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Analysis of urinary retention caused by selective β3-adrenoceptor agonists using the Japanese Adverse Drug Event Report database (JADER)

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Overactive bladder (OAB) is a frequent chronic disorder which impairs quality of life by frequent, uncontrollable urination. Newly developed selective β3-adrenoceptor agonists (sβ3-agonists) have the same efficacy in treating OAB but significantly fewer side effects than the traditionally used anti-muscarinics. However, safety data on these compounds are scarce. In this study, we analysed the occurrence of adverse effects in patients taking sβ3-agonists and their characteristics using the JADER database. The most frequently reported adverse effect associated with the use of sβ3-agonists was urinary retention [mirabegron; crude reporting odds ratios (ROR): 62.1, 95% confidence interval (CI): 52.0–73.6, P<0.001, vibegron; crude ROR: 250, 95% CI : 134–483, P<0.001]. Data from patients with urinary retention were stratified by sex. In both men and women, the rate of urinary retention was higher when using the mirabegron/anti-muscarinic drug when compared to mirabegron monotherapy; its occurrence was higher in men with a history of benign prostatic hypertrophy than in those without. Weibull analysis showed that approximately 50% of sβ3 agonist-induced urinary retention occurred within 15 days after initiation of treatment, and then gradually decreased.
Although sβ3-agonists are useful against OAB, they may induce several side effects, especially urinary retention, which can further evolve into more severe conditions. Urinary retention occurs more frequently in patients concomitantly taking medication that either increases urethral resistance or has organic factors that block the urethra. When using sβ3-agonists, the concomitantly used medications and underlying diseases should be thoroughly reviewed, and safety monitoring should be instituted early during the treatment.

1. Introduction

Overactive bladder (OAB) is a chronic disease that impairs the quality of life of patients, owing to urinary urgency, frequency, and nocturia, especially in the elderly (Robinson and Cardozo, 2019). Anti-muscarinic drugs (anti-muscarinics) are the most commonly used first-line agents in the treatment of OAB, owing to their well-established efficacy (Chapple et al. 2008). However, they have been associated with side effects such as urinary retention, dry mouth, and constipation (Hegde 2006). Subsequently, selective β3-adrenoceptor agonists (sβ3-agonists) have been developed and used. Activation of β3-adrenergic receptors in the bladder by sβ3-agonists results in bladder relaxation, thereby relieving the symptoms of OAB (Leone Roberti Maggiore et al. 2014). They seem to be as effective as frequently used anti-muscarinics and cause significantly fewer bothersome side effects including anticholinergic effects such as dry mouth (Kelleher et al. 2018). In the past, there have been reports of severe adverse drug reactions about sβ3-agonists in randomized controlled trials and in post-marketing surveillance, albeit at a lower frequency (Kennelly et al. 2022; Kelleher et al. 2018; Cui et al. 2014; Nozawa et al. 2018). However, the background of the patient and the concomitant use of other medication are unknown owing to the limited number of cases (Kato et al. 2019). Furthermore, mirabegron and vibegron, sβ3-agonists efficient in treating OAB, are highly used for outpatients. Therefore, collecting information on adverse drug reactions is difficult. However, information on factors predisposing to adverse effects when using sβ3-agonists is important for ensuring the safety of the many patients treated for OAB with these therapeutical agents. In this study, we used the Japanese Adverse Drug Event Report database (JADER), which collects information on adverse drug reactions voluntarily reported to the Pharmaceuticals and Medical Devices Agency (PMDA), thus including adverse drug reactions during outpatient use. Using the JADER database, we analysed the occurrence of adverse drug reactions during treatment with sβ3-agonists, taking into consideration the characteristics of the patients who experienced the reactions and the concomitant use of other medication.

2. Investigations and results

2.1. Analysis of adverse events induced by sβ3-agonists and anti-muscarinics

Of the 380,604 cases reported between April 2012 and December 2020, 779 cases were associated with the use of mirabegron, 46 cases with vibegron, and 1,462 cases with anti-muscarinics. Among them, the significant safety signals associated with sβ3-agonists included the following: urinary retention (mirabegron, crude reporting odds ratios (ROR): 62.1, 95% CI: 52.0–73.6, P<0.001; vibegron, crude ROR: 250, 95% CI: 134–483, P<0.001); the signals for cardiac arrhythmia (mirabegron, crude ROR: 5.19, 95% CI: 3.95–6.72, P<0.001); and hypertension (mirabegron, crude ROR: 6.83, 95% CI: 4.89–9.32, P<0.001) (Table 1). Among the cases in which anti-muscarinics were the suspected drugs, the significant signals included the following: urinary retention (crude

