5-6 hours)
- Intermediate-acting agents (half-life 6-24 hours), as alprazolam, clonazepam, lorazepam, estazolam and temazepam
- Long-acting agents (half-life >24 hours), including flurazepam, diazepam and quazepam.

The BZD volumes of distribution are large and in many cases are increased in elderly patients, requiring special attention in this population. They are also drugs which cross through the placenta and are excreted in the breast milk.

Benzodiazepines are largely metabolized by the hepatic cytochromes (CYP), mainly CYP3A4 and 2C19. Because the active metabolites of some BZD are biotransformed more slowly than the original components, the duration of action of many BZD has scant relationship with the elimination half-time of the original drug administered, as in the case of flurazepam. Conversely, the biotransformation rate of agents which are inactivated by the initial reaction is an important determinant of their duration of action, including oxazepam, lorazepam, temazepam, triazolam and midazolam. (12-16)

Hypertensive crisis and use of benzodiazepines

Consultations for severe HTN in the emergency departments are frequent. A recent meta-analysis found that in this context, the prevalence of hypertensive emergencies (in which BP elevation is associated with acute target organ damage (TOD) is 0.3%, while the so-called hypertensive emergencies (BP elevation not associated with TOD) are even more frequent and estimated at 0.9% (17) The REHASE study, carried out in Argentina, showed that the prevalence of severe hypertension without TOD was 9% of all emergency services consultations; an episode of stress was recognized in 46% of the population within the 48 hours prior to developing severe hypertension (18).

It is important to recall that many acute BP elevations can be reactive or transient due to sympathetic stimulation (stress, pain, urinary retention), a poor assessment technique or manifestation of white coat HTN. (19)

The challenge for the physician in the emergency ward is to decide which is the best therapeutic plan. This determines that some patients receive oral antihypertensive treatment associated or not to a BZD and others only rest and are discharged with alarm recommendations.

To date, several studies have evaluated different therapeutic strategies in patients presenting with high BP without TOD, but most have scarce statistical power.

In 2005, a double blind, randomized clinical trial was published in Brazil, including 100 patients who attended the emergency department at Hospital Universitario Oswaldo Crus with symptoms associated to systolic blood pressure (SBP) between 180 and 220 mmHg and/or diastolic blood pressure (DBP) between 110 and 120 mmHg. Patients were randomly assigned to receive symptomatic medication (dipyrone or diazepam) or antihypertensive medication (captopril). The proportion of patients treated with symptomatic medication who achieved BP reduction and returned home was like that of patients treated with antihypertensive medication. (20) On the same year, another research group obtained similar results in a double blind, randomized clinical trial, evaluating 36 60-year-old patients admitted to the emergency department with elevated BP (over 190/100 mmHg), who were divided into two groups randomly assigned to oral diazepam 5 mg or sublingual captopril 25 mg. The results demonstrated that both treatments were equally tolerated and in both groups the BP reduction was similar. (21)

A research team led by Dr. Sun Keun Park published in 2017 a prospective, randomized, controlled study evaluating the effect of BP reduction using rest alone versus oral antihypertensive treatment in patients admitted to the emergency department due to a hypertensive urgency. Patients were randomized into two groups; one received 40 mg telmisartan and the other placebo. Both groups had to remain at rest in a room for 2 hours. In this study, the BP reduction of patients at rest was similar to that of the group receiving the antihypertensive medication. (22) In the same sense, the previously mentioned REHASE study showed that among the 816 patients attending an

emergency department without EOD, 32% responded to rest [with 20% reduction of the initial mean blood pressure (MBP)] without need of antihypertensive agents.

