The Current State and Future Prospects of Population Pharmacokinetic Research in Post-marketing Clinical Studies in Japan

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Population pharmacokinetics (PPK) is a useful approach to the evaluation of drug pharmacokinetics in patients and is a widely used method for the evaluation of pharmacokinetics in clinical trials. PPK uses a statistical model to calculate population parameters, their variance, and covariates from sparse and unbalanced data in a large target population. Population parameters can subsequently be used to establish individual prescribing regimens for specific patients. Post-marketing clinical studies using PPK analysis have been reported by medical and academic institutions in order to complement the poor pharmacokinetics information, thus increasing the available pharmacokinetics information. However, because, in many cases, PPK information is not indicated in the package insert (PI), pharmacokinetics information such as pharmacokinetics parameters and associated variable factors is insufficient. We investigated what kind of new information was obtained in the post-marketing clinical studies using PPK analysis and whether these PPK results were described in Japan PI and/or interview form (IF). We showed that many post-marketing clinical studies were conducted as a single-center and observational study in order to supplement deficient pharmacokinetics data. Also, most PPK results obtained from post-marketing studies were not included in Japan PI and/or IF presumably due to lack of quality of PPK models. If sufficient post-marketing clinical studies using high-quality PPK models are performed, PPK models based on patients with diverse backgrounds, which take inter-individual variability into consideration, can be constructed and PPK information can contribute to the proper use of drugs and the promotion of individualized treatment strategies.

Key words—population pharmacokinetics; post-marketing; package insert; interview form

INTRODUCTION

Following the publication of the guidance on population pharmacokinetics (PPK) (1999)1) and guidance on exposure-response (2003)2) by the Food and Drug Administration (FDA), guideline on clinical pharmacokinetic studies (2001)3) and guideline on PPK/PD analysis (2019)4) by the Ministry of Health, Labour and Welfare of Japan, the use of PPK methods for the PK evaluation of new drugs for approval in Japan and abroad has increased.5–7) Furthermore, post-marketing clinical studies using PPK analysis have been reported by medical and academic institutions in order to complement the poor pharmacokinetics (PK) information, which increases the availability of PK information. In the U.S.A., the PPK data are frequently listed in drug label, although this is less often the case in Japan.8) Healthcare professionals pointed out that PK information such as parameters and associated variable factors described in Japan package insert (PI) is insufficient9,10) under the existing conditions.

A general limitation of PK data from clinical trials11) is that it is difficult to apply the findings to all the patient populations with complex and multiple backgrounds. Therefore, PPK data obtained in post-marketing clinical studies can complement the existing information on PK parameters and their variable factors for the following reasons: (1) PK information, including that from studies conducted for new drug applications (NDA) for drug approval, is often not fully disclosed by pharmaceutical companies,8) (2) PK information is rarely collected in post-marketing studies, though post-marketing surveillance and clinical trials on efficacy and safety may be required as a condition for approval.12)

In this study, we aimed to examine the state of PPK research in post-marketing clinical studies in Japan.
and investigated what kind of new information was obtained in the post-marketing clinical studies using PPK analysis and whether these PPK results are described in Japan PI and/or interview form (IF).

**METHODS**

**Selection of Analysis Object**  
Clinical research papers using PPK analysis were extracted from the Ichushi-Web [Search formula; (“population pharmacokinetic analysis” (in Japanese) or “population pharmacokinetics” (in Japanese) or “PPK analysis” (in Japanese) or “population pharmacokinetic”) and “original paper” (in Japanese)]. We excluded studies conducted by pharmaceutical companies, studies conducted outside of Japan, studies on methodology, and studies with a different definition of PPK (e.g., palmoplantar keratoderma). As a result, studies on post-marketing clinical studies using PPK analysis in Japan conducted by medical and academic institution were extracted.

