A question based approach to drug development

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CHAPTER 9

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Pharmacodynamics and pharmacokinetics of a single oral dose of nitrazepam in healthy male and female volunteers. An interethnic comparative study between Japanese and Caucasian volunteers

Abstract

BACKGROUND Potential interethnic differences in drug disposition and effects between Japanese and Caucasians hamper the registration in Japan of medications already used in Western countries. A systematic comparison of potential mechanisms of differences in drug response between racial groups can facilitate the transition of drugs between ethnic groups.

OBJECTIVES To compare the pharmacodynamics and pharmacokinetics of a single oral dose of nitrazepam (5 mg) in 8 Japanese and 8 Caucasian matched healthy males and females, in a double-blind, placebo-controlled, cross-over study.

METHODS The study was performed in a Japanese and a Dutch centre, using the same methods and study design. Japanese and Caucasian subjects were individually matched for gender, age and body stature. Drug effects were measured with saccadic and smooth pursuit eye movements and visual analogue lines obtained from the scales of Bond and Lader.

RESULTS There were no pharmacokinetic differences between the Japanese and Caucasian subjects. Clearance was 0.91±0.165 and 1.17 ±0.492 ml/min/kg, and $t_{1/2}$ was 22.1±4.96 and 21.5±7.51 hr, respectively. Pharmacokinetic parameters showed no significant correlation with age, height or weight. The average time-effect-curves for the different parameters were comparable between the groups. Compared to placebo, both groups showed similar significant reductions in average peak velocity (-75±40 vs -85±24 °/sec; M ± SD), and increases in saccadic inaccuracy (2.3±2.1 vs 2.1±0.9%) and reaction time (17.1±13.3 vs 18.2±14.4 msec). Visual analogue scores showed clear sedation in the Caucasians, but non-significant effects in the Japanese subjects. Smooth pursuit did not change significantly in either group. Slopes and intercepts of concentration-effect relationships for saccadic peak velocity showed considerable intersubject variability, but no clear differences between the two groups.

CONCLUSIONS The pharmacokinetics and pharmacodynamics of nitrazepam are similar in healthy Japanese and matched Caucasian subjects. Interethnic comparative studies are feasible and provide meaningful information about potential racial differences in disposition and action of drugs. Such studies can form a rational basis for comparative clinical trials.

Introduction

Drug responsiveness may differ among racial and ethnic groups. For some compounds and drugs, like alcohol, propanolol and debrisoquin, these differences are caused by genetic diversity in factors such as drug
ref. 1 metabolism or pharmacodynamic sensitivity. In other cases, interethnic differences may not be predictable. This may obstruct the transition of drug information from the ethnic group in which they have been developed to another. The possibility of interracial differences in drug disposition and effect has contributed to the policy of the Japanese Ministry of Health and Welfare, Koseisho, to require the repetition of a major part of the drug development programme in Japanese subjects, before an agent used abroad
ref. 2 can also be registered in Japan. Considering the difficulties in organising
ref. 3 clinical trials in Japan, it would in many instances be more rational to identify the factors that systematically determine interindividual and interethnic differences in drug responsiveness, and to adapt subsequent clinical trials or treatment regimens accordingly.

Several systematic differences in determinants of drug responsiveness can be distinguished. Average body stature differs between Japanese and Caucasians, and this is an important determinant of the disposition of many drugs. Genetic diversity in drug metabolism or action are other potential sources of variability in drug response between the Caucasian and Japanese populations. The identification of potential interethnic differences in the disposition or action of a drug that has already been widely studied in the Western market, and is considered for registration in Japan, could therefore start with a comparative study of Caucasian and Japanese subjects. Systematic comparative 'bridging' studies are in line with the increasing globalisation of drug development, that is brought about by the implementation of the International Conference on Harmonisation Guidelines on Good Clinical Practice (ICH-GCP), in numerous countries including Japan. 'Bridging' studies are advocated in the draft ICH guidelines on ethic factors
ref. 4 in the acceptability of foreign clinical data. In such comparative studies, research methods would have to be identical and subjects would have to be carefully matched for demographic factors that are known to influence drug disposition. The present study is aimed to test the feasibility of such an approach, by studying the pharmacokinetics and pharmacodynamics of the benzodiazepine nitrazepam in Caucasian subjects, carefully matched to the participants of a study in Japan, using the same methods and study design. The Japanese trial was performed prior to the Caucasian part of the study,
ref. 5 which allowed the matching of subjects and methods among the two

studies. The eye movement methods used in this study were carefully matched during a mutual exchange programme among investigators of the two research centres, but the studies were otherwise performed independently.

