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Evaluation of syncope association with α_1-adrenoceptor blockers in males using the FAERS database: impact of concomitant hypertension

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Previous studies have revealed an association between the administration of α_1-adrenoceptor blockers (α1Bs) and episodes of syncope in patients with benign prostatic hyperplasia (BPH). The objective of the present study was to evaluate the association between α1Bs and syncope in BPH patients with hypertension using two different pharmacoepidemiological indices. Using the US Food and Drug Administration Adverse Event Reporting System, we analyzed the whole dataset and subsets for specific indications, including hypertension, diabetes, and dyslipidemia, for males older than 40 years. The drugs of interest were alfuzosin, doxazosin, and terazosin as non-selective α1Bs and silodosin and tamsulosin as selective α1Bs. The reporting odds ratio (ROR) and information component (IC) were used for signal detection. The association between the non-selective α1Bs and syncope was observed for all the items examined. The results obtained using the whole dataset, as well as the diabetes and dyslipidemia subsets, were same for the selective and non-selective α1Bs in terms of the association with syncope, while no association with syncope was observed for both silodosin [ROR: 1.09, 95% confidence interval (CI): 0.61–1.93; IC: 0.10, 95% CI: –0.72–0.92] and tamsulosin (ROR: 1.08, 95% CI: 0.90–1.30; IC: 0.10, 95% CI: –0.17–0.37) in patients with hypertension. The data suggested that α1Bs, even those with receptor subtype selectivity, were associated with syncope. Thus, careful attention should be paid when prescribing α1Bs, especially to patients who do not take medications for hypertension.

1. Introduction

Syncope is a transient global cerebral hypoperfusion associated with the loss of consciousness. Syncope is caused by a fall of blood pressure and is characterized by a rapid onset, short duration, and spontaneous complete recovery (Moya et al. 2009). Based on its three principal causes, syncope is pathophysiologically classified into reflex syncope, syncope due to orthostatic hypotension, and cardiac syncope (Moya et al. 2009). Some episodes of syncope may be accompanied by pre-symptoms such as dizziness, sweating, and visual disturbance. Depending on the causative disease, syncope is not directly life-threatening, but it may lead to occasional severe injuries or major morbidities (Bänsch et al. 1998; Bhatia et al. 1999).
α_1-Adrenoceptor blockers (α1Bs) are the most frequently prescribed drugs for the treatment of benign prostatic hyperplasia (BPH) (Lepor et al. 2012). Although α1Bs are effective, it is well known that they can induce hypotension and dizziness, which occasionally lead to severe adverse events, such as falls, fractures, and syncope (Bird et al 2013; Chrischilles et al 2001). Currently, α1Bs with selectivity for α_1-adrenoceptor subtypes are used more frequently than non-selective ones. Selective α1Bs have been designed to be less effective for the α_{1B} subtype, which regulates blood pressure via arterial smooth muscles, and more effective for the bladder neck and prostate gland through the α_{1A} subtype and/or for the smooth muscle tone through the α_{1D} subtype (De Mey et al. 1999; Hatano et al. 1994; Schwinn et al. 2000).
Spontaneous reporting systems have been recognized as primary tools for pharmacovigilance, as they reflect the realities of clinical practice (Poluzzi et al. 2012; Sakaeda et al. 2013). Among the spontaneous reporting systems currently available to the public, the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) is one of the world's largest databases. A spontaneous reporting system can be used to evaluate drug-associated adverse events *via* disproportionality analysis, by calculating the reporting odds ratio (ROR) (van Puijenbroek et al. 2002; Suzuki et al. 2015; Ohyama et al. 2017) and Bayesian confidence propagation neural network method based on an information component (IC) (Bate et al. 1998; Takada et al. 2016). Additionally, in the disproportionality analysis of a spontaneous adverse event reporting system, it is useful to utilize subset analysis, which may help mitigate the effects of confounding factors on signal detection (Grégoire et al. 2008; Raschi et al. 2013; Umetsu et al. 2015).
In our previous report (Ohyama et al. 2018), using the Japanese Adverse Drug Event Report (JADER) database, the spontaneous reporting system of adverse drug events in Japan, syncope was found to be only associated with selective α1Bs (naftopidil, silodosin, and tamsulosin) but not with non-selective α1Bs (prazosin, bunazosin, terazosin, urapidil, and doxazosin). One of the reasons for the results contradicting the α_1-adrenoceptor subtype selectivity theory may be the existence of some reporting bias so that theoretically likely adverse events are too common to be reported. Indeed, there are relatively fewer reports on non-selective α1Bs than on selective α1Bs with regard to syncope in the JADER database (Ohyama et al. 2018). Meanwhile, in terms of indications for α1Bs in Japan, all non-selective α1Bs are indicated for hypertension, whereas selective α1Bs are only indicated for BPH. Therefore, the objective of the present study was to evaluate the association of non-selective and selective α1Bs with syncope in patients with hypertension in the FAERS database.

