—Regular Articles—

Analysis of Pharmacokinetic Data Provided in Japanese Package Inserts and Interview Forms Focusing on Urinary Excretion of Pharmacologically Active Species

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In optimizing oral pharmacotherapy for patients with renal failure, information on actual urinary excretion ratio of the unchanged drug, which is obtained by dividing a urinary excretion ratio by a bioavailability after oral dose, is quite helpful. In addition, urinary excretion ratio of the active species is sometimes equally important where metabolites have a pharmacological potency. In the present study, we conducted a survey of Japanese package inserts and interview forms of drugs, which is being prescribed at the University of Tokyo Hospital, on pharmacokinetic data that enables an estimation of actual urinary excretion ratio. The total urinary excretion of a drug was documented in 70.1% of package inserts and 84.5% of interview forms, respectively. The total urinary excretion is often measured by radioactivity and thus includes its metabolites and degradation products. However, inclusion of degradation products/metabolites was described explicitly for 43.7% and 66.2%, and the absolute fraction of the unchanged drug or degradation product/metabolite was given only for 29.0% and 48.9% in package inserts and interview forms, respectively. The pharmacological activity of metabolite(s) was documented for 19.8% and 54.3%, and the oral bioavailability was described only for 5.7% and 30.6% in respective documents. For some drugs, the time period for the urine collection was too short to evaluate the urinary excretion ratio. With regard to 65 drugs (38.7%), more detailed information on urinary excretion was found in published books, but not provided in the package inserts or interview forms. It is hoped that more distinct and sufficient descriptions on the urinary excretion and bioavailability will be associated to the package inserts and the interview forms in future, for safe and efficient use of prescription drugs.

Key words——pharmacokinetic data; package insert; interview form; drug information

INTRODUCTION

In Japan, package inserts are the only legal source of information on clinical drugs regulated under the Pharmaceutical Affairs Law, and interview forms provide supplementary information for safer and more effective pharmacotherapy. One of problems of these documents is that the information on the pharmacokinetic characteristics differs from one to another and, in some package inserts, the information is insufficient to conduct a dose adjustment in pharmacotherapy. This is due to, at least partly, absence of criteria or consensus in Japan for the necessary description of information on the pharmacokinetics and drug interactions in these documents.

In the present study, we evaluated the documentation of package inserts and interview forms in terms of the pharmacokinetic data those are essential to optimize the pharmacotherapy. The kidney and liver are the major organs which are responsible for the elimination of drugs. It is quite important, therefore, to evaluate the contribution of these two organs to the elimination of drugs for estimation of the optimal dosage for successful pharmacotherapy. In particular, for optimization of oral dosage in patients with renal failure, it is essential to obtain information on the actual urinary excretion ratio of the unchanged drug that is assumed as a quotient of the urinary excretion ratio (Xu) divided by the oral bioavailability (F). The excretion of a drug depends more on the urinary route as Xu/F increases. For drugs those are predominantly excreted into the urine as the unchanged form, the dosage could be optimized considering a creatinine clearance of each patient.[1] Where pharmacological potency of the drug relies heavily on its metabolite which is excreted preferentially into the urine, the dosage may need to be decreased carefully for renal failure patients. For this type of drugs including prodrug, the actual urinary excretion of active species is also important. In the

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present study, we investigated the current status of the description of the pharmacokinetic data in the Japanese package inserts and interview forms, focusing on whether or not sufficient data have been provided for determination of the actual urinary excretion ratio.

METHODS

We investigated the package inserts and interview forms of 504 oral agents which are prescribed at the University of Tokyo Hospital. Combination agents were excluded from the present analysis. The package inserts and interview forms were investigated to see if the following pharmacokinetic data were provided: (1) the total amount of drug and its degradation products/metabolites excreted in the urine, (2) the fraction of unchanged drug, degraded and/or metabolized drug in the urine, (3) bioavailability, (4) pharmacological activity of metabolite(s), and (5) the time period for the determination of the amount excreted in the urine. The package inserts and interview forms were the latest editions available in March, 2004. When the pharmacokinetic data were not documented in the interview forms, the material provided in textbooks, PDR (The physician's desk reference)[2] and Martindale (The complete drug reference by Martindale),[3] were investigated. In addition, the descriptions of the pharmacokinetic data in the package inserts and interview forms were analyzed in terms of the sale year of each drug.

