Study Group on Ethnic Factors in Clinical Data from East Asian Populations

Masahiro Tohkin, Ph.D.

National Institute of Health Sciences

Tokyo, Japan

Scope of the Research

- Purpose

  To Clarify the Ethnic Factors on the Clinical Data among East Asian Populations

- Members

  NIHS, PMDA, JPMA, Academia, Japan CRO Assocn.

Initial Working Questions

Ethnic difference in a medicine's response (ICH-E5 guideline)

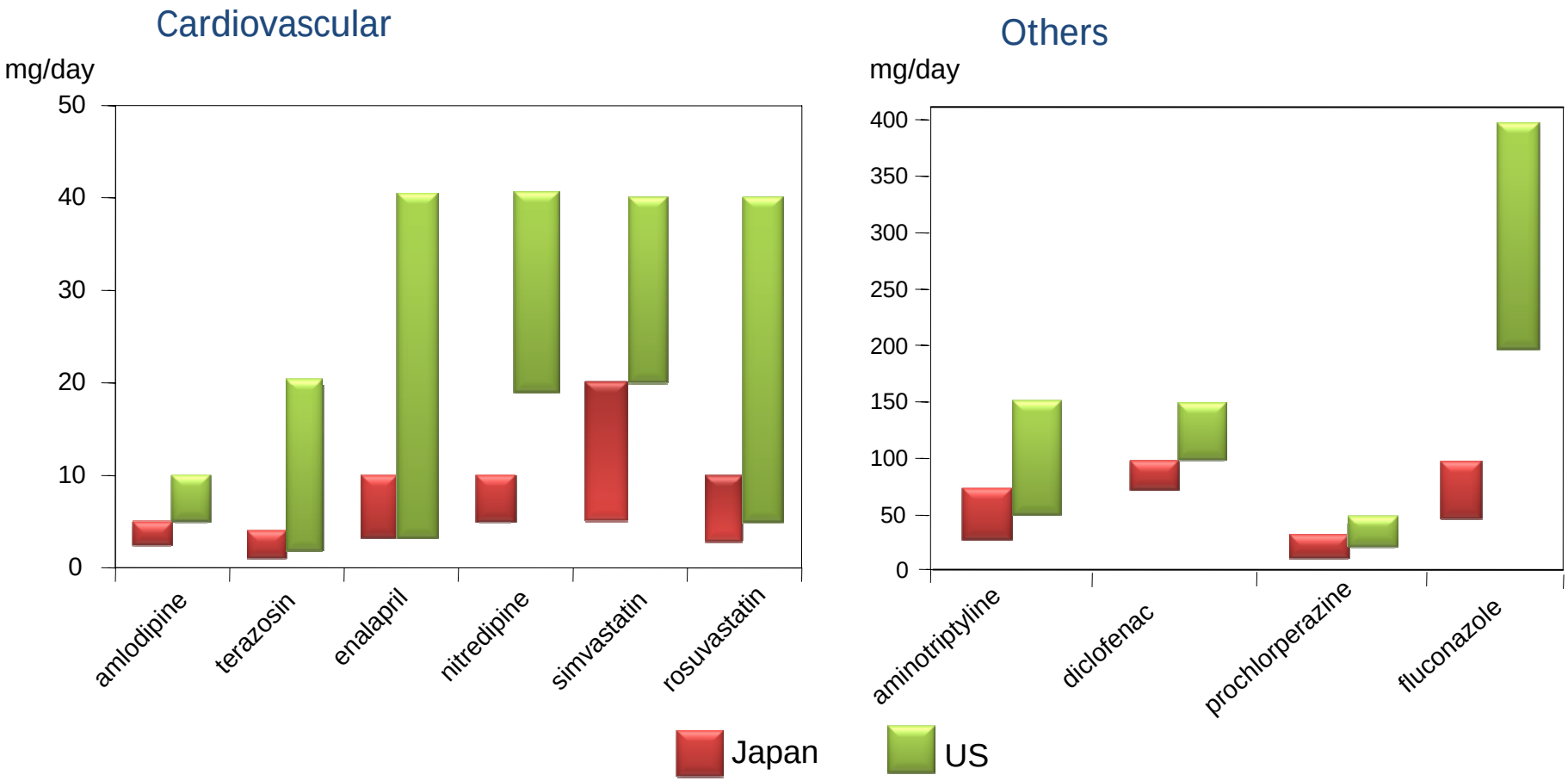
> Although ethnic differences among populations may cause differences in a medicine's safety, efficacy, dosage or dose regimen, many medicines have comparable characteristics and effects across regions.

