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Onset Time Profiles for Syncope Associated with α_1-Adrenoceptor Blockers in Males: Analysis of a Spontaneous Adverse Drug Event Database

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Abstract

Background: α_1-Adrenoceptor blockers (α1Bs) are used for the treatment of benign prostatic hyperplasia and hypertension, but they are known to cause hypotension-related adverse events. The objective of the present study was to evaluate the onset time profiles for syncope associated with the use of α1Bs. **Methods:** We analyzed the data obtained from the Japanese Adverse Drug Event Report (JADER) database for a period from April 2004 until November 2016 and calculated reporting odds ratios (RORs) for eight α1Bs available on the Japanese market, using disproportionality analysis. Moreover, time information recorded in the JADER database was analyzed to evaluate the onset times of adverse events. **Results:** In total, 186,724 reports for males older than 20 years were analyzed. Significant RORs for syncope, with 95% confidence intervals, were obtained for naftopidil (2.53, 1.81 - 3.53), silodosin (4.24, 2.37 - 5.20), and tamsulosin (2.22, 1.75 - 2.81). The median onset times of syncope for naftopidil, silodosin, and tamsulosin were 37, 26, and 108 days, respectively. The shape parameters obtained by fitting the data for the three α1Bs to the Weibull distribution were all less than 1.0, indicating that all these drugs could be classified as the early failure type. The cumulative incidence rates showed that the onset times of syncope tended to be similar among the three α1Bs. **Conclusions:** Patients treated with selective α1Bs should be closely monitored for 100 days, especially in the first 20 to 40 days after initiation of silodosin or naftopidil. This information may be useful for patients and healthcare professionals in preventing syncope due to the use of selective α1Bs.

Keywords

Reporting Odds Ratio, Adverse Drug Event Report Database, Syncope, α_1-Adrenoceptor Blocker

1. Introduction

α_1-Adrenoceptor blockers (α1Bs) are most commonly indicated for the treatment of benign prostatic hyperplasia (BPH) but can also be used for the treatment of hypertension because of their ability to decrease blood pressure. These drugs are divided into two groups, depending on whether they display selectivity for α_1-adrenoceptor subtypes (**Table 1**). The guidelines of the Japanese Society of Hypertension (JSH) [1] [2] [3] recommend that non-selective α1Bs are preferably used for hypertensive patients with BPH; however, the indications of α1Bs for the treatment of hypertension are becoming more restricted [4] [5]. In contrast, selective α1Bs are used as first-line therapies for BPH [6]. α_1-Adrenoceptors are classified into three subtypes. The α_{1A} subtype primarily regulates the smooth muscle tone and is expressed in the bladder neck and prostate gland [7] [8]; the α_{1B} subtype regulates arterial smooth muscles which mediate blood pressure; and the α_{1D} subtype is expressed in the detrusor muscle and sacral spinal cord, both involved in bladder filling [7] [8] [9]. Since selective α1Bs can only target the prostate gland or bladder smooth muscle, they are expected to generate fewer adverse drug events, such as dizziness, hypotension, and syncope, than do non-selective α1Bs.

Syncope is defined as "a transient loss of consciousness due to transient global cerebral hypoperfusion characterized by rapid onset, short duration, and spontaneous complete recovery" [10]. A fall in systolic blood pressure to 60 mmHg or lower is associated with syncope in the absence of compensatory mechanisms and inadequate automatic regulation of systemic or cerebral blood flow [11]. Syncope leads to falls, which can cause minor injuries or major morbidities. Indeed, 17% of the patients with syncope visited an emergency department with bruises or lacerations on the head and face [12]; fractures and motor vehicle accidents due to syncope have also been reported [13] [14].

Adverse event databases are repositories of information, overseen by regulatory authorities of each country and used to quickly find adverse events caused by marketed drugs. The Japanese Adverse Drug Event Report (JADER) database, managed by the Pharmaceutical and Medical Devices Agency (PMDA), which is the regulatory authority in Japan, is a publicly available database, suitable for analyzing adverse events.

Depending on circumstances, spasmodic loss of consciousness can cause substantial injuries, such as bone fractures, hospitalizations, and fatalities. As reported previously [15] [16] [17] [18], if an adverse event (e.g., syncope) is attributable to a drug, knowing in advance the approximate onset time and tendency

Table 1. α_1-Adrenoceptor blockers available on the market in Japan.