RESULTS

Subjects We investigated 504 agents which met our criteria. The agents investigated were classified as the central nervous system (102 agents, 20.2%), cardiovascular (101 agents, 20.0%), metabolic disorder (42 agents, 8.3%), synthetic antimicrobial (35 agents, 6.9%), gastrointestinal (32 agents, 6.3%), hormonal (28 agents, 5.6%), antibacterial (27 agents, 5.4%), antiallergic (25 agents, 5.0%), antitumor (23 agents, 4.6%), respiratory system (20 agents, 4.0%), peripheral nervous system (18 agents, 3.6%), and others (51 agents, 10.1%) (Fig. 1).

Documentation in Package Inserts and Interview Forms Table 1 shows the descriptions of the urinary excretion ratio, bioavailability and pharmacological activity of metabolite(s) in Japanese package inserts and interview forms. The total amount of drugs and their degradation products and/or metabolites excreted in the urine was documented in 70.1% and 84.5% of the package inserts and interview forms, respectively. The presence of degradation products and/or metabolites in the urine was documented in 43.7% and 66.2% of the package in-

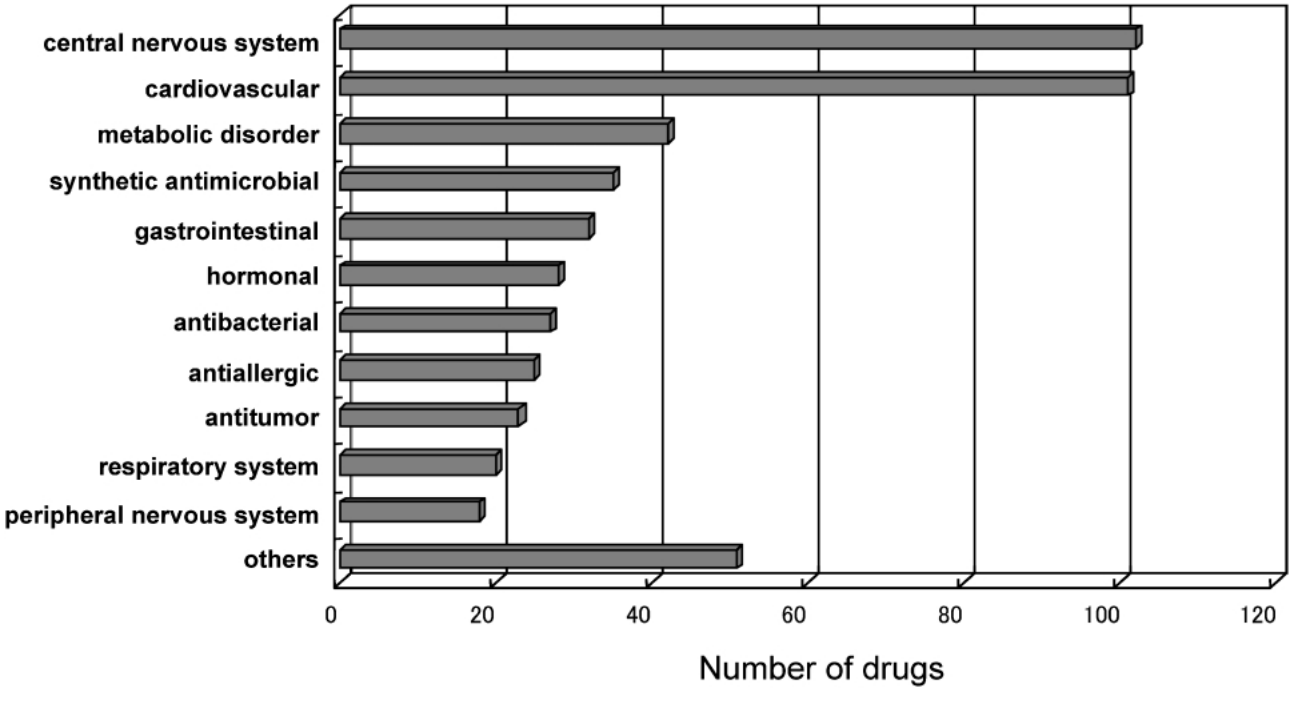

Fig. 1. The Pharmacological Classification of Drugs Surveyed in This Study

Table 1. Descriptions of the Urinary Excretion Ratio, Bioavailability and Pharmacological Activity of Metabolite (s) in Japanese Package Inserts and Interview Forms*

n	Package insert 504	Interview form 497
Urinary excretion ratio		
Quantitatively described†	146 (29.0%)	243 (48.9%)
Qualitatively described‡	74 (14.7%)	86 (17.3%)
Not defined	133 (26.4%)	91 (18.3%)
Not described	151 (29.9%)	77 (15.5%)
Bioavailability		
Described	29 (5.8%)	152 (30.6%)
Not described	475 (94.2%)	345 (69.4%)
Pharmacological activity of metabolite (s)		
Described	100 (19.8%)	272 (54.3%)
Not described	404 (81.2%)	225 (45.7%)

* The number of drugs and percent in the total are indicated. † An example of quantitative description: about 78% of an oral dose is excreted in urine within 24 hrs. ‡ Examples of qualitative description: mainly excreted in urine; a small amount excreted in urine.

serts and interview forms, respectively, although the absolute values of the fraction of unchanged drugs or degradation products/metabolites in the urine were documented in only 29.0% and 48.9% of cases, respectively. The bioavailability values were documented in 5.8% and 30.6% of cases, respectively. The pharmacological activities of metabolite(s) were documented in 19.8% and 54.3% cases, respectively. In 1.8% and 2.6% of the package inserts and interview forms, respectively, it was mentioned that the drug is hardly metabolized.