Questions

1. How about East Asian populations who have genetically similar but culturally or environmentally different backgrounds?

2. If there might be a difference among East Asian populations, what kinds of drugs show the difference?

Comparison of Daily Doses in Japan and US



US dose are higher than Japan dose in 33 % drugs.

What are Ethnic Factors? (ICH E5 Guideline)

Classification of intrinsic and extrinsic ethnic factors

INTRINSIC		EXTRINSIC
Genetic	Physiological and pathological condition	Environmental
Gender		Climate
Height Body weight		Sunlight Pollution
	Liver Kidney Cardiovascular functions	Culture Socioeconomic status Educational status Language
ADME Receptor sensitivity		Medical practice Disease definition/Diagnostic Therapeutic approach Drug compliance
Race		
		Smoking Alcohol
Genetic polymorphism of the drug metabolism		
		Food habit Stress
Genetic diseases	Diseases	Regulatory practice/GCP Methodology/Endpoints

A Medicine's Sensitivity to Ethnic Factors (ICH E5)

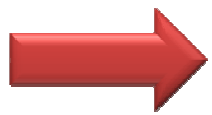
1. Non-linear pharmacokinetics
2. A steep pharmacodynamic curve for both efficacy and safety
3. A narrow therapeutic dose range
4. Highly metabolized, especially through a single pathway
5. Metabolism by enzymes known to show genetic polymorphism
6. Administration as a prodrug, with the potential for ethnically variable enzymatic conversion
7. High inter-subject variation in bioavailability
8. Low bioavailability, thus more susceptible to dietary absorption effects
9. High likelihood of use in a setting of multiple co-medications
10. High likelihood of use, e.g., analgesics and tranquilizers

Discussion Points

- Pharmacokinetics
- Pharmacodynamics

  (Exposure-Response)

- Safety



Clinical Trials

Phase I and II

Phase III
Post Marketing

Research on Pharmacokinetics (ongoing)

Data Source

- Clinical trial data

  Not as much Chinese and Korean PK or bioequivalence data in JPMA.

