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Population Pharmacokinetic Analysis of Daikenchuto, a Traditional Japanese Medicine (Kampo) in Japanese and US Health Volunteers[S]

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ABSTRACT

We constructed population pharmacokinetic (PK) models for the five constituents of daikenchuto (DKT), a traditional Japanese herbal medicine. Data were collected from two randomized PK studies conducted in Japan and the United States. Participants received single oral doses of 2.5 g, 5 g, and 10 g of DKT. The plasma concentrations of five DKT constituents—hydroxy-α-sanshool (HAS), hydroxyl-β-sanshool (HBS), 6-shogaol (6S), 10-shogaol (10S), and ginsenoside Rb_1 (GRB1)—were determined by liquid chromatography-tandem mass spectrometry. A total of 1859 samples from 55 participants (US, *n* = 36; Japanese, *n* = 19) were included in the analysis. Population PK models of HAS, HBS, 6S, and 10S were best described by a one or two-compartment model with a bolus input. On the other hand, the model of GRB1 was best described by a one-compartment model with nonlinear extravascular input. Among the covariates evaluated, body mass index (BMI) and age were found to influence oral clearance (CL/F) and volume of distribution (Vd/F) for HAS and HBS, respectively. The influence of body weight on CL/F and Vd/F for 6S was demonstrated. Marked differences were observed in mean plasma concentrations of HAS and HBS between Japanese and US participants. However, the simulation results indicated that the difference in plasma concentrations may be attributed to the difference in demographic factors such as BMI, body weight, and age, whereas ethnic difference between the Japanese and US participants was considered minimal.

Introduction

Daikenchuto (DKT) is a traditional Japanese herbal medicine that consists of extracted three botanical raw materials: Japanese pepper, processed ginger, and ginseng radix (Kono et al., 2009). Since its approval as a prescription drug in 1986 by the Japanese Ministry of Health, Labor and Welfare, DKT has been widely used by gastroenterologists and surgeons for the treatment of various gastrointestinal disorders, such as postoperative ileus and obstructive bowel disease (Itoh et al., 2002; Ohya et al., 2003; Kono et al., 2009). Consequently, the gastrointestinal effects of DKT have become a vibrant area of clinical and basic research in recent years.

Several animal studies have reported that the ameliorating effects of DKT on laparotomy or chemically induced intestinal dysmotility and postoperative intestinal adhesion were abrogated by atropine, a 5-hydroxytriptamine(4) antagonist (Tokita et al., 2007), and a transient receptor potential-channel antagonist (Tokita et al., 2011), respectively, suggesting that the promotility and antiadhesion effects of DKT likely occur via the activation of 5-hydroxytriptamine(4) receptors and transient receptor potential channel. Further, recent studies have addressed the possibility that DKT increases intestinal blood flow and ameliorates colitis via calcitonin gene-related peptide or adrenomedullin (Murata et al., 2002; Kono et al., 2008, 2010, 2011). The wide range of medicinal actions of DKT has been attributed to its multiple active constituents such as sanshools, shogaols, and ginsenosides. On the basis of a number of reports indicating the ameliorating effect of DKT in various animal gastrointestinal disease models, several double-blind, placebo-controlled, randomized trials in patients with postoperative paralytic ileus, refractory functional constipation, irritable bowel syndrome, or Crohn's disease are currently being conducted in Japan (JFMC39-0902, JFMC40-1001, and JFMC42-1002 funded by the Japanese Foundation For Multidisciplinary Treatment of Cancer) and in the United States (NCT00871325, NCT01139216, NCT01388933, and NCT01348152) with the US Food and Drug Administration approval of DKT as an investigational new drug. Among these studies, one recent study reported that DKT has a prokinetic effect in healthy volunteers (Manabe et al., 2010).

Despite widespread use in clinical practice, the pharmacokinetic (PK) knowledge of DKT is limited. Iwabu et al. (2010) reported that 44 compounds derived from DKT were detected in the plasma and urine after oral administration of DKT by using the liquid chromatography-tandem mass spectrometry. Moreover, Munekage et al. (2011) reported

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ABBREVIATIONS: AUC, area under the curve; BMI, body mass index; BQL, below the quantification limit; CL1/F, oral clearance of the central compartment; CL2/F, intercompartmental clearance; DKT, daikenchuto; GRB1, ginsenoside Rb_1; HAS, hydroxy-α-sanshool; HBS, hydroxy-β-sanshool; K_a, first-order absorption rate constant; PK, pharmacokinetic; RSE%, relative standard error of estimation; 6S, [6]-shogaol; 10S, [10]-shogaol; V1/F, volume of distribution for the central compartment; V2/F, volume of distribution for the peripheral compartment.

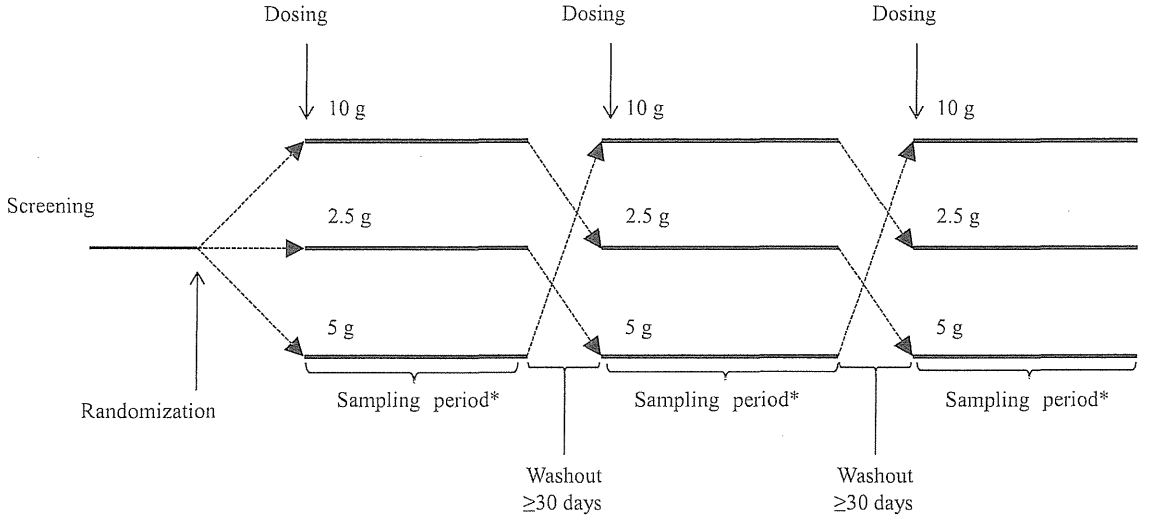

Fig. 1. Study design chart. *Japanese study: predose, 0.25, 0.5, 1, 2, 3, 4, 8, 12, 24, and 48 hours. US study: predose, 0.25, 0.5, 1, 2, 3, 4, 8, 12, 24, 48, 72, 96, and 168 hours.

the plasma concentration profiles of six pharmacologically active constituents of DKT—hydroxy-α-sanshool (HAS), hydroxyl-β-sanshool (HBS), 6-shogaol (6S), 10-shogaol (10S), ginsenoside Rb_1 (GRB1), and ginsenoside Rg_1—in Japanese healthy volunteers.

In recent years, the population PK approach has been used for the development of various pharmaceuticals (Williams and Ette, 2000). This approach can identify the measurable factors that cause changes in the dose-concentration relationship and the extent of these changes (Willliams and Ette, 2000). In this study, we first sought to develop the population PK models for the five constituents of DKT using the plasma concentration data obtained from healthy volunteers participating in the Japanese or US study. We then determined whether potential interethnic differences in the PK of DKT existed between the study populations.

Materials and Methods

Clinical Trials and Data Collection. Data were collected from two randomized, open-label, three-arm, three-period crossover studies in Japan and the United States. Participants received single oral doses of 2.5, 5, and 10 g of DKT after fasting for 12 hours at each period. A washout period of greater than 1 month followed period I and period II, preceding the administration of the next dose of the study drug. All foods and drinks (including spices) containing ginseng, Japanese pepper, and ginger were strictly prohibited from 3 days before dispensing the study medication until completion of each treatment phase. Overall study design is summarized in Fig. 1.

TABLE 1

Disposition and demographics of the study participants (healthy volunteers)

	Japanese Study (TJ-100-4-2)	US Study (TU100CPT4)
Total no. of subjects	19	36
2.5 g	18	33
5 g	19	34
10 g	19	33
Participant Demographics		
Gender (male/female)	14/5	28/8
Age[a] (yr)	22 (20, 37)	42 (21, 56)
Body weight[a] (kg)	58 (44.5, 72.5)	81.1 (50.0, 97.8)
Body mass index[a] (kg/m^2)	20.9 (18.5, 24.1)	26.9 (19.1, 29.9)

[a] Data represent median (minimum, maximum).

In the Japanese study, 19 healthy volunteers enrolled, 18 completed the study, and a total of 560 observations at 0.25, 0.5, 1, 2, 3, 4, 8, 12, 24, and 48 hours after dosing were used for the population PK analysis. Three participants did not meet the eligibility criteria of the study. The effects of these data were evaluated by final population models as sensitivity analysis.

In the US study, 36 healthy volunteers enrolled, 30 completed the study, and a total of 1299 observations at 0.25, 0.5, 1, 2, 3, 4, 8, 12, 24, 48, 72, 96, and 168 hours after dosing were collected. Data from one subject were excluded from the data set for the model building of GRB1 because the concentration-time profile showed a pharmacokinetically unreliable pattern. However, the entire data set was re-evaluated using final population models.

Disposition and demographics of the participants are summarized in Table 1. The content of each DKT constituent in the study medication was comparable between the two studies (Table 2).

Determination of Plasma Concentration of DKT Constituents. The concentrations of five DKT constituents—HAS, HBS, 6S, 10S, and GRB1—were determined by a validated liquid chromatography-tandem mass spectrometry method as reported by Munekage et al. (2011). The limits of the quantification were 0.01 ng/ml for HAS, HBS, and GRB1 and 0.02 ng/ml for 6S and 10S.