Methods

Subjects

Caucasian subjects were individually matched with Japanese volunteers of a previous study, for gender (four males, four females), age (intended allowed difference up to 5 yrs), height (up to 5 cm) and weight (up to 5%). The study was performed according to the Declaration of Helsinki and approved by the Medical Ethics Review Board of Leiden University Medical Center and the Institutional Review Board of Showa University.

Study design and group size estimation

The study was designed as a double-blind, randomised, placebo-controlled cross-over trial with a two-week washout period. The study was independently performed in two research institutes in The Netherlands and in Japan. The sample size of four male and four female healthy volunteers was based upon the size of the Japanese study group. Based on the extensive previous experience with CNS-effects of benzodiazepines, this sample size was expected to allow the detection of nitrazepam effects using saccadic peak velocity. The sample size would allow the detection of a 24% difference in Clearance/kg between the two groups, with a power of 80% using an ½ of 5%. The power was less for the pharmacodynamic parameters.

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Drugs

Nitrazepam was administered as 5 mg capsules, at which it is registered as a hypnotic in the Netherlands and in Japan. The nitrazepam capsules and identical appearing placebo capsules were from the same batch for the Japanese and the Caucasian study (Shionogi Co, Tokyo, Japan), and the same randomisation order was used. The drugs were given orally, with a glass of water (with the subject in a comfortable sitting position), under fasted conditions, followed by a lunch after 4 hours. On all occasions, the

time of ingestion of the trial medication was between 09:00 and 10:00 AM local time. Other medications, illicit drugs, alcohol, tobacco, or xanthine-containing foods and beverages were not allowed during the study, except oral contraceptives and occasional paracetamol.

Pharmacodynamic Determination

The primary pharmacodynamic parameters were determined from saccadic eye movements, which have been shown to be highly sensitive to benzodiazepines. In addition, smooth pursuit eye movements and visual analogue scales of sedation and unsteadiness were assessed. The conditions and methods for these analyses were the same for the Japanese and the Caucasian part of the study. Subjects were instructed not to use alcoholic or xanthine-containing products within 24 hours before drug administration, and to limit the consumption of these products and maintain a regular diurnal rhythm for one week before each study day. Subjects were acquainted with the procedures during a training session, prior to the first study occasion.

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EYE MOVEMENTS Saccadic eye movements and smooth pursuit eye movements were recorded 10 min before drug intake and at 30- 45- 60- 75- 90- 105- 120- 135- 150- 165- 180- 240- 360- and 480 min after administration. Recordings of eye movements were performed in a quiet room with ambient illumination. Recordings and analyses of saccadic eye movements and smooth pursuit eye movements were conducted with a microcomputer-based system for sampling and analysis of eye movements, and were performed as described previously with adaptions as described below. In both centres, the same equipment was used for stimulus display, signal collection and amplification (Nihon Kohden Corporation, Tokyo, Japan). Sampling, analogue-to-digital conversion and analysis of eye movement signals were also performed with the same equipment and software (Cambridge Electronics Design, Cambridge, UK). Disposable silver-silver chloride electrodes were applied on the forehead and beside the lateral canthi of both eyes of the subject for registration of the electro-oculographic signals. Skin resistance was reduced to less than 5 kOhm before application of the electrodes. Head movements were restrained using a fixed head support. The target consisted of an array of light emitting diodes on a bar, fixed at 50 cm in front of the head support. Saccadic eye movements were recorded for stimulus amplitudes of: 10, 15 and 20 degrees to either side. Eleven saccades were recorded for each stimulus amplitude with interstimulus intervals varying randomly between 3 and 6 seconds. Average peak saccadic

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velocity of all artifact-free saccades were used as the primary parameter. For smooth pursuit eye movements the target moved sinusoidally at frequencies ranging from 0.3 to 1.1 Hz in steps of 0.1 Hz. The amplitude of target displacement corresponded to 20 degrees eyeball rotation to both sides. Four cycles are recorded for each stimulus frequency. The time in which the eyes were in smooth pursuit of the target were calculated for each frequency and expressed as a percentage of stimulus duration. The average percentage of smooth pursuit for all stimulus frequencies was used as efficacy parameter.