**Extraction and Summarization of Data**

**Extraction of data**  
We extracted data on the drug name, research purpose, number of centers, subjects and total samples, type of study and newly found information in the study from the published research papers. In addition, PK information was extracted from Japan PI, IF, NDA review report (RR) and common technical document (CTD) (hereafter “Japan application data”) of the target drugs.

**Study classification**  
The identified studies were classified by the number of centers (single, multiple, or unknown), therapeutic category, and research design (interventional, observational, or unknown), as well as by research purpose.

**Number of subjects and total samples**  
From each study, data on the number of subjects and total samples were extracted. Next, the average number of subjects and total samples were calculated and statistically compared between single-center and multiple-center using a Wilcoxon rank-sum test (5% significance level).

**Newly found information from post-marketing clinical studies using PPK analysis**  
Newly found information in each study was extracted and categorized as follows: (1) development of a new PPK model in patients in clinical practice, (2) identification of factors requiring dose adjustment, (3) modification of PPK model, and (4) others. Also, PK information, presence or absence of PPK information and covariate information were extracted from Japan application data. Furthermore, we investigated whether newly found information from the post-marketing clinical studies using PPK analysis had been incorporated into Japan PI and IF.

**Quality of PPK research in post-marketing clinical studies**  
We determined whether the studies in the present research met the following criteria: (1) it was conducted as a multi-center study with more than 30 subjects, (2) unified measurement of blood (serum, plasma) concentration of drug was applied among different centers and throughout the investigation period, (3) blood samples were collected at around time to reach the maximum drug blood concentration following drug administration ($t_{\text{max}}$) and elimination half-life ($t_{\text{1/2}}$), (4) information on the construction of the PPK model and on the accuracy from the base model to the final model were provided, and (5) formula of the final PPK model was included.

The criterion (1) was set because it is necessary to consider whether PPK parameters estimated at a single-center can be used by patients at other centers. As for the (2), it was set considering the fact that there are cases where measurement methods are different among centers, and that, in some studies collecting blood concentration data retrospectively, a measurement method different from the current wide use is employed. Because there are cases where the peak drug concentration is related to clinical efficacy, and cases where the duration of certain drug concentration is related to clinical efficacy, we set the criterion (3). As for the criteria (4) and (5), it is important to show information about the process of and reason for the final PPK model selection to judge its validity, and to show the final PPK model equations for basic PK parameters to estimate PK parameters of individual patients and specific groups. So we set them.

**RESULTS**

Of the 244 papers identified on the Ichushi-Web as of March 2, 2017, we excluded 46 studies conducted by pharmaceutical companies, 10 studies conducted outside of Japan, 85 studies which were studies on methodology or studies with a different PPK definition. The remaining 103 studies were selected for the analysis.

**Study Breakdown**  
Table 1 shows the breakdown of the studies. Of a total of 47 identified drugs,
Table 1. Study Breakdown

| Classification                                      | Number of studies |
|-----------------------------------------------------|-------------------|
| Number of drugs                                     | 47                |
| Year of issue                                       |                   |
| - 1990                                              | 15                |
| 1991–2000                                           | 6                 |
| 2001–2010                                           | 48                |
| 2011–                                               | 37                |
| Therapeutic Category of Drugs in Japan 87           |                   |
| 1 Agents affecting nervous system and sensory organs | 12                |
| 11 Agents affecting central nervous system          | 12                |
| 2 Agents affecting individual organs                |                   |
| 21 Cardiovascular agents                            | 17\(^a\)          |
| 22 Respiratory organ agents                         | 8                 |
| 24 Hormones                                         | 1                 |
| 3 Agents affecting metabolism                       | 15                |
| 39 Other agents affecting metabolism                | 15\(^b\)          |
| 4 Agents affecting cellular function                |                   |
| 42 Antineoplastics                                  | 8                 |
| 44 Allergic agents                                  | 7                 |
| 6 Agents against pathologic organisms and parasites  |                   |
| 61 Antibiotics                                      | 34                |
| 62 Chemotherapeutics                                | 5                 |
| 7 Agents not mainly for therapeutic purpose         |                   |
| 72 Intracorporeal diagnostic agents                 | 2                 |
| 8 Narcotics                                         | 1                 |
| 81 Alkaloidal narcotics                             | 1                 |
| Number of centers                                   |                   |
| Single-center                                       | 63                |
| Multi-center                                        | 23                |
| Unknown                                             | 17                |
| Research design                                     |                   |
| Intervenational                                     | 32                |
| Observational                                       | 64                |
| Unknown                                             | 7                 |
| Research purpose\(^c\)                              |                   |
| No or insufficient reports/studies on PPK and PPK/PD | 22                |
| It is necessary to search for suitable dosage       | 16                |
| Overestimation or underestimation by the current model (including software) | 18 |
| Insufficient consideration of influence factors     | 19                |
| PK in the special population is not examined or insufficient | 38 |
| Pediatric                                           | 13                |
| Geriatric                                           | 2                 |
| Hepatic/renal impairment                            | 4                 |
| Patient (including under special circumstances)     | 13                |
| Japanese                                            | 9                 |
| Others\(^d\)                                        | 9                 |

