Original Article

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Lack of information on gender differences in the package inserts of prescription drugs in Japan

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SUMMARY The package inserts of prescription drugs provide essential information for the proper administration of pharmacotherapy. The incidence of adverse reactions for several drugs is known to be higher in women than in men. However, no studies have examined whether information on gender differences is included in Japanese package inserts. Therefore, this study investigated information on gender differences in the package inserts of Japanese prescription drugs, using the drug information database JAMES provided by the Medical Information System Development Center and the Japan Pharmaceutical Information Center. Non-proprietary names of prescription drugs were yielded 1,679 in Japan. Of the 1,679 ingredients in package inserts of prescription drugs, 76 (4.5%) included information on gender differences. The number of inserts that contained information on gender differences in the "DOSAGE AND ADMINISTRATION," "ADVERSE REACTIONS," and "PHARMACOKINETICS" sections was 3, 16, and 62, respectively. Furthermore, in the "ADVERSE REACTIONS" section, 15 of the 16 inserts mentioned a higher frequency of adverse reactions in women compared with men. Importantly, most of the inserts with information on gender differences in the "PHARMACOKINETICS" section mentioned a higher area under the curve for women than for men. Most of the package inserts of prescription drugs with information on gender differences provide useful information aimed at preventing risks in women. However, there is an extreme lack of information on gender differences in the package inserts of prescription drugs in Japan, and we consider enhancing information on gender difference as an urgent issue.

Keywords gender-specific medicine, sex differences, adverse reaction, ethical drugs

1. Introduction

The incidence of adverse reactions for several drugs is known to be higher in women than in men (*1,2*). Gender differences in pharmacokinetics, including differences in drug absorption and metabolic enzyme expression rates between men and women, have also been reported (*3*).

In the 1950s and 1960s, thalidomide, which was initially administered as a hypnotic drug, caused numerous birth defects worldwide. In the 1970s, diethylstilbestrol, which was administered as an anti-miscarriage drug, resulted in numerous reports of reproductive disorders in mothers and their growing daughters. In response, the U.S. Food and Drug Administration (FDA) published guidelines in 1977 to exclude women from clinical trials (*4*). In 1985, physicians who were concerned about the lack of data on women's health suggested the need for biomedical research on women (*5*). In 1986, a notice was issued requesting the collection of data on women in clinical trials (*6,7*). Since 2000, there has been a growing awareness in Japan of the importance of gender-specific pharmacotherapy. The number of medical facilities with women's outpatient clinics is gradually increasing in Japan.

In the U.S., considering that adverse reactions of the hypnotic drugs zolpidem are more common in women, the FDA issued a notice setting the initial dosage of zolpidem at different doses for men and women (*8,9*). Since then, the package insert has indicated lower starting doses for women than for men, but the Japanese package insert has no such indication and the initial doses are the same for men and women.

The package inserts of prescription drugs provide

essential information for the proper administration of pharmacotherapy and are one of the most accessible sources of drug information for health care professionals in Japan. The Ministry of Health, Labour and Welfare has provided instructions regarding the sections and numbers that should be included in the package insert of prescription drugs in Japan (*10*).

Although the promotion of gender-specific medicine is critical, the actual state of information on gender differences in the "DOSAGE AND ADMINISTRATION," "ADVERSE REACTIONS," and "PHARMACOKINETICS" sections of the package inserts of prescription drugs in Japan is not known. Therefore, the purpose of this research was to investigate the actual state of information on gender differences in the package inserts of prescription drugs in Japan and to clarify issues from the viewpoint of information in promoting gender-specific medicine.

2. Materials and Methods

2.1. Methods for searching the package inserts of prescription drugs

We investigated information on gender differences in the package inserts of prescription drugs, using the drug information database JAMES provided by the Medical Information System Development Center and the Japan Pharmaceutical Information Center. The research was conducted using the data of prescription drug package inserts in Japan that were last revised before December 2022. The search terms were "gender," "gender difference," "men," and "women" in Japanese. The contents of package inserts that returned hits with the search terms in the "DOSAGE AND ADMINISTRATION," "ADVERSE REACTIONS," and "PHARMACOKINETICS" sections of the package inserts were reviewed, and drugs with information on gender differences were extracted. In addition, data on animal experiments were excluded from this study.