Population Pharmacokinetic Model Building. Population PK analysis was performed using the Phoenix NLME (version 1.3; Certara L.P., St. Louis, MO) by the Laplacian method. One- or two- compartment models with or without extravascular input were examined for exploration of the mean structure of the modeling. The basic PK parameters used in this study were oral clearance of the central compartment (CL1/F), volume of distribution for the central compartment (V1/F), intercompartmental clearance (CL2/F), volume of distribution for the peripheral compartment (V2/F), and first-order absorption rate constant (K_a). Nonlinear absorption coefficient (b) was introduced for GRB1 population PK modeling as a power of dose (see Supplemental Model Equation 5).

TABLE 2

Content of each constituent in study medication, daikenchuto (μg/g).

Data represent mean ± S.D.

	Japanese Study (TJ-100-4-2)	US Study (TU100CPT4)
HAS	591 ± 7	534 ± 6
HBS	100 ± 1	114 ± 2
6S	162 ± 1	167 ± 3
10S	43.3 ± 0.6	42.9 ± 2.1
GRB1	128 ± 2	155 ± 2

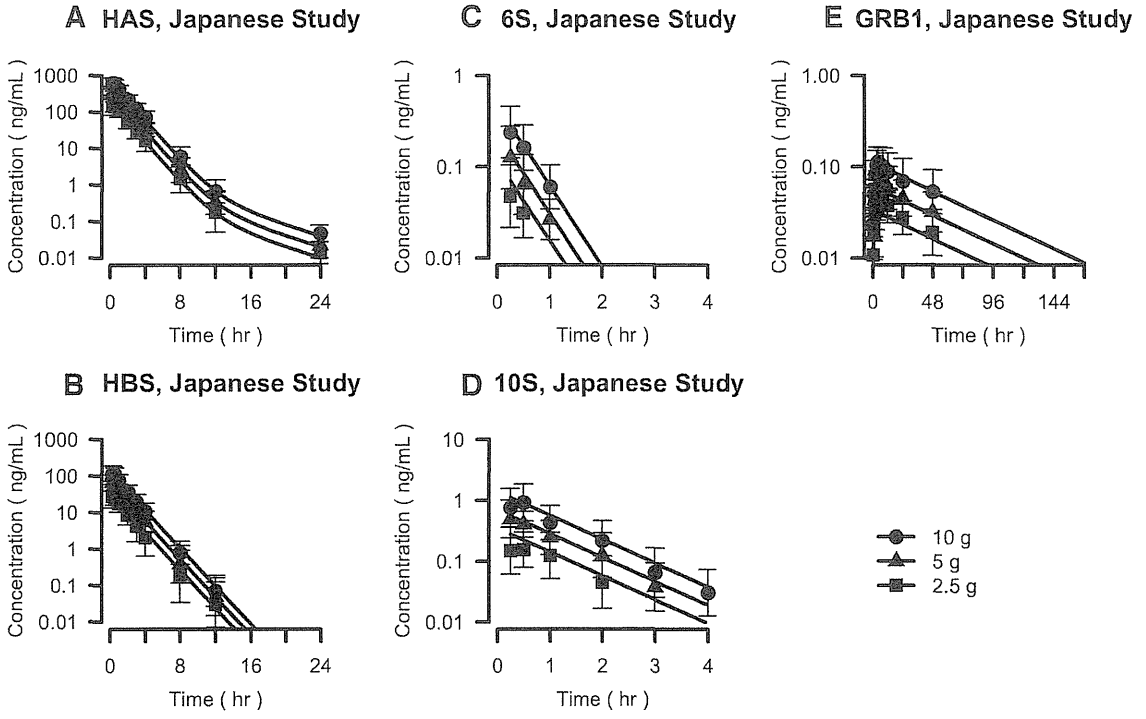

Fig. 2. Mean plasma concentration of five daikenchuto constituents in Japanese healthy volunteers. (A) HAS, (B) HBS, (C) 6S, (D) 10S, and (E) GRB1. Each symbol represents mean ± S.D. of observed concentration. Solid line indicates the model predicted concentration using the median values as covariate.

The interoccasion variability and the interindividual variability were modeled by lognormal distribution using eq. 1:

$$P_{ikj} = tvP_{ik} \cdot \exp(\eta ioc_{ikj} + \eta_{ik}) \quad (1)$$

where P_{ikj} is the k_{th} pharmacokinetic parameter for the i_{th} individual during the j_{th} period, tvP_{ik} is the covariate adjusted typical value of the k_{th} parameter, ηioc_{ikj} is a interoccasion variability, and η_{ik} is a interindividual variability. η_{ik} is Gaussian random deviate for the i_{th} individual in the k_{th} parameter with mean 0 and standard deviation ω_k. ηioc_{ikj} is an independent Gaussian random deviate

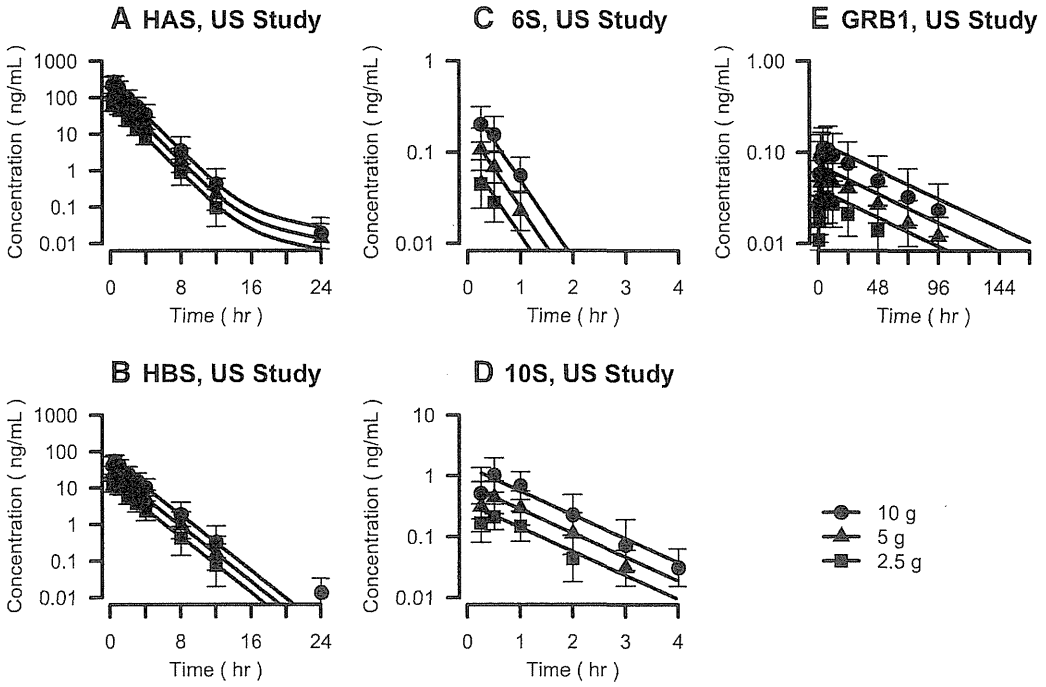

Fig. 3. Mean plasma concentration of five daikenchuto constituents in US healthy volunteers. (A) HAS, (B) HBS, (C) 6S, (D) 10S, and (E) GRB1. Each symbol represents mean ± S.D. of observed concentration. Solid line indicates the model predicted concentration using the median values as covariate.

TABLE 3

Summary of final population PK parameters for five constituents of daikenchuto

PK Model	HAS	HBS	6S	10S	GRB1
	2-Compartment (Bolus input)	1-Compartment (Bolus input)	1-Compartment (Bolus input)	1-Compartment (Bolus input)	1-Compartment (Nonlinear extravascular input)
Population Mean Parameter					
V1/F (l)	$13.2 \cdot \left(\frac{BMI}{24.7}\right)^{1.90} \cdot \left(\frac{AGE}{35}\right)^{0.402}$	$14.4 \cdot \left(\frac{BMI}{24.7}\right)^{2.19} \cdot \left(\frac{AGE}{35}\right)^{0.560}$	$4259 \cdot \left(\frac{WT}{71.8}\right)^{0.933}$	309	4384
CL1/F [(l/h)]	$7.69 \cdot \left(\frac{BMI}{24.7}\right)^{1.68} \cdot \left(\frac{AGE}{35}\right)^{0.322}$	$6.95 \cdot \left(\frac{BMI}{24.7}\right)^{1.37} \cdot \left(\frac{AGE}{35}\right)^{0.389}$	$8451 \cdot \left(\frac{WT}{71.8}\right)^{0.841}$	279	66.2
V2/F (l)	$0.281 \cdot \left(\frac{BMI}{24.7}\right)^{0.828} \cdot \left(\frac{AGE}{35}\right)^{0.509}$	—	—	—	—
CL2/F (l/h)]	0.0343	—	—	—	—
K_a (h^{-1})	—	—	—	—	0.719
b	—	—	—	—	0.862
Interoccasion Variability (CV%)					
$\omega ioc_{V1/F}$	13.9	24.1	—	—	36.3
$\omega ioc_{CL1/F}$	15.9	28.6	—	—	—
$\omega ioc_{V2/F}$	36.1	—	—	—	—
Interindividual Variability (CV%)					
$\omega_{V1/F}$	16.2	20.7	30.7	44.1	52.5
$\omega_{CL1/F}$	23.0	25.3	26.7	46.8	45.3
$\omega_{V2/F}$	15.4	—	—	—	—
ω_{Ka}	—	—	—	—	71.1
Correlation Coefficient					
V1/F vs. CL1/F	0.982	0.994	0.789	0.731	0.553
V1/F vs. V2/F	0.736	—	—	—	—
V2/F vs. CL1/F	0.824	—	—	—	—
V1/F vs. K_a	—	—	—	—	0.792
CL1/F vs. K_a	—	—	—	—	0.0162
Residual Error [S.D. (ng/ml) for additive, CV% for proportional]					
$\sigma_{additive}$	0.00481	0.0125	0.00558	0.0115	—
$\sigma_{proportional}$	21.6	21.1	35.7	54.1	32.0

—, not estimated; CV%, percent coefficient of variation.

for the i_{th} individual in the k_{th} parameter during the j_{th} period with mean 0 and standard deviation ωioc_k

The residual variability was described by the proportional error model (eq. 2) or combined proportional and additive model (eq. 3). The proportional error model is

$$C_{obs,ijt} = C_{ijt} \cdot (1 + Eps_{ijt}), \quad (2)$$

where $C_{obs,ijt}$ is the plasma concentration observed in the i_{th} individual, at time t after the drug administration during the j_{th} period. C_{ijt} is the predicted plasma concentration, and Eps_{ijt} is a random variable which is normally distributed with mean 0 and standard deviation σ.

