Metoprolol oxidation polymorphism in a Korean population: comparison with native Japanese and Chinese populations

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We examined metoprolol oxidation capacity in 218 unrelated, healthy Korean subjects using the 8 h urinary metabolic ratio (MR) of metoprolol to α -hydroxymetoprolol after an oral dose of 100 mg metoprolol tartrate. The results were compared with those from 295 Japanese and 107 mainland Chinese whose metoprolol oxidation capacities were assessed in a similar manner. The frequency of occurrence of poor metabolisers (PMs) was 0.5% (1/218) in the Korean, 0.7% (2/295) in the Japanese and 0% in the Chinese population. However, the respective mean ($\pm$ s.d.) MRs (0.84 ± 1.14 and 0.87 ± 0.90) in the Korean and Japanese extensive metabolisers (EMs) were significantly ($P < 0.001$) less than that in the Chinese EMs (2.81 ± 2.35), and the mode of the distribution histogram and the probit plot of data for Chinese EMs were shifted to the right compared with those for Korean and Japanese EMs. The results indicate that Koreans, like Japanese and mainland Chinese, have a much lower frequency of the PM phenotype of debrisoquine/sparteine-type oxidation compared with that reported for Caucasian populations. Chinese EMs appear to have a lower capacity to metabolise metoprolol to α -hydroxymetoprolol compared with Korean or Japanese EMs.

Keywords metoprolol pharmacogenetics Oriental populations interethnic difference

Introduction

A marked interethnic difference in the incidence of the poor metaboliser (PM) phenotype of debrisoquine, sparteine or metoprolol has been observed (Eichelbaum & Gross, 1990; Horai & Ishizaki, 1988a; Kalow, 1991; Lou, 1990). We have recently reported that Japanese and mainland Chinese have a relatively low frequency of the PM phenotype for metoprolol oxidation (Horai *et al.*, 1989) compared with a white British population (Iyun *et al.*, 1986; McGourty *et al.*, 1985), and that the metabolic capacity differs between the extensive metabolisers (EMs) of the two Oriental populations (Horai *et al.*, 1989). Whether these findings are applicable to other Far Eastern Oriental groups of similar ethnic origin is not known. Therefore, we have extended these studies to Korean subjects.

Methods

Subjects

A total of 620 subjects were studied. They were drawn from three different native, Oriental ethnic origins: 218 unrelated healthy Koreans (167 men and 51 women; 19 to 40 years of age; 23.3 ± 3.1 years, mean $\pm$ s.d.) residing in the Chinju and Seoul areas; 295 unrelated healthy Japanese (172 men and 123 women; 18 to 48 years of age; 21.4 ± 3.4 years) residing in the Tokyo area; and 107 unrelated healthy Chinese Han subjects (77 men and 30 women; 19 to 32 years of age; 20.5 ± 2.1 years) residing in the Changsha area, Hunan, People's Republic of China. They were laboratory personnel and medical or nursing school students. The study protocol was approved by the local ethics committees of the three

countries. None of the subjects had any history of bronchial asthma, had experienced any recent illness, or was on any medication for at least 1 week before and during the study. The metoprolol oxidation capacities were reported previously for 262 of the 295 Japanese (Horai *et al.*, 1988a) and for 98 of the 107 mainland Chinese subjects (Horai *et al.*, 1989).

Determination of phenotype

After an overnight fast, each subject emptied his or her bladder and took a single oral dose of 100 mg metoprolol tartrate (Betacloc®, Yuhan Pharmaceutical Co., Ltd, Seoul, in the Korean subjects; Seloken®, Fujisawa Pharmaceutical Co., Ltd, Osaka, in the Japanese and Chinese subjects). Urine samples were collected over the next 8 h; urine volume was measured and aliquots (10 ml) were frozen at -20°C until analysed. Samples from both Korea and mainland China were packed in dry ice and flown to Tokyo. All of the samples were still frozen on arrival at the National Medical Center in Tokyo where they were assayed.