All studies \((N=103)\). PPK: population pharmacokinetics, PD: pharmacodynamics, PK: pharmacokinetics. \(^a\) A paper of a drug falling into the therapeutic category number 21 and 22 was classified as 21. \(^b\) Four papers of drugs falling into the therapeutic category number 39 and 42 were classified as 39. \(^c\) Papers with multiple purposes were counted for each of the corresponding categories. \(^d\) Others include studies conducted with backgrounds such as “only a single-center study had been conducted” and “only a few subjects had been included”.
Table 2. Number of Subjects and Number of Total Samples

| Number of total samples per study | Number of subjects per study | $p$ value |
|-----------------------------------|-----------------------------|-----------|
| Number of data | Median (Q1–Q3) | Mean ± S.D. | | Number of data | Median (Q1–Q3) | Mean ± S.D. | $p$ value |
| Single-center $(n = 63)$ | 60 | 45.50 (19–65) | 56.93 ± 77.23 | $p = 0.00307$ | 39 | 111.00 (61.00–220.5) | 154.18 ± 127.77 | $p = 0.00498$ |
| Multi-center $(n = 24)$ | 24 | 70.00 (42.75–107.25) | 84.17 ± 54.16 | 19 | 188.00 (127.5–401.0) | 312.16 ± 259.13 |

All studies ($N = 103$). Q1: 25 percentile, Q3: 75 percentile.

Newly Found Information from Post-marketing Clinical Studies Using PPK Analysis

Fig. 1. Newly Found Information from Post-marketing Clinical Studies Using PPK Analysis

(1) Development of a new PPK model based in patients in clinical practice; (2) Identification of factors requiring dose adjustment; (3) Modification of PPK model; (4) Others (including validation for software, comparison of version of software or PPK models, examination of prediction accuracy, etc.). PPK: population pharmacokinetics, PK: pharmacokinetics.

17 drugs were subject to the therapeutic drug monitoring (TDM). For the research purpose, 38 studies were conducted for “PK in a special population is not examined or insufficient”, 22 studies for “no or insufficient reports, studies on PPK and PPK/pharmacodynamics (PD)” and 16 studies for “overestimation or underestimation by the current PPK model (including software)”. Number of Subjects and Total Samples The number of centers was reported for 87 of the identified studies. The results comparing number of subjects and total samples for single-center and multi-center studies are shown in Table 2. Both the number of total samples and number of total samples per study were significantly larger in multi-center studies than in single-center studies. Newly Found Information from Post-marketing Clinical Studies Using PPK Analysis Newly found information reported in the selected post-marketing studies using PPK analysis are shown in Figs. 1
Table 3. PPK Related Information from Post-marketing Clinical Studies Reflectable to Package Insert [All studies (N = 103)]