2.2. Methods for identifying the number of non-proprietary names in prescription drugs

The number of prescription drugs was calculated using the individual drug code, known as the "YJ code," in order to identify the number of non-proprietary names. The YJ code is a 12-digit alphanumeric code. Because the first 7 digits of the YJ code are identical for the same non-proprietary names, the number of prescription drugs with the same first 7-digits were counted as one non-proprietary name. When both brand-name and generic drugs were available, information from the package insert of the brand-name drug was used. Drugs with different YJ codes were counted as one component. As an exception, we visually confirmed and counted drugs with the same non-proprietary name but having different formulations as well as drugs with different salts (different non-proprietary name but the same active ingredient) and biosimilar drugs as one drug.

In this study, we excluded drugs classified as topical drugs for local action and ingredients for preparation (*e.g.*, white soft sugar for taste correction) because they have no systemic action. In addition, drugs containing multiple active ingredients, including combination products and infusion solutions, as well as blood products were excluded.

3. Results

3.1. Number of drugs with information on gender differences in package inserts

To explore the information on gender differences, we calculated the number of prescription drugs using the YJ code. Our study yielded 1,679 non-proprietary names of prescription drugs in Japan (Figure 1). Of these, there were 76 drugs (4.5%) with information on gender differences in the package inserts. The number of drugs

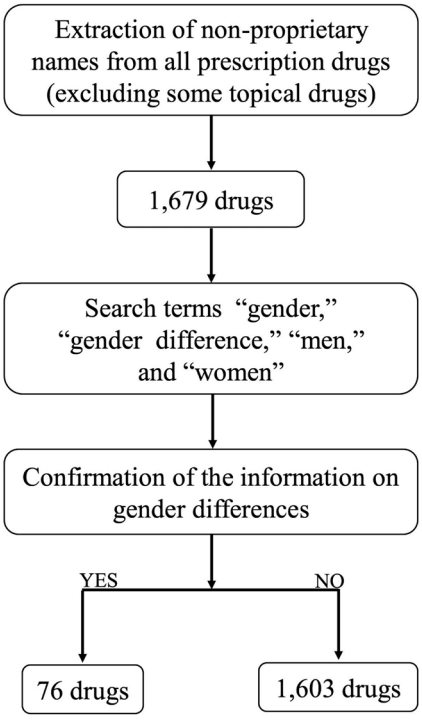

Figure 1. Process for extracting information on gender differences in the package inserts of prescription drugs. The number of prescription drugs was calculated using the YJ code. Excluded drugs were classified as topical drugs for local action and ingredients for preparation. In addition, drugs containing multiple active ingredients, including combination products and infusion solutions, as well as blood products were excluded. Non-proprietary names of prescription drugs were yielded 1,679 in Japan. The search terms were "gender," "gender difference," "men," and "women" in Japanese. The contents of package inserts that returned hits with the search terms were reviewed, and drugs with information on gender differences were extracted. Of these, there were 76 drugs with information on gender differences in the package inserts.

that included information on gender differences in the "DOSAGE AND ADMINISTRATION," "ADVERSE REACTIONS," and "PHARMACOKINETICS" sections was 3, 16, and 62, respectively (Figure 2). In addition, there were 4 drugs, ramosetron hydrochloride, pioglitazone hydrochloride, mirabegron, and nevirapine, with information on gender differences across multiple sections.

3.2. Drug package inserts describing gender differences in the "DOSAGE AND ADMINISTRATION" section

The package inserts of 3 drugs, metreleptin, pioglitazone hydrochloride, and ramosetron hydrochloride, mentioned gender differences in the "DOSAGE AND ADMINISTRATION" section (Table 1). Metreleptin, a leptin hormone with higher blood secretion levels

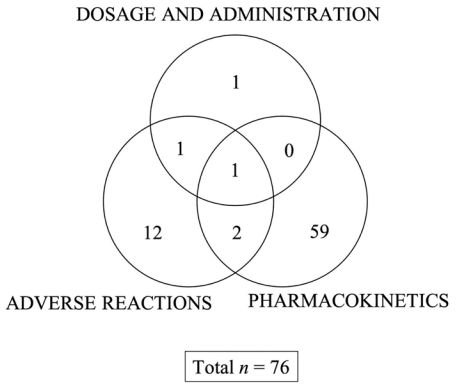

Figure 2. Venn diagram; breakdown of the 76 drugs and sections with information on gender differences in the drug package inserts. There were 76 drugs with information on gender differences in the package inserts. The number of drugs that included information on gender differences in the "DOSAGE AND ADMINISTRATION," "ADVERSE REACTIONS", and "PHARMACOKINETICS" sections was 3, 16, and 62, respectively. In addition, there were 4 drugs with information on gender differences across multiple sections.

in women than in men, was set at a higher dose in women than in men. Ramosetron hydrochloride was set at a lower dose for women than for men. In the "PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION" section, it was recommended that the starting dosage of pioglitazone hydrochloride be lower in women than in men.