2. Investigations and results

A total of 1,186,456 reports were extracted from the FAERS database for males older than 40 years. The total numbers of the reports registered with the terms *Hypertension, Hyperglycaemia/new*

onset diabetes mellitus, and *Dyslipidaemia* were 75,689, 86,569, and 52,816, respectively.

The data of statistical analysis of the association of syncope with non-selective and selective α1Bs, based on the reports for the whole dataset and hypertension, diabetes, and dyslipidemia subsets, are presented for ROR and IC in Fig. 1. Both signal scores, with 95% confidence intervals (CIs), suggested that the non-selective α1Bs were significantly associated with syncope in all the datasets (ROR: 2.67, 95% CI: 2.49–2.86; IC: 1.33, 95% CI: 1.23–1.43 for the whole data; ROR: 2.19, 95% CI: 1.92–2.50; IC: 1.00, 95% CI: 0.80–1.19 for hypertension; ROR: 2.04, 95% CI: 1.56–2.68; IC: 0.95, 95% CI: 0.55–1.36 for diabetes; and ROR: 1.64, 95% CI: 1.21–2.24; IC: 0.65, 95% CI: 0.20–1.10 for dyslipidemia). However, significant associations with syncope were only found for the selective α1Bs in the whole dataset (ROR: 2.04, 95% CI: 1.91–2.17; IC: 0.96, 95% CI: 0.87–1.06), as well as in the subsets for diabetes (ROR: 1.65, 95% CI: 1.25–2.17; IC: 0.67, 95% CI: 0.27–1.07) and dyslipidemia (ROR: 1.70, 95% CI: 1.33–2.18; IC: 0.69, 95% CI: 0.33–1.05) but not in that for hypertension (ROR: 1.08, 95% CI: 0.91–1.29; IC: 0.10, 95% CI: –0.16–0.36). The results of statistical analysis for individual α1Bs are presented in Table 1.

3. Discussion

In a previous study (Ohyama et al. 2018), using the spontaneous adverse event reporting system in Japan, we have reported that syncope was only associated with selective α1Bs, which are indicated for BPH, but not with non-selective α1Bs, among which some are also indicated for hypertension. In the present study, to clarify the results in accordance with the α_1-adrenoceptor subtype selectivity theory, we conducted subset analysis by extracting data from the FAERS database for some indications, including hypertension. The association of syncope with non-selective α1Bs and with those selective for BPH was examined using two different disproportionality analysis measures.

Subset data for a population of patients with some risk factors and diseases are useful for evaluating the association of drug–adverse event in disproportionality analysis (Umetsu et al. 2015). Therefore, we analyzed not only the whole dataset but also subsets for diabetes and dyslipidemia to mitigate the influence of confounding factors for hypertension.

