FORUM

A Survey of Clinical Pharmacokinetic Studies of 17 Cardiovascular Drugs in Japanese New Drug Approvals Between 2000 and 2007

Susumu NAKADE^{*1} Akinori YAMAUCHI^{*1} Naoki HONDA^{*1}
Junsaku KITAGAWA^{*1} Tomoya OHNO^{*1} Chihiro AMANO^{*1}
Yasuo KODAMA^{*2} and Mikio OGAWA^{*1}

^{*1} Pharmacokinetic Research Laboratories, Ono Pharmaceutical Co., Ltd., Ibaraki, Japan

^{*2} Laboratory of Bio-Pharmaceutics, Faculty of Pharmaceutical Sciences, Josai International University, Chiba, Japan

We analyzed the current status of clinical pharmacokinetic (PK) studies in new drug applications (NDA) by evaluating 17 cardiovascular (CV) drugs that were approved between 2000 and 2007 in Japan since CV drugs were one of the largest categories to be submitted. All summaries of data had been submitted by applicants and were freely accessible on the website of the Pharmaceuticals and Medical Devices Agency (PMDA). The clinical PK studies were divided into 12 categories: single-dose, multiple-dose, food-effect, elderly, gender difference, mass balance, absolute bioavailability, target patients, liver impairment, renal impairment, drug-drug interaction, and population PK studies. The median number of clinical PK studies per new molecular entity (NME) excluding single-dose, multiple-dose, and food-effect studies was 13.5, and foreign data accounted for 86% of the study results. A relatively high proportion of PK studies in Japanese subjects were observed in elderly volunteers and target patients; however, a dependency on foreign data was noted in the other PK study categories. The effect of the guidance "*Clinical PK Studies of Pharmaceuticals*" by the Ministry of Health, Labour and Welfare on implementation of clinical PK studies could not be fully assessed, since there were only three NMEs approved prior to issuance of the guidance. The median number of clinical PK studies per NME was approximately three times higher for drugs for lifestyle-related diseases than that for other drugs. In recent NDA reviews by the PMDA, the trend to emphasize a relationship between PK and safety with respect to drug-drug interactions and/or special populations was noted.

Key words: pharmacokinetics, cardiovascular drug, new drug application, population pharmacokinetics

Introduction

Clinical pharmacokinetic (PK) studies in Japan have historically consisted mainly of single-dose, multiple-dose, and food effect studies that were essential components of a new drug application (NDA). Meanwhile, PK studies that investigated the properties of compounds such as drug-drug interaction studies, special population PK studies, and population PK studies were not routinely conducted. The utility of PK information had not been sufficiently recognized until the issuance of the ICH-E5 guideline¹⁾ in 1998. The guideline brought a concept of bridging strategy and PK (PK/PD) data gained prominence in drug development. As the significance of PK in drug development was increasingly recognized, the Ministry of Health, Labour and Welfare (MHLW) of Japan issued the first guidance for clinical PK studies in drug development, "*Clinical PK Studies of Pharmaceuticals*" (MHLW-PK guidance)²⁾ in 2001. To analyze the current status of

clinical PK studies in NDAs, we surveyed 17 cardiovascular (CV) drugs approved between 2000 and 2007 in Japan. CV drugs were selected due to the predominant number of NDAs submitted to the MHLW.

Summary of 17 CV drugs

Seventeen CV drugs were approved from January 2000 to December 2007 in Japan (Table 1). All summaries of data submitted by applicants were freely accessible on the website.³⁾ Three NMEs (New Molecular Entities) were approved before (2000-2001) and 12 NMEs were approved after (2002-2007) the MHLW-PK guidance was issued, respectively. Therapeutic drugs for hypertension and hypercholesterolemia (eight NMEs) accounted for approximately half of all NMEs. Table 2 summarizes the implementation of 12 types of clinical PK studies for each NME. For the three basic studies, single-dose, multiple-dose, and food-effect studies, foreign data were surveyed