In a prospective, single blind, randomized, controlled study, Yilmaz et al. compared oral treatment with alprazolam versus captopril in 53 patients admitted to the emergency department with diagnosis of hypertensive urgency. Different from other works, this study not only considered evaluating BP measurements by an oscillometric method but also used validated scales, to define those patients who in addition to HTN presented some sign/symptom of anxiety. It was noteworthy that in this group of patients, 92% of participants presented, according to the cited scales, some trait of anxiety. In both groups, BP was similarly reduced with the intervention, but the reduction of anxiety was more effective in the groups receiving alprazolam. (23)

The evidence is clearer in those situations in which the patient is suspected to present symptoms associated with autonomic hyperactivity by amphetamine, methamphetamine or cocaine intoxication. The clinical condition is characterized by HTN, tremors, agitation, and convulsions, and can lead to a stroke, acute myocardial infarction (AMI) or aortic dissection. In this case, BZD treatment should be indicated from the onset, with drugs such as intramuscular lorazepam or midazolam, and once the intravenous access is achieved, initiate diazepam. (24) Phentolamine, a competitive alfa blocking agent for intravenous administration, is recommended in case of additional need for antihypertensive treatment, and when this is not available, use nicardipine or nitroprusside. (25) Alternatively, clonidine can be used, which in addition to its sympatholytic actions has sedative effects. In the event of accompanying coronary ischemia associated to cocaine consumption, aspirin added to BZD is recommended in nitroglycerine treatment.(26)

Chronic use of benzodiazepines and long-term effects on blood pressure

Small studies and reviews have been carried on the chronic use of BZD as antihypertensive treatment, with dissimilar results.

A double blind, randomized study published in 2018, evaluated 25 healthy participants between 65 and 74 years of age, treated with diazepam 5 mg or placebo, administered at night. At the end of 4 weeks, office BP and ambulatory BP monitoring (ABPM) values did not differ. Blood pressure values during the night were higher in the diazepam group than in the one treated with placebo: higher SBP (7.6%, $p<0.01$) and DBP (5.8%, $p<0.05$), and similar results were obtained for heart rate (HR): 6.6% higher in the diazepam group ($p<0.05$). The HR in the group receiving diazepam remained high during the morning, while during the afternoon and the first hours of the night, the values of SBP, DBP and HR were similar in both groups. The authors concluded that these effects probably depend of an increase in the sympathetic impulse mediated by diazepam and a decrease in the vagal tone that could have clinical relevance due to the role of BP and HR increase as independent predictors of cardiovascular morbidity and mortality. (27)

In the same year, a retrospective article of 4629 patients studied the association between chronic BZD consumption (3 months) and ABPM values. Patients were divided into a group of 524 individuals receiving anxiolytics and a control group consisting of the rest of the patients. Eighty-one percent of patients in the BZD group were over 60 years of age, more frequently female, presented diabetes and consumed a higher number of antihypertensive agents. After adjusting for sex, age, number of antihypertensive drugs and comorbidities, a greater BP reduction (both systolic and diastolic) was demonstrated during 24 hours in the group consuming BZD. The reduction was similar for short and long half-life drugs. However, total mortality and cardiovascular events (secondary objective at 42-month follow-up) were similar between both groups. In addition to the different number of individuals between both groups, another weakness of this study was that it did nor evaluate the adverse effects of BZD. (28)

Costa et al. published in 2019 a study evaluating the effect on ABPM and HR in 37 patients receiving bromazepam 3 mg alone, in combination with propranolol 40 mg or placebo for 2 weeks. The nighttime SBP and DBP values were not affected by bromazepam alone compared with placebo, but were significantly reduced with propranolol alone and associated with bromazepam. On the other hand, nighttime HR reduction was significantly greater in patients receiving propranolol, while it increased in those taking bromazepam alone or together with propranolol. The authors considered that the increase in HR observed with bromazepam depends on a reduction in the vagal tone mediated by this psychotropic drug, which could have clinical relevance, particularly in already at-risk hypertensive subjects. (29)