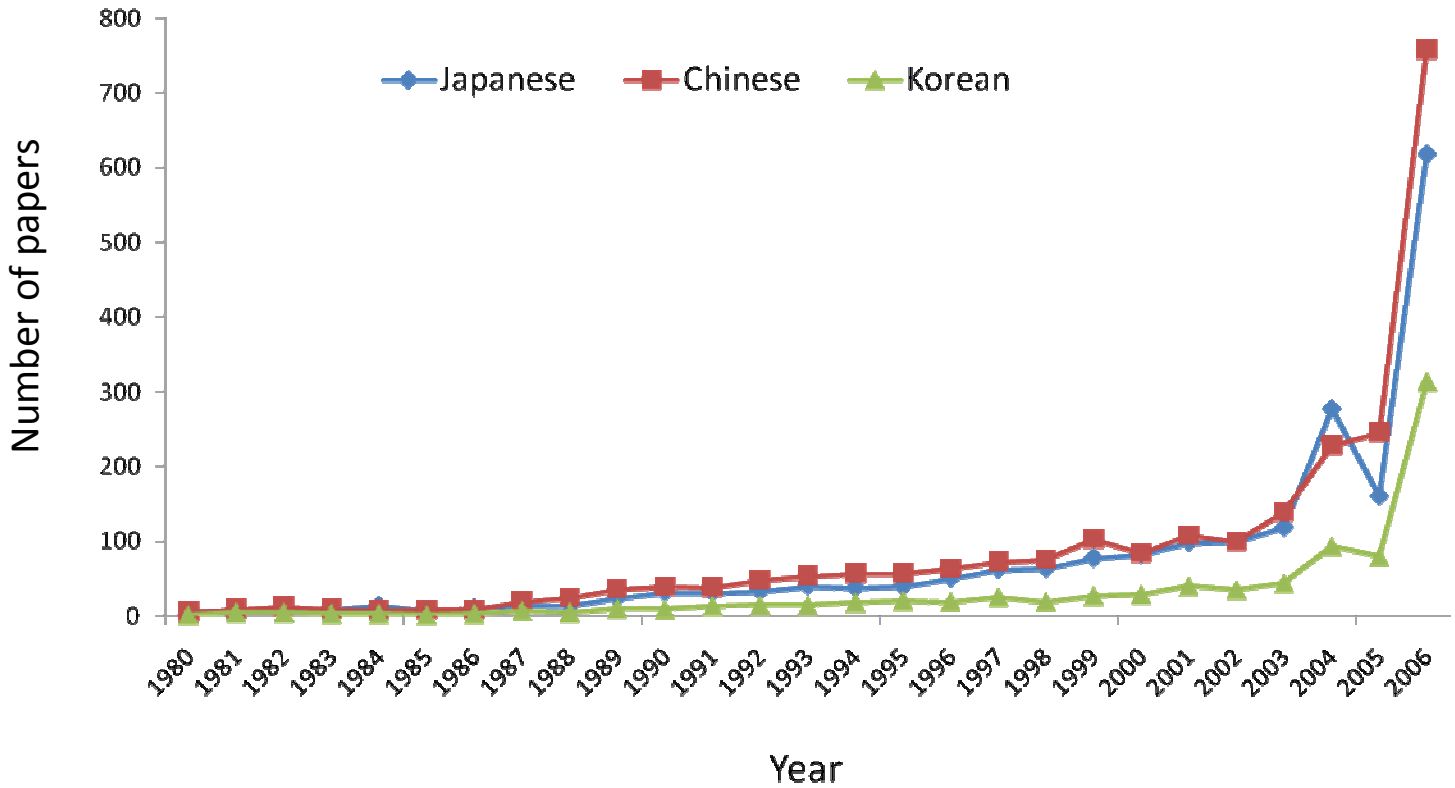
- Literature-based Comparison

  Genetic Polymorphisms of Major Drug Metabolizing Enzymes
  → Saito Y. *et al*

  PK Parameters → Google Scholar search

  Japanese, Chinese, Korean PK parameters of 42 drugs

Number of original articles related to clinical pharmacokinetic studies in Japanese, Chinese, and Korean



Genetic polymorphisms and allelic frequencies of major drug metabolizing enzymes in East Asians

Enzyme					Allelic frequency			
Name	Alelle	Nucleotide Change	Amino Acid change	Activity change	Japanese	Korean	Chinese	Caucasians
CYP2C9	*3	1075A>C	Ile359Leu	reduced	0.026	0.030	0.038	0.078
CYP2C19	*2	681G>A	slicing defect	none	0.289	0.264	0.399	0.150
	*3	636G>A	Trp212Stop	none	0.117	0.088	0.062	<0.001
CYP2D6	*5	whole deletion		none	0.053	0.051	0.072	0.041
	*10	100C>T	Pro34Ser	reduced	0.367	0.470	0.513	0.025
CYP3A4	*4	352A>G	Ile118Val	reduced	ND	ND	0.014	ND
	*5	653C>G	Pro218Arg	reduced	ND	0.002	0.006	ND
	*16	554C>G	Thr185Ser	reduced	0.015	0.002	ND	ND
	*18	878T>C	Leu293Pro	substrate -dependent	0.028	0.017	0.015	ND
CYP3A5	*3	IVS3-237A>G	slicing defect	severely reduced	0.756	0.758	0.736	0.919
UGT1A1	*6	211G>A	Gly71Arg	reduced	0.154	0.220	0.185	0.003
	*28	-54_-39A$(TA)_6$TAA >A$(TA)_7$TAA		reduced	0.112	0.115	0.118	0.342
	*60	-3279T>G		reduced	0.257	0.268	0.320	0.473