A. Interventional studies

| Evaluation criteria | Journal A (1995) | Journal B (2008) | Journal C (2012) |
|---------------------|------------------|------------------|------------------|
| (1) Number of centers | ≥ 2              | 2                | 2                |
| Number of subjects (total samples) | 33 (106)         | 32 (145)         | 95 (101)         |
| (2) Measuring method | HPLC             | HPLC             | HPLC             |
| (3) Validity of sampling points* | Yes              | Yes              | Yes              |
| (4) Method of confirmation of model accuracy | —Superposition of measured value and calculated value —Judgement by AIC and OBJ function —Residual of measured value and calculated value —Judgement by bootstrap method and OBJ function |
| Model construction informationb | Yes              | Yes              | Yes              |
| (5) Final model formula | Yes (ke, Vd/F)  | Yes (CL, Vc, Q, Vp) | Yes (CL/F, Vd/F) |

HPLC: high performance liquid chromatography, OBJ: objective function, ke: elimination rate constant, CL, CL/F: clearance, Vd/F: distribution of volume, AIC: Akaike’s information criterion, Vc: central volume of distribution, Q: inter-compartmental clearance, Vp: peripheral volume of distribution. * Whether or not blood samples were collected around t_{max} and/or t_{1/2}. b Information of software, construction and selection of PPK model, and background for covariate evaluation.

B. Observational studies

| Evaluation criteria | Journal D (1990) | Journal E (2012) | Journal F (2015) |
|---------------------|------------------|------------------|------------------|
| (1) Number of facilities | 12               | 2                | 3                |
| Number of subjects (total samples) | 33 (107)         | 51 (353)         | 132 (292)        |
| (2) Measuring method | FPIA (kit)       | HPLC             | FPIA (kit)       |
| (3) Validity of sampling points* | Yes              | Yes              | Yes              |
| (4) Method of confirmation of model accuracy | —Judgement by ME, MAE, RMSE and OBJ function —Judgement by 95% confidence intervals of estimates —Judgement by Good of fit —Judgement by bootstrap method and OBJ function |
| Model construction informationb | Yes              | Yes              | Yes              |
| (5) Final model formula | Yes (CL)         | Yes (CL/F, Vd/F) | Yes (CL, Vc, Vp, Q) |

FPIA: fluorescence polarization immunoassay, ME: mean prediction error, MAE: mean absolute error, RMSE: root mean square error, CL, CL/F: clearance, Vd/F: distribution of volume, Vc: central volume of distribution, Vp: peripheral volume of distribution, Q: inter-compartmental clearance. * Whether or not blood samples were collected around t_{max} and/or t_{1/2}. b Information of software, construction and selection of PPK model, and background for covariate evaluation.

When PPK analysis was not included in Japan application data, the newly found information was classified into categories (1) and (2). The detailed breakdown of these 2 categories, “information on the patients’ PK” was the largest with 40 reports.

On the other hand, when PPK analysis was included in Japan application data, the newly found information was classified into categories (2) and (3). Many reports classified into these 2 categories suggested different covariates from those specified in Japan application data. Reports pointing out “different diseases” include studies in which PPK models in pediatric patients were developed in addition to the existing PPK data for adult patients; those pointing out “different age group” include studies in which PPK models for different diseases from the existing ones were developed.

PPK Related Information from Post-marketing Clinical Studies Reflectable to Japan PI To investigate the feasibility of including PPK data in Japan PI and/or IF, each study was assessed according to the criteria defined in section “Quality of PPK research in post-marketing clinical studies”. Six stud-
ies were found to meet all the criteria for the inclusion of PPK data in Japan PI and/or IF [Tables 3 (A) and (B)].

Among the studies subject to the present research, there was only one study whose PPK analysis data was shown in Japan IF. This study did not meet the criteria. No PPK analysis data from post-marketing clinical studies were reflected in Japan PI.