In 2021, the same authors published another study evaluating cardiovascular parameters (24-hour SBP, DBP and HR) after 2-week alprazolam and lorazepam consumption (used as hypnotics) in mild hypertensive patients. The study included 32 individuals, between 40 and 65 years of age, with SBP between 140 and 160 mmHg and/or DBP between 90 and 99 mmHg, with no medical treatment, without other comorbidities and with normal values in depressive and anxiety disorder scales. Alprazolam versus placebo, lorazepam versus placebo and placebo versus placebo consumption were compared for a period of 2 weeks each. Each group underwent ABPM after each period. There were no 24-hour SBP, DBP and HR changes among patients, except nighttime DBP, which was significantly higher in patients receiving lorazepam. (30)

Mendelson et al. retrospectively analyzed 4938

ABPM studies evaluating the use of BZD in the previous 3 months. Results showed that in patients ≥60 years, the regular consumption of BZD was significantly associated with lower SBP and DBP, while in younger patients BZD did not have a significant association with BP. The investigators point out that despite no increase in mortality was found with BZD, caution is required in their prescription in elderly patients due to a greater risk of falls, fractures, or syncope. (31)

A retrospective analysis was published in 2020 on this topic in 538 patients ≥60 years, 6% of which were regularly receiving BZD. Use of these drugs was associated with greater SBP reduction 10 seconds after standing up, independently of sex, age, concomitant antihypertensive drugs and level of frailty, leading to the conclusion that elderly persons taking BZD can be at greater risk or orthostatic hypotension, perhaps due to an exaggerated immediate fall of BP. Therefore, use of BZD should be avoided in persons at greater risk of falls. (32)

CONCLUSION

Benzodiazepines are among the more frequently prescribed psychotropic drugs

It is a growing health care problem in several countries around the world, especially related to an increased number of deaths for overdose associated with BZD consumption and to the need for consultations in the emergency department due to disorders linked with their use. These increases have been produced simultaneously with the elevated rate of BZD prescription. (33)

Thus, this extensive bibliographic review on BZD use in HTN, clearly reveals that they are drugs that should be used in the treatment of anxiety disorders and under medical supervision. Their use as antihypertensive agents would only be relegated to cases in which BP elevation were the consequence of sympathomimetic drug consumption, or in cases in which BP elevation is not associated with TOD and is the product of an anxiety condition, for example, a panic attack. In these cases, the physician will use them with this criterion and under no concept the patient should continue the prescription as antihypertensive treatment.

We should recall that they are not harmless drugs. The American Geriatrics Society (AGS) placed BZD in a list of drugs that should be avoided in patients over 65 years, (34) since they could be associated with higher increase of mortality. Although there is no concluding evidence, it is clear that they are related to an enhanced risk of fractures, with the elevated morbidity and mortality this fact entails in the geriatric population.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web/Additional material.)

Ethical considerations

Not applicable.

REFERENCES

1. Roest AM, Martens EJ, de Jonge P, Denollet J. Anxiety and risk of incident coronary heart disease: a meta-analysis. J Am Coll Cardiol 2010;56:38-46. https://doi.org/10.1016/j.jacc.2010.03.034

2. Cohen BE, Edmondson D, Kronish IM. State of the Art Review: Depression, Stress, Anxiety, and Cardiovascular Disease. Am J Hypertens 2015;28:1295-302. https://doi.org/10.1093/ajh/hpv047

3. Pan Y, Cai W, Cheng Q, Dong W, An T, Yan J. Association between anxiety and hypertension: a systematic review and meta-analysis of epidemiological studies. Neuropsychiatr Dis Treat 2015;11:1121–30. https://doi.org/10.2147/NDT.S77710

4. Johnson HM. Anxiety and Hypertension: Is There a Link? A Literature Review of the Comorbidity Relationship Between Anxiety and Hypertension. Curr Hypertens Rep 2019;21:66. https://doi.org/10.1007/s11906-019-0972-5