α1 Subtype receptor selectivity	Drug name	Indication	
		Hypertension	Benign prostatic hyperplasia
Non-selective			
	Prazosin	+	+
	Bunazosin	+	–
	Terazosin	+	+
	Urapidil	+	+
	Doxazosin	+	–
Selective			
	Naftopidil	–	+
	Silodosin	–	+
	Tamsulosin	–	+

for occurrence of such an event would allow the patient to be alerted and avoid or minimize the potential injury. Therefore, to evaluate the onset time of syncope due to α1B usage, a disproportionality analysis was performed in this study to examine the association between α1B use and syncope in males. Furthermore, for each drug for which statistical significance was detected, its onset time profile was evaluated using the time information available in the JADER database.

2. Materials and Methods

2.1. Data Source

The data recorded in the JADER database from April 2004 to November 2016 were downloaded from the PMDA website. The database consists of four data sets: patient demographic information (DEMO), drug information (DRUG), adverse event (REAC), and primary disease (HIST). A flowchart of the steps involved in the construction of a data analysis table is provided in **Figure 1**. In the present study, we only extracted data for males over 20 years old.

2.2. Study Drugs and Definition of Adverse Events

The drugs of interest were eight α1Bs (prazosin, bunazosin, terazosin, urapidil, doxazosin, naftopidil, silodosin, and tamsulosin) available on the market in Japan. The route of administration was limited to oral administration. The adverse events listed in REAC are based on the medical terminology used in the Medical Dictionary for Regulatory Activities (MedDRA) as preferred terms (PTs). PTs also include various conditions as lowest level terms (LLTs). For the detection of syncope, we used "syncope" (PT 10042772) and "loss of consciousness" (PT 10024855), which includes "transient loss of consciousness" (LLT 10077573), as LLTs from the MedDRA ver. 18.0.

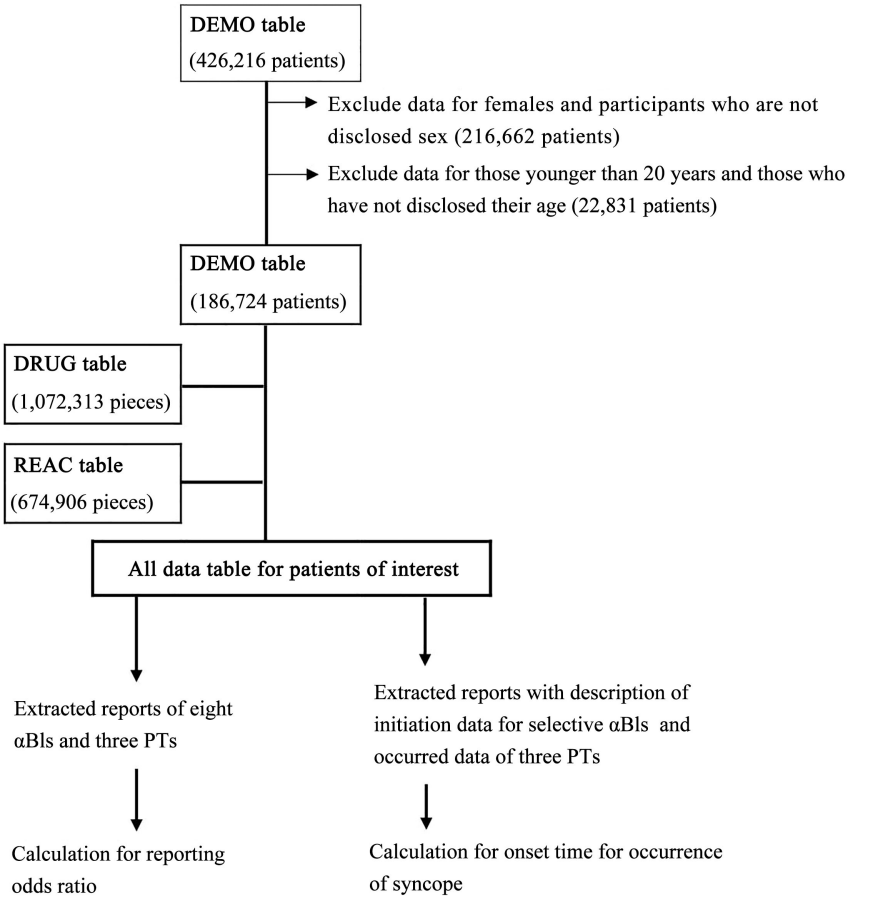

Figure 1. Flowchart of the steps involved in the construction of a data analysis table.

