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Pattern of utilization of benzodiazepines in patients with hypertension: a pilot study

Upotreba benzodiazepina kod bolesnika sa hipertenzijom: pilot studija

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Abstract

Background/Aim. The analysis of drug prescribing in general practice in Serbia showed that the use of benzodiazepines is most frequently associated with hypertension. The aim of this study was to establish the correlation of the characteristics of patients with hypertension to antihypertensive drug therapy, and the intake of benzodiazepines. **Methods.** A special questionnaire was used for interviewing the patients (n = 171) chronically treated for hypertenson. Statistical tests used were χ^2-test and Student's t-test. **Results.** No differences were noted in terms of age, gender, education, body weight, smoking habits and blood pressure (155±4.9/100±2.7 mmHg vs. 160±2.2/105±3.7 mmHg), between the group I (antihypertensive drugs+benzodiazepines: n = 79), and the group II (antihypertensives only: n = 92). The patients taking benzodiazepines received a lower number of different antihypertensive drugs (2.3±0.09 vs. 2.7±0.10; $p < 0.01$), but the total antihypertensive drug load was significantly greater than in the group II (2.6±0.10 vs. 1.9±0.15 defined daily doses (DDD)/patient/day; $p < 0.01$). Benzodiazepines were taken for anxiety (62%) and hypertension (21%), rarely for insomnia, mostly once a day, at bedtime. About half the patients took benzodiazepines regularly for months or years aware of the risk for addiction. Diazepam was used by 82% of the patients. The average daily exposure to benzodiazepines was 0.45±0.05 DDD/patient/day. The drug was bought without prescription in 25% of the patients, and without consulting a physician in 12% of them. **Conclusion.** The study confirmed a close association of hypertension with the use of benzodiazepines. The frequent use of benzodiazepines in the patients with hypertension might be caused by an inadequate response to antihypertensive drug therapy, besides anxiety and insomnia. The therapeutic efficacy of a long-term use of low doses of benzodiazepines in hypertension requires further investigation.

Key words:
benzodiazepines; diazepam; hypertension; drug utilization review; family practice.

Apstrakt

Uvod/Cilj. Analiza propisivanja lekova u opštoj praksi u Srbiji pokazala je da je primena benzodiazepina najčešće povezana sa terapijom hipertenzije. Cilj ovog istraživanja bio je da ustanovi korelaciju karakteristika bolesnika sa hipertenzijom i njihove antihipertenzivne terapije, kao i korišćenja benzodiazepina. **Metode.** Bolesnici (n = 171) koji su se hronično lečili od hipertenzije intervjuisani su korišćenjem specijalno pripremljenog upitnika. Korišćene statističke metode bile su χ^2 test i Student *t* test. **Rezultati.** Između bolesnika grupe I (antihipertenzivni lekovi + benzodiazepini; n = 79) i grupe II (samo antihipertenzivni lekovi; n = 92) nisu nađene razlike u smislu prosečne starosti, zastupljenosti polova, nivoa obrazovanja, gojaznosti, pušačkih navika i visine krvnog pritiska (155±4,9/100±2,7 mmHg : 160±2,2/105±3,7 mmHg). Bolesnici koji su uzimali benzodiazepine (grupa I) primali su manji broj antihipertenzivnih lekova (2,3±0,09 : 2,7±0,10; $p < 0,01$), ali je ukupno opterećenje antihipertenzivnim lekovima kod njih bilo značajno veće nego kod bolesnika grupe II (2,6±0,10 : 1,9±0,15 definisanih dnevnih doza – DDD/bolesnik/dan; $p < 0,01$). Bolesnici su uzimali benzodiazepine zbog anksioznosti (62%) i hipertenzije (21%), retko zbog nesanice, najčešće u pojedinačnoj dnevnoj dozi i to uveče pred spavanje. Oko polovine ispitanika benzodiazepine je uzimalo redovno, više meseci ili godina, uz obaveštenost o mogućnosti razvoja zavisnosti. Diazepam je lek koji je koristilo 82% bolesnika. Prosečno dnevno opterećenje benzodiazepinima iznosilo je 0,45±0,05 DDD/bolesnik/dan. Bez recepta je benzodiazepine nabavljalo 25% bolesnika, a 12% bez ikakve konsultacije sa lekarom. **Zaključak.** Rezultati rada potvrđuju da postoji značajna veza između hipertenzije i primene benzodiazepina. Učestaloj primeni benzodiazepina kod bolesnika sa hipertenzijom verovatno doprinosi i neadekvatan odgovor na antihipertenzivnu terapiju. Terapijska efikasnost hronične primene malih doza benzodiazepina kod hipertenzije zahteva dalja istraživanja.

Ključne reči:
benzodiazepini; diazepam; hipertenzija; lekovi, korišćenje, izveštaji; medicina, opšta.