5. Delucchi AM, Majul CR, Vicario A, Cerezo GH, Fábregues G. Registro Nacional de Hipertensión Arterial. Características epidemiológicas de la hipertensión arterial en la Argentina. Estudio RENATA 2. Rev Argent Cardiol 2017;85:354-60. http://dx.doi.org/10.7775/rac.es.v85.i4.11061

6. Yilmaz S, Pekdemir M, Tural U, Uygun M. Comparison of alprazolam versus captopril in high blood pressure: a randomized controlled trial. Blood Press 2011;20:239-43. https://doi.org/10.3109/08037051.2011.553934

7. Grossman E, Nadler M, Sharabi Y, Thaler M, Shachar A, Shamiss A. Antianxiety treatment in patients with excessive hypertension. Am J Hypertens. 2005;18:1174-7. https://doi.org/10.1016/j.amjhyper.2005.03.728

8. Craske MG, Stein MB. Anxiety. Lancet 2016;388:3048-59. https://doi.org/10.1016/S0140-6736(16)30381-6

9. Estudio Nacional Informe de Resultados N° 1 en población de 12 a 65 años, sobre Consumo de Sustancias Psicoactivas Argentina 2017. SEDRONAR

10. Hayhoe Benedict, Lee-Davey James. Tackling Benzodiazepine Misuse Bmj 2018; 362:K3208. https://doi.org/10.1136/bmj.k3208

11. AlDawsari A, Bushell TJ, Abutheraa N, Sakata S, Al Hussain S, Kurdi A. Use of sedative-hypnotic medications and risk of dementia: A systematic review and meta-analysis. Br J Cln Pharmacol. 2022;88:1567-89. https://doi.org/10.1111/bcp.15113

12. Goodman & Gilman. Las Bases Farmacológicas De La Terapéutica (12a Edición). Laurence Brunton, Bruce A. Chabner.

13. Fernández García A, González Viña A, Peña Machado MA. Bases científicas para el uso de las benzodiazepinas. Rev Cubana Med Gen Integr 2003;19

14. Sigel E, Ernst M. The Benzodiazepine Binding Sites of GABAA Receptors. Trends Pharmacol Sci 2018;39:659-71. https://doi.org/10.1016/j.tips.2018.03.006

15. Balon R, Starcevic V. Role of Benzodiazepines in Anxiety Disorders. Adv Exp Med Biol 2020;1191:367-88. https://doi.org/10.1007/978-981-32-9705-0_20

16. Griffin CE 3rd, Kaye AM, Bueno FR, Kaye AD. Benzodiazepine pharmacology and central nervous system-mediated effects. Ochsner J 2013;13:214-23.

17. Astarita A, Covella M, Vallelonga F, Cesareo M, Totaro S, Ventre L, et al. Hypertensive emergencies and urgencies in emergency departments: a systematic review and meta-analysis .J Hypertens. 2020;38:1203-10. https://doi.org/10.1097/HJH.0000000000002372

18. Rodríguez P, Flaherty MO, Forcada P, Grassi D, Díaz M, Ferrante D, y cols . Estudio REHASE. Rev Argent Cardiol 2006;74:102-8.

19. Marín M, Bendersky M, Paéz O, Obregon S, Rodríguez P, Cerezo G, y col. Consenso Argentino de Hipertensión Arterial. Rev Argent Cardiol 2018;86(Supl 2):1-53.

20. Goncalves De Lima S, Simoes Do Nascimento L, Nobre Dos Santos Filho C, Militao De Albuquerque MFP; Guimaraes EV. Hipertensión Arterial Sistémica En Urgencias. El Uso De Fármacos Sintomáticos Como Tratamiento Alternativo. Arq Bras Cardiol 2005;85. https://doi.org/10.1590/S0066-782X2005001500008

21. Grossman E, Nadler M, Sharabi Y, Thaler M, Shacar A, Shamiss A. Antianxiety Treatment In Patients With Excessive Hypertension.