Table 1: Analysis of adverse events induced by sβ3-agonists and anti-muscarinics

Adverse events	Total reported cases	sβ3-agonists								Anti-muscarinics			
		Mirabegron				vibegron							
		Case	Ratio (%)	Crude ROR (95% CI)	*p-value*	Case	Ratio (%)	Crude ROR (95% CI)	*p-value*	Case	Ratio (%)	Crude ROR (95% CI)	*p-value*
	380,604	779				46				1,462			
Urinary retention	2,169	191	24.5	62.1 (52.0–73.6)	*< 0.001*	27	58.7	250 (134–483)	*< 0.001*	823	56.3	365 (322–412)	*< 0.001*
Hypertension	3,263	43	5.52	6.83 (4.89–9.32)	*< 0.001*	1	2.17	2.57 (0.06–15.1)	*0.33*	10	0.68	0.78 (0.38–1.45)	*0.57*
Cardiac arrhythmias	6,505	64	8.22	5.19 (3.95–6.72)	*< 0.001*	3	6.52	4.01 (0.80–12.5)	*0.044*	50	3.42	2.02 (1.49–2.68)	*< 0.001*
Delirium	1,763	7	0.90	1.95 (0.78–4.05)	*0.10*	0	–	–	–	20	1.37	2.96 (1.80–4.61)	*< 0.001*
Dry eye	414	0	–	–	–	0	–	–	–	11	7.52	7.03 (3.47–12.7)	*< 0.001*
Dry mouth	158	1	0.13	3.11 (0.08–17.6)	*0.28*	0	–	–	–	23	1.57	44.3 (27.0–69.4)	*< 0.001*
Constipation	579	3	0.39	2.55 (0.52–7.50)	*0.12*	0	–	–	–	23	1.57	10.7 (6.73–16.3)	*< 0.001*

*sβ3-agonists: selective β3-adrenoceptor agonists; anti-muscarinics: anti-muscarinic drugs; ROR: reporting odds ratios; CI: confidence intervals.

ROR: 365, 95% CI: 322–412, *P*<0.001), cardiac arrhythmias (crude ROR: 2.02, 95% CI: 1.49–2.68, *P*<0.001), delirium (crude ROR: 2.96, 95% CI: 1.80–4.61, *P*<0.001), dry eye (crude ROR: 7.03, 95% CI: 3.47–12.7, *P*<0.001), dry mouth (crude ROR: 44.3, 95% CI: 27.0–69.4, *P*<0.001) and constipation (crude ROR: 10.7, 95% CI: 6.73–16.3, *P*<0.001) (Table 1).

2.2. Analysis of the characteristics of patients with urinary retention using information collected from JADER database

The frequency and mechanisms of urinary retention are different in men and women, owing to differences in the urinary drainage system (Hernández Hernández et al. 2013). Therefore, the present analysis was conducted separately by sex. Significant safety signals were observed for all sβ3-agonists and anti-muscarinics. In a multivariate logistic regression analysis in males, the occurrence of urinary retention was associated with reporting year (adjusted ROR: 1.13, 95% CI: 1.10–1.16, P<0.001), age (≥70 years, adjusted ROR: 1.48, 95% CI: 1.25–1.76, P<0.001), use of mirabegron (adjusted ROR: 66.8, 95% CI: 35.6–125, P<0.001), the use of vibegron (adjusted ROR: 276, 95% CI: 104–733, P<0.001), the use of anti-muscarinics (adjusted ROR: 420, 95% CI: 354–500, P<0.001) and the presence of BPH (adjusted ROR: 4.10, 95% CI: 3.47–4.84, P<0.001) (Table 2). In females, the occurrence of urinary retention was associated with age (≥70 years, adjusted ROR: 1.73, 95% CI: 1.34–2.22, P<0.001), the use of mirabegron (adjusted ROR: 125, 95% CI: 63.7–244, P<0.001), the use of vibegron (adjusted ROR: 88.0, 95% CI: 32.9–235, P<0.001), the use of anti-muscarinics (adjusted ROR: 262, 95% CI: 213–321, P<0.001) (Table 2). In male patients with BHP, the concomitant use of mirabegron (*P* = 0.022) was detected as significantly increasing the risk of urinary retention; additionally, the concomitant administration mirabegron and anti-muscarinics (P<0.001) in male and female patients were significant (Table 2).

2.3. Analysis of the characteristics of patients with urinary retention receiving sβ3-agonists

To evaluate the characteristics of patients with urinary retention using mirabegron, we included 779 cases (male: 438 cases, female: 341 cases) listed in JADER as associated with sβ3-agonists use.