Of 353 agents described documented urinary excretion of package inserts, the time period of urine collection for the calculation of the urinary excretion ratio was documented in 80.0%. However, in 105 agents (37.1%), the time period for the collection of urine was less than 5 times of the plasma half-life. The period was less than twice of the plasma half-life in 16 agents (5.7%). The presence of degradation products and/or metabolites in urine, bioavailability, and pharmacological activity of metabolites were less frequently documented in package inserts and interview forms as time passed since the drug's approval (Fig. 2).

Comparison of the Description in Package Inserts and Interview Forms with that in References We investigated the description provided by the PDR and Martindale for the 168 agents for which the description in interview forms was not sufficient to calculate the urinary excretion ratio. In the PDR, 41 of these agents (24.4%) were listed and sufficient information was provided in 20 of cases (11.9%). On the other hand, in Martindale, 160 agents (95.2%) were listed, and the sufficient information was documented in 62 cases (36.9%). Collectively, information on urinary excretion of unchanged drug or degradation product/metabolite was documented for 65 agents (38.7%) in these reference books. Typical cases, in which information on urinary excretion was not documented in package inserts nor in interview forms but on reference books, are exemplified in Table 2.

DISCUSSION

In the wake of the fatal accidents involving patients receiving Sorivudine and 5-fluorouracil in 1993,[4] it was pointed out that the readability of the package inserts was not excellent, as far as from viewpoints of physicians and pharmacists, not only due to their information provided but also due to differences in formats among drug manufacturers. Therefore, in 1994, the Ministry of Health and Welfare, which is presently referred to as the Ministry of Health, Labor and Welfare, organized a research group to review the prescription drug package inserts and produce a uniform format. All package inserts were renewed according to this new format by the end of 1999. In addition, the Japanese Society of Hospital Pharmacists established a subcommittee in 1996 to review the interview forms, and a new format of the interview forms was announced in September, 1998. Along with the revision of the format, the quantity and quality of information were much improved in both the package inserts and interview forms, and healthcare professionals came to regard them as very important sources for the successful clinical application of drugs. However, the criteria for the description of information on the pharmacokinetics and drug interactions are not clear enough, even in the current format, and are sometimes insufficient to estimate the drug disposition in clinical use. It has been pointed out that some Japanese package inserts do not provide sufficient information on dosage of antibiotics in patients with renal failure[5] and on drug interactions[6,7] compared with the foreign package inserts.