Ajh 2005;18:1174-7. https://doi.org/10.1097/HJH.0000000000001340
22. Park SK, Kim WJ, Lee DY, Lee SY, Park HS, Kim HW, et al. Comparing The Clinical Efficacy Of Resting And Antihypertensive Medication In Patiens Of Hypertensive Urgency: A Randomized, Control Trial. J Hypertens 2017;35:1474-80. https://doi.org/10.1097/HJH.0000000000001340
23. Yilmaz S, Pekdemir M, Tural U, Uygun M. Comparison of alprazolam versus captopril in high blood pressure: a randomized controlled trial. Blood Press. 2011;20:239-43. https://doi.org/10.3109/08037051.2011.553934.
24. Kotliar C, Redón I Mas J, Brandani L, Obregón S. Manual de Hipertensión arterial secundaria. Claves y Algoritmos. 1º ed. 2019.
25. Van den Born BH, Lip GYH, Brguljan-Hitij J, Cremer A, Segura J, Morales E, et al. ESC Council on hypertension position document on the management of hypertensive emergencies. Eur Heart J Cardiovasc Pharmacother 2019;5:37-46. https://doi.org/10.1093/ehjcvp/pvy032
26. McCord J, Jneid H, Hollander JE, de Lemos JA, Cercek B, Hsue P, et al; American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology. Management of cocaine-associated chest pain and myocardial infarction: a scientific statement from the American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology. Circulation 2008;117:1897-907. https://doi.org/10.1161/CIRCULATIONAHA.107.188950
27. Fogari R, Costa A, Zoppi A, D'Angelo A, Ghiotto N, Battaglia D, et al. Diazepam as an oral hypnotic increases nocturnal blood pressure in the elderly. Aging Clin Exp Res 2019;31:463-8. https://doi.org/10.1007/s40520-018-0991-0
28. Mendelson N, Gontmacher B, Vodonos A, Novack V, Abuajaj M, Wolak A, et al. Benzodiazepine Consumption Is Associated with Lower Blood Pressure in Ambulatory Blood Pressure Monitoring (Abpm): Retrospective Analysis of 4938 Abpms. Am J Hypertens 2018;31:431-7. https://doi.org/10.1093/ajh/hpx188
29. Costa A, Bosone D, Cotta Ramusino M, Perini G, Ghiotto N, Zoppi A, et al. Effect of Evening Bromazepam Administration on Blood Pressure and Heart Rate in Mild Hypertensive Patients. Pharmacology 2019;10:1-6. https://doi.org/10.1159/000499371
30. Costa A, D'angelo A, Cotta Ramusino M, Perini G, Bosone D, Derosa G, et al. Effects of Oral Administration of Alprazolam and Lorazepam as Hypnotics on Cardiovascular Parameters In Hypertensive patients. J Clin Psychopharmacol 2021;41. https://doi.org/10.1097/JCP.0000000000001362
31. Mendelson N, Gontmacher B, Vodonos A, Novack V, Abu-AjAj M, Wolak A, et al. Benzodiazepine Consumption is Associated with Lower Blood Pressure in Ambulatory Blood Pressure Monitoring (ABPM): Retrospective Analysis of 4938 ABPMs. Am J Hypertens 2018;31:431-7. https://doi.org/10.1093/ajh/hpx188
32. Rivasi G, Kenny RA, Ungar A, Romero-Ortuno R. Effects of benzodiazepines on orthostatic blood pressure in older people. Eur J Intern Med. 2020;72:73-8. https://doi.org/10.1016/j.ejim.2019.10.032
33. Votaw VR, Geyer R, Rieselbach MM, McHugh RK. The epidemiology of benzodiazepine misuse: A systematic review. Drug Alcohol Depend. 2019;200:95-114. https://doi.org/10.1016/j.drugalcdep.2019.02.033
34. By the American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc 2015;63:2227-46. https://doi.org/10.1111/jgs.13702