Table 2: The univariate and multiple-logistic regression analysis of urinary retention

			Total	Case	Ratio (%)	Crude ROR (95% CI)	Adjusted ROR (95% CI)	*p-value*
Male			196,227	1,453	0.74			
	Reporting year		–	–	–	–	1.13 (1.10–1.16)	*< 0.001*
	Age							
		0–19 years	12,179	19	0.16	0.20 (0.12–0.31)	0.49 (0.30–0.80)	*0.004*
		20–29 years	4,497	5	0.11	0.15 (0.047–0.34)	0.42 (0.17–1.01)	*0.053*
		30–39 years	7,368	23	0.31	0.41 (0.26–0.62)	1.17 (0.75–1.81)	*0.49*
		40–49 years	13,488	53	0.39	0.51 (0.38–0.67)	1.28 (0.93–1.76)	*0.14*
		50–59 years	22,354	88	0.39	0.50 (0.40–0.62)	1.15 (0.88–1.50)	*0.32*
		60–69 years	48,057	226	0.47	0.56 (0.49–0.65)	reference	–
		>=70 years	86,831	1,039	1.2	3.12 (2.78–3.51)	1.48 (1.25–1.76)	*< 0.001*
	Drugs							
	sβ3-agonists							
		mirabegron	438	123	28.1	56.6 (45.1–70.6)	66.8 (35.6–125)	*< 0.001*
		vibegron	27	21	77.8	979 (282–4161)	276 (104–733)	*< 0.001*
	anti-muscarinics		874	592	67.7	476 (409–566)	420 (354–500)	*< 0.001*
		fesoterodine	562	501	89.1	1761 (1205–2475)	–	–
		imidafenacin	29	5	17.2	28.0 (8.34–75.1)	–	–
		oxybutynin	15	6	40	89.7 (26.3–281)	–	–
		propiverine	60	19	31.7	62.9 (34.4–111)	–	–
		solifenacin	187	51	27.3	52.1 (36.8–72.8)	–	–
		tolterodine	23	11	47.8	123 (49.4–307)	–	–

	Underlying diseases						
	BPH	10,801	463	4.28	8.34 (7.44–9.34)	4.10 (3.47–4.84)	*< 0.001*
	Interactions						
	mirabegron*Age (>=70 years)	–	–	–	–	0.91 (0.48–1.75)	*0.78*
	mirabegron*BPH	–	–	–	–	0.58 (0.36–0.93)	*0.022*
	mirabegron*anti-muscarinics	–	–	–	–	0.008 (0.004–0.015)	*< 0.001*
Female		184,377	716	0.39			
	Reporting year	–	–	–	–	1.03 (0.99–1.07)	*0.067*
	Age						
	0–19 years	11,260	23	0.2	0.50 (0.32–0.77)	1.23 (0.77–1.98)	*0.38*
	20–29 years	6,867	24	0.35	0.90 (0.57–1.35)	1.98 (1.24–3.16)	*0.004*
	30–39 years	11,783	24	0.2	0.51 (0.32–0.76)	1.12 (0.70–1.79)	*0.63*
	40–49 years	16,163	46	0.28	0.71 (0.52–0.96)	1.59 (1.10–2.31)	*0.014*
	50–59 years	21,476	56	0.26	0.64 (0.48–0.85)	1.41 (0.99–2.00)	*0.055*
	60–69 years	37,679	87	0.23	0.54 (0.42–0.67)	reference	–
	>=70 years	79,149	456	0.58	2.34 (2.00–2.74)	1.73 (1.34–2.22)	*< 0.001*
	Drugs						
	mirabegron	341	68	18.7	64.6 (47.7–86.4)	125 (63.7–244)	*< 0.001*
	vibegron	19	6	31.6	119 (37.1–338)	88.0 (32.9–235)	*< 0.001*
	anti-muscarinics	588	231	39.3	243 (204–298)	262 (213–321)	*< 0.001*
	fesoterodine	253	166	65.6	647 (481–834)	–	–
	imidafenacin	39	5	12.8	37.9 (11.6–98.3)	–	–
	oxybutynin	17	4	23.5	79.2 (18.8–257)	–	–
	propiverine	36	12	33.3	131 (59.1–273)	–	–
	solifenacin	235	40	17	55.6 (38.3–79.5)	–	–
	tolterodine	10	4	40	172 (35.6–738)	–	–
	Interactions						
	mirabegron * Age (>=70 years)	–	–	–	–	0.59 (0.29–1.22)	*0.16*
	mirabegron * anti-muscarinics	–	–	–	–	0.010 (0.005–0.019)	*< 0.001*

*sβ3-agonists: selective β3-adrenoceptor agonists; anti-muscarinics: anti-muscarinic drugs; BPH: benign prostatic hyperplasia; ROR: reporting odds ratios; CI: confidence intervals.
To construct the logistic model for males, the reporting year, age group, drugs (sβ3-agonist), use of anti-muscarinic, underlying BPH and interactions mirabegron*Age (>=70 years), mirabegron*BPH, and mirabegron*anti-muscarinics were coded. To construct the logistic model for females, the reporting year, age group, drugs (sβ3-agonist), use of anti-muscarinic, and interactions mirabegron*Age (>=70 years) and mirabegron*anti-muscarinics were coded. The adjusted RORs were calculated in independent models for each sβ3-agonist. Furthermore, the adjusted RORs for other factors were calculated using the mirabegron model.