The combined proportional and additive model is

$$C_{obs,ijt} = C_{ijt} + Eps_{ijt}(1 + C_{ijt} \cdot CMix\ Ratio), \quad (3)$$

where the proportional error component is obtained as the product of Eps_{ijt} and CMixRatio.

Once the basic model was selected, the influences of covariates were evaluated by a stepwise procedure based on the likelihood ratio test using $P < 0.05$

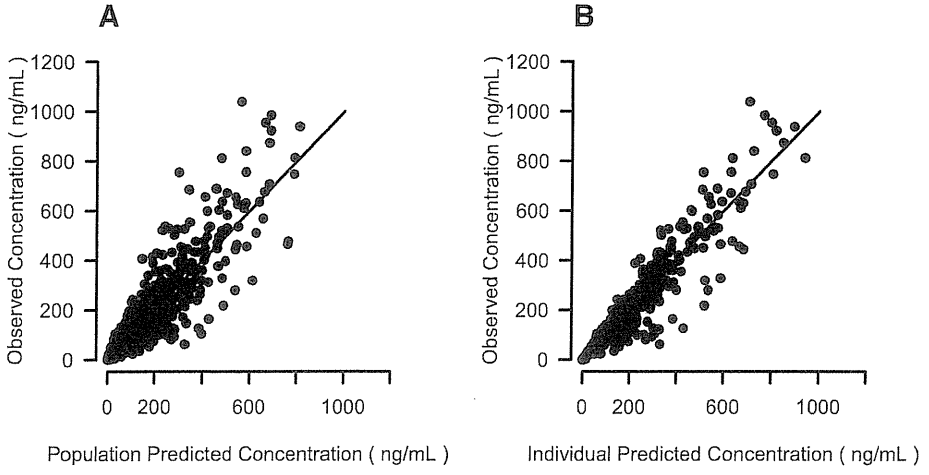

Fig. 4. Goodness-of-fit plot for HAS. (A) Observations plotted against population predicted concentrations. (B) Observations plotted against individual predicted concentrations.

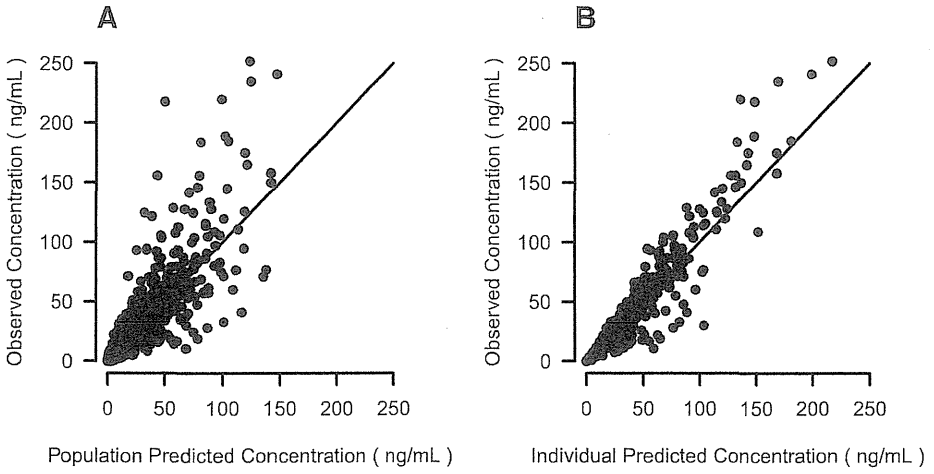

Fig. 5. Goodness-of-fit plot for HBS. (A) Observations plotted against population predicted concentrations. (B) Observations plotted against individual predicted concentrations.

as entry criterion. The covariates evaluated were the individual's age, body weight, body mass index (BMI), gender, and participation in the Japanese or US study (interstudy difference).

The influences of continuous covariates (age, body weight, and BMI) onto the k_{th} parameter were described as a power model as shown in eq. 4:

$$tvP_{ik} = tvP_k \cdot \left(\frac{Age_i}{Median\ Age}\right)^{dP_kdAge} \cdot \left(\frac{WT_i}{Median\ WT}\right)^{dP_kdWT} \cdot \left(\frac{BMI_i}{Median\ BMI}\right)^{dP_kdBMI} \quad (4)$$

where tvP_k is a typical value of k_{th} parameter; WT is the body weight; and dP_kdAge, dP_kdWT, and dP_kdBMI, are the fixed effect parameters for the age, body weight, and BMI.

The influences of categorical covariate (gender and study identifier) were described as eq. 5:

$$tvP_{ik} = tvP_k \cdot \exp(dP_kdGender*G_{female}) \cdot \exp(dP_kdStudy*S_{US}), \quad (5)$$

where G_{female} is a dummy variable which took on a value of 1 if the gender of the subject was female and 0 otherwise. Likewise S_{US} is a dummy variable which took on a value of 1 if the study was conducted in the United States and 0 otherwise.

The BQL (below the quantification limit) values were treated as the left censored data and used in the model fitting procedure via the maximum likelihood method (Beal, 2001).

Model Validation. Bootstrap resampling method (Ette, 1997) and visual predictive check method (Post et al., 2008) were used to evaluate the accuracy and robustness of our models. A total of 1000 resamplings was executed for the bootstrap method, and a total of 1000 replicates of the original data set were simulated for the predictive check method to generate the predicted concentration values and the 95% prediction interval.

Results

Demographics and disposition of the study participants are summarized in Table 1. The population PK analysis included a total 1859 samples from 55 participants. There were marked differences in subject demographics.

Figures 2 and 3 demonstrate observed (mean +/− S.D., presented as dots) and the model predicted (population mean values, presented as solid lines) plasma concentration-time profiles of the five DKT constituents (HAS, HBS, 6S, 10S, and GRB1) after a single oral dose of DKT in healthy Japanese and US adults. Noticeable differences were observed in the mean plasma concentrations of HAS and HBS between the Japanese and US participants.

Final population PK parameters are summarized in Table 3.

Population PK model of HAS was best described by a two-compartment model with a bolus input (see Supplemental Model Equation 1). Interoccasion variability and interindividual variability were estimated for V1/F, CL1/F, and V2/F. The interindividual variation of PK

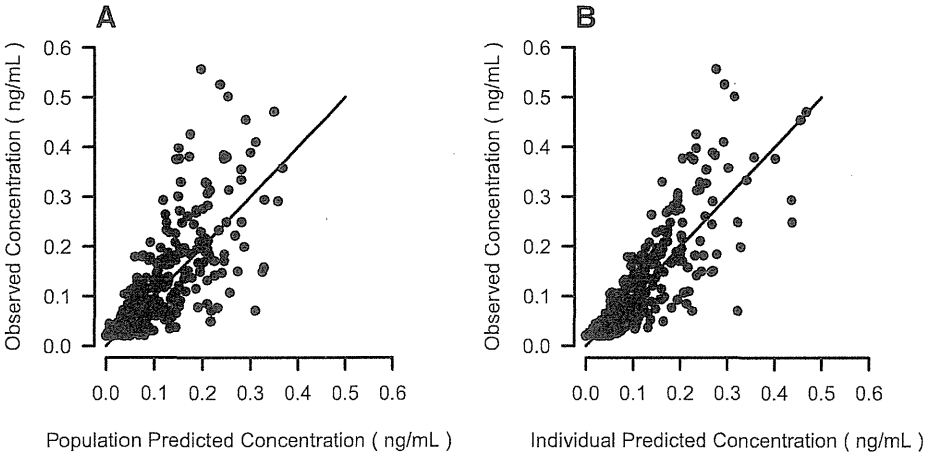

Fig. 6. Goodness-of-fit plot for 6S. (A) Observations plotted against population predicted concentrations. (B) Observations plotted against individual predicted concentrations.

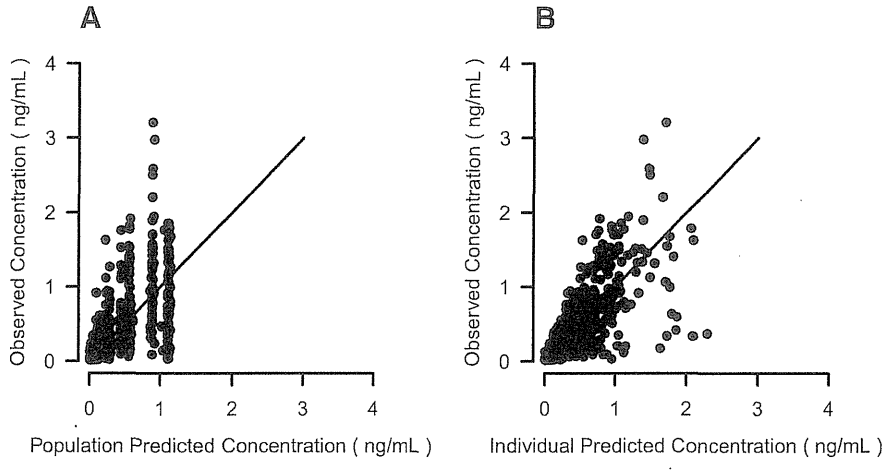

Fig. 7. Goodness-of-fit plot for 10S. (A) Observations plotted against population predicted concentrations. (B) Observations plotted against individual predicted concentrations.

parameters showed a positive correlation. A combined proportional and additive model was selected to describe the residual variability. BMI and age were the covariates affecting V1/F, V2/F, and CL1/F. The relative standard error of estimation (RSE%) for the fixed effect parameters stayed within the range from 2.7 to 32.7%, and the RSE% of random effect parameters ranged from 7.8 to 45.5% (Supplemental Table 1). Goodness-of-fit plot for the final population PK model showed no remarkable biases (Fig. 4). The visual predictive check plots indicated that the predictive concentrations displayed a good fit with the observed concentrations (Supplemental Fig. 1). The resampling successfully converged in the bootstrap evaluation, and the estimated parameters from bootstrap were similar to the parameters obtained from the final model (Supplemental Table 1).

