ORIGINAL ARTICLE

The Frequency of Prescription of Immediate-Release Nifedipine for Elderly Patients in Germany

Utilization Analysis of a Substance on the PRISCUS List of Potentially Inappropriate Medications

Ingrid Schubert, Rebecca Hein, Sascha Abbas, Petra Thürmann

SUMMARY

Background: Immediate-release nifedipine is on the PRISCUS list of drugs that should not be given to elderly patients. We studied the use of this calcium-channel blocker under real-life conditions.

Methods: In 2009, we carried out a cross-sectional study based on the Statutory Health Insurance Sample AOK Hesse/KV Hesse with a sample size of 260 672 insurees. We used an anatomic-therapeutic-chemical classification (C08) to identify prescriptions for calcium-channel blockers. We determined from brand names and dosage forms whether nifedipine was prescribed in an immediate-release or sustained-release formulation.

Results: Among insurees over age 65, the prevalence of treatment with immediate-release and sustained-release nifedipine was 0.9% and 1.0%, respectively. Immediate-release nifedipine was usually (75%) given in a single administration. 46% of patients receiving immediate-release nifedipine also received another calcium-channel blocker. Patients who received immediate-release nifedipine tended to take more cardiovascular drugs than those who received sustained-release nifedipine (6 or more cardiovascular drugs were taken by 30% and 16%, respectively). Among all medical diagnoses related to hypertension, two were significantly more common among patients taking immediate-release nifedipine than among those taking sustained-release nifedipine: hypertensive crisis (OR 4.26, 95% CI 2.45–7.40) and hypertensive heart disease (OR 1.82, 95% CI 1.04–3.19).

Conclusion: Our analysis demonstrates that immediate-release nifedipine is being prescribed to elderly patients in Germany, albeit mostly in a single administration. In view of the risks and the availability of alternative drugs, stricter adherence to the PRISCUS recommendations in this case should be stressed in continuing medical education.

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PMV Research Group, Department for Child and Adolescent Psychiatry and Psychotherapy, University of Cologne: Dr. rer. soc. Schubert, Dr. sc. hum. Hein, Dr. sc. hum. Abbas

Clinical Pharmacology, Witten/Herdecke University, Philipp Klee-Institute of Clinical Pharmacology—HELIOS Clinic Wuppertal: Prof. Dr. med. Thürmann

The 2010 published PRISCUS list—a specifically German list of potentially inappropriate medications (PIM) (1)—summarizes drugs which, according to a multidisciplinary panel of experts, should be replaced with less risky alternative drugs when treating elderly patients (65 years and older). Immediate-release nifedipine is listed among these 83 drugs. This rationale is mainly based on previous studies that showed an increased mortality and myocardial infarction risk for elderly patients when immediate-release nifedipine was taken together with other antihypertensive drugs (2–5). The study by Pahor et al. showed that the adjusted relative risk for all cause mortality in elderly patients with hypertension (≥71 years) treated with immediate-release nifedipine, as compared to those treated with beta-blockers, was 1.7 (95% confidence interval [CI]: 1.1–2.7) (3). Maxwell et al. (2) reported that nifedipine administration increased overall mortality, given either as immediate-release (hazard ratio [HR]: 1.64; 95% CI: 0.88–3.03) or sustained-release (HR: 2.07, 95% CI: 1.11–3.85), in patients treated with antihypertensive drugs (65 years and older), as compared to treatment with beta-blockers. The immediate-release preparation is also included in the update for the Beers list developed in the United States (6), and in the list developed in France and published by Laroche et al. (2007) (7), of potentially inappropriate medications. For the Beers list update (2002), experts evaluated the severity of unwanted hypotension events during therapy with immediate-release nifedipine to be high (6). Laroche et al. (2007) (7) listed the reasons for including nifedipine (and nicardipine) in the PIM list for treating elderly (≥75 years) as orthostatic dysregulation, myocardial infarction, and stroke.