In the multivariate logistic regression analysis of male patients, significant associations with urinary retention were observed for reporting year (adjusted ROR: 1.20, 95% CI: 1.10–1.31, P<0.001), the concomitant use of anti-muscarinics (adjusted ROR: 3.67, 95% CI: 1.97–6.85, P<0.001), and the presence of BPH (adjusted ROR: 2.43, 95% CI: 1.53–3.86, P<0.001) (Table 3). In the analysis of female patients, a significant association was observed for the concomitant use of anti-muscarinics (adjusted ROR: 2.59, 95% CI: 1.36–4.95, P=0.004) (Table 3).

2.4. Characteristics of urinary retention among patients with BPH

We evaluated the characteristics of urinary retention across 10,806 cases listed in the JADER, for patients in which BPH was the underlying disease. In the multivariate logistic regression analysis, significant associations were observed between urinary retention and reporting year (adjusted ROR: 1.09, 95% CI: 1.04–1.15, P<0.001), the use of mirabegron (adjusted ROR: 27.4, 95% CI: 19.2–39.2,

Table 3: Analysis of each factor related to urinary retention among patients receiving sβ3-agonists

		Total	Case	Ratio (%)	Crude ROR (95% CI)	Adjusted ROR (95% CI)	*p-value*
Male		438	123	28.1			
	Reporting year	–	–	–	–	1.20 (1.10–1.31)	*< 0.001*
	Age						
	0–19 years	0	0	–	–	–	–
	20–29 years	0	0	–	–	–	–
	30–39 years	2	0	–	–	–	–
	40–49 years	4	0	–	–	–	–
	50–59 years	18	3	16.7	0.50 (0.091–1.82)	0.55 (0.13–2.42)	*0.43*
	60–69 years	46	12	26.1	0.89 (0.41–1.85)	reference	–
	>=70 years	368	108	29.3	1.52 (0.81–3.03)	1.02 (0.50–2.10)	*0.96*
	Anti-muscarinics	53	28	52.8	3.41 (1.82–6.42)	3.67 (1.97–6.85)	*< 0.001*
	fesoterodine	14	12	85.7	14.4 (3.13–134)	–	–

	imidafenacin	3	0	–	–	–	–
	oxybutynin	2	1	50	2.22 (0.028–175)	–	–
	propiverine	5	4	80	9.04 (0.88–448)	–	–
	solifenacin	30	12	40	1.78 (0.76–4.06)	–	–
	tolterodine	0	0	–	–	–	–
	Underlying diseases						
	BPH	202	73	36.1	2.10 (1.35–3.30)	2.43 (1.53–3.86)	*< 0.001*
Female		341	68	19.9			
	Reporting year	–	–	–	–	1.11 (1.00–1.24)	*0.049*
	Age						
	0–19 years	0	0	–	–	–	–
	20–29 years	1	0	–	–	–	–
	30–39 years	1	0	–	–	–	–
	40–49 years	5	2	40.0	2.72 (0.22–24.2)	2.50 (0.34–18.2)	*0.37*
	50–59 years	10	2	20.0	1.00 (0.10–5.19)	1.13 (0.20–6.50)	*0.89*
	60–69 years	43	9	20.9	1.05 (0.42–2.40)	reference	–
	>=70 years	281	55	19.6	0.88 (0.43–1.90)	0.97 (0.43–2.19)	*0.94*
	Anti-muscarinics	55	19	34.5	2.54 (1.27–5.00)	2.59 (1.36–4.95)	*0.004*
	fesoterodine	6	4	66.7	8.39 (1.17–94.7)	–	–
	imidafenacin	4	0	–	–	–	–
	oxybutynin	2	0	–	–	–	–
	propiverine	3	1	33.3	2.02 (0.034–39.3)	–	–
	solifenacin	40	14	35.0	2.46 (1.11–5.26)	–	–
	tolterodine	2	0	–	–	–	–

*sβ3-agonists: selective β3-adrenoceptor agonists; anti-muscarinics: anti-muscarinic drugs; BPH: benign prostatic hyperplasia; ROR: reporting odds ratios; CI: confidence intervals.
To construct the logistic model for males, the reporting year, age group, use of anti-muscarinic, and underlying BPH were coded. To construct the logistic model for females, the reporting year, age group, and use of anti-muscarinic were coded. The adjusted RORs were calculated in independent models for each sβ3-agonist. Furthermore, the adjusted RORs for other factors were calculated using the mirabegron model.