Table 1 List of 17 cardiovascular drugs approved from 2000 to 2007 in Japan

No.	Nonproprietary name	Target disease	Approval year	Review status	Bridging study	Mechanism of action
1	Valsartan	Hypertension	2000	Normal	No	Angiotensin II receptor antagonist
2	Sumatriptan	Migraine	2000	Normal	No	Serotonin receptor agonist
3	<i>Edaravon</i>	Acute cerebral infarction	2001	Normal	No	Free radical scavenger
4	Esmolol hydrochloride	Supraventricular tachyarrhythmia	2002	Normal	No	β blocker
5	Telmisartan	Hypertension	2002	Normal	No	Angiotensin II receptor antagonist
6	<i>Landiolol hydrochloride</i>	Atrial fibrillation, atrial flutter, sinus tachycardia	2002	Normal	No	β blocker
7	<i>Pitavastatin calcium</i>	Hypercholesterolemia	2003	Normal	No	HMG-CoA reductase inhibitor
8	Rizatriptan benzoate	Migraine	2003	Normal	Yes	Serotonin receptor agonist
9	<i>Azelmidipine</i>	Hypertension	2003	Normal	No	Calcium channel blocker
10	Sevelamer hydrochloride	Hyperphosphataemia	2003	Normal	No	Phosphate binder
11	Olmesartan medoxomil	Hypertension	2004	Normal	No	Angiotensin II receptor antagonist
12	Bosentan hydrate	Pulmonary arterial hypertension	2005	Orphan	Yes	Endothelin-1 receptor antagonist
13	Rosuvastatin calcium	Hypercholesterolemia	2005	Normal	Yes	HMG-CoA reductase inhibitor
14	<i>Mozavaptan hydrochloride</i>	Hyponatremia	2006	Orphan	No	Vasopressin V2 antagonist
15	Clopidogrel bisulfate	Ischemic cerebrovascular disease	2006	Rapid	No	ADP receptor antagonist
16	Ezetimibe	Hypercholesterolemia	2007	Normal	No	Niemann-Pick C1-like 1 protein inhibitor
17	Eplerenone	Hypertension	2007	Normal	No	Aldosterone receptor antagonist

The drugs approved only in Japan are indicated in italics.

only if Japanese data were not included. Sevelamer hydrochloride was excluded from the analysis, since it is a nonabsorbable poly-cation polymer, which is not absorbed into systemic circulation after oral administration. The median number of clinical PK studies per NME (excluding the three basic studies) was 13.5. Foreign data accounted for 86% of the studies.

1) Single and multiple-dose studies

A single or multiple dose study in healthy young adults was conducted for all NMEs, with the exception of sevelamer. A placebo treatment was included in approximately 70% of studies, and the median number of subjects administered an active drug per group was six. Only bosentan hydrate was studied in Japanese expatriates and non-Japanese subjects. Many PK analysts have been interested in a method to evaluate dose proportionality of PK parameters because there currently is no universal consensus on a method. Although a power model (one NME) and linear model (three NMEs) were used for the statistical evaluation, many NMEs were visually evaluated. The findings indicate that there is difficulty in evaluating dose proportionality from a statistical analysis perspective.

2) Food-effect studies

A food-effect study in healthy young adults was conducted for all oral NMEs, with the exception of

sevelamer. All studies were conducted in male subjects, and the median number of subjects was 9 (range 6–20). The effect of food was evaluated by a statistical analysis ($n=10$) and a visual assessment ($n=2$). Statistical analyses included confidence intervals ($n=5$), t-tests ($n=3$), and ANOVA ($n=2$).

When developing oral drugs, a food effect study in Japanese subjects is important because of the difference in dietary intake between ethnic groups. However, in the bosentan study, only foreign data from non-Japanese subjects was submitted. The reason for this is unknown but bosentan's orphan status may be a factor.

With the exception of olmesartan medoxomil, for which the effects of both standard and high-fat diets were investigated, the other NMEs only evaluated the effect of a standard diet. There is no MLHW guidance for food-effects studies similar to those that exist in the United States and the European Union.^{4,5)} According to the regulatory guidance in these regions, the standard trial design and analytical method is defined as a high-fat diet, $n=12$ or more, and utilizing a confidence interval in the statistical analysis. In general, all food-effect studies in Japan have a similar trial design except for using high-fat diet.