ND: not detected

Saito Y *et al.* Current Pharmacogenomics 2007, **5**, 49-78

Ethnic Difference in Pharmacokinetics (1)

CYP2C19

Omeprazole/5-hydroxyomeoprazole

Ethnicity group	n	Mean of metabolic ratio	range	Ratio
Native Japanese	100	2.06	0.34-37.47	1
1st-generation Japanese	83	1.79	0.4-36.29	0.87
3rd-generation Japanese	93	2.52	0.38-27.12	1.22
Korean	98	2.04	0.51-32.87	0.99
Chinese	143	1.86	0.39-37.19	0.9
Caucasian	100	0.68	0.16-22.48	0.33

These phenotypes depend on the genotypes of *CYP2C19*

Myrand SP *et al*. Clin Pharmacol Ther (2008) Jan 30 [Epub]

Ethnic Difference in Pharmacokinetics (2)

Rosuvastatin

Population	Dose (mg/day)	n	Cmax (ng/mL)	AUC (ng·h/mL)	Reference
Japanese	10	6	7.87	126	RinshoIyaku, 21, 187–203, 2005
	20	6	20.5	209	
	40	6	41.5	404	
White	20	6	10.7	103	
	40	6	38	291	
Chinese	10	20	11	123	Chin J New Drugs Clin Rem, 25, 912, 2006
White	40	36	25	216	Clin Pharmacol Ther, 78, 330–341, 2005
Chinese	40	35	59.1	500	
Malay	40	35	50	413	
Indian	40	35	42	353	

PGx can not explain the difference at this stage.

Ethnic Difference in Pharmacokinetics (3)

Tolterodine (sustained release capsule)