In the present study, we evaluated the documentation of package inserts and interview forms in terms of the pharmacokinetic data which are essential to op-

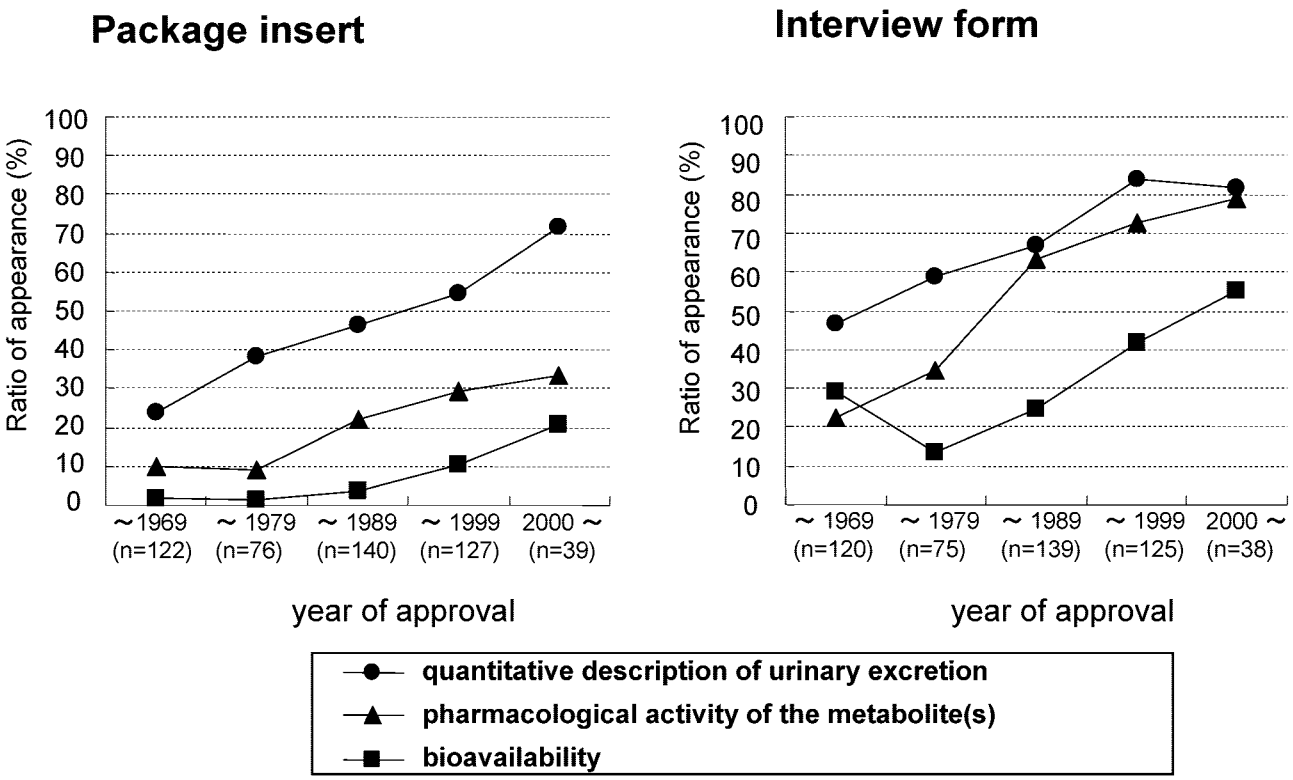

Fig. 2. Change in Appearance Ratio of Quantitative Information of Pharmacokinetics in Japanese Package Inserts and Interview Forms