3.3. Drug package inserts describing gender differences in the "ADVERSE REACTIONS" section

The package inserts of 16 drugs mentioned gender differences in the "ADVERSE REACTIONS" section (Table 2). Fifteen of the 16 drugs were described as having a higher incidence of adverse reactions in women than in men. Antiviral drugs were the most common therapeutic category, with 6 drugs, while the others were 1 drug each. Severe lactic acidosis and severe hepatomegaly (fatty liver) due to fat deposition were the most frequently reported adverse reactions for antiviral drugs (5 drugs). An increased frequency of adverse reactions in women was noted in the package inserts of 4 drugs, emedastine fumarate, lansoprazole, sodium ferrous citrate, and theophylline. The only drug that was reported to have more adverse reactions in men than in women was the anti-arrhythmic drug verapamil hydrochloride.

3.4. Drug package inserts describing gender differences in the "PHARMACOKINETICS" section

The package inserts of 62 drugs mentioned gender differences in the "PHARMACOKINETICS" section (Table 3). Many of the drugs were described as having higher blood concentrations or lower clearance (CL) in women than in men. In addition, some package inserts stated that there were no differences in pharmacokinetics between men and women. We counted the number of medicines for these parameters. Of these, 31 drugs (50%)

Table 1. List of drugs with information on gender differences in the "DOSAGE AND ADMINISTRATION" section of the package inserts for prescription drugs (*n* = 3)

Non-proprietary name of drug	Therapeutic Category[a]	Dosages
metreleptin (genetical recombination)	other hormone preparations (including anti-hormone agents)	The usual dose of metreleptin is 0.04 mg/kg for men, 0.06 mg/kg for women under 18 years of age, and 0.08 mg/kg for women over 18 years of age by subcutaneous injection once daily.
pioglitazone hydrochloride	diabetes agent	Since edema has been reported relatively frequently in women, when administering to women, it is desirable to pay attention to the occurrence of edema and start administration at 15 mg once daily.
ramosetron hydrochloride	other gastrointestinal drugs	<Diarrhea-type irritable bowel syndrome in men> The usual adult male dosage is 5 μg of ramosetron hydrochloride administered orally once daily. The dosage may be adjusted according to the symptoms, but the maximum daily dose should not exceed 10 μg. <Diarrhea-type irritable bowel syndrome in women> The usual dose for adult women is 2.5 μg of ramosetron hydrochloride administered orally once daily. The dose can be increased if the effect is insufficient, but the maximum daily dose should not exceed 5 μg.

[a]For the medicinal efficacy classification of pharmaceutical ingredients, we used the "Therapeutic category number" used in Japan.

Table 2. List of drugs with information on gender differences in the "ADVERSE REACTIONS" section of the package inserts for prescription drugs (*n* = 16)

Non-proprietary name of drug	Therapeutic Category[a]	Incidence	Adverse reactions
abacavir sulfate	antiviral drug	W > M	Severe lactic acidosis and severe hepatomegaly (fatty liver) due to fat deposition
emedastine fumarate	other allergy medications	W > M	Frequency of adverse reactions
emtricitabine	antiviral drug	W > M	Severe lactic acidosis and severe hepatomegaly (fatty liver) due to fat deposition
lamivudine	antiviral drug	W > M	Severe lactic acidosis and severe hepatomegaly (fatty liver) due to fat deposition
lansoprazole	agent for peptic ulcer	W > M	Frequency of adverse reactions
mirabegron	other urogenital and anal medications	W > M	Prolongation of QTc interval
moxifloxacin hydrochloride	synthetic antibacterial agent	W > M	Prolongation of QT interval
nevirapine	antiviral drug	W > M	Development of rash or liver dysfunction
pioglitazone hydrochloride	diabetes agent	W > M	Edema, fractures
ramosetron hydrochloride	other gastrointestinal drugs	W > M	Constipation and hard stools
sodium ferrous citrate	inorganic preparations	W > M	Frequency of adverse reactions
temocapril hydrochloride	antihypertensive	W > M	Cough
tenofovir disoproxil fumarate	antiviral drug	W > M	Severe lactic acidosis and severe hepatomegaly (fatty liver) due to fat deposition
theophylline	bronchodilator	W > M	Frequency of adverse reactions
verapamil hydrochloride	antiarrhythmic drug	M > W	Decreased LH and testosterone levels in the blood
zidovudine	antiviral drug	W > M	Severe lactic acidosis and severe hepatomegaly (fatty liver) due to fat deposition