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Introduction

An increased use of benzodiazepines (BZDs) has been recorded over the past decade in Serbia, with diazepam reaching the first place on the list of the most frequently prescribed drugs [1, 2]. The analysis of prescribing of BZDs in general practice in Serbia showed that diazepam was most frequently prescribed to the patients with hypertension, often without mentioning any other indication (e.g. anxiety or insomnia) [1]. A long-term use of BZDs associated with hypertension has been pointed out in some other studies [3, 4]. Although a high utilization of BZDs has been correlated to various comorbidity and risk factors [5–7], as well as to the doctors' prescribing habits [8], the use of BZDs in hypertension remains controversial [9].

The aim the present study was to analyze the pattern of utilization of BZDs by interviewing the chronically treated patients with hypertension. An attempt was made to establish a possible correlation of the intake of BZDs with some characteristics of the patients, as well as with the antihypertensive drug therapy.

Methods

A questionnaire has been prepared for the assessment of utilization of BZDs in patients with hypertension. However, exact data on the duration of antihypertensive therapy longer than 5 years were not available, neither from the records of patients nor from the patients directly. Therefore, the patients (n = 171) who claimed to be treated for hypertension between 5 and 10 years approximately were included in this study.

The patients with hypertension were interviewed by the physicians at the Institute for Nephrology and Haemodyalysis, the Clinical Center Niš, and at the Institute for Cardiovascular Diseases, the Clinical Center of Serbia, Belgrade.

The first part of the questionnaire included general data (age, gender, body weight, education level, smoking habits) and the blood pressure measured at the check-up. The names, as well as daily doses of all antihypertensive drugs used by the patients before this visit were recorded. These data were obtained from the patients lists as noted by the physicians.

The second part of the questionnaire included questions about the use of BZDs in the period before the check-up. These questions were answered by the patients in order to establish the "real life" pattern of the use of BZDs.

The questionnaire filling-up was anonymous: the patients were informed in advance that their names would not be recorded.

Based on the usage of BZDs, two groups of patients were analyzed: the group I included patients treated with antihypertensive drugs and BZDs, and the group II included patients treated with antihypertensive drugs only.

The general characteristics of patients, as well as the use of antihypertensive drugs were compared between the group I, and the group II.

The therapy for hypertension was analyzed regarding the type, as well as the number of different antihypertensive drugs used by each patient per day (monotherapy, 2, 3, 4 or 5 drugs per day).

A total exposure to antihypertensive drugs of each individual patient was expressed as a sum of the number of defined daily doses (DDD) of all the antihypertensive drugs regularly used (DDD/patient/day). First, the number of DDD per day for every antihypertensive drug for each patient was calculated. If a patient was taking two or more antihypertensive drugs, the number of DDD of all antihypertensive drugs was added up. Next, for each group of the patients, the average number of DDD of antihypertensive drugs ±standard error of the mean (SEM) was calculated.

The defined daily dose is a widely accepted statistical unit for measuring drug consumption. It is the amount of a drug which is most often used for the main indication. It is independent from the mechanism of drug action, from size of package, commercial drug name, in some cases from the pharmaceutical formulation, and from its price [10]. Since hypertension is the main indication for most drugs used by our patients, the use of DDD may be considered as appropriate measure of the total antihypertensive drugs load.

The same method was used to express the utilization of BZD.

For testing the differences between groups, the χ^2-test was performed for nonparametric values and the Student's *t* test for parametric values. Only statistically significant differences ($p < 0.05$) are shown in the text.

Results

Out of the total number of patients treated for hypertension (n = 171), benzodiazepines were used by 46.2% (n = 79).

There were no significant differences in general characteristics of patients (age, gender, education level, body weight, smoking habits) between the group that used only antihypertensive therapy, and the group that used both, the antihypertensive therapy and the BZD. Also, the values of arterial blood pressure at the check-up were similar in these two groups (155±4.9 /100±2.7 mmHg in the group I, and 160±2.2 / 105±3.7 mmHg in the group II) (Table 1).

Antihypertensive drugs (diuretics, ACE inhibitors, calcium antagonists) as monotherapy were prescribed in about 22% of the patients in both groups. The polytherapy (daily use of 2, 3, 4 or 5 drugs) comprised various combinations of diuretics, beta-blockers, calcium channel antagonists and ACE inhibitors (Table 2).

The analysis of the prescribed antihypertensive therapy showed that the patients taking BZDs received significantly smaller average number of different antihypertensive drugs (2.3±0.09 vs. 2.7±0.10; $p < 0.01$). However, antihypertensive drug load expressed as the number of DDD/patient/day, in patients taking BZDs was significantly greater than in the group of patients using BZDs (2.6±0.10 vs. 1.9±0.15 DDD/patient/day; $p < 0.01$) (Table 3).