Urinary concentrations of metoprolol and α -hydroxy-metoprolol were measured by h.p.l.c. (Horai *et al.*, 1988b). Metoprolol oxidation phenotype was assessed according to the $\log_{10}$ urinary metoprolol/ α -hydroxy-metoprolol ratio (log MR). Subjects with log MR of > 1.10 or MR > 12.6 were defined as PM according to the criteria proposed from a British population study (McGourty *et al.*, 1985).

Data analysis

To compare metoprolol oxidation capacities among the three populations, the following variables were evaluated using the non-parametric Kruskal-Wallis test followed by the Wilcoxon signed-rank test: urinary excretions of metoprolol and α -hydroxymetoprolol expressed as % dose and urinary MR. Frequency distributions and probit plots (cumulative frequency distribution) were constructed for the log MR data as reported previously (Horai & Ishizaki, 1988b). Statistical significance was defined as $P < 0.05$. The data are given as mean $\pm$ s.d.

Results

The frequency distributions of $\log_{10}$ 8 h urinary metoprolol/ α -hydroxymetoprolol ratios (log MRs) observed in the three Oriental populations are shown in Figure 1, indicating that in each case the frequency of the PM phenotype of metoprolol was very low. Thus, one of the 218 Korean subjects (0.5% with a 95% confidence interval of 0.1 to 2.6%) and two of the 295 Japanese subjects (0.7% with a 95% confidence interval of 0.2 to 2.4%) were PMs with a log MR > 1.10 , and no PM was found amongst the 107 Chinese subjects. In addition, it is clear that the mode of the distribution of data for Chinese EMs is shifted to the right compared with the modes for the Korean and Japanese EMs (Figure 1).

Figure 2 shows probit plots of the log MRs. Because plots coincided for the Korean and Japanese subjects,

Figure 1 Frequency distributions of the $\log_{10}$ 8 h urinary metoprolol to α -hydroxymetoprolol ratio (log MR) in 218 Korean (upper panel), 295 Japanese (middle panel) and 107 Chinese subjects (lower panel).

The arrows indicate the antimode defined for a white British population (McGourty *et al.*, 1985).

the data are displayed separately to contrast the inter-ethnic difference, i.e., Koreans vs Chinese and Japanese vs Chinese (Figure 2, upper and lower panels, respectively). Consistent with the data in Figure 1 the probit plot for the Chinese EMs was shifted to the right compared with those for both Korean and Japanese EMs. As indicated in both Figures 1 and 2, individuals with a very high ability to oxidise metoprolol (log MR < -1) were apparent among the Korean and Japanese groups: nine (4.1%) of the 217 Korean EMs and 6 (2.0%) of the 293 Japanese EMs. In contrast, there was no EM with a log MR < -1 and the lowest log MR was -0.65 among the 107 Chinese EMs.

There were significant ($P < 0.001$) differences in the mean urinary recoveries of metoprolol and α -hydroxymetoprolol between the Korean/Japanese and Chinese EMs. The former excreted more α -hydroxymetoprolol ($6.2 \pm 3.2\%$ and $4.9 \pm 2.1\%$) than metoprolol ($3.5 \pm 2.8\%$ and $3.4 \pm 2.5\%$, respectively), whereas Chinese EMs excreted more metoprolol ($6.7 \pm 4.5\%$) than α -hydroxymetoprolol ($3.5 \pm 2.4\%$). This resulted in a statistically significant ($P < 0.001$) difference in the mean MR between the Korean (0.84 ± 1.14)/Japanese (0.87 ± 0.90) and Chinese EMs (2.81 ± 2.35). Korean and Japanese EMs had MR values that varied over a

Figure 2 Probit plots of the $\log_{10}$ 8 h urinary metoprolol to α -hydroxymetoprolol ratio in 218 Korean vs 107 Chinese subjects (upper panel) and in 295 Japanese vs 107 Chinese subjects (lower panel).

Circles, squares and triangles indicate the data from the Korean, Chinese and Japanese subjects, respectively. The open circle and triangles represent poor metabolisers in the Korean and Japanese subjects, respectively.

300–320-fold range, whereas Chinese EMs had MR values varying over a 53-fold range.

Discussion

The results indicate that Koreans, like Japanese and Chinese, have a very low frequency of the PM phenotype of metoprolol oxidation compared with white British subjects (Iyun *et al.*, 1986; McGourty *et al.*, 1985).

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