The model for HBS, 6S, and 10S was best described by a one-compartment population PK model with a bolus input (see Supplemental Model Equations 2–4). Interindividual variability was estimated for V1/F and CL1/F. Regarding the interindividual variations of these two parameters, a positive correlation emerged for all constituents. Interoccasion variability was calculated for only HBS. A combined proportional and additive model was selected to describe the residual variability. For HBS, BMI and age affected V1/F and CL1/F as covariate. Similarly, body weight was incorporated into V1/F and CL1/F for the 6S model. However, the model for 10S retained no significant covariates. The RSE% for the parameters stayed within the range of 2.7 to 33.2% (Supplemental Tables 2–4). Goodness-of-fit plot for the final population PK model of HBS (Fig. 5) and 6S (Fig. 6) indicated no remarkable biases. The plots of the 10S model implied that the model contained a slight asymmetry at high concentrations (Fig. 7). The visual predictive check plots indicated that there were good agreements between the predicted and observed concentrations (Supplemental Figs. 2, 3, and 4). The resampling successfully converged in the bootstrap evaluation, and the estimated parameters from bootstrap were similar to the parameters obtained from the final model (Supplemental Tables 2–4).

The population the PK model of GRB1 was best described by a one-compartment model with nonlinear extravascular input (see Supplemental Model Equation 5). Interindividual variability was estimated for V1/F, K_a, and CL/F. The interoccasion variability was calculated for V1/F. No statistically significant covariate was incorporated into the model. For all estimated parameters, RSE% was considered acceptable (within the range of 2.6 to 30.0%), except for the covariance between K_a and CL1/F, which showed greater RSE% as a result of the mean value being nearly zero (Supplemental Table 5). Residuals of population prediction and the observed value showed log-normal distribution. On the other hand, individual post hoc estimation and observed value showed no remarkable biases (Fig. 8). The visual predictive check plots indicated that the predictive concentrations were well fitted to the observed concentrations (Supplemental Fig. 5). The

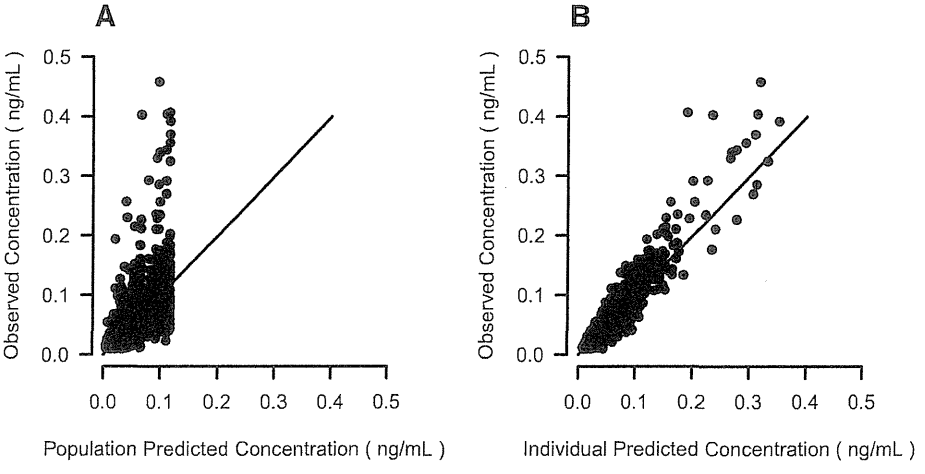

Fig. 8. Goodness-of-fit plot for GRB1. (A) Observations plotted against population predicted concentrations. (B) Observations plotted against individual predicted concentrations.

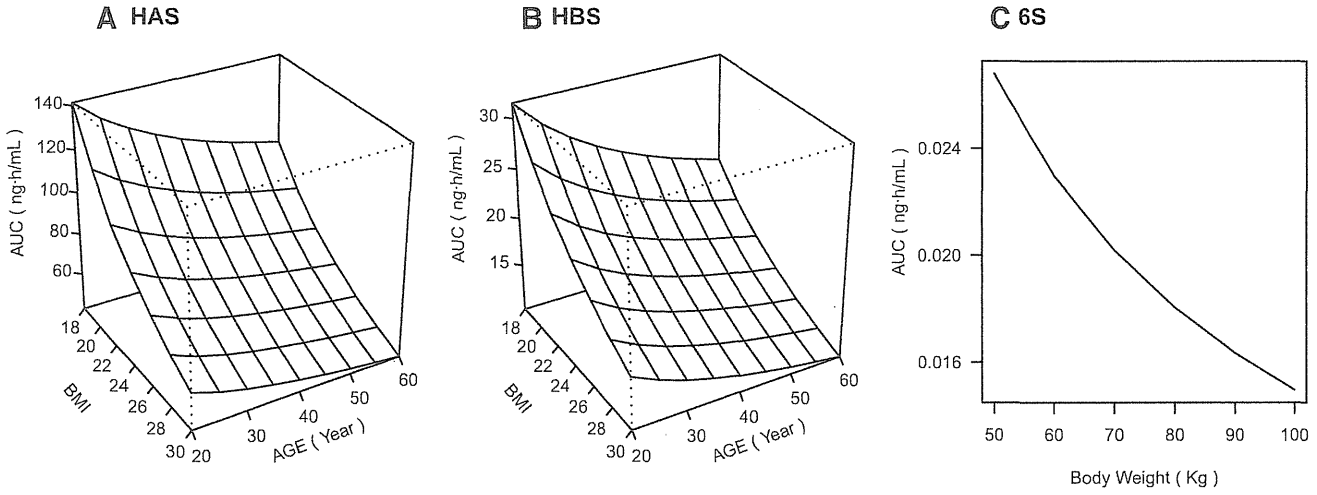

Fig. 9. Influence of covariates on calculated AUCs of DKT constituents. (A) HAS, (B) HBS, and (C) 6S.

resampling successfully converged in the bootstrap evaluation, and the estimated parameters from bootstrap were similar to the parameters obtained from final model (Supplemental Table 5).

Figure 9 indicates that the influence of covariates on the calculated area under the curve (AUC) of DKT constituents HAS, HBS, and 6S. BMI showed a pronounced influence on the AUCs of HAS and HBS.

Discussion

We analyzed six pharmacologically active constituents of DKT—HAS, HBS, 6S, 10S, GRB1, and GRG1 in respective Japanese and US PK studies. Population PK models were constructed for the five constituents, but not for GRG1, because most of the GRG1 concentrations fell below the quantification limit (BQL).

When the first-order absorption model and the bolus input model were evaluated as population PK models for HAS, HBS, 6S, and 10S, the bolus input model was found to best describe the PK of these constituents. This was because the t_{max} was observed in many subjects at the first sampling point, which occurred at an early time point of 15 minutes. Wade et al. (1993) reported that when no data are present in the absorption phase, the misspecification of the rate of drug absorption or the model used to describe drug absorption has little consequence on the estimation of the remaining population parameters. On the other hand, the goodness-of-fit plot of the model for 10S indicated that the predicted plasma concentrations overestimated the observed plasma concentrations at the highest predicted plasma concentration (i.e., the first sampling point), based on participants who were actually observed during the absorption phase. Without incorporating the absorption phase into the model, the plasma level in the proximity of C_{max} was unpredictable. Although the modeling is limited to an elimination phase, the model is still considered applicable to the PK characterization of the compound with a short absorption phase.

As reported previously in Japanese PK study (Munekage et al., 2011), nonlinearity was observed in AUC of GRB1, but dose-dependence in half-life was not; therefore, a nonlinear absorption model was assumed for the GRB1 analysis. As a result, nonlinear parameter (b) showed a significant value, and the AIC value indicated a better fit compared with the model not assuming the nonlinear parameter. Estimated b value below 1 suggested the convex dose-concentration relationship.

The BQL data included in the dataset were used for the analysis. Although useful information is included in the BQL data, there are concerns regarding the possible bias caused by the mishandling of BQL data. (Hing et al., 2001; Byon et al., 2008). Beal (2001) reported an overview of ways to fit a PK model in the presence of BQL data. The method applied conditional likelihood estimation to the observations above BQL and the likelihood for the data being above the BQL were maximized with respect to the model parameters. Phoenix NLME (Pharsight, St. Louis, MO), which was the analysis software used in this study, implemented this method. We therefore treated BQL data as left censored data and used them in the model fitting procedure via the maximum likelihood method.

Among the covariates evaluated, BMI, age, and body weight affected CL/F and Vd/F for HAS, HBS, and 6S. The three-dimensional plot (Fig. 9) of the covariate relationship with AUC indicated that BMI was the most important covariate to explain the AUC variability of HAS and HBS because the AUCs decreased by 2-fold when the BMI increased by 2-fold from 18 to 30. The package insert of DKT in Japan describes that the dosage may be adjusted according to the patient's age, body weight, and symptoms, and our findings support this statement. However, it is necessary to judge in consideration of clinical meaning about the necessity for dosage adjustment by more detailed examination, including the clinical study on efficacy and safety.

Remarkable differences were observed in mean plasma concentrations of HAS and HBS between the Japanese and US participants (Figs. 2 and 3). However, interstudy difference has not been selected for the final models of all constituents of DKT. On the other hand, the simulated plasma concentrations at the median value of covariates in each study could reproduce the study difference observed. These results suggest that the difference in the plasma levels between the study populations could be explained by the difference in terms of demographic factors such as BMI and age rather than by interethnic differences between the Japanese and the US habitants.

The likelihood ratio test is frequently used as the criteria for the selection of covariates. The possibility of type 1 error inflation in the likelihood ratio test has been cautioned (Wählby et al., 2001). Therefore, a very low P value such as $P < 0.001$ is often used as the significance level. Nevertheless, as the first exploratory analysis of DKT via population modeling, we set a criterion of P value at 0.05 to increase the probability of detecting a greater number of covariates that might influence the PK parameters. To protect against the inclusion of false covariates, more evaluations are needed.

Pharmacokinetic information is very useful to characterize a medication and is indispensable to determine the proper use of the medication. However, the clinical effects of herbal medicines are complex because of the presence of numerous constituents. We therefore constructed PK models for five constituents of a single formulation that simultaneously contains constituents with very different PK properties, as seen from constituents with a short half-life, such as shogaols and sanshools, compared with those with a long half-life, such as ginsenosides. To extrapolate our findings effectively to a wider population, further investigation of the relationship between PK and efficacy is warranted.

The results from this study are useful and are a preliminary step toward a more comprehensive pharmacokinetic/pharmacodynamic study in patients.