Table 2 State of implementation of clinical PK studies for cardiovascular drugs in Japanese new drug applications

No.	Nonproprietary name	Ethnicity	Study												
			SD	MD	Food	Elderly	Gender	MB	BA	Patient Full	Patient Sparse	Liver	Kidney	DDI	PPK
1	Valsartan	JP non-JP	○	○	○	-	-	-	-	-	-	-	▲	-	-
2	Sumatriptan	JP non-JP	○	○	-	-	-	-	-	-	-	-	-	-	-
3	Edaravon	JP non-JP	○	○	-	▲	-	-	-	○	-	-	-	-	-
4	Esmolol hydrochloride	JP non-JP	○	-	-	○	-	-	-	-	○	-	-	-	-
5	Telmisartan	JP non-JP	○	○	○	-	-	-	-	○2	-	-	○	-	○
6	Landiolol hydrochloride	JP non-JP	○	○	-	-	-	-	-	○	-	-	-	-	-
7	Pitavastatin calcium	JP non-JP	○	○	○	○	-	-	-	-	○	○	-	○	-
8	Rizatriptan benzoate	JP non-JP	○	○	○	●	○	-	-	○3	-	-	●	○4	○2
9	Azelidipine	JP non-JP	○	○	○	-	-	-	-	○2	-	-	○	○3	-
10	Sevelamer hydrochloride	JP non-JP	-	-	-	-	-	-	-	-	-	-	-	-	-
11	Olmesartan medoxomil	JP non-JP	○	○	○	○	-	-	-	○2	-	-	○	-	▲
12	Bosentan hydrate	JP non-JP	○	○	-	-	-	-	-	○3	●	○	-	●10	-
13	Rosuvastatin calcium	JP non-JP	○	○	○	-	-	-	-	○	-	-	○	○2	○5
14	Mozavaptan hydrochloride	JP non-JP	○	○	○	-	-	-	-	-	○2	○	-	○13	●
15	Clopidogrel bisulfate	JP non-JP	○	○	○	-	-	-	-	-	-	-	-	-	-
16	Ezetimibe	JP non-JP	○	○	○	○	●2	-	-	-	-	●	●2	○19	●
17	Eplerenone	JP non-JP	○	○	○	-	-	-	-	-	-	-	●	-	●

SD = single-dose study, MD = multiple-dose study, Food = food-effect study, Elder = elderly study, Gender = gender difference study, MB = mass balance study, BA = absolute bioavailability study, Patient = target patients study, Liver = hepatic impairment study, Kidney = renal impairment study, DDI = drug-drug interaction study, PPK = population pharmacokinetic analysis, JP = Japanese, non-JP = non Japanese.
 ○ formal data, ● reference data, ▲ undetermined
 When several studies were performed under the same category, the number of study is indicated on the right.

3) Elderly PK studies

Twelve PK studies in healthy elderly subjects were conducted in 11 NMEs (69%). Five of these were performed in Japanese subjects. With regard to the number of PK studies that specifically included Japanese subjects, elderly PK studies were the second most frequently studied after PK studies in the target population. Six studies included only male subjects while the other five included both male and female subjects, and one was unknown. The median number of subjects per group was 11.5 (5–16). Except for studies involving edaravon and pitavastatin, the effect of age was evaluated based on statistical analyses that included confidence intervals ($n=2$), t -tests ($n=1$), and ANOVA ($n=3$).

4) Gender difference PK studies

Seven studies in six NMEs (38%) were conducted to evaluate the effect of gender in non-elderly, healthy subjects. Only rizatriptan benzoate was studied in Japanese subjects. This could be because the rizatriptan AUC value in females is approximately 1.3-fold higher than that in males, and most of the target patients were women. The median number of subjects per group was 12 (8–17). The effect of gender was evaluated using confidence intervals ($n=3$) and ANOVA ($n=3$).

5) Mass balance studies

Thirteen mass balance studies were conducted in 11 NMEs (69%), none of which were conducted in Japanese subjects. All studies, with the exception of that involving sevelamer, were conducted in male subjects. The sevelamer study included young and elderly male and female subjects. The combination of different age and gender groups suggests that an extensive mass balance study was conducted for sevelamer to demonstrate its characteristic as a nonabsorbable drug.

6) Absolute bioavailability studies

Ten absolute bioavailability studies were conducted in six NMEs (38%). Only rosuvastatin calcium was studied in both Japanese and non-Japanese subjects, while others evaluated non-Japanese subjects only. The rosuvastatin PK results showed that its plasma concentrations in Japanese subjects were approximately two times higher than those in non-Japanese subjects. Thus, absolute bioavailability was key component of the bridging strategy in the new drug development of rosuvastatin in Japan.