VISUAL ANALOGUE SCALES Subjective drug effects are often quantified with a set of 10 cm visual analogue scales as described by Norris, and Bond and Lader. These visual analogue scales have not been validate for Japanese subjects. Therefore, the six indicators most relative to sedation were translated into Japanese, to assess three domains of sedation with two indicators each: mental sedation (Alert-Drowsy and Muzzy-Clear headed), tranquillisation (Calm-Excited and Tense-Relaxed) and physical sedation (Well coordinated-Clumsy and Lethargic-Energetic). These indicators corresponded to numbers 1,2,4,5,6,12 in the scales of Norris, and numbers 1,2,4,5,6,10 in the Bond and Lader scales. Visual analogue scales were completed at the times of blood sampling: before administration and at 30- 60- 90- 120- 150- 180- 240- 360- 480- and 1440 min (24 hours) after drug administration.

ref. 7
ref. 8

Blood sampling

Before drug intake, a cannula was inserted into a forearm vein, kept patent with saline after each blood sample. Blood samples (9 ml) were collected in Li heparin tubes. Plasma concentrations of nitrazepam were measured in blood samples taken at the following times: two just before drug administration (one extra for HPLC calibration) and at 30- 60- 90- 120- 150- 180- 240- 360- 480- and 1440 min (24 hours) after administration.

Analyses

DRUG CONCENTRATION ANALYSIS Plasma concentrations of nitrazepam were analysed separately in both centres, using the same HPLC-method.

ref. 9-10

PHARMACOKINETIC, PHARMACODYNAMIC AND STATISTICAL ANALYSES The pharmacokinetic and statistical analyses were performed in a single centre, using the original Japanese and Caucasian raw data. Eye movement parameters were analysed as areas under the effect curve calculated using the linear trapezoidal rule over 0-240 min divided by 240 min to obtain a weighted average response. For each group (Japanese/ Caucasian) separately, placebo results were compared to nitrazepam using paired Student t-tests. Groups were compared by analysing the difference compared to placebo using unpaired Student t-tests. Differences between groups are presented with 95% confidence intervals (95% CI). Model independent nitrazepam pharmacokinetic parameters (C_{max}, t_{max}, $AUC_{(0\text{-}24h)}$, $AUC_{(0\text{-}\infty)}$, Cl_{sys}, Cl_{sys}/kg and $t_{½}$) were calculated using WinNonlin (V1.1; Scientific Consulting, Inc., Apex, NC, USA) using automatic detection of the terminal part of the curve to be used for log-linear regression. Parameters were compared between groups using unpaired t-tests. $AUC_{(0\text{-}\infty)}$ and C_{max} were analysed after log-transformation, and the resulting difference was back-transformed, yielding an estimate of percentage increase with the associated 95% confidence interval (95% CI).

Correlations between anthropometric measures (age, height, weight) and PK parameters were performed using Pearson's and Spearman's correlation coefficients. Statistical analysis and calculations were performed using SPSS for Windows V6.1.2 (SPSS, Inc., Chicago, IL). Areas under the effect curve were calculated using BMDP/Dynamic V7.0 (BMDP Statistical Solutions Ltd, Cork, Ireland).

Results

Subjects

The eight Caucasian subjects had and average age of 23.3 (range 19-27) years, a weight of 58.3 (48.0- 82.0) kg and a height of 167.0 (157.0-179.5) cm. The Japanese demographic characteristics were 22.8 (range 18-26) years, 56.4 (45.0- 78.0) kg and 164.1 (155-178) cm. Differences between some matched subjects slightly exceeded the intended maximal values: age differed by 6 yrs in two cases, weight by 10% in one and 6.5% in two cases (but less than 5 kg in each), and height by 6 cm in one case.