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Authorship Contributions

Participated in research design: Munekage, Ichikawa, Kitagawa, Kono, Hanazaki.

Conducted experiments: Munekage, Ichikawa, Kitagawa, Hanazaki.

Performed data analysis: Ishihara, Uehara, Watanabe.

Contributed to the writing of the manuscript: Munekage, Ichikawa, Kitagawa, Ishihara, Uehara, Watanabe, Kono, Hanazaki.

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Clinical Study

Infliximab Extends the Duration until the First Surgery in Patients with Crohn's Disease

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Background/Aims. While biological drugs are useful for relieving the disease activity and preventing abdominal surgery in patients with Crohn's disease (CD), it is unclear whether the use of biological drugs in CD patients with no history of abdominal surgery is appropriate. We evaluated the effects of infliximab and other factors on extending the duration until the first surgery in CD patients on a long-term basis. *Methods.* The clinical records of 104 CD patients were retrospectively investigated. The cumulative nonoperation rate until the first surgery was examined with regard to demographic factors and treatments. *Results.* The 50% nonoperative interval in the 104 CD patients was 107 months. The results of a univariate analysis revealed that a female gender, the colitis type of CD, and the administration of corticosteroids, immunomodulators, or infliximab were factors estimated to improve the cumulative nonoperative rate. A multivariate analysis showed that the colitis type and administration of infliximab were independent factors associated with a prolonged interval until the first surgery in the CD patients with no history of abdominal surgery. *Conclusions.* This study suggests that infliximab treatment extends the duration until the first surgery in CD patients with no history of abdominal surgery. The early use of infliximab before a patient undergoes abdominal surgery is therefore appropriate.

1. Introduction

Crohn's disease (CD) is a chronic inflammatory bowel disease whose etiology remains unclear. Deep and refractory ulcers frequently develop in the small intestine in CD patients, often causing severe complications, including abdominal abscesses and ileus. Open surgery is sometimes required to relieve the patient's conditions, including ileus due to severe stricture, refractory abscesses, and fistulas, which lead to a deterioration of the general condition and quality of life in the patients, as well as severe intestinal bleeding [1]. Recent advances in therapeutic strategies have led to the development of biological agents, such as infliximab and adalimumab, that have improved the success rate of inducing remission and are useful as maintenance therapy in patients with refractory CD [2–6]. The administration of biological agents also reduces the rate of complications and extends the duration from the first to the second surgery [7–10]. Because the traditional therapeutic approach for treating CD is based on a step-up strategy [11], the administration of treatment with biological drugs is recommended in patients who fail to respond to conventional therapy, but not patients who exhibited mild to moderate disease activity without a history of abdominal surgery. Recently, D'Haens et al. reported in a 2-year randomized trial that the percentage of newly diagnosed patients without a need for corticosteroid

treatment or surgery at six and 12 months was significantly higher in the group administered infliximab [12]. This short-term observation suggests that the use of infliximab in CD patients, who were diagnosed within the past four months, can increase the duration of remission and extend the duration until the first surgery. Conversely, Jones and Finlayson evaluated the Nationwide Inpatient Sample in the US and concluded that, during the period of adoption of infliximab as a novel CD treatment, the overall rate of bowel resection either remained relatively stable or moderately decreased [13]. Domènech et al. retrospectively reviewed the clinical outcomes of newly diagnosed Crohn's disease patients before and after infliximab availability and concluded that infliximab availability did not reduce the need for surgery or the development of disease-related complications [14]. It remains unclear whether the early use of biological drugs decreases the risk of the first surgery in CD patients.

The present retrospective study investigated factors affecting the interval from the time of diagnosis to the first surgery, including patient demographics, type of disease, and treatment procedures, in CD patients with no history of abdominal surgery.

2. Methods

2.1. Patients. Written informed consent was obtained from all identified patients, and the study was approved by the institutional review board of Asahikawa Medical University. The clinical records of 104 patients who were diagnosed as having CD at Asahikawa Medical University between February 1982 and October 2011 were retrospectively investigated. The diagnosis of CD was made based on the combination of the clinical course and the colonoscopy, double balloon endoscopy, small bowel enterolysis, and histological findings. Typical lesions of CD, including longitudinal ulcers and a cobblestone appearance in the small and/or large intestine, were observed on endoscopy in all patients. Intestinal strictures, fistula formation, and abdominal abscesses were also observed in the patients. These findings were also referenced for the diagnosis of CD. Data regarding patient demographics, treatments, and operative findings were collected by A.S., who did not participate in the diagnosis, medical examination, or treatment of the patients. The onset of the disease was defined as the time of appearance of symptoms caused by CD. The date of disease onset was used to divide the patients into two groups, those treated before 2001 and those treated after 2002, because infliximab became clinically available in Japan in 2002. Patients who received infliximab four or more times, corticosteroids as remission induction therapy, or immunomodulators for one or more months were classified as belonging to the infliximab-positive, corticosteroid-positive, or immunomodulator-positive groups, respectively. These agents were administered in patients resistant to 5-aminosalicylate treatment and/or those who requested these drugs.

2.2. Cumulative Nonoperative Rate until the First Surgery. The abdominal surgeries performed in this study included intestinal resection, strictureplasty, colostomy, and ileostomy. The demographic and treatment-related factors were retrospectively compared with the cumulative nonoperative rate until the first surgery. In the patients who did not undergo surgery, the interval from diagnosis to the end of the study was defined as the nonoperative time (March 2012). In the patients who underwent either single or multiple surgeries, the interval from diagnosis to the first surgery was defined as the nonoperative time.

2.3. Statistical Analyses. The Kaplan-Meier method was used to test the cumulative nonoperative rates and the data related to each factor were statistically analyzed using the log-rank test. A Cox proportional hazards model was used to calculate the hazard ratios of the factors identified to estimate the frequency of surgery. A P value of <0.05 was considered to be statistically significant (two-sided test).

3. Results

3.1. Patient Demographics and Treatments. Seventy-one male and 33 female patients were included in this study. Sixty-seven (64%) patients exhibited lesions in both the small and large intestines (ileocolitis type), 28 (27%) patients had lesions in the small intestine only (ileitis type), and nine (9%) patients had lesions in the large intestine only (colitis type). The age at disease onset ranged from 10 to 66 years, with a median of 22 years. The date of disease onset was before 2001 in 74 patients and after 2002 in 30 patients. Corticosteroids, immunomodulators, and infliximab were administered in 33 (32%), 37 (36%), and 39 (38%) of the patients before the first surgery, respectively. A total of 16 of the 74 patients who had disease onset before 2001 and 23 of the 30 patients who had disease onset after 2002 took infliximab. Sixty-nine patients (66%) underwent one or more surgeries (Table 1). A total of 134 surgeries were performed. Ileal or jejunal resection was performed in 76 patients, strictureplasty was performed in 10 patients, and colostomy or ileostomy was performed in six patients. Combination surgeries were performed in 42 patients (Table 2).

3.2. Clinical Factors Associated with the Cumulative Nonoperative Rate. The cumulative nonoperative rate among all 104 patients is shown in Figure 1. The 50% nonoperative interval was 107 months. The relationships between the clinical factors, such as gender, the location of the lesions, the age at disease onset and treatments, and the cumulative nonoperative rate, were analyzed. The results of a univariate analysis of the cumulative nonoperative rate based on the presence or absence of each clinical factor are shown in Table 3. The analysis revealed that a female gender, the colitis type of CD, and the administration of corticosteroids, immunomodulators, or infliximab were factors estimated to improve the cumulative nonoperative rate (Figure 2). A multivariate analysis showed the colitis type of CD and the administration of infliximab to be independent factors associated with a prolonged interval until the first surgery. The hazard ratios of the colitis type of CD and the administration

Table 1: Patient demographics and treatments (104 cases).

	Number of patients (n = 104)
Sex	
Male	71 (68%)
Female	33 (32%)
Type of disease	
Ileitis	28 (27%)
Ileocolitis	67 (64%)
Colitis	9 (9%)
The age of onset	
Median	22
Range	10–66
The history of corticosteroid use until the first operation	
(+)	33 (32%)
(−)	71 (68%)
The history of immunomodulator use until the first operation	
(+)	37 (36%)
(−)	67 (64%)
The history of infliximab use until the first operation	
(+)	39 (38%)
(−)	65 (62%)
The history of enteral nutrition	
(+)	96 (92%)
(−)	8 (8%)
Bowel surgery	
(+)	69 (66%)
(−)	35 (34%)

of infliximab were 0.086 (0.011–0.657) and 0.256 (0.122–0.540), respectively (Table 4).

4. Discussion

The present study showed that the administration of infliximab extends the duration until the first surgery in CD patients who have not previously undergone abdominal surgery. This suggests that the administration of infliximab is useful in CD patients with no experience with abdominal surgery. While the usefulness of biological drugs for inducing and maintaining remission of CD and extending the duration from the first to the second surgery has been established [2, 3, 10], it remains unclear whether these biological drugs should be administered in CD patients with no history of abdominal surgery. Recently, D'Haens et al. reported in a 2-year open-label-randomized trial that the percentage of CD patients who were diagnosed within four months in clinical remission and were neither receiving corticosteroids nor requiring surgery at six and 12 months was significantly higher in

Table 2: Surgical procedures performed in 69 patients with Crohn's disease (total: 134 operations).

	Total of 134 operations
Bowel resection	76
Strictureplasty	10
Colostomy or ileostomy	6
Bowel resection and strictureplasty	27
Bowel resection and colostomy (or ileostomy)	13
Strictureplasty and colostomy (or ileostomy)	1
Bowel resection and strictureplasty and colostomy (or ileostomy)	1

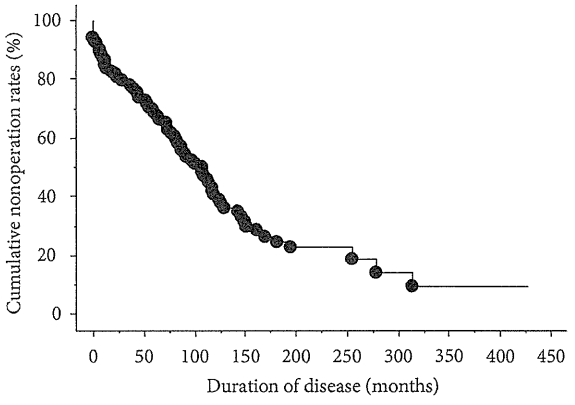

Figure 1: The cumulative nonoperative rate among all 104 patients. The nonoperative rate was inversely proportional to the duration of the disease.

the group treated with infliximab [12], thus suggesting that the early use of infliximab can improve the short-term outcomes of CD. The present study supports the notion that infliximab treatment can improve both the long-term and short-term outcomes in CD patients, even when the patient has no history of abdominal surgery.