Inclusion of an active substance in a PIM list, if it is available on the market, is not primarily linked to the number of prescriptions written for it. However, the question about the importance of individual drugs within the spectrum of therapies arises when implementing PIM lists.

The annual German Drug Prescription Report (*Arzneiverordnungs-Report*) for 2010 revealed a significant increase in the use of nifedipine-like calcium channel blockers (dihydropyridines) since 2004, which the

authors claimed is due to long-acting dihydropyridines, and especially to amlodipine (8). The number of defined daily doses prescribed for immediate-release nifedipine is still decreasing and is only 4% of that for dihydropyridine prescriptions (8). The information given in the Drug Prescription Report provides a first important indication for the use of a substance group; however, since it lacks person related data, it cannot be used to determine patient exposure, such as to immediate-release nifedipine. The goal of this study, therefore, was to assess the treatment prevalence for calcium channel blockers, and specifically for nifedipine (both sustained- and immediate-release preparations), as well as to determine the number of prescriptions written for immediate-release nifedipine for insurees of AOK Hesse in 2009.

Methods

This study was conducted based on the Statutory Health Insurance Sample AOK Hesse/KV Hesse. In agreement with Germany's data protection regulations, an 18.75% random sample of all insurees of AOK Hesse was taken (9). From this extensive data set, the core data of the insurees (age, sex, insurance period), their outpatient diagnoses, and the drug data including the prescribing physician group were evaluated.

Treatment prevalence represented the percentage of the insurees who, in the observation year (2009), received at least one prescription of either a calcium channel blocker (Anatomical Therapeutic Chemical Classification [ATC] C08), or a dihydropyridine (C08CA) or nifedipine (C08CA05). Nifedipine drug products were separated into sustained- or immediate-release types, based on the medication name and the dosage form. Drop solutions were classified as immediate-release, while injectable solutions were excluded from the analysis. Prescription amounts were determined by the number of prescribed daily doses, which for example for nifedipine is internationally established to be 30 mg (10).

Data were organized in a database (MSSQL Server 2008 on Windows Server 2003) and analyzed using SQL. Frequency estimates are given as percentages. Wilson score interval was used to calculate 95% confidence intervals for proportions (11).

Results

The study population included a total of 260 672 people who were continuously insured in 2009, with an average age of 45 years (standard deviation [SD]: 24.2) (men, 43 years, SD: 23.2; women, 47 years, SD: 24.9). The percentage of those aged 65 years and over—the population for which the PRISCUS list was developed—was 27.4% (n = 71 367; men, 40.9%, women, 59.1%). The treatment prevalence for calcium channel blockers was 9% for all age groups, and 24% for the ≥65-year-old group. This therapy was received somewhat more frequently by women aged 65 years or older (25%; 10% for all age groups) compared to men (23%; 8% for all age groups). The *Table* shows the treatment prevalence for calcium channel blockers overall, and specifically for dihydropyridine and nifedipine. Clearly, dihydropyridine is highly used among the calcium channel blockers.

Slightly fewer than 8% of all insurees, and 21% of those in the ≥65-year-old group, received at least one prescription in 2009 for a calcium channel blocker from the nifedipine-like group. A treatment prevalence of nifedipine (all types) of 0.7% (women, 0.8%; men, 0.5%) was observed for all age groups, and of 1.8% (women, 2.0%; men, 1.6%) in the ≥65-year-old group. Nearly 54% (912/1700) of patients treated with nifedipine (equivalent to 0.3% of the insurees) received immediate-release nifedipine (*Table*). A much higher proportion of women 65 years and older received immediate-release nifedipine than men (of 1.1% compared to 0.6%, respectively).

Prescriptions were made primarily by the general practitioner for both types of formulation (sustained-release nifedipine, 93%; immediate-release nifedipine, 91%). Only 3% of prescriptions for either formulation type were written by an internist.