Pharmacodynamic Determinations

SACCADIC EYE MOVEMENT The average time-corrected area-under-the-effect-curves (AUECS) for saccadic and smooth pursuit eye movements after placebo- and nitrazepam-treatment in the two groups are presented in Table 1. In both groups, saccadic peak eye movements showed clear treatment effects, as shown in Table 2. The average placebo-corrected time curves of saccadic peak velocity for the Japanese and Caucasian subjects were comparable between the two groups (Figure 1). Comparison of the two groups showed no significant differences in any of these parameters (Table 2).

TABLE 1 **Eye movement AUECS (0-240min) for Japanese and Caucasian subjects**

	JAPANESE			CAUCASIAN		
Parameter	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**
Nitrazepam						
Inaccuracy (%)	10.3	2.1	8	8.2	3.0	8
Peak velocity (°/sec)	301.5	33.2	8	315.8	33.4	8
Reaction time (ms)	221.2	18.7	8	219.3	10.0	8
Smooth pursuit (%)	59.0	12.2	7	48.9	14.9	8
Placebo						
Inaccuracy (%)	8.5	2.2	7	6.1	2.2	8
Peak velocity (°/sec)	375.3	48.4	7	400.7	49.8	8
Reaction time (ms)	204.9	17.2	7	201.1	15.5	8
Smooth pursuit (%)	60.5	14.0	8	50.4	16.7	8

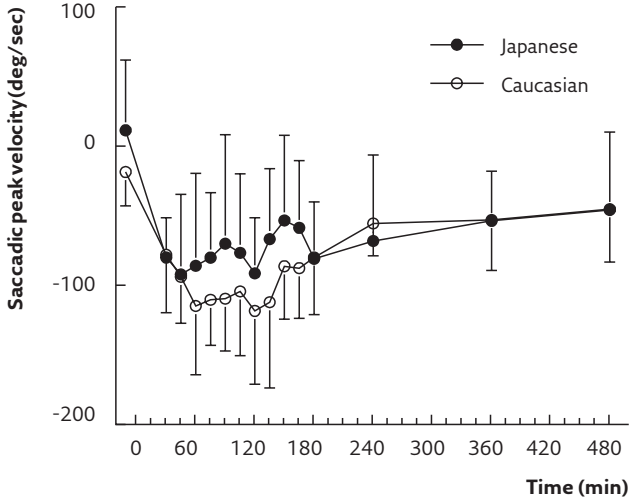
TABLE 2 **Treatment effects on eye movements for Japanese and Caucasian subjects**

	JAPANESE		CAUCASIAN		DIFFERENCE	
Parameter	**Mean**	**95 % CI**	**Mean**	**95 % CI**	**Mean**	**95 % CI**
Nitrazepam-Placebo						
Inaccuracy (%)	2.3	(0.3, 4.2)	2.1	(1.3, 2.8)	0.2	(-1.8, 2.2)
Peak velocity (°/sec)	-74.5	(-111.4, -37.6)	-85.0	(-105.2, -64.8)	10.5	(-28.3, 49.3)
Reaction time (ms)	17.1	(4.8, 29.4)	18.2	(6.1, 30.2)	-1.1	(-16.5, 14.4)
Smooth pursuit (%)	-2.4	(-8.6, 3.8)	-1.5	(-7.7, 4.7)	-0.9	(-8.8, 7.1)

SMOOTH PURSUIT The smooth eye movement AUEC data for the Japanese and Caucasian subjects are represented in Table 1. Both groups failed to show significant nitrazepam effects, as shown in Table 2. Also, no differences in treatment effects were detected between the two ethnic groups.

VISUAL ANALOGUE SCALES The individual time-effect curves for visual analogue scores showed clear sedative effects in the Caucasians. In contrast, the effects were non-significant in the Japanese subjects, and often the reverse of the Caucasian effect. It was concluded that the two ethnic groups had interpreted the visual analogue scales differently, and no comparative analysis was made.

FIGURE 1 **Average (+ SD) saccadic peak velocity-time curves for Japanese (●) and Caucasian (○) subjects, shown as difference from placebo**



Pharmacokinetic determinations

The mean nitrazepam concentration-time profiles for both Japanese and Caucasian subjects are presented in Figure 2. The pharmacokinetic parameters are shown in Table 3. Clearance (M±SD) was 0.91±0.165 and 1.17±0.492 ml/min/kg and $t_{½}$ was 22.1±4.96 and 21.5±7.51 hr, in the Japanese and Caucasian groups, respectively.