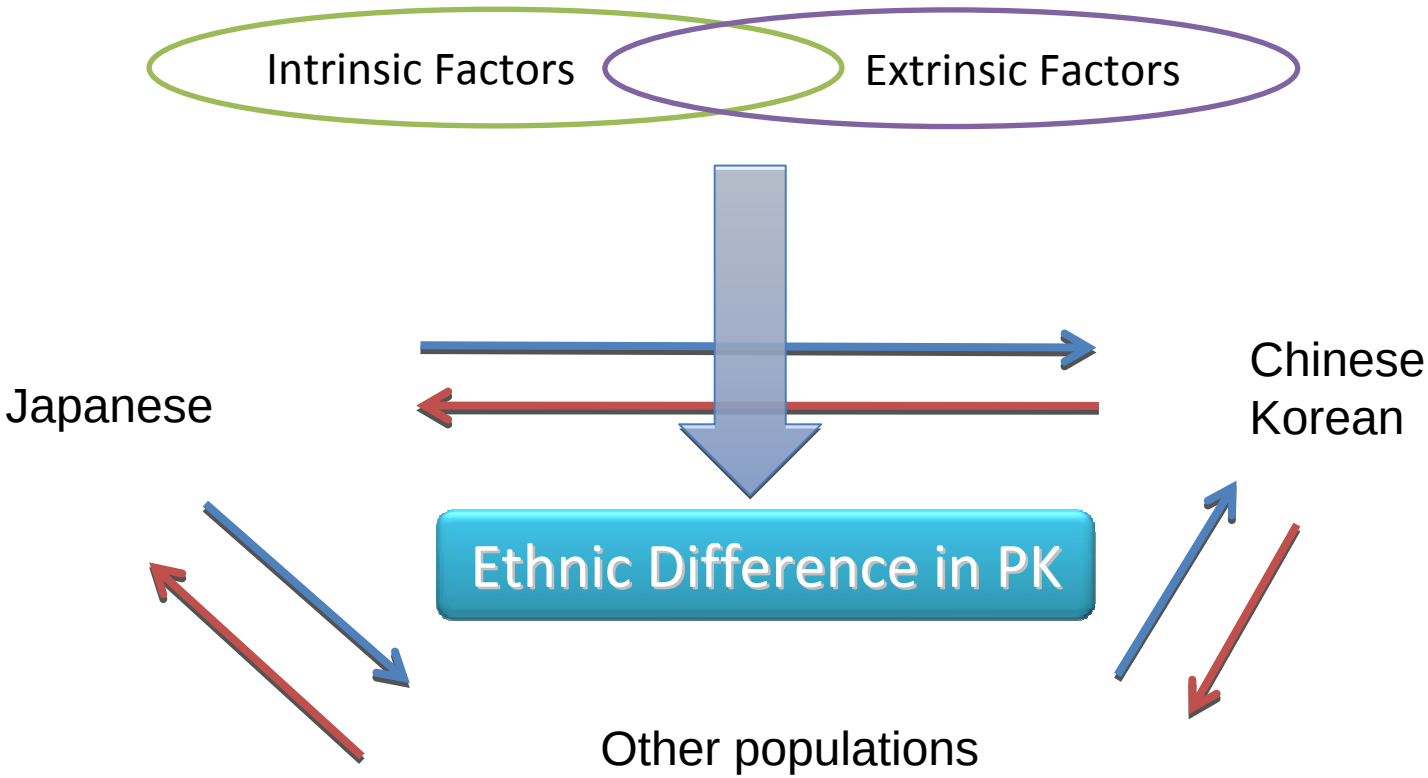
	Parent Compound			Active Metabolite		Free Form	
	Dose mg	Cmax ng/mL	AUC ng·h/mL	Cmax ng/mL	AUC ng·h/mL	Cmax nM	AUC nM·h
Japanese	2	1.12	13	0.76	8.77	1.07	12.5
Caucasian*	2	2.53	40.3	1.28	13.7	1.31	15.2
Korean	2	1.48	18.2	1.18	15	1.61	20.5
Japanese	4	1.3	14.8	1.68	19.2	2.07	23.9
Caucasian	4	2.57	26.8	2.27	25.1	2.7	30.3
Korean	4	2.83	33.2	2.12	27.4	2.65	33.9
Japanese	6	2.87	26.7	3.34	34.8	4	42.8
Caucasian	6	2.03	19.5	3.19	33	3.92	40.1
Korean	6	4.38	45.5	3.85	41.6	5.15	55.7

* Contains 2 poor metabolizers

PMDA Review report (2006)

PGx of *CYP2D6* can not explain the difference between Japanese and Korean.

Ethnic Difference in Pharmacokinetics
(Research Strategy)



Research on Pharmadynamics (future plan)

ICH-E5 described ……

In contrast to the pharmacokinetics of a medication, where differences between populations may be attributed primarily to intrinsic ethnic factors and are readily identified, the pharmacodynamic response (clinical effectiveness, safety, and dose-response) may be influenced by both intrinsic and extrinsic ethnic factors and this may be difficult to identify except by conducting clinical studies in the new region .

Pharmacodynamics study targets

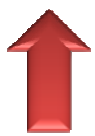
Clinical Trial Data

- Clear and objective markers of pharmacological effects. (e.g. anti-diabetic drug, anti-hypertensive drug *etc*.)
- PK profile.

Research on Drug Safety (future plan)

Comparison of Drug Safety

- Adverse drug reaction during the clinical trials (for relatively high frequent ADRs)
- Adverse drug reaction during the post marketing surveillance（for relatively low frequent ADRs）



Medical practice, Reporting system *etc*.

Clinical Trial Data

Cooperation with Chinese & Korean Counterparts

Clinical Trial Data

PK/PD data of Japanese Population

(PMDA & JPMA)

+

PK/PD data of Chinese and Korean Populations

Clarify Ethnic Factors in Clinical Data