2.3. Data Analysis

2.3.1. Reporting Odds Ratio (ROR)

RORs, safety signal indexes for adverse drug events, were calculated using a data mining algorithm, (a:c)/(b:d) [19] [20] [21] [22], where the letters refer to the following: a) individuals who were administered the drug of interest (e.g., an α1B) and experienced an adverse event (e.g., syncope); b) individuals who were administered the drug of interest but did not experience the adverse event; c) individuals who were not administered the drug of interest but experienced the adverse event; and d) individuals who were not administered the drug of interest and did not experience the adverse event. The signal was considered significant when the estimated ROR and the lower limit of the corresponding 95% confidence interval (CI) were greater than 1.0.

2.3.2. Onset Times of Adverse Events

The onset time of an adverse event was calculated by adding 1 day to the number of days from the time of initiation of the drug of interest until the occurrence of the adverse event using the time information recorded in the JADER database. After the data with incomplete adverse event or prescription initiation dates were excluded, box plots of the relationships between the drugs and onset times

of the adverse event were created, and the median data were compared for different drugs.

Furthermore, a Weibull distribution was used to evaluate the expression profile of the adverse event using the Weibull shape parameter test [15] [23] [24]. The Weibull distribution is expressed using a scale parameter, α, and a shape parameter, β. The scale parameter α represents the scale of the distribution function. A larger scale value stretches the distribution, while a smaller scale value shrinks the data distribution. The shape parameter β represents the change in the hazard over time. There are three types of failure, according to the value of β, as follows: $\beta < 1$ indicates that the hazard increases at an early stage but subsequently decreases (early failure type); $\beta = 1$ indicates that the hazard is constant over the time of exposure (random failure type); and $\beta > 1$ indicates that the hazard increases over time (wear-out failure type). Plots of the cumulative incidence of syncope for the α1B drugs were constructed using the Kaplan–Meier method.

We set the maximum number of days to the onset of adverse events to 730. Data analysis was performed using JMP Pro 13.0 (SAS Institute, Inc., Cary, NC, USA).

3. Results

3.1. JADER Data

The JADER data, containing 426,216 reports from April 2004 to November 2016, were downloaded from the PMDA website. After extracting data for males older than 20 years, 186,724 reports (41.8% of the data) were used for analysis. Numbers of reports in the JADER database by age groups of the male patients analyzed in this study are described in Table 2.

3.2. ROR Values

Ninety-six reports were extracted for prazosin, 57 for bunazosin, 50 for terazosin, 252 for urapidil, 1,929 for doxazosin, 1,678 for naftopidil, 1,627 for silodosin, and 3,965 for tamsulosin. There were 288 reports of syncope and 1,346 reports of loss of consciousness as adverse events. After cases with identical identification numbers were excluded from the analysis, the associations between α1Bs and syncope were determined, and the results are shown in Table 3. The ROR values (95% CI) for α1Bs that were found to be statistically significant for syncope were 2.53 (1.81 - 3.53) for naftopidil, 4.25 (3.25 - 5.60) for silodosin, and 2.22 (1.75 - 2.81) for tamsulosin (Table 3).

3.3. Onset Times of the Adverse Event

Box plots with the median values of the onset times of the adverse event are shown in Figure 2. The median numbers of days (with interquartile ranges) for syncope were 37 (4 - 184) for naftopidil, 26 (4 - 391) for silodosin, and 108 (15 - 341) for tamsulosin.

The results of the Weibull distribution analysis for the three drugs are summarized in Table 4. The lower limits of the 95% CI for the shape parameter β were all <1, indicating the early failure type. The cumulative incidence rates of syncope, generated by the Kaplan–Meier method for naftopidil, silodosin, and tamsulosin, are shown in Figure 3. Although naftopidil and tamsulosin administration resulted in the earliest and latest onsets of syncope, respectively, in the first 350 days, the overall onset times of syncope were similar among the three α1Bs.

Table 2. Numbers of reports in the JADER database by age groups of the male patients analyzed in this study.

	Number of reports	Percent
Total	186,724	100.00
Sex		
Male	186,724	100.00
Age (years)*		
20 - 29	5,651	3.03
30 - 39	10,119	5.42
40 - 49	14,854	7.96
50 - 59	27,541	14.75
60 - 69	50,327	26.95
70 - 79	53,152	28.47
80 - 89	21,681	11.61
90 - 99	1,859	1.00
100>	36	0.02
Adult	663	0.36
The aged	841	0.45

*Age groups correspond to those provided in the DEMO table.

Table 3. Signal detection for α_1-adrenoceptor blockers associated with syncope.