7) Target patients PK studies

A total of 14 full PK studies in patients with the target disease were conducted in seven NMEs (44%). There were two types of PK evaluations: stand-alone tests ($n=10$) in which pharmacokinetics were evaluated in human

pharmacology studies and add-on tests ($n=3$) in which the pharmacokinetics was evaluated as part of therapeutic exploratory or confirmatory studies (one study was unknown). PK evaluation using sparse sampling was performed for eight studies of five NMEs (31%). The majority of the studies evaluated trough concentrations during repeated administration. The pharmacokinetics in Japanese patients (regardless of whether full PK or sparse sampling was done) was evaluated in nine NMEs (56%). Target patient PK studies had the highest proportion of Japanese data among all clinical PK studies, excluding the three basic studies. Each of the four NMEs (landiolol hydrochloride, pitavastatin calcium, azelnidipine, and mozavaptan hydrochloride) approved only in Japan, evaluated PK in Japanese patients. In many cases of domestic drug development, clinical PK data, particularly in healthy subjects or special populations, has been limited (Table 2). Our analysis determined that the difficulties in conducting certain studies such as liver impairment studies resulted in a higher tendency to evaluate the PK in target patients.

8) Hepatic and renal impairment PK studies

Fifteen PK studies in patients with hepatic impairment were conducted in 13 NMEs (81%). Only pitavastatin was studied in Japanese subjects. Since recruiting subjects is difficult, it is rare to conduct a hepatic impairment PK study in Japanese subjects. Although hepatic impairment PK studies were not included in the original NDA package of pitavastatin or azelnidipine, the study results were submitted as additional data during their respective NDA reviews. Fourteen PK studies in patients with renal impairment were conducted in 11 NMEs (69%). Five NMEs (valsartan, telmisartan, azelnidipine, olmesartan, and eplerenone) included data from Japanese subjects. These five NMEs are all therapeutic drugs for hypertension. This can be attributed to the issuance of ICH-E12A “Principles for Clinical Evaluation of New Antihypertensive Drugs”, in which PK studies in hypertensive patients with renal impairment is an essential requirement.

9) Drug-drug interaction studies

A total of 114 drug-drug interaction studies were conducted in 15 NMEs (94%). Seven studies in four NMEs (pitavastatin, azelnidipine, mozavaptan, and ezetimibe) were performed in Japanese subjects. The studies conducted in Japan have a common feature in that either the NME or the concomitant drug is a domestic drug that is not approved in western countries. Although the drug-drug interaction studies were not included in the original NDA packages for pitavastatin or azelnidipine, the study

Table 3 List of concomitant drugs in drug-drug interaction studies

Nonproprietary name	Major elimination pathway or major metabolic enzymes	Concomitant drugs
Valsartan	Bile excretion	amlodipine, atenolol, cimetidine, digoxin, furosemide, hydrochlorothiazide, indomethacin, glibenclamide, warfarin,
Sumatriptan	Monoamine oxidase A	alcohol, flunarizine, moclobemide, propranolol, selegiline
Esmolol hydrochloride	Esterase	digoxin, morphine, warfarin
Telmisartan	Bile excretion	amlodipine, digoxin, glibenclamide, hydrochlorothiazide, ibuprofen, paracetamol, simvastatin, warfarin,
Pitavastatin calcium	Bile excretion	<u>cyclosporine</u> , fenofibrate, gemfibrozil
Rizatriptan benzoate	Monoamine oxidase A	ergotamine, metoprolol, moclobemide, nadolol, oral contraceptive, paroxetine, propranolol
Azelnidipine	CYP3A4	<u>grapefruit juice</u> , <u>itraconazole</u> , <u>simvastatin</u>
Sevelamer hydrochloride	—	digoxin, enalapril, metoprolol, warfarin
Olmesartan medoxomil	Bile excretion	amlodipine, antacid, atenolol, atorvastatin, digoxin, glibenclamide, hydrochlorothiazide, pravastatin, simvastatin, warfarin
Bosentan hydrate	CYP2C9, 3A4	cyclosporine, digoxin, glibenclamide, ketoconazole, oral contraceptive, simvastatin, warfarin
Rosuvastatin calcium	Bile excretion	antacid, cyclosporine, digoxin, erythromycin, fenofibrate, fluconazole, gemfibrozil, itraconazole, ketoconazole, oral contraceptive, warfarin
Mozavaptan hydrochloride	CYP3A4	<u>dextromethorphan</u> , <u>itraconazole</u>
Clopidogrel bisulfate	CYP3A4, 1A2, 2C19, 2B6	antacid, antipyrine, atenolol, aspirin, cimetidine, digoxin, enalapril, estrogen, heparin, naproxen, nifedipine, phenobarbital, theophylline, warfarin,
Ezetimibe	Bile excretion	antacid, atorvastatin, cerivastatin, cholestyramine, cimetidine, cyclosporine, digoxin, fenofibrate, fluvastatin, gemfibrozil, glipizide, intravenous probe (midazolam), lovastatin, oral probe (caffeine, tolbutamide, dextromethorphan, diamino diphenyl sulfone), oral contraceptive, <u>pitavastatin</u> , pravastatin, rosuvastatin, simvastatin, warfarin
Eplerenone	CYP3A	antacid, clarithromycin, cyclosporine, digoxin, erythromycin, fluconazole, grapefruit juice, ketoconazole, midazolam, oral contraceptive, saquinavir, simvastatin, St Jones' wart, verapamil, warfarin