The analysis of patients taking BZDs (group I) showed that the reason for taking BZDs was most often anxiety and

Table 1

General characteristics of patients treated with antihypertensive drugs with and without benzodiazepines

Characteristic		Group I (antihypertensive drugs + benzodiazepines) (n = 79)	Group II (only antihypertensive drugs) (n = 92)
Age (years)		52.5±1.2	53.8±1.1
Gender	(male)	53.2 %	58.7%
	(female)	46.6 %	41.3%
Education			
University		27.5%	22.3%
Secondary school		52.7%	48.5%
Primary school		19.6%	29.2%
Smokers		37.9%	44.6%
Non-smokers		62.1%	55.4%
Body mass index > 30		15.2%	10.9%
Arterial blood pressure		155±4.9 / 100±2.7 mmHg	160±2.2 / 105±3.7 mmHg

Table 2

Average number of antihypertensive drugs used in therapy of hypertension

Number of antihypertensive drugs	Group I (antihypertensive drugs + BZD) n = 79	Group II (only antihypertensives) n = 92
One drug (monotherapy)	18 (22.8%)	20 (21.7%)
ACE inhibitors	10	13
β blockers	6	7
Ca antagonists	2	0
Two drugs	22 (27.8%)	2 (2.2%)
Three drugs	36 (45.6%)	54 (58.7%)
Four drugs	3 (3.8%)	16 (17.4%)

Table 3

Number of antihypertensive drugs and total antihypertensive drug load expressed as the number of Defined Daily Doses/day/patient in patients treated with antihypertensive drugs with and without benzodiazepines

Parameters	Group I (antihypertensive drug + benzodiazepines) (n = 79)	Group II (only antihypertensive drugs) (n = 92)
Average number of antihypertensive drugs day patient	2.3±0.001*	2.7±0.001†
Average number of DDD of all antihypertensive drugs/day/patient	2.6±0.20*	1.9±0.35†

*$p < 0.05$; †$p < 0.01$

hypertension, and rarely insomnia (Table 4). There were not any clear indications for BZDs prescribing in patients' charts. On the other hand, a dosing regime of BZDs was mainly once a day, predominantly taken at bedtime. Most patients had been using BZDs for sevaral months or years, about one half of the patients regularly, and the other half when needed. Hardly half of them were aware of the risk of getting addicted to drugs. Most of the patients took BZDs on their doctors' recommendation. Almost one fourth of patients used to buy BZDs without prescription. Of all the BZDs on the market, diazepam was used by the majority (83%) of the patients. The exposure to BZDs, expressed as an average number of DDDs of BZDs was 0.45±0.05 DDD/patient/day.

Discussion

Our results showed that the patients treated chronically for hypertension with or without BZDs, at the check-up, had similar values of arterial blood pressure, independent from the intake of BZDs. Also, between these two groups of patients, there were no significant differences in terms of age, gender, education, smoking habits nor body mass index. The analysis of antihypertensive therapy in both groups indicated that the therapeutic approach was, generally, in accordance with the guidelines for antihypertensive therapy [11]. On the other hand, the average values of arterial blood pressure at the check-up (155/100 and 165/105 mmHg) showed that, in both groups of the patients, the recommended target values

Table 4

Pattern of benzodiazepine (BDZ) utilization in patients treated for hypertension

Parameter	Percentage of the number of patients taking benzodiazepines (n = 79)	
Reason for taking BDZ	Anxiety	62.2 %
	Hypertension	20.7 %
	Insomnia	17.1 %
Daily dosage	At bedtime	77.2 %
	In the morning	19.3 %
	In the morning and at bedtime	3.5 %
Are BZD taken regularly	As needed	58.2 %
	Every day	41.8 %
Duration of therapy with BZD	Several years	31.6 %
	Several months	43.0 %
	Less than a month	25.4 %
Knowledge about the addiction potential of BZD	Yes	51.9 %
	No	48.1 %
BZD are obtained or bought	On prescriprtion	75.9 %
	Without prescription	24.1 %
Who prescribed or suggested the use of BZD	General practitioner	43.0 %
	Specialist	40.5 %
	Self medication	12.7 %
	Other persons	3.8 %
Which BZD drug was used	Diazepam	82.2 %
	Bromazepam	11.4 %
	Other	6.4 %
Most frequently used daily dose of BZD	Diazepam (n = 65)	
	5 mg	72.4 %
	2 mg	23.1 %
	10 mg	4.5 %
	Bromazepam (n = 9)	
	3 mg	68.9%
	1.5 mg	31.1%
Average number of DDD* of BDZ per day per patient	0.42±0.05 DDD*/patient/day	

*Defined Daily Doses

for the therapy of hypertension (140/90 mmHg or lower) had not been achieved. This research was not aimed to investigate the antihypertensive therapy *per se*, but, as more important, to point out that patients adherence to a therapeutic regimen, as well as their dietary habits and lifestyles, had not been taken into consideration. It is well known that all these factors can significantly influence a therapeutic outcome. This has been proved by the findings that 53% of patients with hypertension in the USA do not comply with the prescribed therapy [12].