M, men; W, women; [a]For the medicinal efficacy classification of pharmaceutical ingredients, we used the "Therapeutic category number" used in Japan.

included information on gender differences in the area under the curve (AUC) (Figure 3). Next were 29 drugs (47%) for maximum blood concentration (C_{max}), 14 drugs (23%) for blood concentration half-life ($T_{1/2}$), 17 drugs (27%) for CL, 6 drugs (9.7%) for volume of distribution, and 6 drugs (9.7%) for protein binding as well as 8 drugs (13%) that referred to "overall pharmacokinetics." Many package inserts included information on gender differences in the pharmacokinetic parameters AUC, C_{max}, CL, and $T_{1/2}$. About half of the drugs provided AUC and C_{max} data. The number of coverages of information for each of the four pharmacokinetic parameters by component was confirmed by a Venn diagram, and it was found that only two drugs, nevirapine and tigecycline, included all four parameters, while 10 drugs included three parameters (Figure 4). The other 50 drugs included two or fewer pharmacokinetics parameters with information on gender differences.

4. Discussion

In this study, we investigated the status of information on gender differences in the package inserts of prescription drugs marketed in Japan on a non-proprietary name basis. Information on gender differences in the "DOSAGE AND ADMINISTRATION," "ADVERSE REACTIONS," and "PHARMACOKINETICS" sections was available for 76 drugs (Figure 1). This number represents approximately 4.5% of the 1,679 prescription drugs in Japan, indicating for the first time that there is an extreme lack of information on gender differences in the package inserts of prescription drugs in Japan.

In the "DOSAGE AND ADMINISTRATION" section of the package inserts, there were three drugs for which the dosages for men and women differed (Table 1). The dosages of ramosetron hydrochloride and pioglitazone hydrochloride were set lower because adverse reactions are more likely to occur in women than in men. In clinical studies of pioglitazone hydrochloride in Japan conducted up to the time of its approval (15 mg, 30 mg, or 45 mg of pioglitazone hydrochloride once daily), edema occurred in 3.9% (26/665) of men and 11.2% (72/643) of women who received the drug alone or in combination with other diabetes drugs excluding insulin (*11*). In addition, edema occurred in 13.6% (3/22) of men and 28.9% (11/38) of women when pioglitazone hydrochloride was administered with insulin. The information included in the pioglitazone hydrochloride package insert may reflect the results of this clinical trial.

In the "ADVERSE REACTIONS" section of the package inserts, it was found that the incidence of adverse reactions differed between men and women for 16 drugs. Of these, the incidence of adverse reactions was higher in women for the 15 drugs other than verapamil hydrochloride. Among them, "severe lactic acidosis and severe hepatomegaly (fatty liver) due to fat deposition" in the "antiviral drug" category was much more common among women. It has been reported that the probability of hepatic impairment with nevirapine is higher in women (*12*); this report has also been cited in the human immunodeficiency virus treatment guidelines in Japan (*13*). It is expected that as information on gender differences becomes more complete, it will be included in guidelines for the treatment of other diseases as well.