α1Bs are notorious for causing hypotension-related adverse events, occasionally leading to falls, fractures, and syncope (Bird

Table 1: Association of individual α_1-adrenoceptor blockers with syncope in the analyzed datasets

Set/subset	α1Bs	Cases (n)	Total (n)	ROR	95% CI	IC	95% CI
Whole							
	Non-selective						
	Alfuzosin	184	4,075	2.43	2.09–2.82	1.22	1.01–1.44
	Doxazosin	336	8,389	2.15	1.93–2.40	1.06	0.90–1.22
	Terazosin	362	5,763	3.47	3.11–3.86	1.70	1.55–1.86
	Selective						
	Silodosin	86	2,010	2.29	1.85–2.84	1.14	0.82–1.45
	Tamsulosin	971	26,209	2.01	1.88–2.15	0.95	0.85–1.04
Hypertension							
	Non-selective						
	Alfuzosin	33	492	1.93	1.35–2.75	0.85	0.34–1.37
	Doxazosin	133	2,188	1.76	1.47–2.11	0.74	0.48–1.00
	Terazosin	90	857	3.20	2.56–4.00	1.51	1.18–1.83
	Selective						
	Silodosin	12	307	1.09	0.61–1.93	0.10	–0.72–0.92
	Tamsulosin	124	3,201	1.08	0.90–1.30	0.10	–0.17–0.37
Diabetes							
	Non-selective						
	Alfuzosin	6	265	1.31	0.58–2.95	0.32	–0.79–1.42
	Doxazosin	35	852	2.46	1.75–3.46	1.19	0.69–1.68
	Terazosin	12	431	1.63	0.91–2.89	0.61	–0.20–1.43
	Selective						
	Silodosin	3	154	1.12	0.36–3.53	0.12	–1.35–1.58
	Tamsulosin	51	1,780	1.69	1.28–2.25	0.70	0.29–1.12
Dyslipidemia							
	Non-selective						
	Alfuzosin	7	290	1.41	0.66–2.99	0.41	–0.63–1.44
	Doxazosin	23	782	1.74	1.14–2.65	0.72	0.12–1.33
	Terazosin	13	485	1.57	0.90–2.74	0.57	–0.21–1.36
	Selective						
	Silodosin	13	157	5.19	2.93–9.19	1.91	1.10–2.72
	Tamsulosin	57	2,326	1.46	1.11–1.91	0.49	0.10–0.89

α1Bs: α₁-adrenoreceptor blockers; ROR: reporting odds ratio; CI: confidence interval; IC: information component

et al. 2013; Chrischilles et al. 2001). In general, patients who were treated with other antihypertensive medications, prior to α1Bs, would show an increased risk of hypotension-related adverse events (Bird et al. 2013; Chrischilles et al. 2001). However, our results showed that drug-associated syncope was not detected in patients with concomitant hypertension only taking selective α1Bs. Some other reports partially support our results. Thus, Lai et al. (2015, 2016) reported, using claims data in Taiwan, that in patients without concomitant prescriptions of antihypertensive agents, α1B therapy was associated with statistically significant risks of hip/femur fractures and ischemic stroke during the early initiation period, which was not observed in patients with concomitant prescriptions of antihypertensive agents. A possible explanation of our results is that patients with hypertension may have an excited sympathetic nerve system, making them tolerant to the inadvertent hypotensive effects induced by the administration of α1Bs. At the same time, patients without hypertension may have weak or no adequate regulation of systemic or cerebral blood flow to be able to tolerate the inadvertent hypotensive effect caused by α1Bs.

Analysis of individual α1Bs showed no signals for alfuzosin and terazosin in patients with diabetes and dyslipidemia (Table 1). The reasons are unclear but may be related to the characteristics of these drugs. Terazosin has been reported to produce no clinically significant changes in systolic and diastolic blood pressure in normotensive patients (Kirby 1998). Alfuzosin, in spite of the lack of significant receptor subtype selectivity, has been reported to display the lowest hypotensive activity among α1Bs when administered intravenously to conscious normotensive rats at doses 3 to 10 times higher than those necessary to induce significant urethral relaxation (Roehrborn et al. 2001). Although alfuzosin has been reported to be clinically uroselective, in the present study, it was classified as a non-selective α1B based on the receptor subtype theory (Shibata et al. 1995; Takei et al. 1999).