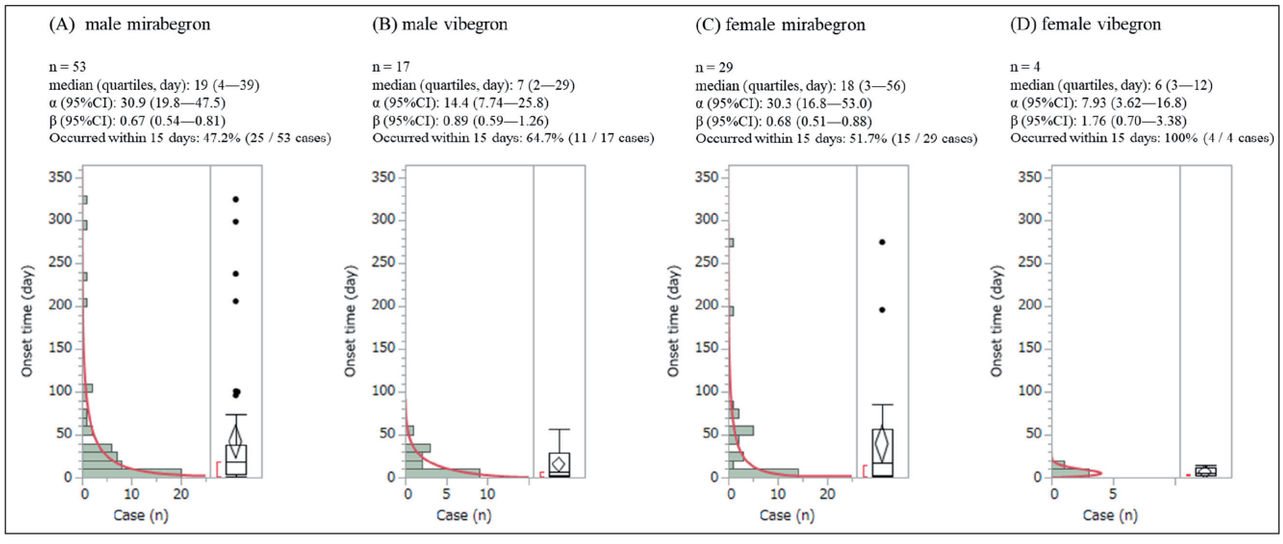

Fig.: Urinary retention cases associated with sβ3-agonists in the JADER database according to onset time.

P<0.001), the use of vibegron (adjusted ROR: 191, 95% CI: 53.9–673, P<0.001) and the use of anti-muscarinics (adjusted ROR: 145, 95% CI: 107–198, P<0.001). The concomitant use of mirabegron and anti-muscarinics (P<0.001) increased the occurrence of urinary retention when compared to the monotherapy (Table 4).

2.5. Onset time of selective β3-adrenoceptor agonists-associated urinary retention

The time-to-onset profiles are depicted in the Fig. The onset of urinary retention induced by sβ3-agonists was analysed using a Weibull distribution analysis. The median and quartiles of time to urinary retention were as follows: mirabegron male, 19 (4–39) days; mirabegron female, 18 (3–56) days; vibegron male, 7(2–29) days; and vibegron female, 6(3–12) days. The scale parameters were as follows: mirabegron male, α=30.9, 95% CI: 19.8–47.5, β=0.67, 95% CI: 0.54–0.81; mirabegron female, α=30.3, 95% CI: 16.8–53.0, β=0.68, 95% CI: 0.51–0.88; vibegron male, α=14.4, 95% CI: 7.7–25.8, β=0.89, 95% CI: 0.59–1.26; and vibegron female, α=7.9, 95% CI: 3.6–16.8, β=1.76, 95% CI: 0.70–3.38. Urinary retention occurred within 15 days from the first administration of treatment with mirabegron in 47.2 % of males (25/53)

Table 4: Analysis of each factor related to urinary retention among patients with BPH

		Total	Case	Ratio (%)	Crude ROR (95% CI)	Adjusted ROR (95% CI)	*p-value*
		10,806	463	4.28			
Reporting year		–	–	–	–	1.09 (1.04–1.15)	*0.001*
Age							
	0–19 years	0	0	–	–	–	–
	20–29 years	2	0	–	–	–	–
	30–39 years	1	0	–	–	–	–
	40–49 years	31	2	6.45	1.54 (0.18–6.13)	1.03 (0.12–8.90)	*0.96*
	50–59 years	253	7	2.77	0.63 (0.25–1.33)	1.55 (0.68–3.56)	*0.30*
	60–69 years	1,822	60	3.29	0.73 (0.54–0.96)	reference	–
	>=70 years	8,697	394	4.53	1.40 (1.08–1.85)	1.13 (0.81–1.58)	*0.49*
Drugs							
sβ3-agonists							
	mirabegron	196	71	36.2	14.8 (10.8–20.3)	27.4 (19.2–39.2)	*< 0.001*
	vibegron	17	15	88.2	173 (40.0–1592)	191 (53.9–673)	*< 0.001*
anti-muscarinics		297	212	71.4	101 (76.2–137)	145 (107–198)	*< 0.001*
	fesoterodine	176	161	91.5	366 (212–666)	–	–
	imidafenacin	9	4	44.4	18.0 (3.56–83.7)	–	–
	oxybutynin	8	4	50	22.5 (4.18–121)	–	–
	propiverine	22	11	50	22.8 (8.93–58.4)	–	–
	solifenacin	73	28	38.4	14.7 (8.75–24.4)	–	–
	tolterodine	9	4	44.4	18.0 (3.56–83.7)	–	–
Interactions							
	mirabegron * anti-muscarinics	–	–	–	–	0.027 (0.011–0.069)	*< 0.001*

*sβ3-agonists: selective β3-adrenoceptor agonists; anti-muscarinics: anti-muscarinic drugs; BPH: benign prostatic hyperplasia; ROR: reporting odds ratios; CI: confidence intervals.
To construct the logistic model, the reporting year, age group, drugs (sβ3-agonist), use of anti-muscarinic, and interaction mirabegron*anti-muscarinics were coded. The adjusted RORs were calculated in independent models for each sβ3-agonist. Furthermore, the adjusted RORs for other factors were calculated using the mirabegron model.

and 51.7% of females (15/29); similarly, urinary retention occurred with vibegron in 64.7% of males (11/17) and 100% of females (4/4) patients.