Table 3. List of drugs with information on gender differences in the "PHARMACOKINETICS" section of the package inserts for prescription drugs (n = 62)

Non-proprietary name of drug	Therapeutic Category[a]	Women/Men							
		AUC	C_{max} (C_{ss})	$T_{1/2}$	CL	Distribution volume	Protein binding rate	Overall pharmaco-kinetics	Remarks
apixaban	anticoagulant	1.15	1.18	-	-	-	-	-	
apremilast	metabolic drugs not elsewhere classified	1.31	1.08	-	-	-	-	-	
aripiprazole	psychoneurotic agent	-	-	-	-	-	-	M = W	
azithromycin hydrate	antibiotic preparation	-	-	1.68	-	-	-	-	
bevacizumab	other oncologic drugs	-	-	-	0.79	0.82	-	-	
bilastine	other allergy medications	M = W[c]	M = W[c]	-	-	-	-	-	
cabergoline	anti parkinsonian	1.06	0.09	1.16	-	-	-	-	
celecoxib	antipyretic analgesic anti-inflammatory agent	1.88	1.88	-	-	-	-	-	Elderly people
cetuximab	other oncologic drugs	-	-	-	0.75	-	-	-	
cinacalcet hydrochloride	metabolic drugs not elsewhere classified	-	-	-	-	-	0.99	-	Calculated from average
dabigatran etexilate methanesulfonate	anticoagulant	1.50 >	-	-	-	-	-	-	
darunavir ethanolate	antiviral agent	1.17	-	-	-	-	-	-	
dexmedetomidine hydrochloride	hypnotic sedative, anti-anxiety drug	-	-	-	-	-	M = W	-	
dolutegravir sodium	antiviral agent	-	-	-	-	-	-	1.2[b] >	
dotinurad	gout remedy	1.29	1.15	1.02	-	-	-	-	
eldecalcitol	vitamin A and D agents	-	-	-	M = W	-	M = W	-	
eltrombopag olamine	metabolic drugs not elsewhere classified	1.5[b]	-	-	-	-	-	-	
entecavir hydrate	antiviral agent	-	-	-	M = W	-	-	-	
febuxostat	gout remedy	1.12	1.24	-	-	-	-	-	
fesoterodine fumarate	other genitourinary and anal drugs	M = W	M = W	-	-	-	-	-	Elderly people
fluvoxamine maleate	psychoneurotic agent	2.97	2.61	-	0.33	-	-	-	6-11 years old, 50 mg/day[d]
gadobutrol	other diagnostic agents (excluding *in-vitro* diagnostic agents)	1.10[c]	-	0.91[c]	1.02[c]	-	-	-	Elderly people
gemcitabine hydrochloride	antimetabolite	-	-	2.08	0.34	-	-	-	
icatibant acetate	other allergy medications	1.26	1.26	-	-	-	-	-	
imidafenacin	other genitourinary and anal drugs	-	-	-	M = W	-	-	-	
lacosamide	antiepileptic drug	1.13[c]	1.19[c]	0.83[c]	-	-	-	-	Elderly people
leflunomide	metabolic drugs not elsewhere classified	-	(1.29)	-	-	-	-	-	(C_{ss})
linezolid	synthetic antibacterial agent	-	W > M	M = W	M ≥ W	M > W	-	-	
lorazepam	antiepileptic drugs	-	-	-	-	-	-	M = W	
maraviroc	antiviral agent	-	M = W	-	-	-	-	-	
mianserin hydrochloride	psychoneurotic agent	-	-	-	-	-	M = W	-	
midazolam	antiepileptic drugs	-	-	0.71	1.70	1.31	-	-	
minodronic acid hydrate	metabolic drugs not elsewhere classified	-	M = W	-	-	-	-	-	
mirabegron	other genitourinary and anal drugs	1.38	1.44	-	-	-	-	-	
mirtazapine	psychoneurotic agent	2.00	-	1.60	-	-	-	-	

AUC, area under the serum concentration-time; C_{max}: maximum serum concentration; C_{ss}, steady-state blood concentration; $T_{1/2}$, elimination half-life; CL, clearance; M, men; W, women; [a] For the medicinal efficacy classification of pharmaceutical ingredients, we used the "Therapeutic category number" used in Japan. [b] The number of digits after the decimal point conforms to the numerical value stated in the package insert. [c] For drugs with approximate pharmacokinetic descriptions for male and female in the package insert, detailed numerical information was calculated with reference to the "Interview Form," which is a comprehensive information form provided by the pharmaceutical company to supplement information that is inadequate in the prescription drug's package insert. [d] No gender differences were provided in adolescent data.