The analysis of $AUC_{(0\text{-}24h)}$, $AUC_{(0\text{-}\infty)}$ and C_{max} after log-transformation and back-transformation of the resulting difference showed that Japanese $AUC_{(0\text{-}24h)}$ was 33.6 % higher (95% CI -1.1, 80.7 %), Japanese $AUC_{(0\text{-}\infty)}$ was 26.3 % higher (95% CI -5.8, 69.4 %) and Japanese C_{max} was 15.9 % higher (95% CI -18.0, 63.7 %). Similar interracial comparisons of clearance and

clearance/kg showed that Caucasian clearance was 26 % higher (95% CI -6, 99 %) and Caucasian clearance/kg was 22 % higher (95% CI -10, 67 %). None of these pharmacokinetic differences reached statistical significance between the two racial groups after paired -or unpaired comparison. The correlations between anthropometric measures (age, weight, height) and pharmacokinetic parameters were not statistically significant.

FIGURE 2 **Average (+ SD) nitrazepam concentration-time curves for Japanese (●) and Caucasian (○) subjects**

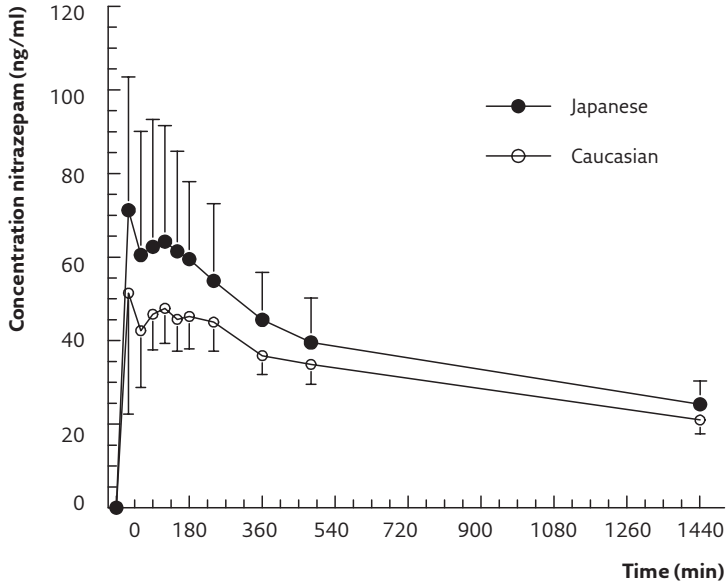


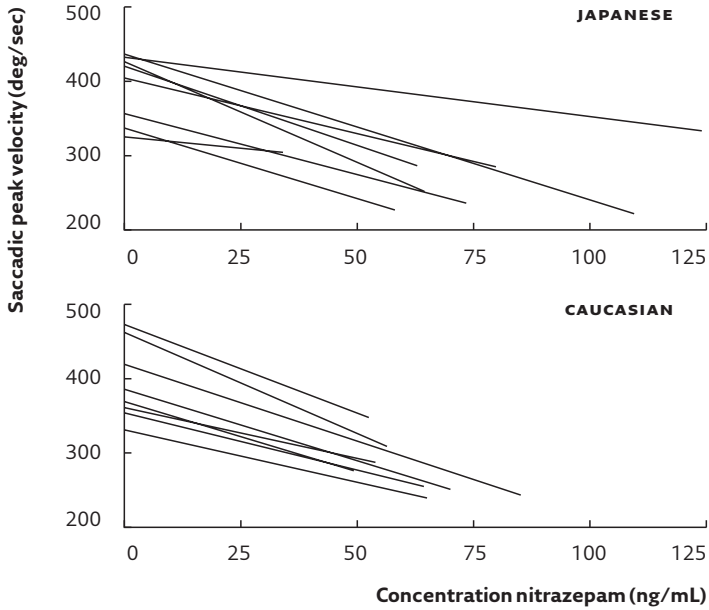
TABLE 3 **Pharmacokinetic parameters for Japanese and Caucasian subjects, obtained by model independent analysis**