3. Discussion

In this study, we analysed the occurrence of side effects associated with sβ3-agonists using the JADER database. Safety signals such as urinary retention, hypertension, and arrhythmia were detected following administration of sβ3-agonists, with urinary retention being the most frequently reported. The results also suggest that the urinary retention observed with sβ3-agonists therapy may be associated with a history of BPH and concomitant use of anti-muscarinics. The novelty of this study is that the urinary retention observed in patients taking sβ3-agonists was associated with both the background of the patient and the use of concomitant anticholinergic medication. We believe this information is important for ensuring the safety of the treatment of OAB.

OAB is a condition that presents with storage symptoms such as urinary urgency. The lower urinary tract is dually innervated by the autonomic nervous system: during urinary storage, the voiding muscles relax *via* β3-adrenergic receptors upon sympathetic stimulation; during voiding, they contract *via* muscarinic receptors upon parasympathetic stimulation (Nomiya and Yamaguchi 2003; Takeda et al. 1999; Yamanishi et al. 2002). Thus, sβ3-agonists relax the bladder by activating β3-adrenergic receptors (Takasu et al. 2007). sβ3-Agonists and anti-muscarinics reduce urinary frequency and urge incontinence, and are used as pharmacotherapy for OAB. Although sβ3-agonists are highly selective for β3 receptors in the bladder, there is a concern that they may interfere with the activity of β1 receptors, which are predominantly present in the heart and coronary vessels, causing cardiovascular adverse events (Katoh et al. 2016). In this study, signals such as hypertension and arrhythmia were detected with sβ3-agonists. Patients with underlying cardiovascular disease may require tight blood pressure control and reduced cardiac workload, and caution may be needed when recommending sβ3-agonists for them. Conversely, previously used anti-muscarinics suppressed cholinergic activity, resulting in specific anticholinergic adverse effects, which sβ3-agonists are less likely to cause (Chapple et al. 2020). In the present study, safety signals detected with anti-muscarinics, but not with sβ3-agonists, included dry mouth, constipation, dry eye, and delirium. These results suggest that anti-muscarinics and sβ3-agonists produce different adverse events. Therefore, their use should be differentiated according to the characteristics and risks of patients, such as their other underlying diseases.

Urinary retention is one of the most serious adverse events induced by anti-muscarinics (Remick 1988; Verhamme et al. 2008). Several randomized clinical trials and systematic reviews indicate that sβ3-agonists have a lower incidence of urinary retention than anti-muscarinics (Chapple et al. 2020; Remick 1988; Verhamme et al. 2008; Wang et al. 2019). However, these studies were statistically unsatisfactory. Furthermore, the association between urinary retention and administration of sβ3-agonists, the background of the patient, and the concomitantly used medication was unclear because these studies did not include a statistically sufficient number of patients nor patients with risk factors for urinary retention.

In this study, we found urinary retention to occur not only following the administration of anti-muscarinics, but also with that of sβ3-agonists. β-Adrenergic agonists may cause urinary retention because the external urethral sphincter has β2 receptors, and their stimulation results in contraction of the sphincter and increase of urethral resistance (Rodrigue et al. 2016). Mirabegron and vibegron, which are used for the treatment of OAB, are highly selective for β3 receptors, but also have intrinsic activity towards β2 receptors, which may contribute to the development of urinary retention (Morita et al. 2000). Further investigations are needed to clearly understand this phenomenon.