There are some limitations in this study. First, we extracted the α1B data based on the drug only and did not consider formulations, e.g., with different effective times, since we tried to examine differences in adverse events associated with α1Bs based on the receptor subtype theory (Shibata et al. 1995; Takei et al. 1999). Second, because of the inadequate number of reports, we could not analyze another concomitant disease and naftopidil. Third, in general, spontaneous reporting databases have their intrinsic limitations, such as underreporting, reporting bias, the lack of detailed clinical information, and the lack of certainty that the reported events are due to the drugs (Wise et al. 2009). Therefore, careful consideration is needed when interpreting results obtained from a database. On the other hand, analysis using a spontaneous reporting system has many advantages for detecting a tendency for a drug–adverse event association (Fujita 2009), including the availability of information on coadministration of various drugs and indications in patients, reflecting medical practice.

Our results suggest that even selective α1Bs are associated with syncope, except in patients with concomitant hypertension. Therefore, careful attention should be paid when prescribing α1Bs, especially to patients who do not take medications for hypertension.

Table 2: Preferred terms for three indications, hypertension, diabetes, and dyslipidemia, used in the present study for the analysis of the FAERS database

Indication	Preferred Term	Code
Hypertension		
	Blood pressure increased	10005750
	Essential hypertension	10015488
	Hypertension	10020772
Diabetes		
	Blood glucose increased	10005557
	Diabetes mellitus	10012601
	Diabetes mellitus inadequate control	10012607
	Diabetic ketoacidosis	10012671
	Diabetic metabolic decompensation	10074309
	Glucose tolerance impaired	10018429
	Glucose urine present	10018478
	Glycosuria	10018473
	Glycosylated haemoglobin increased	10018484
	Hyperglycaemia	10020635
	Impaired fasting glucose	10056997
	Insulin resistance	10022489
	Insulin-resistant diabetes	10022491
	Insulin-requiring type 2 diabetes mellitus	10053247
	Ketoacidosis	10023379
	Ketosis	10023391
	Ketosis-prone diabetes mellitus	10023392
	Latent autoimmune diabetes in adults	10066389
	Pancreatogenous diabetes	10033660
	Type 1 diabetes mellitus	10067584
	Type 2 diabetes mellitus	10067585
Dyslipidemia		
	Blood cholesterol abnormal aemia	10005423
	Blood cholesterol increased	10005425
	Blood triglycerides abnormal	10005837
	Blood triglycerides increased	10005839
	Diabetic dyslipidaemia	10070901
	Dyslipidaemia	10058108
	High density lipoprotein abnormal	10020051
	High density lipoprotein decreased	10020060
	Hypercholesterolaemia	10020603
	Hyperlipidaemia	10062060
	Hypertriglyceridaemia	10020869
	Hypo HDL cholesterolaemia	10068961
	LDL/HDL ratio increased	10077917
	Lipid metabolism disorder	10061227
	Lipids abnormal	10024588
	Lipids increased	10024592
	Lipoprotein (a) abnormal	10054023
	Lipoprotein (a) increased	10081354
	Low density lipoprotein abnormal	10024901
	Low density lipoprotein increased	10024910
	Remnant hyperlipidaemia	10038316
	Total cholesterol/HDL ratio abnormal	10058633
	Total cholesterol/HDL ratio increased	10058630
	Type I hyperlipidaemia	10060749
	Type II hyperlipidaemia	10045254
	Type III hyperlipidaemia	10060751
	Type IIa hyperlipidaemia	10045261
	Type IIb hyperlipidaemia	10045263
	Type IV hyperlipidaemia	10060753
	Type V hyperlipidaemia	10060755
	Very low density lipoprotein increased	10047361