Immediate-release nifedipine accounted for about 30% of all nifedipine prescriptions but only for 12% of all prescribed daily doses, since the majority of immediate-release nifedipine (75%) was prescribed only once with few daily doses. Only 7% of the 912 immediate-release nifedipine recipients received five or more prescriptions during the year. On average, sustained-release nifedipine was prescribed almost continuously, with 314 daily doses, while immediate-release nifedine was prescribed on average only for 39 daily doses per beneficiary.

Patients with immediate-release nifedipine prescriptions did not necessarily also receive a prescription for sustained-release preparation: Only 5% of these patients were documented as receiving a prescription for sustained-release nifedipine, and 46% for another calcium channel blocker.

Patients who were treated with immediate-release nifedipine differed from those with sustained-release preparations with respect to the number of different drugs that affect the cardiovascular system (ATC C, 5th level) that they received during the observation year: Almost 30% of those treated with immediate-release nifedipine were prescribed six or more different active ingredients. In contrast, this was observed for only 16% of the group treated with sustained-release nifedipine.

Of all coded diagnoses of hypertension, outpatients who received immediate-release nifedipine were significantly more likely than those who received sustained-release nifedipine to be diagnosed with hypertension crisis (ICD 10: I10.91, OR: 4.26, 95% CI: 2.45–7.40) and hypertensive heart disease (ICD 10; I11.90; OR: 1.82; 95% CI: 1.04–3.19). A diagnosis of hypertension crisis was documented in less than 8% of patients treated with immediate-release nifedipine (10.3% for the ≥65-year-old group) and in 2% of patients who received a sustained-release formulation (4.1% for the ≥65-year-old group).

TABLE

Percentage of insurees with calcium channel blockers (total and subgroups) according to age group (2009)*

Age	Calcium channel blocker		Dihydropyridine		Nifedipine					
					Total		Sustained-release		Immediate-release	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
0–39	248	0.2 (0.2–0.3)	216	0.2 (0.2–0.2)	25	0.0	11	0.0	14	0.0
40–59	3777	5.2 (5.1–5.4)	3479	4.8 (4.7–5.0)	216	0.3 (0.3–0.3)	65	0.1 (0.1–0.1)	157	0.2 (0.2–0.3)
60–79	13 741	20.6 (20.2–20.9)	12 123	18.1 (17.8–18.4)	969	1.4 (1.4–1.5)	504	0.8 (0.7–0.8)	490	0.7 (0.7–0.8)
≥80	5687	28.5 (27.8–29.1)	4876	24.4 (23.8–25.0)	490	2.5 (2.3–2.7)	256	1.3 (1.1–1.5)	251	1.3 (1.1–1.4)
Total	23 453	9.0 (8.9–9.1)	20 694	7.9 (7.8–8.0)	1700	0.7 (0.6–0.7)	836	0.3 (0.3–0.3)	912	0.3 (0.3–0.4)
>65	17 215	24.1 (23.8–24.4)	15 006	21.0 (20.7–21.3)	1313	1.8 (1.7–1.9)	700	1.0 (0.9–1.1)	651	0.9 (0.8–1.0)

Reference population: n = 260 672; * multiple entries

Discussion

To the best of our knowledge, this is the first study that identifies the prevalence of nifedipine treatment, and specifically, of immediate-release nifedipine. Long-term therapy with immediate-release nifedipine is considered to be obsolete in guidelines and in the literature (12–14). Nonetheless, in this study slightly fewer than 1% of elderly patients (aged 65 and over), who are particularly vulnerable to adverse drug events, received this dosage form. Treatment with immediate-release nifedipine, in contrast to that with sustained-release nifedipine, usually occurred with a single prescription and, according to the data analyzed here, was apparently prescribed in addition to other kinds of antihypertensive drugs.