In our study, 46% of the patients who were taking antihypertensive drugs, were also taking BZDs, most of them following medical advice. It has already been shown that a high utilization of BZDs frequently coincides with hypertension, especially in older population [1, 5, 13]. Besides, there are some indicators that BZDs can stabilize blood pressure fluctuations in patients with unstable hypertension [14]. In this context, it is interesting to note that about 20% of our patients were taking BZD drugs only because they believed in their beneficial effect on hypertension, without mentioning any other symptoms. However, the number of these patients was rather small, and this problem, anyhow, requires further investigation. Pharmacoepidemiological studies of antihypertensive drugs utilization are based mostly on the number of drugs per patient per day used in the therapy [4, 15]. In our study, the average number of different antihypertensive drugs was significantly smaller in the group taking BZDs. In addition, an attempt was made to analyze antihypertensive therapy using the concept of daily drug load (total number of DDD/patient/day) [16].

The total antihypertensive drug load was significantly greater in the patients taking BZDs. One of the possible explanation was that the patients experiencing resistance to antihypertensive therapy had increased daily dosage of antihypertensive drugs and used BZDs as adjuvant therapy which ultimately reduced blood pressure to the same level as in the group not taking BZDs.

Most of the patients were taking BZDs following an initial medical advice. As the reason for taking BZDs, most of the patients stated anxiety (62%) and insomnia (17%). So far, the results of the studies of the correlation between anxiety and hypertension have been controversial. A positive correlation between psychological characteristics of a person, anxiety and hypertension has been suggested [15]. On the other hand, the results of Friedman et al. [6] showed that, in terms of psychological characteristics (personality type A, anxiety, aggression etc.), there is no difference between patients with hypertension and normotensive persons. The fact that in our study almost half of the patients were chronically adding benzodiazepines to antihypertensive therapy, indicated a correlation between hypertension and psychological factors, such as anxiety and insomnia. However, it is not clear whether anxiety and insomnia are independent clinical entities coexisting with hypertension, or may be the result of poorly controlled hypertension [17, 18].

It is, also, important to reconsider one more aspect of the utilization of BZDs. The recommended doses of diazepam in the treatment of anxiety are 4–40 mg/day divided in two doses at least [19]. In our study, the patients with hypertension were usually taking BZDs as a single daily dose at bedtime (77%), although only 17% of the patients claimed that they needed BZDs as hypnotic drugs. In most of the patients who had been taking BZDs regularly or when needed for several months or years, the average daily dose of diazepam

was less than a half of the recommended (defined) daily dose for the treatment of anxiety. It is well known that the tolerance to hypnotic effects of BZDs develops after several weeks of the usage, while anxiolytic effect persists much longer. Rickels and Schweizer et al. [20, 21] have shown that all patients who were taking BZDs over a 8-year period (without increasing a dose), expressed some withdrawal symptoms once the therapy had been abruptly discontinued. About 25% of these patients could not stop taking BZDs, because of the severity of withdrawal syndrome. A long term, constant use of small doses of BZDs indicated their low addictive potential in our patients. However, on the basis of the well known pharmacological and pharmacokinetic characteristics of diazepam and other BZDs, it was easy to suppose that a long term use of low single doses of BZDs, at least in some of our patients, could have been prompted by the need to prevent unrecognized mild withdrawal symptoms, which might have also been manifested by anxiety, nervousness or insomnia.

The absolute domination of diazepam over other BZDs was the consequence of its constant availability on the market, low price and popularity among both the patients and doctors. Over a 10-year period, the utilization of BZDs doubled, whereas the utilization of diazepam alone trebled in Serbia [1]. Art the same time, we noted no significant increase in the use of non-BZD hypnotics, which, together with short-acting anxiolytics have a dominant role in the therapy of insomnia [22] and anxiety [23] in the developed countries.

About 24% of the interviewed patients buy BZDs without prescription, and about 12% have started to take BZDs without consulting the doctor. The posibility to buy drugs without prescription and self-medication are common practice in our country [1]. The lack of control of drugs on the market is not rare in the developing countries, and also in those in transition [22]. On the other hand, self-medication is a widespread phenomenon, related to an increasing number of over-the-counter (OTC) drugs on the market and alternative methods of healing[24].

Conclusion

This study confirmed a close association between hypertension and the use of BZDs. It might be that, besides anxiety and insomnia, an inadequate response to antihypertensive drug therapy contribute to the frequent use of BZD in hypertension. However, the therapeutic efficacy of a long term use of small doses of BZDs in hypertension urges for further investigation.

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