The studies conducted in Japanese subjects are underlined.

Results of drug-drug interaction studies were not included in landiolol and edaravon NDAs.

results were submitted as additional data during their respective NDA reviews. The median number of drug-drug interaction studies per NME was 7 (2–21). Table 3 lists the concomitant drugs used in these interaction studies for each NME. Digoxin and warfarin were the most frequently administered concomitant drugs and both drugs are recommended in the ICH-E7 guideline “Studies in Support of Special Populations : Geriatrics”.⁶⁾ Following these two drugs, simvastatin was the next most frequently administered concomitant drug. This might be attributed to the fact that simvastatin is often coadministered with CV drugs and is a substrate of CYP3A4.⁷⁾

10) Population PK studies

Five population PK analyses were performed in four

NMEs (25%). Of these, two NMEs included Japanese data in the population PK analysis. This rate of population PK analysis is comparable to that of all NDAs submitted between 1999 and 2006 (16.4%).⁸⁾

11) Pharmacogenomic studies

The effect of cytochrome P450 gene polymorphisms was not assessed. For rosuvastatin, the relations between plasma drug concentrations and OATP-C (organic anion transport polypeptide C) gene polymorphism was assessed in Japanese patients (n=39) and foreign patients (n=264) to investigate the basis of ethnic differences. OATP-C is a transporter that functions to enhance hepatic uptake of rosuvastatin, as well as pravastatin and simvastatin.^{9,10)} OATP-C gene polymorphism, however,

Table 4 Effect of the MHLW-PK guidance and target disease on the implementation of clinical PK studies

	Elderly ^a	Gender ^a	MB ^a	BA ^a	Patient ^a (full)	Patient ^a (sparse)	Liver ^a	Kidney ^a	DDI ^a	PPK ^a
Before MHLW-PK guidance (2000–2001)	1/2/3	0/1/3	0/1/3	0/1/2	1/1/3	0/0/3	0/2/3	1/1/3	0/2/3	0/0/3
After MHLW-PK guidance (2002–2007)	4/9/13	1/5/13	0/10/13	1/5/11	4/6/13	4/5/13	1/11/13	4/10/13	3/12/13	2/4/13
Hypertension & Hypercholesterolemia (Lifestyle-related disease)	3/7/8	0/5/8	0/7/8	1/5/8	3/3/8	2/3/8	1/8/8	5/7/8	3/8/8	2/4/8
Other diseases	2/4/8	1/1/8	0/4/8	0/1/5	2/4/8	2/2/8	0/5/8	0/4/8	1/6/8	0/0/8

^aElder = elderly study, Gender = gender difference study, MB = mass balance study, BA = absolute bioavailability study, Patient = target patients study, DDI = drug-drug interaction study, Liver = hepatic impairment study, Kidney = renal impairment study, PPK = population pharmacokinetic analysis. A number in these columns indicates the number of NMEs conducting Japanese study/the total number of NMEs conducting the concerned study/the number of target NMEs.

was not related to plasma rosuvastatin concentrations in this study. This pharmacogenomic investigation may be conducted to support the basis for successful bridging, as well as in the evaluation of ethnic differences in bioavailability.