Interestingly, patients with immediate-release nifedipine prescriptions were more likely to have had a hypertensive crisis reported, than those with prescriptions for a sustained-release preparation. Additionally, those with immediate-release nifedipine received more antihypertensive drugs overall, which may indicate difficulties in controlling blood pressure. These findings suggest that the reason for prescribing did not require continuous treatment with immediate-release nifedipine. This approach conforms with the recommendations of professional societies (12–14) to avoid immediate-release nifedipine. Perhaps patients were intended to use this to independently treat such occasional blood pressure spikes themselves. Such therapy, however, is not covered by guidelines.

According to current definitions and recommendations, hypertensive crises—which as a rule present with severe clinical symptoms such as encephalopathy or pulmonary edema—must be supervised and monitored in intensive care. Asymptomatic hypertensive

emergencies, on the other hand, can be treated for example with GTN spray or with orally administered immediate-release nifedipine, but only under medical supervision and not through self-medication by patients. However, for occasional high blood pressure that does not require immediate therapy, no recommendations for treatment are available, but rather only advice for further diagnostic evaluations (see guidelines).

This analysis confirmed the results of the global data (see Drug Prescription Report [8]), which indicated that nifedipine plays a less important role among the calcium channel blockers. However, in contrast to those data, this study provides information for:

- the number of recipients
- the prescribed daily doses per recipient
- additional features for treated patients.

In view of the long-standing critical assessment of prescribing immediate-release preparations, the question arises as to why this situation is still continuing. Answering this would require in-depth analyses of comorbidity, adherence, and clinical data. This goes beyond the scope of this routine data analysis, which is meant to primarily draw attention to the problem.

Even though the number of recipients is low as compared to some other drugs listed in PRISCUS (1), the present analysis reveals a clinically relevant problem in everyday clinical practice, which is perhaps not sufficiently covered in the guidelines. When implementing the PRISCUS list and developing advanced training material, therefore, the problems related to treating high blood pressure spikes with immediate-release nifedipine should be outlined, and treatment alternatives for this should be indicated.

It should be mentioned that this study was limited to a single health insurance provider and region. However, since the ratios of different dihydropyridines according to daily doses found in this study—5 874 752 (C08CA01) : 298 446 (C08CA05): 672 280 (C08CA08) : 1 078 054 (C08CA13)—correspond to those from the Drug Prescription Report (8), we believe that these results can be generalized.

Conclusion

Although the number of prescribed daily doses for immediate-release nifedipine is fortunately decreasing overall, immediate-release nifedipine is still being used as antihypertensive medication on demand, particularly for the elderly. This underscores the necessity to indicate alternatives to immediate-release nifedipine in the PRISCUS list. In case of exaggerated blood pressure, treatment regimens should be reconsidered and patient inquiries should be made about therapy adherence. In addition, other differential diagnoses might need to be considered. According to current guidelines, the administration of immediate-release nifedipine is not to be justified except in special situations. The data presented here should stimulate further analysis on the reasons for prescribing.

KEY MESSAGES

- Immediate-release nifedipine is listed by PRISCUS as a potentially inappropriate medication.
- According to data from health insurance providers, about 1% of ≥65-year-old insurees received at least one prescription of immediate-release nifedipine in 2009; this was used mainly as an antihypertensive medication on demand.
- Direct use by patients as an antihypertensive medication on demand is neither recommended in the guidelines of professional societies nor mentioned under alternative uses in the PRISCUS list.
- In case of blood pressure spikes, patients should be questioned for the therapy regimen and adherence; where required, differential diagnosis should be carried out to clarify the situation.

Conflict of interest statement

The PMV Research Group received research funding from government departments, insurance funds, physician associations, foundations, Gesundes Kinzigtal GmbH, and pharmaceutical industry (Abbott, Lilly, Bayer-Schering, Sanofi-Aventis, Merz, and Novo-Nordisk).

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Corresponding author
Dr. rer. soc. Ingrid Schubert
PMV forschungsgruppe an der Klinik und
Poliklinik für Psychiatrie und Psychotherapie
des Kindes- und Jugendalters der Universität zu Köln
Herderstr. 52–54
50931 Köln, Germany
Ingrid.Schubert@uk-koeln.de