Although the present study demonstrated the efficacy of infliximab treatment, the period of disease onset may have influenced the duration from disease onset to the first surgery. After 2002, the availability of infliximab treatment is not the only factor that changed from the previous era. The types and characteristics of microorganisms causing infectious colitis and the eating habits and lifestyle factors affecting the pathology of inflammatory diseases have been changed over the past two decades in Japan. Therefore, the present study investigated the influence of the date of disease onset on the duration until the first surgery, the results of which showed that the date of disease onset is not a significant factor affecting the duration until the first surgery in CD patients. An evaluation of the Nationwide Inpatient Sample conducted in the US concluded that, during the period of adoption of infliximab as a novel CD treatment, the overall rate of bowel resection either remained relatively stable or moderately decreased [13]. Domènech et al. also reviewed the clinical

Table 3: Factors associated with the nonoperative rate until the first surgery (univariate analysis).

	Number of patients (n = 104)	50% nonoperation time (months)	P value
Sex			
Male	71	84	<0.05
Female	33	142	
Type of disease			
Ileitis/ileocolitis	95	98	<0.05
Colitis	9	Undefined	
The age of onset			
Less than 20	39	117	N.S.
20 or more	65	98	
The date of onset			
Before 2001	74	107	N.S
After 2002	30	Undefined	
Corticosteroid			
(+)	33	126	<0.05
(−)	71	91	
Immunomodulator			
(+)	37	169	<0.05
(−)	67	84	
Infliximab			
(+)	39	256	<0.05
(−)	65	78	

Undefined: nonoperation time is greater than 50% at the last time point. N.S.: not significant.

Table 4: Factors associated with the nonoperative rate until the first surgery (multivariate analysis).

		Hazard ratio	95% CI
Sex	Female	0.605	0.339–1.081
Type of disease	Colitis	0.086	0.011–0.657
Corticosteroid	(+)	0.912	0.519–1.604
Immunomodulator	(+)	1.057	0.569–1.966
Infliximab	(+)	0.256	0.122–0.540

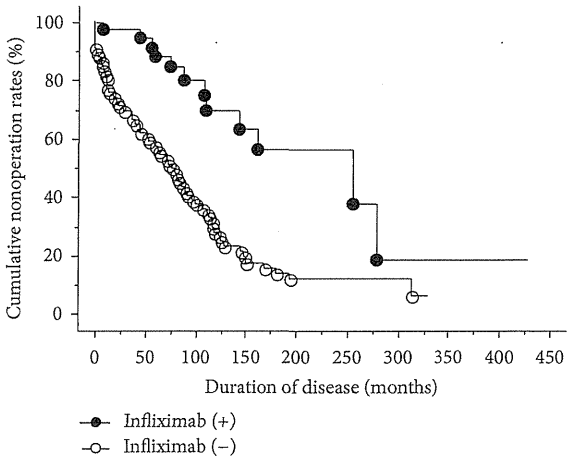

Figure 2: The results of a univariate analysis of the cumulative nonoperative rate based on the presence or absence of infliximab treatment. The univariate analysis revealed that the administration of infliximab is a factor estimated to improve the cumulative nonoperative rate.

outcomes of newly diagnosed Crohn's disease patients before and after infliximab availability in a retrospective study and concluded that infliximab availability did not reduce the need for surgery [14]. These investigations and the present study therefore indicate that the date of disease onset is not a strong factor affecting the duration until the first surgery in CD patients. Further long-term prospective studies of large numbers of CD patients with no history of abdominal surgery are needed to confirm the significance of biological agents in improving the cumulative nonoperative rate in CD patients.

In this study, while the univariate analysis revealed that the administration of corticosteroids and immunomodulators affected the duration until the first surgery, the multivariate analysis did not identify these treatments to be independent factors. Therefore, these therapies are not very useful for treating CD patients with no history of abdominal surgery in comparison to the administration of infliximab. The administration of corticosteroids has been shown to be effective for inducing remission in patients with CD [15–20]. However, it is well known that the administration of corticosteroids is associated with various side effects. Corticosteroids should be used as short-term therapy only when other treatments are ineffective. Although the administration of immunomodulators alone is useful for maintaining CD [21, 22], combination therapy with immunomodulators and infliximab has been shown to be more effective for this purpose [23]. Because immunomodulators were used in combination with infliximab in most cases in the present study,

the multivariate analysis did not identify immunomodulators to be an independent factor.

In summary, the results of the present study suggest that infliximab treatment has the potential to extend the duration until the first surgery. This implies that the administration of infliximab in CD patients with no history of abdominal surgery, even in CD patients with no experience with abdominal surgery, can improve the outcomes, including the cumulative nonoperative rate. Further randomized, controlled trials are needed to establish the appropriate timing of the initiation of infliximab treatment and determine the optimal dose, schedule, and duration of the administration of these biological drugs.

Conflict of Interests

The authors declare that they have no conflict of interests.

Authors' Contribution

Aki Sakatani and Mikihiro Fujiya contributed equally to this study.

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消化器外科と漢方

Gastroenterological surgery and Kampo

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●要旨●漢方薬は日本固有の薬物であり，医療用漢方薬とそれ以外に分けられ，消化器外科医は前者を使用すべきである。漢方薬は西洋薬と根本的に異なり，基礎研究を経ずに成長，変遷してきたため誤解が生じやすい。技術革新のおかげで漢方薬の薬物動態が明らかとなり，薬効機序解明も一気に進んできた。臨床試験においてもプラセボ対照としたハイエビデンスの臨床試験が多く行われるようになり，国際学会でも注目されるようになってきた。西洋薬に対する信頼感に匹敵するレベルに到達するのも時間の問題である。それを牽引するのは日本の消化器外科医の責務である。

● key words：漢方薬，西洋薬，エビデンス，大建中湯，抑肝散

はじめに

消化器外科における漢方の導入や有用性，今後の展望について総論的に解説を述べるが，最初に，漢方初学者であった私が，医療用漢方薬の基礎的研究を始めたときには十分理解ができていなかった点で，質問などを受けながら理解してきたことをポイントごとに述べる。また，登場する漢字の読み方についても一部かなを追記した。

漢方の登場

漢方という名前が登場したのは比較的新しく，江戸時代にオランダから伝わった西洋医学を蘭方医学とし，古来中国から伝わってきた中医（ちゅうい）や日本古来の医学を含めて漢方（漢方医学）として区別しはじめたのが最初である。したがって，漢方は中医を巧みに取り入れた日本伝統医学そのものである[1)]。漢方は診断学なども含めたものであるため，薬剤そのものは漢方薬と呼んでいるが，狭義の漢方は薬を指すこともあり，混乱が生じている。とくにマスコミでは漢方と漢方薬を同列に扱う傾向が強く注意を要する。

医療用漢方薬

われわれ消化器外科医がもっとも多く使用している大建中湯（だいけんちゅうとう）は医療用漢方薬である。しかし同じ名前のものが薬局でも市販されているだけでなく，同じ医療用漢方薬，大建中湯でも発売する医薬品会社の違いによって量や内容にも違いがある。そもそも大建中湯が当時の厚生省から許可を得て保険収載されたのは1986年である。医療用漢方薬はすべて抽出，つまり生薬（しょうやく）と呼ばれる薬草の原材料を決められた配合比で混ぜ，高温の熱水で成分を抽出するプロセスが行われ，抽出液を乾燥させ飲みやすく加工したものである。

さらに，ロットごとによる効果の違いを最小限にするための工夫や安全性についても国が定めた基準に準拠していることは当然であるが，一部のメーカーでは

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表 1　西洋薬と漢方薬の違い

西洋薬	単一成分	単一標的	治療効果 副作用なし
		意図しない 多標的	治療効果と 重篤な副作用
漢方薬	複数成分	意図した 多標的	治療効果と 少ない副作用

単一成分 →	基礎研究 →	臨床試験 第Ⅰ相・第Ⅱ相 →	臨床試験 第Ⅲ相 →	西洋薬
複数成分 →	臨床試験 第Ⅰ相・第Ⅱ相 →	臨床試験 第Ⅰ相・第Ⅱ相 →	臨床試験 第Ⅰ相・第Ⅱ相 →	漢方薬

世界中の農薬，抗生物質，重金属などが混入していないか生薬の段階で検査している[1]。いまだに多くの生薬は輸入，とくに中国からのものが多く，他の食品同様，安全性が危惧されるため，厳重かつ慎重な対応が必要である。この点で大いに危惧されるのが医療用漢方薬以外の薬局処方や個人で輸入した生薬原材料を使用した場合，安全性は確保できていないためアレルギーや重篤な副作用が出現する可能性がある[1]。したがって，消化器外科医が使用すべき漢方薬は医療用漢方薬に限定すべきである。

大建中湯をTU-100として米国食品医薬品局(FDA)が臨床治験薬として認可した際に副作用の再調査をツムラに依頼し行った結果，2010～2012年の２年間，3,400例で1.9%の副作用の発現率であった。重篤なものはなく，安全性がきわめて高いことが改めて確認された。大建中湯の構成生薬はすべて食品として使用されている人参，山椒，乾姜（かんきょう）なので副作用が少ないのも当然であるといえる。

漢方薬と西洋薬の違い

漢方薬の薬理効果研究を行うなかで西洋薬との違いが明らかとなってきた（**表 1**）。西洋薬のほとんどは単一成分で作られているが，その理想は単一成分が単一のターゲットに対して単一の効果を発揮し，副作用を起こさない薬，つまり優秀なサッカー選手が１人でドリブルしシュートし得点するのである。残念ながら現実は単一の成分が開発時には思いもしなかったターゲットに作用し，副作用を発現してしまうことがほとんどである。一方，漢方薬は２種類以上の生薬が基本で，多数の成分が含まれており，その理想は多成分が多数のターゲットに対して効果を発揮する，つまり，パスを中心としたチームワークで得点するのに似ている。