	JAPANESE			CAUCASIAN			DIFFERENCE	
Parameter	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**95% CI**
$t_{½}$ (min)	1329	298	8	1292	450	8	36.5	(-378.9, 451.9)
t_{max} (min)	93.8	74.2	8	101.5	71.4	8	-7.75	(-85.89, 70.39)
C_{max} (ng/ml)	75.8	28.9	8	62.1	11.7	8	13.7	(-11.1, 38.5)
Clearance (ml/min)	50.8	11.4	8	65.6	22.6	8	-14.8	(-34.6, 5.1)
Clearance/kg (ml/min/kg)	0.91	0.17	8	1.17	0.49	8	-0.26	(-0.68, 0.16)

Concentration-effect relationships

The individual nitrazepam concentration-time profiles could not be adequately described using standard pharmacokinetic models. Individual plots of saccadic peak velocity against concomitant (linearly interpolated) nitrazepam concentration revealed possible hysteresis in some subjects, possible proteresis in others and no sign of either in the rest. No indications were present to consider a concentration-effect model that was more complex than a simple linear association. Figure 3 shows the plots using standard linear regression for both Japanese and Caucasian subjects.
The mean slopes of the plots of the Japanese subjects were 0.26 (95% CI -0.32, 0.84)° $sec^{-1}ml{\cdot}ng^{-1}$ less steep than the corresponding slopes for the Caucasian subjects (-1.66±0.69 vs -1.91±0.48° $sec^{-1}ml{\cdot}ng^{-1}$). The intercepts for the Japanese subjects were 2.0 (95% CI -43.2, 39.2)°/sec lower than for Caucasian subjects (392.5±45.6 vs 394.5±51.9°/sec). The Caucasian slopes were 24.2 (95% CI -20.2, 93.2) % steeper than the Japanese. Both the slopes and the intercepts were not statistically different by paired and unpaired comparison.

FIGURE 3 **Slopes of linear relationships between nitrazepam concentrations and saccadic peak velocities for Japanese and Caucasian subjects**



Discussion

The objectives of the study were to compare the pharmacokinetics and CNS-pharmacodynamics of a single oral dose of nitrazepam 5 mg between Caucasian and Japanese male and female volunteers, matched for gender, age and body stature. Nitrazepam was chosen because it is a widely used benzodiazepine in both regions, but the pharmacokinetics in the Japanese population have not been reported. In addition, nitrazepam is partly metabolised in the liver by enzymes that exhibit polymorphism subject to interracial differences. The study did not represent a formal 'bridging' study for registration purposes, but was intended to assess the feasibility of such studies as international enterprises.

ref. 11-12
ref. 4

Nitrazepam is metabolised by reduction of the nitro group to the corresponding amine, followed by acetylation to the acetamido-compound. The first step is catalysed by cytochrome P450 isoenzymes, which show considerable interethnic variation, *e.g.* of the CYP2E1 and CYP2C sub-families, such as CYP2C19. Polymorphism of these isoenzymes could theoretically lead to differences in nitrazepam effects. The second metabolic step is catalysed by N-acetyltransferase, which is also polymorphic and potentially subject to interracial differences. Based on the activity of N-acetyltransferase (NAT2), individuals can be distinguished as fast or slow acetylators. Ninety percent of the Japanese people are fast acetylators, compared to less than 50% of the Europeans. More rapid metabolism in Japanese subjects could theoretically reduce the duration of action of the parent compound relative to Caucasians; both NAT2 metabolites are inactive. Demographic factors may also contribute to interethnic pharmacokinetic differences. Body stature may influence the disposition of drugs like nitrazepam, while gender and age can cause differences in drug metabolising enzymes.

ref. 13
ref. 14-15
ref. 16-17
ref. 18
ref. 19
ref. 18
ref. 20

Most of these pharmacokinetic factors, which can contribute to interracial variability in drug action, can be determined in the ethnic group where the drug was initially developed. The identification and quantification of such 'ethnically sensitive' factors can thus provide a rational basis for subsequent designs of clinical trials or treatment regimens in other populations, if the factors affecting drug disposition are also known in the new population. However, pharmacodynamic differences remain difficult to predict, and comparative studies such as the current one may elucidate unexpected interethnic differences in drug action. The design and size of such studies obviously depend on the drug in question, but identification of 'ethnically

sensitive' compounds should ideally be performed during the early phases of drug development. The current study was a phase I-type investigation, intended to test the feasibility and informativeness of interregional interethnic pharmacokinetic/ pharmacodynamic studies. The draft ICH guidelines on ethnic factors indicate that comparative studies can be performed within the original region, in a population representative of the new region, *e.g.* immigrants. However, this may eliminate only part of the ethnic variability between the two regions, since many habits of culture, feeding *etc.* which may influence drug effects, will have been adopted by the immigrants. Therefore, comparative studies are best performed in the original populations, which however necessitates careful matching of subjects, study designs and methodology.