Drug name	Total number of reports	Number of cases	Reporting ratio (%)	ROR	95% CI
Prazosin	96	0	0	–	–
Bunazosin	57	1	1.75	2.03	0.28 - 14.7
Terazosin	50	0	0	–	–
Urapidil	252	5	1.98	2.31	0.95 - 5.60
Doxazosin	1929	17	0.88	1.01	0.63 - 1.64
Tamsulosin	3965	74	1.87	2.22	1.75 - 2.81
Naftopidil	1678	36	2.15	2.53	1.81 - 3.53
Silodosin	1627	57	3.50	4.25	3.25 - 5.60

The definition of syncope included syncope (PT 10042772) and loss of consciousness (PT 10024855). Cases with identical identification numbers were excluded from the analysis since a single report included several drugs from the same category. Reporting ratio (%) = Number of cases/Total number of reports × 100. ROR: reporting odds ratio. 95% CI: 95% confidence interval.

Table 4. Weibull shape parameters of onset times of syncope due to α_1-adrenoceptor blockers.

Drug name	Number of cases	Scale parameter α (95% CI)	Shape parameter β (95% CI)
Naftopidil	28	91.6 (41.1 - 195)	0.52 (0.38 - 0.69)
Silodosin	45	97.2 (51.2 - 179)	0.51 (0.40 - 0.63)
Tamsulosin	30	162 (90.2 - 282)	0.69 (0.50 - 0.90)

95% CI: 95% confidence interval.

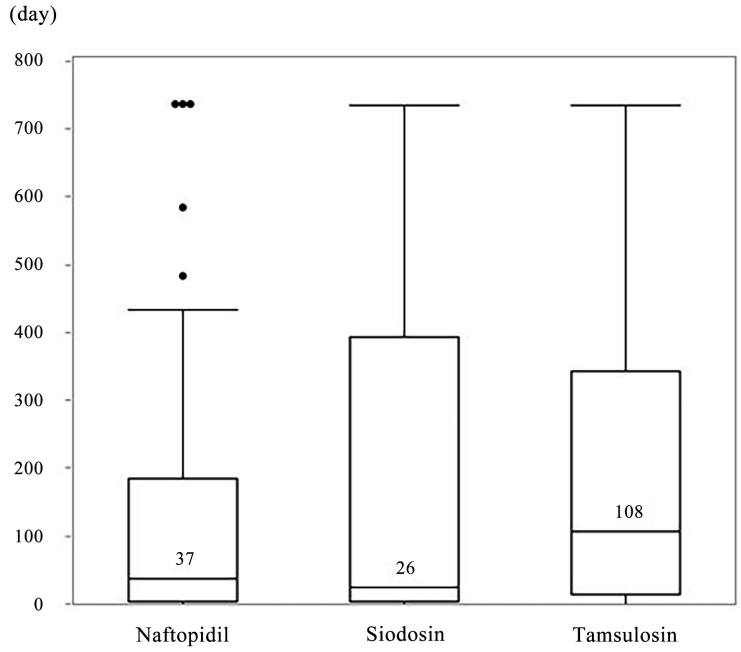

Figure 2. Box plots for the onset times of syncope due to α_1-adrenoceptor blockers. The number in each box represents the median number of days to onset of syncope.

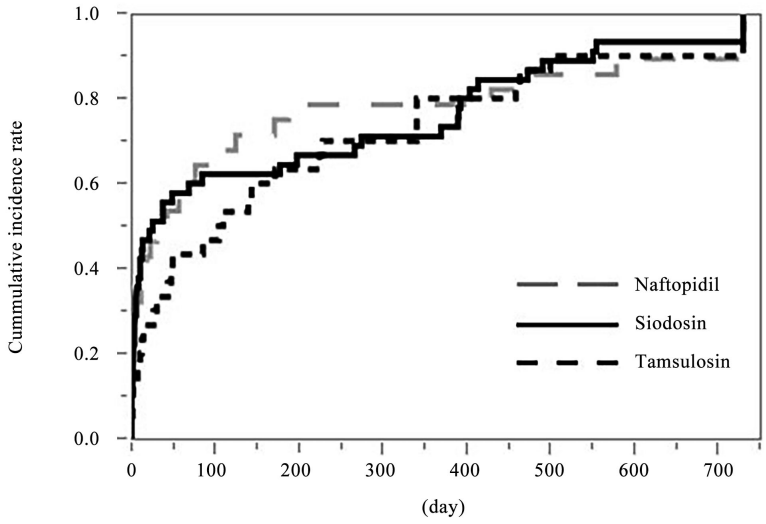

Figure 3. Cumulative incidences of syncope due to α_1-adrenoceptor blockers.

4. Discussion

Knowing in advance the approximate onset times of adverse events would be useful information to avoid those. In the present study, we evaluated the onset time profiles of syncope due to the use of individual *α*1Bs.