副作用は重篤なものは少ないが，その理由は薬として完成する過程が西洋薬とはまったく異なるからである（表 1）。西洋薬では候補となる成分の薬理作用，薬物動態試験，毒性試験などが行われてから臨床試験を行い薬効，副作用の発現について検証され完成し，さらに市販後副作用調査も行われる。一方，漢方薬は最初に臨床試験が繰り返し行われ，効果がより強く，副作用がより少ない生薬の組み合わせを長期にわたり検討が行われ，最終的にはレスポンダー，つまり漢方で診断される患者だけに投与されてきた。したがって，薬理作用，薬物動態は必然的に後回しになってしまった。副作用の発現が少ないのも当然であるが，漢方の診断法，つまり誰がレスポンダーかわからない消化器外科医にとって“副作用も少ないからまずは使って効果があればOK”ということになってしまった。完成して何百年以上もたった今，漢方薬の薬理作用機序，薬物動態試験がやっと行われることになったのである。

最近のテクノロジーの進歩がなければできない研究ではあるが，消化器外科医をはじめ多くの医師が漢方薬に対して懐疑的であった理由の第一はこの点にあるといえる。さらに，現代医療では欠かせないプラセボ使用によるエビデンスレベルの高い臨床試験がきわめて少ないということも助長してきた要因といえる。

漢方薬のエビデンス

10年前と比較した結果，漢方薬の臨床試験において量だけでなく質においてもプラセボを対照とした二

表2　漢方のエビデンス・タイプ分類（2013年2月現在）

レベル	エビデンスのタイプ	2002年	現在
Ⅰa	ランダム化比較試験のメタ分析	0	1
Ⅰb	ランダム化比較試験	2	31
Ⅱa	よくデザインされた非ランダム化比較試験	4	12
Ⅱb	よくデザインされた準実験的研究	1	9
Ⅲ	よくデザインされた非実験的記述研究	2	3
Ⅳ	専門家委員会の報告や意見，権威者の臨床経験	3	5

重盲検試験が行われることが多くなってきた（表2）。エビデンスレベルがもっとも高いⅠaであるランダム化比較試験のメタ分析で薬効が証明された漢方薬，抑肝散（よくかんさん）について簡単に説明する。

抑肝散の“肝”は心や精神を意味し，いらつきや興奮を制御する働きがある。消化器外科領域だけでなく，手術や治療の適応年齢が高齢化し，高齢者特有の問題点が重要視されてきた。とくに認知症をすでに発症している場合，手術後や抗癌剤治療中にせん妄，徘徊など異常行動を起こす場合が少なくない。また，認知症がない場合でも手術や抗癌剤のストレスで異常行動を起こす場合もある。作用メカニズム的に抑肝散の予防投与，治療に用いることが推奨される。抑肝散は異常行動を起こすメカニズムのなかで神経興奮作用をもつグルタミン酸という神経伝達物質の再吸収を行っているグリア細胞のグルタミン酸トランスポーターを活性化してグルタミン酸の作用を抑制する働きをもっていることが明らかとなり，その有効成分まで明らかとなっている。

これまで西洋薬では向精神薬が頻用されてきたが，ターゲットがグルタミン酸でなく，ADLに影響を及ぼすドパミンやセロトニン神経系であったため，薬剤自体による生活の質の低下が顕著であり，使用が難しかった。一方，抑肝散はADLに影響を与えることがないため使用が容易である。ランダム化比較試験のメタ分析で抑肝散の認知症による異常行動，すなわち妄想，幻覚，興奮，攻撃性などの抑制効果が明らかとなっている[2]。

抑肝散は有効生薬に甘草（かんぞう）を含んでいるため，その副作用は長期連用で発現する可能性があるので電解質異常に要注意である。抑肝散の効果は持続性があるため，中止してもしばらく抑制効果は継続されることが明らかとなっている。最近，緩和医療における麻薬使用量が増加しているが，麻薬による異常行動は看過できない副作用であり，緩和医療における解決できない大きな問題点となっている。抑肝散の効果が期待できる可能性が少数例だが報告され，今後のプラセボ試験などが期待される。

漢方薬のエビデンス構築ストラテジー

西洋薬の新薬開発とほぼ同様の基礎的・臨床的エビデンスレベルが構築されつつある漢方薬として抑肝散，大建中湯，六君子湯（りっくんしとう），茵蔯蒿湯（いんちんこうとう），半夏瀉心湯（はんげしゃしんとう），牛車腎気丸（ごしゃじんきがん）などがあげられる。そのなかで，今後行われるであろう，すべての漢方薬のエビデンス構築に共通したストラテジーを理解するために，もっとも進んでいる大建中湯を1例として取り上げて，大建中湯のエビデンス構築のプロセスを経時的に紹介する。

大建中湯の“中”は消化管を意味し，消化管を大いに建て直すという意味である[1]。130種類以上ある医療用漢方薬のなかでもっとも多く使用されている漢方薬である。ちなみに次に多く使用されているのは抑肝散である。大建中湯の薬効生薬は人参，山椒，乾姜の3種類と他の漢方薬のなかでもきわめて少ない。製品中の割合では3種類合わせても10%未満で，残り90%はマルトースやラクトースなど糖類で構成されている。辛み成分を飲みやすくするためと考える。

最初に薬効機序が注目されたのが腸管運動への作用に関してである。比較的多くの基礎研究が行われ，神経関連因子の誘導が行われることが明らかとなった。しかしながら，鼓腸で「腹部膨満感の改善」という点に関してエビデンスは乏しく，研究は停滞していた。一方，遅れていた「腹部の冷えの改善」という点に関して，腸管血流改善を中心とした基礎研究が精力的に展開された。最初に注目されたのは，カルシトニンファ

ミリーペプチドで，神経組織由来のCGRP（calcitonin gene related peptide）である。CGRPはもっとも強い血管拡張作用をもつペプチドとして知られている。そこで神経ペプチドCGRPが「腹部の冷えの改善」作用に関与しているという仮説を元に研究が進み，仮説は立証されることになった[3]。さらに受容体に関してCGRP受容体関連因子も大建中湯によって刺激を受けることが明らかとなった[3]。CGRPの受容体は恒常的に存在せず，未成熟な受容体CRLR（calcitonin receptor-like receptor）が成熟化するプロセスが必要で，その成熟化にはRAMP（receptor activity-modifying membrane protein）が必須である。そのRAMPには3種類のタイプがあり，RAMP1が出現し成熟化に関与するとCGRP受容体になるが，RAMP2，RAMP3が成熟化に関与するとCGRPと同じカルシトニンファミリーペプチドであるADM（adrenomedullin）の受容体に変化することが報告されていた。われわれの実験結果から大建中湯によってRAMP1, 2, 3いずれも増加することが明らかとなり，カルシトニンファミリーペプチドの2つのペプチド，CGRPとADMおよびその受容体関連因子が大建中湯の血流改善機序に関与している可能性が高まった[3]。

両ペプチドの生理学的作用の共通点は多く，強い末梢血管拡張作用もその1つである。さらにCGRPは腸管運動亢進作用，分泌作用があり，ADMには抗炎症性サイトカイン作用がある。したがって，大建中湯の複数成分が多くのターゲットに作用を解明するうえできわめて重要な鍵となる内因性ペプチドであると考えられる。両ペプチドの大きな違いは産生部位である。CGRPは主に神経終末など神経組織，ADMは主に上皮細胞，平滑筋細胞など非神経組織である。そこで大建中湯が腸管粘膜上皮細胞と感覚神経終末を刺激することでADMとCGRPおよび受容体関連因子が動員され血流増加が起こることが推察された。

次に成分レベルでの解析を進めるため腸管粘膜上皮培養細胞を用いた結果，腸管上皮細胞がADMを産生，放出することを確認し，大建中湯によって濃度依存性，時間依存性にADM産生，放出が起こり，生薬レベルでは山椒と乾姜がADM産生，放出を起こすことを確認できた。さらに山椒と乾姜の主成分のランダム試験を行い，hydroxy-α-sanshoolと6-shogaolが有効成分であることが判明した[4]。次に腸管粘膜上皮細胞に対する刺激機序を明らかにした。そのヒントは生体センサーであるTRP（transient receptor potential）チャネルである。このTRPチャネルは自然物の多くが特有のチャネルを刺激するアゴニストとなっている。たとえば，冷覚に関するTRPM8チャネルのアゴニストはメントールである。冷湿布で冷たいと感じるのは血流が低下するのではなく，冷湿布に含まれるメントールによってTRPM8チャネルが刺激され冷たいと感じるのである。漢方の原料となる自然物にも多くのTRPチャネルに対する刺激物が含まれているという仮説を立て，ADM産生，放出に関与するhydroxy-α-sanshoolと6-shogaolが文献的検索を行った結果，TRPA1とTRPV1という2つのチャネルのアゴニストであることが判明した。そこで腸管粘膜上皮細胞にこの2つのチャネルが発現しているか否かを検討した結果，TRPA1のみ強く発現し，TRPA1のアゴニストで刺激するとADMが放出されることが判明した[5]。TRPV1や他のTRPチャネルのアゴニストではまったく反応しないことから，hydroxy-α-sanshoolと6-shogaolがTRPA1チャネルを介してADMを刺激していることが確認された[5]。

一方，TRPA1チャネルを高発現している粘膜上皮細胞としてエンテロクロマフィン細胞があり，この細胞はセロトニンを分泌して腸管運動を亢進させることが知られている。そこで，大建中湯の腸管運動亢進作用がこのエンテロクロマフィン細胞のTRPA1チャネルを刺激し，セロトニン分泌を促していると考え，研究を進めた結果，hydroxy-α-sanshoolと6-shogaolがTRPA1チャネルを介してエンテロクロマフィン細胞からセロトニン分泌を促していることが明らかとなった。つまり，大建中湯は腸管粘膜上皮細胞からADMとセロトニンを放出させることで腸管血流増加と腸管運動亢進作用を発現させている可能性が強く示唆された。

さらに，最近のわれわれの研究で乾姜の成分が強いPGE_2抑制作用があることが示唆されている。PGE_2は腸管運動の重要な担い手である輪状筋の動きを抑制することが知られていることから，大建中湯の術後早期の麻痺性イレウスに効果をもたらしている機序として魅力的である。しかしながら，これら有効成分がどのようなルートで標的細胞に到達するのかは薬物動態試験を行うまで不明のままであった。薬物動態試験は西洋薬開発では初期段階で行われるが，漢方薬でも薬効機序解明には必須であることは疑いようもない事実である。