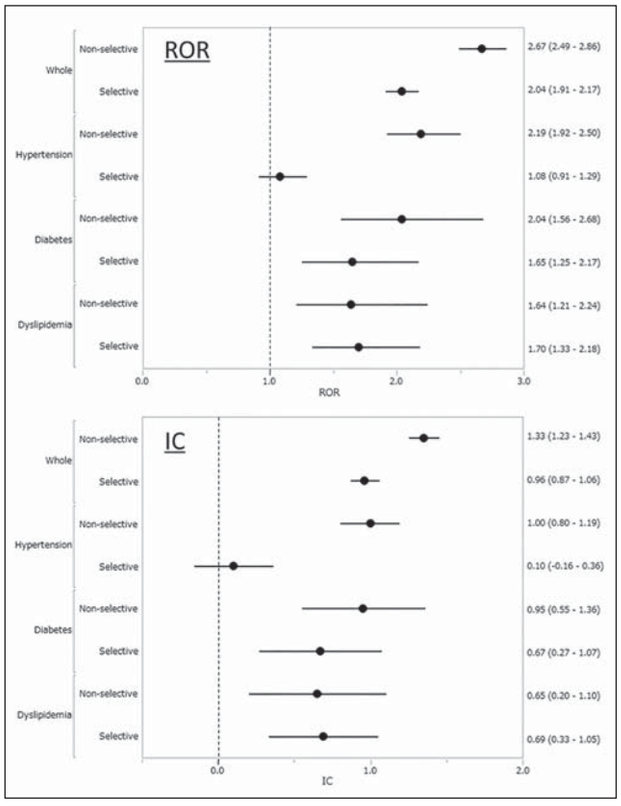

Fig. 1: Association of non-selective and selective α_1-adrenoceptor blockers with syncope in the analyzed datasets. ROR: reporting odds ratio; CI: confidence interval; IC: information component

4. Experimental

4.1. Data source

The FAERS data from January 2004 to December 2015 were downloaded from the FDA website (https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html). The FAERS database consists of the following seven datasets: patient demographic and administrative information (DEMO), drug/biologic information (DRUG), adverse events (REAC), patient outcomes (OUTC), report sources (RPSR), start and end dates of drug therapy (THER), and indications for use/diagnosis (INDI). All drug names in the DRUG table were changed to their respective generic names using the drug database, Drugs.com (https://www.drugs.com), and its name collecting function because the FAERS database contains generic names and their respective brand names used in the reporting countries. To apply the latest case identification numbers, redundant numbers were deleted in accordance with the FDA recommendations.

4.2. Drugs of interest

The drugs of interest were alfuzosin, doxazosin, and terazosin as non-selective α1Bs and silodosin and tamsulosin as selective α1Bs, which are all indicated for BPH in the United States.

4.3. Definitions of indications and adverse events

The indications for use/diagnosis in INDI and adverse events in REAC are coded using preferred terms (PTs) from the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Standardized MedDRA Queries (SMQs) are groupings of MedDRA terms from one or more "System Organ Class" related to the desired medical state or region of interest. We used SMQs *Hypertension* (SMQ 20000147), *Hyperglycaemia/new onset diabetes mellitus* (SMQ 20000041), and *Dyslipidaemia* (SMQ 20000026) to define the three indications and utilized PTs are summarized in Table 2. We also used "syncope" (PT 10042772) and "loss of consciousness" (PT 10024855) in REAC for the detection of syncope cases.

4.4. Data analysis

The relationship between syncope and each α1B was estimated using disproportionality analysis ROR (van Puijenbroek et al. 2002; Suzuki et al. 2015; Ohyama et al. 2017) and IC (Bate et al. 1998; Takada et al. 2016) values. Signal scores were calculated using a case/non-case method (Almenoff et al. 2007; Sakaeda et al. 2013; Takada et al. 2016). Although both measures use a two-by-two table for frequency counts to calculate signal scores, their algorithms are different, and ROR is frequentist (van Puijenbroek et al. 2002), while IC is Bayesian (Bate et al. 1998). The signal was defined when the lower limit of the 95% CI of ROR exceeded one and that of IC exceeded zero.

Conflicts of interest: None declared.

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