Table 2. Comparison of the Description on Urinary Excretion in Package Inserts and Interview Forms with that in Reference Books

Drug	Package insert	Interview form	PDR	Martindale
Oxybutynin	27.4% (Japanese)		Oxybutynin is metabolized primarily by the cytochrome P450 enzyme systems. Its metabolic products include phenylcyclohexylglycolic acid, which is pharmacologically inactive, and desethyloxybutynin, which is pharmacologically active. Oxybutynin is extensively metabolized by the liver, with less than 0.1% of the administered dose excreted unchanged in the urine. Also, less than 0.1% of the administered dose is excreted as the metabolite desethyloxybutynin.	—
Olanzapine	57% (^{14}C labeled, non-Japanese)		Following oral dose of ^{14}C labeled olanzapine, 7% of the dose of olanzapine was recovered in the urine as unchanged drug. 57% of the dose was recovered in the urine.	About 57% of the dose is excreted in the urine, mainly as metabolites.
Triazolam	82% (non-Japanese)	82% (^{14}C labeled, non-Japanese)	Not listed	Triazolam is excreted in the urine mainly in the form of its conjugated metabolites with only small amount appearing unchanged.
Diltiazem	—	69% (^{14}C labeled, non-Japanese)	Only 2% to 4% of unchanged diltiazem appears in the urine.	About 2 to 4% of a dose is excreted in urine as unchanged diltiazem with the remainder excreted as metabolites in bile and urine.
Granisetron	33.7% (Japanese) 59% (^{14}C labeled, non-Japanese)		Approximately 11% of the orally administered dose is eliminated unchanged in the urine. The remainder of the dose is excreted as metabolites, 48% in the urine and 38% in feces.	It is metabolized in the liver, primarily by 7-hydroxylation, with less than 20 % of a dose recovered unchanged in urine, the remainder being excreted in feces and urine as metabolites.

— : No data provided.

timize the pharmacotherapy of patients with renal failure. The total amount of drug and its degradation products/metabolites excreted into the urine was documented in 70.0 and 84.5% of package inserts and interview forms, respectively. This value is usually determined by examining the total radioactivity excreted in the urine after the administration of radio-labeled drugs, and some of the package inserts and interview forms lacked information about the methodology to determine this value. For example, we can examine the description in the package insert of triazolam (Halcion). The package insert declares that this drug is predominantly eliminated from the body via urinary excretion and, therefore, care is required during its administration to patients with renal failure. However, the major detoxification pathway of triazolam is via intestinal and/or hepatic metabolism, and most of the metabolites are excreted in the urine. The described urinary excretion ratio is including the metabolites, because this value is determined by examining the total radioactivity excreted in the urine after the administration of radio-labeled triazolam. Consequently, the pharmacological effect of triazolam may not be affected by renal function from a pharmacokinetic point of view.

For some drugs, active metabolites are responsible for the pharmacological activity and/or adverse effects. For these drugs, it is important to have information on the pharmacological activity of metabolites. However, a description of the pharmacological activity of metabolites was available only in 19.8% and 54.3% of package inserts and interview forms, respectively. For example, although it is suggested that the pharmacological activity observed after administration of sarpogrelate is ascribed to an active metabolite named M1, ((±)-3-dimethylamino-1-[o-(m-methoxyphenethyl) phenoxy]-2-propanol),[8] no information about the pharmacological activity or the urinary excretion ratio of M1 is available in the package inserts or interview form.