The risk of urinary retention increases with the presence of urinary tract disorders (Hernández Hernández et al. 2013). In particular, BPH is a common cause of urinary retention because the enlarged prostate obstructs the urethra, impairing urine excretion. Administration of sβ3-agonists may further increase urethral resistance, making urinary retention more likely. However, most previous studies have reported safety in phase III trials of patients without underlying disease (Kennelly et al. 2022; Kelleher et al. 2018; Cui et al. 2014; Nozawa et al. 2018). A post-marketing survey of mirabegron in Japan suggested that urinary retention caused by sβ3-agonists is more common in patients with a history of BPH; however, this study did not include statistical studies due to the small number of cases (Nozawa et al. 2018). Therefore, the effect of underlying BPH on the occurrence of urinary retention due to sβ3-agonists is not well understood. Consequently, in this study, we analysed the occurrence of urinary retention due to a history of BPH and coexistence of sβ3-agonists. Urinary retention occurs with different frequencies and by various mechanisms in men and women, owing to differences in the urinary drainage system (Hernández Hernández et al. 2013). Hence, the present analysis was stratified by sex. Furthermore, we stratified male patients by the presence of underlying BPH, analysed the data and found that a history of BPH favours the development of urinary retention in men receiving sβ3-agonists. In some cases of BPH-induced OAB, symptoms might be alleviated by reducing urethral resistance with 5α-reductase inhibitors, α1-receptor antagonists, and other agents. Furthermore, the onset of urinary retention might be inhibited (Edwards, 2008). Therefore, BPH-induced OAB should first be treated with 5α-reductase inhibitors and α1-receptor antagonists to diminish urethral resistance (Cornu et al. 2012; Marshall et al. 2015; Bergman et al. 2015). If this treatment does not improve the symptoms, the use of either anti-muscarinics or sβ3-agonists may be a good therapeutic option (Filson et al. 2013; van Gelderen et al. 2014; Ichihara et al. 2015). The efficacy of sβ3-agonists against OAB may improve when combined with anti-muscarinics (Maruyama et al. 2020; Abrams et al. 2015). The risk of urinary retention alongside concomitant therapy with sβ3-agonists has not been clearly examined or defined in previous studies. Therefore, we pioneered a study analysing the risk of urinary retention with sβ3-agonists and concomitant medications. We observed that combination therapy with antimuscarinics and sβ3-agonists resulted in urinary retention compared to monotherapy with either drug, and a safety signal was detected in the interaction between antimuscarinics and sβ3-agonists in both men and women. Furthermore, this interaction was also detected in the stratified analysis of patients with BPH, in which anti-muscarinics were found to increase urethral resistance by contracting the external urethral sphincter and suppress bladder contraction during voiding. This might cause urinary retention because impairment of the contraction of the external urethral sphincter makes it difficult to urinate (Reynard, 2004). This is a different mechanism of action from that of the aforementioned sβ3-agonists and of organic factors such as BPH. Thus, their combination may synergistically increase the incidence of urinary retention.

The onset time of sβ3-agonists-induced urinary retention is also unclear. Herein, we also analysed this parameter. The results showed that urinary retention induced by sβ3-agonists occurred early after initiation of treatment and gradually decreased thereafter, with 47.2% of males and 51.7% of females with mirabegron cases and 64.7% of males and 100% of females with vibegron cases reported within 15 days after the first drug administration. These data suggest that patients receiving sβ3-agonists should be intensively monitored early during the treatment.

Despite the findings highlighted in this study, certain limitations should be noted. The presence and severity of organic or neurologic underlying disease of the lower gastrointestinal tract may influence the development of urinary retention (Hernández Hernández et al. 2013; Kowalik and Plante 2016); however, information on these factors is not provided in the JADER database. Additionally, quantitative information, such as biochemical test values, were not available. Furthermore, drug dosage was not considered in this study because temporary interruptions or changes in dosage may not be reflected in the database. As for vibegron, evaluation of interaction with concomitant drugs, age, and BPH were not performed because the number of cases was small (46 cases). Although analysis of the timing of onset was conducted, the number of female cases was only 4, and an analysis that mobilizes a large number of cases is needed in the future to obtain reliable results. Furthermore, since the cases in the JADER database were reported spontaneously, only data on patients who presented adverse drug reactions were available, which could lead to a reporting bias. There is a concern that the study data may be based on a different patient sample than that commonly encountered in actual clinical practice. Therefore, the results of this study need to be further evaluated by cohort studies and randomized controlled trials.

In conclusion, sβ3-agonists are effective agents against OAB. However, they carry the risk of developing several side effects, among which urinary retention may develop into a serious condition such as obstructive nephropathy. The present study suggests that concomitant use of anti-muscarinics and a history of BPH may favour the development of urinary retention. We hope that the results of this study will provide useful information for practicians treating OAB.

4. Experimental

4.1. Study design

Data recorded from April 2012 to December 2020 in the JADER database were downloaded from the website of PMDA (http://www.pmda.go.jp/). Mirabegron, the first sβ3-agonist approved in Japan, received its marketing authorization in July 2011. Vibegron, the second sβ3-agonist approved in Japan, received its marketing authorization in November 2018. The JADER dataset consists of four tables containing the following data: (1) patient information, including sex, age, and body weight; (2) administered treatment; (3) adverse events and patient outcomes; and (4) medical history and underlying illnesses. These four tables were integrated using the FUND E-Z Backup Archive (FUND E-Z Development Corporation, NY, USA) (Ishida et al. 2020; Kawada et al. 2022). Cases in which data on sex and age were missing were excluded from this analysis. In the table containing information on "administered treatment", the drugs listed in the adverse event report were categorized into three groups: "suspected drug", "concomitant drug", and "interaction". In the present study, we examined the category "suspected drug".