Table 3. List of drugs with information on gender differences in the "PHARMACOKINETICS" section of the package inserts for prescription drugs (n = 62) (continued)

Non-proprietary name of drug	Therapeutic Category[a]	Women/Men							
		AUC	C_{max} (C_{ss})	$T_{1/2}$	CL	Distribution volume	Protein binding rate	Overall pharmaco-kinetics	Remarks
nalfurafine hydrochloride	other central nervous system drugs	-	-	-	-	-	M = W	-	
naratriptan hydrochloride	vasoconstrictor	1.19 - 1.33	0.99 - 1.39	M = W	-	-	-	-	
nelarabine	antimetabolite	-	-	-	-	-	-	M = W	
nevirapine	antiviral agent	1.13	1.11	0.87	1.24	1.12	-	-	
olanzapine	psychoneurotic agent	-	-	-	M > W	-	-	-	
omarigliptin	diabetes agent	1.20	1.00	-	-	-	-	-	
oxaliplatin	other oncologic drugs	-	-	-	1.09	-	-	-	
oxycodone hydrochloride hydrate	opium alkaloids	1.40	1.40	-	-	-	-	-	
panitumumab	other oncologic drugs	-	-	-	-	M = W	-	-	
pralmorelin hydrochloride	functional test reagent	-	M = W	-	-	-	-	-	
propofol	general anesthetic	-	-	-	-	-	-	M = W	
ramosetron hydrochloride	other gastrointestinal drugs	1.72	1.48	-	-	-	-	-	
rasagiline mesilate	anti parkinsonian	-	-	-	-	-	0.98	-	Calculated from average
remifentanil hydrochloride	synthetic drug	-	-	-	-	0.60	-	M = W (Other than distribution volume)	
rosuvastatin calcium	hyperlipidemia agent	1.10	1.22	-	-	-	-	-	
sertraline hydrochloride	psychoneurotic agent	M = W	1.41	1.16	-	-	-	-	Elderly people
solifenacin succinate	other genitourinary and anal drugs	1.21	-	-	0.83	-	-	-	
sumatriptan succinate	vasoconstrictor	-	-	-	-	-	-	M = W	
telmisartan	antihypertensive agent	0.97, 1.69	1.18, 1.77	-	0.72 (40 mg)	-	-	-	40 mg, 80 mg
temozolomide	alkylating agent	-	-	-	0.95	-	-	-	
teriparatide	thyroid, parathyroid hormone	1.23	1.12	-	-	-	-	-	
thrombomodulin alfa	anticoagulant	-	-	-	-	-	-	M = W	
ticagrelor	other blood and body fluid drugs	1.52 (1.56)	1.37 (1.55)	-	-	-	-	-	(Main metabolite: AR-C124910XX)
tigecycline	antibiotic preparation	1.21	1.20	0.77	0.72	-	-	-	18-50 years old
tolterodine tartrate	other genitourinary and anal drugs	1.16 (1.10)	-	-	-	-	-	-	(Active metabolites: DD01)
topiroxostat	gout remedy	1.26	0.97	1.17	-	-	-	-	
zolmitriptan	vasoconstrictor	1.50	1.50	-	-	-	-	-	

AUC, area under the serum concentration-time; C_{max}: maximum serum concentration; C_{ss}, steady-state blood concentration; $T_{1/2}$, elimination half-life; CL, clearance; M, men; W, women; [a] For the medicinal efficacy classification of pharmaceutical ingredients, we used the "Therapeutic category number" used in Japan. [b] The number of digits after the decimal point conforms to the numerical value stated in the package insert. [c] For drugs with approximate pharmacokinetic descriptions for male and female in the package insert, detailed numerical information was calculated with reference to the "Interview Form," which is a comprehensive information form provided by the pharmaceutical company to supplement information that is inadequate in the prescription drug's package insert. [d] No gender differences were provided in adolescent data.