漢方薬の薬物動態試験

漢方薬の薬物動態試験は不可能であるとされ，まったく行われてこなかったのは計測技術の問題であった。最近の技術革新によって可能となり，漢方薬で最初に薬物動態試験が行われたのは大建中湯である。健康成人で行った結果，大建中湯の有効生薬である山椒のhydroxy-α-sanshoolを含めて多くの成分が大量に瞬時に吸収され，血中濃度が高まることが判明した[6]。乾姜も6-shogaolなど多くの成分が吸収されるが比較的ゆっくり吸収され，その吸収率は山椒の成分に比べてはるかに小さいものであった。一方，人参成分はほとんどが吸収されないが，代謝成分が血中に出現することが明らかとなった。また，肝や腸管にて乾姜の成分の多くが抱合されることも判明した。

次に動物レベルでも吸収試験を行い，同様の結果を得ただけでなく，回腸末端部まで到達した抱合体が腸内細菌によって脱抱合され，再度活性物質となり大腸に到達することが判明した。また，日本人だけでなく白人でも大建中湯の薬物動態試験が行われ，同様の結果が得られた[7]。これまで大建中湯は直接的な働きが主体であると考えられてきたが，吸収されることで効果を発現している部分が相当数あることが推察され，これまで説明できなかった臨床試験結果を説明できるようになった。

高いエビデンスレベルの臨床試験

大建中湯が開腹手術後の腸閉塞の発生や再発を予防し，手術の必要性を減らす効果があることがエビデンスレベルの高いいくつかの臨床試験で証明されているので概説する。

1. クロスオーバー試験

単一施設，胃癌で噴門部切除後の空腸パウチ間置術を行った17例を対象に，大建中湯投与15g/dayあり，なしのランダム化クロスオーバー試験が行われ，大建中湯が液状物，固形物ともに胃からの排出を有意に促進し，パウチによる胃内容物停滞に伴う不快な症状を有意に改善する結果が得られた[8]。

2. プラセボ対照試験

単一施設，154例の消化管開腹手術後早期に腸閉塞をきたした24例（16%）を，大建中湯を2週間15g/day投与した群と，プラセボ投与群に分けたランダム化比較試験が行われ，大建中湯投与群はプラセボ群に比べ，腸閉塞手術の頻度が有意に50%以上減少したという結果が得られている。また，有意差はないものの腸閉塞の再燃頻度は大建中湯投与群で減少傾向が認められた[9]。

全国26施設で行われたプラセボ対照二重盲検試験のDKTフォーラムの1つであるJFMC40-1001試験は肝腫瘍で肝切除した231例を，大建中湯を術後3日目から1週間15g/day投与した群と，プラセボ投与群に分けたランダム化二重盲検試験が行われ，排ガス出現時期を指標に腸管運動再開までの期間を比較した結果，大建中湯群が有意に改善する結果が得られた（2012年米国肝臓学会で発表）。

手術後ではないが，大建中湯にとって大変重要な臨床試験が米国メイヨークリニックで行われた。健康白人60例を対象にプラセボ対照二重盲検試験がラジオアイソトープを使用して行われ，大建中湯を投与した群に有意に結腸排出，小腸運動促進効果を認められた。これまで，12種類の新薬が腸管運動改善薬としてプラセボ投与群に分けたランダム化二重盲検試験が行われたがすべてネガティブな結果で，大建中湯が13番目の新薬として初めてポジティブな結果を出すことに成功した[10]。

今後の展望

現在，大建中湯，抑肝散，六君子湯などを中心に漢方薬の処方数の増加が続いて右肩上がりである。これまでまったく漢方について興味がなかった医師が積極的に処方してきたものと考えられている。一方，医学教育における漢方医学に関する講義が全国80大学医学部すべてで8コマ以上系統的に行われるようになったので，漢方医学教育を受けた医師が増加し，彼らが指導的立場になればさらに多くの漢方薬が使用されるものと推察されている。しかし，警鐘も必要で，使用量が増加すればかつての小柴胡湯（しょうさいことう）による間質性肺炎死亡例発生後のように一気に漢方薬使用にブレーキがかかる可能性がある。漢方薬が薬として出現し，育ってきた時代にはなかった疾患や開腹手術，患者の状態（高齢者など）に投与されるわけで，しっかりと副作用の発現に注意を払う必要性があり，漢方薬だから安全という妄信的な考えは厳に慎み，捨

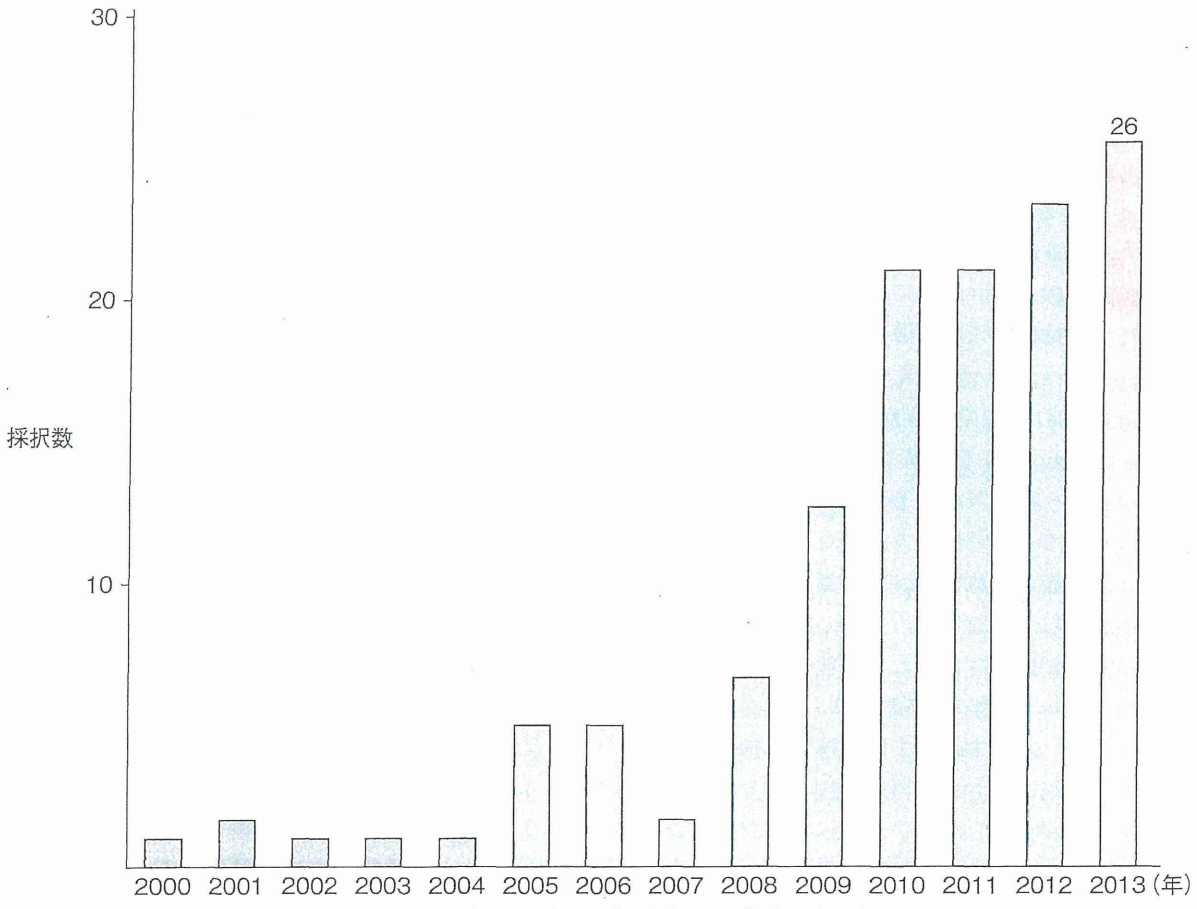

図 1　米国消化器病週間（DDW）漢方薬関連採択演題数推移

て去るべき思い込みであり，とくに漫然とした長期投与は厳禁である。

現在，まだ漢方薬が保険使用でき，西洋薬と一緒に使えるのは日本の医師だけであり，日本伝統薬である漢方薬を消化器外科医が中心となって大いに育て，日本だけでなく，世界中で西洋薬と肩を並べる時代が到来することを期待したい。世界でももっとも大きな国際学会の１つである米国消化器病週間（DDW）での漢方薬の研究発表が急激に増加している。とくに基礎研究結果が出だした2005年以降が顕著で，2010年以降は一気に20演題を突破し，2013年の DDW では過去最高の26演題が採択され，日本だけでなくメイヨークリニック，UCLA などからの演題が登場している（**図 1**）。

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学会案内・お知らせ　告知板　information

第7回 NOTES研究会

日　時：平成25年11月27日(水)　16：00～20：30
会　場：福岡サンパレスホテル＆ホール　2階　パレスルーム
〒812-0021　福岡市博多区築港本町2-1　TEL：092-272-1123（代表）
当番世話人：土岐祐一郎（大阪大学大学院医学系研究科外科学講座消化器外科学）
テーマ：Quo Vadis?
NOTES研究・臨床は見直しの時期に来ていると言えます。我々はこれまでの6年間でNOTESを通じて何を学び，何を学ばなかったのか。我々はこれからどこへ向かおうとしているのか（Quo Vadis?）。第7回研究会は，これまでのNOTES研究・臨床を我々自身で「総括」し，今後の低侵襲内視鏡治療の方向性を見極める場にしたいと思います。
公式HP：http://www.med.osaka-u.ac.jp/pub/gesurg/NOTES07/
プログラム：16：00～16：30　研究助成報告
16：30～18：00　一般講演（公募）
18：00～19：30　特別企画（指定）
19：30～20：30　招請講演（National University of Singapore, Lawrence Ho教授）
会　費：2,000円
演題募集：平成25年7月1日～平成25年10月11日
演題名，発表者（○印），共同演者，所属，発表内容を含め，800字以内で記載いただいたWindows Wordファイルを添付の上，下記アドレスまでE-mailでお申込みください。
演題申込アドレス：notes07@gesurg.med.osaka-u.ac.jp
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