ref. 4

ref. 4

In the current study, subjects were matched for gender, age and body stature, but the study was not designed to characterise the heterogeneity of acetylator status or cytochrome P450 activity in the Japanese and Caucasian populations. This would have required the determination of genetic polymorphism and careful identification of nitrazepam metabolites in much larger samples. In the current study however, relevant differences in drug metabolism would have become evident from differences in pharmacokinetics between the two groups. The results showed no significant pharmacokinetic differences between the two groups, although the 95% confidence intervals were too wide to confirm bioequivalence. Therefore, subtle interethnic differences in drug metabolism cannot be excluded, but these are certainly not as important as the interindividual variability within each ethnic group. Theoretically, sampling errors in this small study could have obscured the detection of ethnic differences in drug disposition. In the Japanese group however this is unlikely, since the most relevant 'ethnically sensitive' metabolic factor in this study, NAT2-activity, is present in 90% of the Japanese population. The Caucasian study group also seems to be representative of the European population, because their pharmacokinetic results agree well with textbook data on nitrazepam ($t_{½}$ 20-28h, t_{max} 45-240 min, clearance 0.86 ± 0.12 ml·min^{-1}·kg^{-1}; *cf.* Table 3).

ref. 21-22

Apart from the mentioned drug-dependent differences, there are also ethnic differences in methodology. An example is the difference in visual analogue scales between the two study groups. Visual analogue scores showed clear sedative effects in the Caucasians, but the majority of Japanese subjects scored a value of approximately zero throughout the study day. It is likely that young Japanese immigrants would have responded more like Caucasians, illustrating the point that interethnic comparative studies are best performed

in the original populations. This requires a thorough validation in particular of subjective methods, such as descriptions of adverse events, visual analogue scales, questionnaires *etc.,* before they can be applied from one population to another. The literal translation of relevant visual analogue scales performed in this study did not take sufficient account of differences in instructions and in sociocultural factors such as subject-investigator-relationships. Validation requirements are more easily met for objective methods, which are therefore more suitable to perform interethnic comparative studies. The eye movement methodology used in this study was carefully adjusted during an intensive mutual exchange programme between the Japanese and Dutch research centres.

Although concentration-effect-relationships could be established only crudely, no significant interethnic variations in pharmacokinetic / pharmacodynamic relationships of nitrazepam were found. Intersubject variability was much larger than interracial variation. However, the results did not meet formal criteria for equivalence. Therefore, they would need confirmation, repetition in special populations (elderly) and extension to some specific situations (drug interactions). If similarity in drug disposition and effects among the ethnic groups is confirmed, data from previous studies of nitrazepam in Caucasian subjects can be translated to the Japanese situation, leading to rational dose adaptations for treatment regimens. This could reduce the need for repetition of large scale studies and would rationalise the dose selection for the ones that are still necessary. Thus, systematic comparative studies could ease the burden for clinical reseach in Japan, where resources that are fully up to the requirements of ICH-GCP are currently limited. The present study shows that interethnic comparative pharmacokinetic/ pharmacodynamic investigations with rigorous similarity in design, subjects and methodology are feasible across different regions. Such studies can make a useful addition to *in vitro* assessment of 'ethnically sensitive' pharmacokinetic differences, not only for global drug development but also in multiethnic societies.