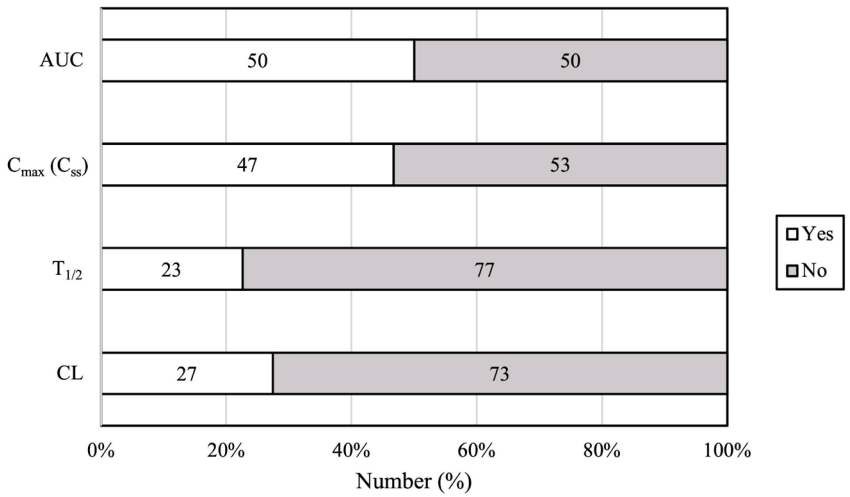

Figure 3. Number of prescription drug package inserts with information on gender differences for each pharmacokinetic parameter (*n* = 62). AUC, area under the serum concentration-time; C_{max}: maximum serum concentration; C_{ss}, steady-state blood concentration; $T_{1/2}$, elimination half-life; CL, clearance. The package inserts of 62 drugs mentioned gender differences in the "PHARMACOKINETICS" section. Of these, 31 drugs (50%) included information on gender differences in the AUC. Next were 29 drugs (47%) for C_{max} and 14 drugs (23%) for $T_{1/2}$ as well as 17 drugs (27%) that referred to CL. We counted the number of medicines for these four parameters. About half of the drugs provided AUC and C_{max} data.

The results of the present study indicated that for many drugs with information on gender differences, a higher incidence of adverse reactions was noted in women compared with men, which is consistent with the findings of many previous studies (*1,2*). This is thought to be due to one of the reasons being the existence of gender differences in the absorption, distribution, metabolism, and excretion (*3*).

The package inserts of 62 drugs mentioned gender differences in the "PHARMACOKINETICS" section. Among the pharmacokinetic data, the AUC was the most frequently reported numerical item. However, as shown in Figure 4, it is clear that this information is not sufficient and is far from being complete. Improving how these items are described is important in preventing adverse reactions caused by higher drug levels in the blood and slower drug elimination.

In the package inserts of prescription drugs, sections on gender differences information are not specified. Therefore, information on gender differences may be included in many different sections of the package inserts, making it difficult to quickly find this information. Among the drugs for which information on gender differences in pharmacokinetics was included in the package inserts, some had a "Gender" sub-item in the "Patients with Specific Backgrounds" sub-section of the "PHARMACOKINETICS" section. To further enhance and use information on gender differences, it would be useful to add a "Gender" sub-section, as well as "Elderly" and "Pediatric", under the "PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS" section of the package insert.

The package inserts of relatively few drugs included information on gender differences. To implement pharmacotherapy considering gender differences, it is necessary to include sufficient information on gender differences in package inserts. Therefore, it will lead to further promotion of gender-specific medicine. Additionally, it might be possible to prevent adverse reactions that occur more frequently in women at the same level as in men by mandating the inclusion of information on gender in the package insert.

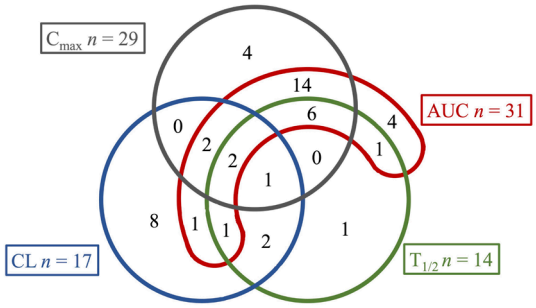

Figure 4. Venn diagram; number of duplications of information on gender differences for each pharmacokinetic parameter (*n* = 62). AUC, area under the serum concentration-time; C_{max}: maximum serum concentration; C_{ss}, steady-state blood concentration; $T_{1/2}$, elimination half-life; CL, clearance. The number of coverages of information for each of the four pharmacokinetic parameters by component was confirmed by a Venn diagram, and it was found that only two drugs included all four parameters, while 10 drugs (AUC, C_{max}, and $T_{1/2}$; 6 drugs, AUC, C_{max}, and CL; 2 drugs, C_{max}, $T_{1/2}$, and CL; 1drug, AUC, $T_{1/2}$, and CL; 1drug) included three parameters. The other 50 drugs included two or fewer pharmacokinetics parameters with information on gender differences.

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