DISCUSSION

PK assessment using PPK methods was included in post-marketing clinical study in some cases, but many of them were based on observational research using TDM data at a single-center. In addition, despite the fact that PPK analysis was conducted for NDA for approval in many cases, the results are not included in Japan PI and IF. This situation is one of the backgrounds for conducting post-marketing clinical studies using PPK method. The present study suggested that PPK analyses were conducted in post-marketing clinical studies to supplement deficient PK data. However, we identified only one study, which was observational, whose PPK data was reflected in Japan IF.

There is a limit to predicting the variation range of blood concentration in patients with various background factors such as age, weight, presence of underlying disease, presence of liver/renal impairment etc. only from the results of Phase 1 studies in healthy volunteers. When any factors related to PK are found as a result of PPK analysis based on PK data in patients with various background factors included in clinical trials, they are expected to be utilized for dose setting as well as monitoring of efficacy and/or safety. However, if such PPK information is not provided in the Japan PI, which is most often referred to by healthcare professionals, it is not likely be utilized by them. We believe that for (1) drugs whose blood concentration affected by liver/renal impairment, body weight, age, etc. or (2) drugs whose dosage need to be adjusted due to large variation in blood concentration, PK information including results of PPK analysis should be presented in the package insert as important information for judging the dosage.

In order to improve provision of PPK information in Japan PIs, quality of PPK models included in post-marketing clinical studies is important. We would propose that such studies should be designed encompassing the following criteria specified at the planning stage: (1) it is conducted as a multi-center study with sufficient subjects to construct a PPK model, (2) unified measurement of blood concentration of drug is applied among different centers and throughout the investigation period, (3) blood samples are collected at around \( t_{\text{max}} \) and \( t_{1/2} \), and at the publishing stage: (4) information on the construction of the PPK model and on the accuracy from the base model to the final model are provided, and (5) formula of the final model is included. If sufficient post-marketing clinical studies using high-quality PPK models are performed, PPK models based on patients with diverse backgrounds, which take inter-individual variability into consideration, can be constructed. If PPK data are subsequently described in Japan PI and/or IF, they can be used by health professionals to ensure proper administration of medicines.

Of the 103 studies, 22 were studied from the perspective of PK/PD (Table 1). To understand the relationship between dose, PK, PD and clinical effects helps to predict efficacy and safety of the drug, and gives information useful for setting appropriate dosages. In the post-marketing clinical studies in medical and academic institutions, not only PPK analysis, but also its relations with PD and clinical effect should be examined because it gives useful information on dose adjustment for patients with any impairment and/or concomitant drugs.

First limitation of this research is that all the included data were retrieved only from the published material. In particular, the research design was estimated from the description of the data source and study method in the published paper, unless it was explicitly described as interventional or observational research. Second limitation is that clinical research papers published in foreign journals were not included in the present study. It was because most post-marketing clinical studies using PPK analysis in Japanese conducted by medical and academic institutions were considered to be published in domestic medical journals. So we might have missed some papers published in foreign journals.

PPK models constructed for NDA for approval are developed using data from subjects who satisfy certain inclusion criteria and therefore can’t be applied to real-world patients with various characteristics. Therefore, post-marketing clinical studies are frequently undertaken by medical and academic institutions to complement the existing PK data, which are
often insufficient. Furthermore, some pharmaceutical companies updated the PPK models by integrating clinical trial data, drug use survey data, and post-marketing survey data.\textsuperscript{21,22} Therefore, it is possible to ensure the quality of post-marketing clinical study using PPK methods, new and/or improved PPK models using the data from these studies could be developed.

If data from PPK models that are applicable to patients in real-world settings are included in Japan PI and/or IF, by which useful PK information for the adjustment of dosage regimens would be provided, PPK information can contribute to the proper use of drugs and the promotion of individualized treatment strategies.

**Conflicts of Interest** Megumi Watanabe-Uchida (Employee of Novartis Pharma K.K), Tatsuya Watanabe (No potential COI to disclose), Mamoru Narukawa (No potential COI to disclose).

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