For more than 10 years since the JSH published its first guidelines on the management of hypertension in 2000 (JSH2000), *α*1Bs had been preferably indicated for hypertensive patients with BPH. However, the guidelines were updated in 2014 to recommend that caution be exercised when treating elderly hypertensive patients [4]. Moreover, the 2015 guidelines for medical treatment and safety in the elderly [5] recommended that *α*1Bs be maximally avoided for elderly patients with hypertension. Thus, the recent indications of *α*1Bs for hypertension are so few that the small numbers of reports remaining in the JADER database are likely to represent the background.

Tamsulosin, naftopidil, and silodosin were shown to be selective for the α_{1B}-adrenoceptor subtype, with 15.3-, 5.4-, and 583-fold higher affinity than that for the α_{1A}-adrenoceptor subtype and 4.6-, 16.7-, and 10.5-fold higher affinity than that for the α_{1D}-adrenoceptor subtype, respectively [25] [26]. However, in the present study, using adverse event data from clinical reports, significant signals were detected for the three selective *α*1Bs, but no significance was found for the non-selective *α*1Bs, including doxazosin, despite a sufficient number of reports. The reasons for these findings are unclear, but one of the likely explanations may be differences in the numbers of reports in the JADER database. As described above, there are relatively few reports on the non-selective *α*1Bs in the JADER database, as compared with those on the selective *α*1Bs. The differences may be due to some reporting biases because it is worth reporting severe adverse events, such as syncope, that are attributable to selective *α*1Bs, whereas orthostatic hypotension, an adverse event caused by non-selective *α*1Bs, is too common to be reported. Furthermore, concomitant medications coadministered for hypertension may be responsible for the findings. Lai *et al.* [27] [28] have reported that during an early period after treatment initiation, *α*1B therapy in patients not taking antihypertensive medications was associated with an increased risk of ischemic stroke and hip/femur fracture, which are severe adverse effects due to *α*1Bs. The non-selective *α*1Bs examined in the present study were supposedly indicated for hypertensive BPH patients. Therefore, it would be unlikely for patients taking antihypertensive medications to experience severe adverse events sequential to orthostatic hypotension.

The median values (with interquartile ranges) of the onset times of syncope were close for naftopidil and silodosin, 37 (4 - 184) and 26 (4 - 391) days, respectively (**Figure 2**). Tamsulosin showed a later onset, 108 (15 - 341) days, than did the other two drugs (**Figure 2**); however, based on the expression profiles of the adverse event, all three *α*1Bs were of the early failure type (**Table 4**). Therefore, patients treated with *α*1Bs should be closely monitored for syncope for 100 days, especially in the first 20 to 40 days after initiation of naftopidil or silodosin.

According to the Weibull shape parameter test, there was anincrease in adverse events at an early stage, indicating that syncope was likely caused by hypotension-related adverse events due to the α_1-adrenoceptor-blocking activity. We also calculated the onset times of orthostatic hypotension-related adverse events, using PTs for orthostatic hypotension (PT 10031127), dizziness (PT 10013573), and dizziness postural (PT 10013578), and the median values (with interquartile ranges) were 8 (1 - 149) for naftopidil, 3 (1 - 11) for silodosin, and 71 (15 - 730) days for tamsulosin (data not shown).Considering the median onsettimes of syncope, one of the precursor symptoms would have preceded the occurrence of syncope. In the clinic, patients with these precursor symptoms can be routinely treated to avoid inadequate regulation of systemic or cerebral blood flow.

There are several limitations in this study. First, the reports examined in this study may have included syncope due to factors other than orthostatic hypotension since syncope is classified into three types, namely, syncope due to orthostatic hypotension, neurallymediated syncope, and cardiac syncope [10]. There is a possibility that we included α1Bs that were administered to patients with cardiac arrhythmias, coronary artery disease, or myocardial infarction. In addition, owing to the background α1B indications, only reports for males were extracted and analyzed. Moreover, spontaneous reporting systems have limitations, including the lack of details needed to assess causal associations, generalized underreporting bias, dependence of the reporting rate on the time of the presence of each drug on the market, exclusion of healthy individuals, and the lack of denominators [19] [29]. We excluded some data because of the missing dates, making it impossible to calculate the onset time. However, despite the unique limitations of spontaneous adverse event reporting systems, our study revealed typical onset times of adverse events.

5. Conclusion

In conclusion, in the present study, we found, using the information from the JADER database, that the use of selective α1Bs was associated with syncope, and the onset time profiles for syncope were similar among the drugs. Therefore, patients treated with selective α1Bs should be closely monitored for 100 days, especially in the first 20 to 40 days after initiation of silodosin or naftopidil. We hope that this information will be useful for patients and healthcare professionals in preventing syncope due to the use of selective α1Bs.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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