First, to evaluate the adverse events associated with the use of either sβ3-agonists or anti-muscarinics, the RORs of each adverse event were calculated. Second, to evaluate the association between the use of sβ3-agonists and anti-muscarinics and the onset of drug-induced urinary retention, the crude RORs were calculated. Subsequently, the interaction of possible factors contributing to the appearance of urinary retention were examined. Third, for the analysis of possible factors associated with urinary retention in patients using sβ3-agonists, we used a multivariate analysis to calculate the crude and adjusted RORs for the following parameters: reporting year, age, concomitantly used drugs, and the presence of benign prostatic hyperplasia (BPH). Fourth, for the analysis of possible factors associated with urinary retention in patients with underlying BPH, we used a multivariate analysis to calculate the crude and adjusted RORs for the following parameters: reporting year, age, and concomitantly used drugs. Finally, we investigated the onset time of urinary retention associated with sβ3-agonists using the Weibull distribution. Because the aetiology of urinary retention may differ depending on sex, all analyses on urinary retention were conducted following the stratification of data by sex. The sβ3-agonists investigated were mirabegron and vibegron, and the anti-muscarinics investigated were fesoterodine, imidafenacin, oxybutynin, propiverine, solifenacin and tolterodine.

4.2. Definition of adverse events and underlying diseases

We used the Medical Dictionary for Regulatory Activities (MedDRA), version 24.0, developed by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use to extract the adverse events and underlying diseases listed in the JADER database. These were defined by preferred terms (PT) and standardized MedDRA queries (SMQ): urinary retention (PT code: 10046555), hypertension (SMQ code: 20000147), cardiac arrhythmias (SMQ code: 20000049), delirium (SMQ code: 20000133), dry eye (PT code: 10013774), dry mouth (PT code: 10043458), constipation (PT code: 10010774) and benign prostatic hyperplasia (PT code: 10004385 and 10004446).

4.3. Analysis of the RORs from the reported data

For the analysis of adverse events, the crude RORs and 95% confidence intervals (CIs) were calculated. The crude RORs were calculated as follows. First, the cases were classified into four groups (a) to (d) as follows: (a) individuals who received the drug of interest and exhibited the adverse event of interest; (b) individuals who received the drug of interest and exhibited other adverse events (of no interest); (c) individuals who received other drugs (of no interest) and exhibited adverse event of interest; and (d) individuals who received other drugs (of no interest) and exhibited other adverse events (of no interest). Next, the crude RORs were calculated using Eq. (1).

Crude ROR = (a /b)/(c/d)

95% CI = exp [log (ROR) ± 1.96 $\sqrt{(1/a) + (1/b) + (1/c) + (1/d)}$ (1)

The RORs were expressed as point estimates with 95% CIs. The data were analysed using Fisher's exact test.

We calculated the adjusted ROR similarly to previous reports (Shimada et al. 2019; Ishida et al. 2022). Additionally, the cases were stratified by age as follows: 0–19, 20–29, 30–39, 40–49, 50–59, 60–69, and ≥70 years. To construct the logistic model, the reporting year, age group, drugs (sβ3-agonist), use of anti-muscarinic, underlying BPH, and interactions were coded. The adjusted RORs were calculated in independent models for each sβ3-agonist. Furthermore, the adjusted RORs for other factors were calculated using the mirabegron model, Eq. (2).

$\text{Log(odds)} = \beta_0 + \beta_1 Y + \beta_2 A + \beta_3 B + \beta_4 M + \beta_5 U + \beta_6 A*B + \beta_7 B*M + \beta_8 U*B$ (2)

Y = reporting year, A = stratified age group, B= sβ3-agonists, M = anti-muscarinics, U = underlying disease

For the analysis of interactions, P values < 0.10 were defined as significant. Other results were considered statistically significant for P values < 0.05. These analyses were performed using JMP 14.0 (SAS Institute, Cary, NC). A signal was detected when the lower limit of the 95% CI of the adjusted ROR exceeded 1.

4.4. Analysis of onset of adverse events

For the time-to-onset analysis, we selected cases with complete information on urinary retention occurrence and prescription start date, in which mirabegron and vibegron were the suspected causative drugs. The onset of adverse events was calculated from the time the patient received their first prescription to the occurrence of urinary retention separately by sex for each drug. A cut-off period of 365 days after the start of administration was used for the analysis (Shimada et al. 2019). The median duration, quartiles, and Weibull shape parameters were used to evaluate the onset data. The scale parameter α of the Weibull distribution determines the scale of the distribution function. A larger scale value (α) stretches the data distribution, whereas a smaller scale value (α) shrinks it. The shape parameter β of the Weibull distribution determines the shape of the distribution function. Larger and smaller shape values produce left- and right-skewed curves, respectively. The shape parameter β of the Weibull distribution was used to indicate the level of hazard over time without a reference population. When β is less than 1 and the upper 95% CI of β less than 1, the hazard is considered to decrease with time. When β is equal to 1, the hazard is estimated to be constant over time. If β is greater than 1 and the lower 95% CI of β greater than 1, the hazard is considered to increase with time (Sauzet et al. 2013). These analyses were performed using JMP 14.0.

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