In addition, the period of the urine collection is also important in evaluating the calculated urinary excretion ratio. The period of urine collection was documented 80.0% of the package inserts and it was found that, in 37.1% of cases (105 agents), the period of collection was less than 5 times of the plasma half-life. For example, for irsogladine maleate (Gaslon N), it is stated that 7% of the dose was excreted in urine during 80 hrs after administration. Although it requires approximately 5 plasma half-lives for most of the drug to be eliminated from the body, 80 hrs for the urine collection is too short, considering the fact that the plasma half-life of this drug is approximately 160 hrs. The value of the urinary excretion ratio of irsogladine maleate (Gaslon N) would be much higher than the reported value (7%) if the urine was collected for a sufficiently long time period. The same conclusion also holds true for perindopril erbumine (Coversyl) (Table 3). Due to practical reasons, it might be prohibitory to collect the urine for a sufficiently long period in a clinical study after administration of a drug which has a very long plasma half-life. If this is the case, a description on resulting urinary excretion should be cautiously made avoiding misunderstanding.

It was also found that there were less information in package inserts and interview forms about the presence of degradation products/metabolites in urine, oral bioavailability and pharmacological activity of metabolites, as longer the time passed after drug approval (Fig. 2). Although the package inserts of all drugs were revised and converted to the new format by the end of December, 1999, and, in addition, the new criteria for the information in the description were set in September, 1998, significant difference was not observed in the pharmacokinetic information in the package inserts between drugs which were introduced to the market before and after the changes of criteria.

We also compared the description of the pharmacokinetic data between package inserts/interview forms and reference books. For 65 drugs (38.7%), the information which is required for the determina-

Table 3. Description Cases of the Period of Urine Collection in Japanese Package Inserts

Irsogladine maleate (Gaslon N®) Plasma half-life: 152 hrs Elimination: About 7% of a dose was excreted in urine during 80 hrs after administration. Approximately 20% of that was unchanged.
Perindopril erbumine (Coversyl®) Plasma half-life of active metabolite (perindoprilat): 57.3 hrs (4 mg), 105.4 hrs (8 mg) Elimination: Within 24 hrs 21—26% of a dose was excreted in urine as unchanged, 3—10% as perindoprilat, and 12—14 % as perindoprilat glucuronide.

tion of urinary excretion ratio was documented in the reference books, but not in package inserts or interview forms. It was found that, although sufficient pharmacokinetic data are available, such information is not given in the package inserts or interview forms. In the case of triazolam (Halcion), Martindale gives the urinary excretion ratio of the parent drug and also information in patients with renal failure. It was found that much more clinically important pharmacokinetic data are given in Martindale compared with package inserts/interview forms.

Following notification by the dean of Pharmaceutical Affairs Bureau (No. 606),[9] it is required that the package inserts for prescription drugs contain pharmacokinetic data on drug absorption, distribution, metabolism and excretion in humans. In addition, it is also required that the interview forms contain data on the bioavailability, presence of active metabolites and pharmacokinetic parameters of active metabolites.[10] However, it was still found that the pharmacokinetic data supplied by the Japanese package inserts and interview forms are not sufficient to evaluate the urinary excretion ratio. In Japan, the regulatory guidelines require the package inserts to be ''as simple as possible''. This is a meaningful recommendation to make the document understandable. But it may have gone too far regarding missing information on pharmacokinetics and urinary excretion.

It should be noted that the urinary excretion data to be documented are not restricted to data from Japanese subjects. The regulatory hurdle hinders administration of radio-labeled drugs in clinical trials in Japan, leading information losses on urinary excretion of some metabolites in Japanese subjects. In these cases, data from foreign countries should be documented as background information. These data are important because they provide useful information for health care professionals.

On June 1st, 2001, the Ministry of Health, Labor and Welfare officially announced a new explanatory document for clinical pharmacokinetic trials.[11] In this guideline, it is recommended that pharmacokinetic data after intravenous administration should be provided as possible to clarify bioavailability, irrespectively of the administration route in clinical use. It is also stated that (1) the ratio and extent of the urinary excretion of the parent drug and its metabolites, (2) the fecal excretion, if appropriate and (3) the hepatic and/or renal clearance values should be determined. In addition, in examining the fecal excretion, attention should be paid to the possibility that the non-absorbed drug is excreted into the feces. From a standpoint of clinical pharmacists, it is our hope that these recommendations are more respected and all clinically important pharmacokinetic information will be given in package inserts and interview forms in future for safe and efficient use of prescription drugs.

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