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REFERENCES

1 Breimer DD. Genetic polymorphisms in drug metabolism, In: Walker S, Lumley C, McAuslane N, eds. The relevance of ethnic factors in the clinical evaluation of medicines. Dordrecht: Kluwer Academic Publishers, 1994: 13-25

2 Anonymous. Japan and foreign clinical data. *Scrip* 1994; 1970: 22

3 Sugii H. Clinical trials in Japan. *GCP Journal* 1997;4(5):19-23

4 Food and Drug Administration. International Conference on Harmonisation; draft guideline on ethnic factors in the acceptability of foreign clinical data. *Federal Register* 1997;62(147):41054-41061

5 Uchida E, Kawamura Y, Yasuda K, Uchida N, Shimada K, Yasuhara H. Effects of nitrazepam on saccadic eye movement in Japanese healthy volunteers. *Thérapie* 1995; 50(suppl.): S169 (Abstract)

6 Van Steveninck AL, Schoemaker HC, Pieters MSM, Kroon R, Breimer DD, Cohen AF. A comparison of the sensitivities of adaptive tracking, eye movement analysis, and visual analogue lines to the effects of incremental doses of temazepam in healthy volunteers. *Clin Pharmacol Ther* 1991; 50: 172-180

7 Norris H. The action of sedatives on brain stem oculomotor systems in man. *Neuropharmacology* 1971; 10: 181-191

8 Bond A, Lader M. The use of analogue scales in rating subjective feelings. *Br J Med Psychol* 1974; 47: 211-218

9 Rovel V, Sanjuan M. Simple and specific high performance liquid chromatographic method for the routine monitoring of clonazepam in plasma. *Ther Drug Monit* 1980; 2(3): 283-287

10 Ho PC, Triggs EJ, Heazlewood V, Bourne DWA. Determination of nitrazepam and temazepam in plasma by high performance liquid chromatography. *Ther Drug Monit* 1983; 5: 303-307

11 Nebert DW. Invited editorial: Polymorphism in drug-metabolizing enzymes: What is their clinical relevance and why do they exist? *Am J Hum Genet* 1997; 60: 265-271

12 Boobis AR. Molecular basis for differences in susceptibility to toxicants: introduction. *Toxicology Letters* 1992; 64/65: 109-113

13 Breimer DD. Pharmacokinetics and metabolism of various benzodiazepines used as hypnotics. *Br J Clin Pharmac*. 1979; 8: 7S-13S

14 Shimada T, Yamazaki H, Mimura M, Inui Y, Guengerich FP. Interindividual variations in human liver cytochrome P-450 enzymes involved in the oxidation of drugs, carcinogens and toxic chemicals: Studies with liver microsomes of 30 Japanese and 30 Caucasians. *J Pharm Exp Ther* 1994; 270: 414-423

15 Kim RB, Yamazaki H, Chiba K, O'shea D, Mimura M, Guengerich FP, et al. In vivo and in vitro characterization of CYP2E1 activity in Japanese and Caucasians. *J Pharm Exp Ther* 1996; 279: 4-11

16 Odani A, Hashimoto Y, Otsuki Y, Uwai Y, Hattori H, Furusho K, Inui K. Genetic polymorphism of the CYP2C subfamily and its effect on the pharmacokinetics of phenytoin in Japanese patients with epilepsy. *Pharmacol Ther* 1997; 62: 287-292

17 Caraco Y, Tateishi T, Wood AJJ. Interethnic difference in omeprazole's inhibition of diazepam metabolism. *Clin Pharmacol Ther* 1995; 58: 62-72

18 Kangas L, Breimer DD. Clinical pharmacokinetics of Nitrazepam. *Clin Pharmacokinet* 1981; 6: 346-366

19 Mrozikiewicz PM, Drakoulis N, Roots I. Polymorphic arylamine N-acetyltransferase (NAT2) genes in children with insulin-dependent diabetes mellitus. *Clin Pharmacol Ther* 1994; 56: 626-634

20 Jochemsen R, van Beusekom BR, Spoelstra P, Janssens AR, Breimer DD. Effect of age and liver cirrhosis on the pharmacokinetics of nitrazepam. *Br J Clin Pharmac* 1983; 15: 295-302

21 Dollery C, Boobis AR, Burley D, Margerison Davies D, Harrison PI, Orme ML'E, et al. (eds) Therapeutic drugs, Volume 2. Churchill Livingstone, Edinburgh, 1991, pp.N98-N100

22 Gilman AG, Rall TW, Nies AS, Taylor P (eds). Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw Hill, New York, 1992, p.1096