12) Effect of the MHLW-PK guidance and target disease on the implementation of clinical PK studies

We compared the trends of clinical PK studies before and after issuance of the MHLW-PK guidance, and between drugs for lifestyle-related disease (hypertension and hypercholesterolemia) and other drugs (Table 4). The median number of clinical PK studies per NME (excluding the three basic studies) before and after the guidance was 5 (2–16) and 16 (1–28), respectively. However, since there were only three NMEs that were approved before the MHLW guideline, the effect of MHLW-PK guidance could not be fully assessed. Meanwhile, the number of NMEs of drugs for lifestyle-related disease and other drugs, except for sevelamer, was almost equivalent, 7 and 8, respectively. Among drugs for lifestyle-related disease, the median number of clinical PK studies per NME was approximately three times higher than that of other drugs. Clinical PK studies of drugs for lifestyle-related diseases were more likely to include Japanese subject data than PK studies for other types of drugs. Long-term administration and polypharmacy are the characteristics of drugs for lifestyle-related disease. Therefore, to assure safety under conditions of wide-ranging clinical use, a large number of clinical PK studies will continue to be required for these drugs.

13) PK-related Issues in NDA review

Based on the assessment report by the Pharmaceuticals

and Medical Devices Agency (PMDA), we categorized the inquiries from the PMDA regarding clinical PK. The noteworthy inquiries were as follows : drug-drug interaction (15 NMEs), administration to patients with hepatic (11 NMEs) and renal impairment (six NMEs). Drug-drug interactions in the main metabolic pathway or main excretion route and/or interaction with frequently administered concomitant drugs were requested in many cases. Inquiries referring to hepatic and renal impairment were to require answers regarding PK and safety considerations and their relevance to labeling. Other issues frequently raised were the effects of age and/or gender on PK and safety (five NMEs) and the relationship between food effect and labeling (five NMEs). Race differences in PK were investigated for rizatriptan and rosuvastatin among the three NMEs that were approved based on the bridging strategy.

Summary and future directions

We surveyed 12 types of clinical PK studies of 17 CV drugs that were approved in Japan between 2000 and 2007. Although the effect of the MHLW-PK guidance on clinical PK studies could not be fully assessed, we found that the NDA package varies widely, depending in part on whether the drug is targeted for a life style-related disease or not. A relatively high proportion of elderly PK studies and target patient PK studies included analyses for Japanese subjects. Other PK study categories were largely dependent on foreign data. This might have been to avoid difficulties associated with the conduct of clinical pharmacological studies in Japan or to prevent data duplication. Until further guidance, it seems likely that future NDAs will remain largely based on foreign PK data. As a result, it

Number of total studies ^b / NME Median (Range)	Foreign studies/ Total studies ^b in all NMEs
5 (2-16)	20/23 (87%)
16 (1-28)	156/186 (84%)
19 (6-28)	119/144 (83%)
6 (1-19)	57/65 (88%)

^bWhen several studies were performed under the same category, all of them were counted.

will continue to be difficult for Japanese physicians to find data for new drugs based on specialized Japanese populations such as those with liver or kidney impairments. One way to bolster Japanese PK data could be to design population PK studies added on long term administration studies. Thus, informative data can be collected in some special populations such as the elderly, both gender, and patients with mild liver or renal impairment. NDA review by the PMDA may have a better outcome if the sponsor proactively evaluates the relationship between PK and safety on drug-drug interaction and/or special population. Moreover, population PK studies are also attractive with respect to cost and development speed, since they are add-on studies and do not require the conduct of separate or additional clinical studies. In the case of drug approved based on a bridging strategy, Japanese postmarketing studies are more important because Japanese data, especially safety data, is not perfect. Population PK analyses will be a powerful tool for characterizing safe and efficacious therapeutic doses of new drugs for target populations. What is essential is that a sufficient amount of PK data is collected to allow appropriate dosing for patients and to help regulatory agencies and pharmaceutical companies better inform patient populations.

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