Age-related changes in trimethadione oxidizing capacity

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The metabolism of trimethadione (TMO) following oral administration (4 mg kg^{-1}) has been studied in 11 young male and 11 elderly male patients. The elimination half-life (h) of TMO was 11.8 ± 1.4 (mean $\pm$ s.e. mean) in the young and 23.5 ± 2.17 in the elderly ($P < 0.01$). Total body clearance ($1 \text{ h}^{-1} \text{ kg}^{-1}$) was 41.4 ± 2.8 in the young and 29.0 ± 2.4 in the elderly ($P < 0.01$). The apparent volume of distribution (1 kg^{-1}) was 0.67 ± 0.03 in the young and 0.65 ± 0.04 in the elderly. Serum dimethadione (DMO)/TMO ratios at 4 h were 0.65 ± 0.03 in the young and 0.46 ± 0.03 in the elderly ($P < 0.01$). These results suggest that *N*-demethylation of TMO is inversely related to age.

Keywords trimethadione metabolism hepatic drug-oxidizing capacity age-related change

Introduction

Trimethadione (TMO) is a neutral compound, exclusively metabolized to DMO by a cytochrome P-450-dependent monooxygenase in the liver, and almost completely absorbed from the gastrointestinal tract when given orally. Neither TMO nor dimethadione (DMO) is bound to plasma protein, and the simultaneous measurement of TMO and its only metabolite, DMO, can be carried out rapidly (Withrow, 1982; Tanaka *et al.*, 1983).

Because of these properties we have used the serum concentration ratios of DMO to TMO as an index of hepatic drug-oxidizing capacity in humans (Kobayashi *et al.*, 1984; Tanaka *et al.*, 1986).

In the present study, drug oxidizing capacity in young and elderly subjects was compared using TMO as a model substrate.

Methods

Subjects and procedures

The subjects comprised a group of 11 young males aged 21–37 (mean 29) years, and a group of 11 elderly males aged 58–76 (mean 68) years. All subjects were Japanese and had been admitted

to Tsukuba Gakuen Hospital (appendicitis; four cases, anal fistula; nine cases, hernia; nine cases). None of them had a history of alcoholism, jaundice, or acute or chronic hepatic disease. None was receiving hepatotoxic drugs or enzyme inducers or had been treated with such drugs prior to the study. The protocol was approved by the Hospital Ethics Committee.

The study was performed in the morning after a 12 h fast. TMO 4 mg kg^{-1} was given orally with 100 ml water, followed by breakfast 2 h later. Blood samples (0.5 ml) for estimation of TMO and DMO were collected at 1, 2, 4, 8, 12 and 24 h after administration of TMO, and centrifuged. The serum was separated and frozen at -20°C until assay.

TMO and DMO assay

Serum TMO and DMO concentrations were measured by a gas-liquid chromatographic method using paramethadione as internal standard (Tanaka *et al.*, 1983).

Pharmacokinetic studies

The half-life ($t_{1/2}$) of TMO was estimated by linear regression analysis. The apparent volume

Table 1 Trimethadione kinetics in relation to age

	Young (n = 11)	Elderly (n = 11)	Normal laboratory values
Subject characteristics			
Age (years)	29 ± 4	68 ± 5	—
Body weight (kg)	58 ± 3.2	52 ± 2.7	—
Smoking (cigarettes/day)	10.5 [7]	5.5 [3]	—
Plasma albumin (g dl ⁻¹)	4.5 ± 0.06	3.9 ± 0.17**	3.7–5.2
SGOT (u l ⁻¹)	14.9 ± 1.52	22.3 ± 2.54*	7–38
SGPT (u l ⁻¹)	16.6 ± 3.34	23.6 ± 6.53	8–40
Kinetic variables for p.o. TMO			
<i>t</i> _{1/2} (h)	11.8 ± 1.4	23.5 ± 2.17**	—
<i>V</i> (l kg ⁻¹)	0.67 ± 0.03	0.65 ± 0.04	—
CL (l h ⁻¹ kg ⁻¹)	41.4 ± 2.83	29.0 ± 2.44**	—

Mean ± s.e. mean, []: Number of smoker

***P* < 0.01, **P* < 0.05 compared with young patients (Wilcoxon Rank Sum Test)

of distribution (*V*) was calculated from the ratio of the dose to the serum drug concentration extrapolated to zero time.

Total body clearance (CL) was calculated from: $CL = 0.693 V/t_{1/2}$.

Statistical analysis

Results were expressed as mean ± s.e. mean. Comparisons between the young and elderly groups were performed using the Wilcoxon rank sum test.

Results

Laboratory data including the results of liver function tests and pharmacokinetic parameters are shown in Table 1.

Plasma albumin levels and serum glutamic oxaloacetic transaminase (SGOT) activities, but not serum glutamic pyruvic transaminase (SGPT) activities were significantly different between the young and the elderly. The mean *t*_{1/2} of TMO was twice as long in the elderly as in the young (23.5 ± 2.17 vs 11.8 ± 1.4 h, mean ± s.e. mean, *P* < 0.01). In the elderly, CL was decreased significantly by 30% compared to the young (29.0 ± 2.44 vs 41.4 ± 2.83 l h⁻¹ kg⁻¹, *P* < 0.01). *V* did not show significant differences between the young and the elderly (0.67 ± 0.03 vs 0.65 ± 0.04, l kg⁻¹, NS).

The serum DMO/TMO ratios at 4 h after oral administration of TMO 4 mg kg⁻¹ in the elderly

were decreased significantly by 30% compared with the young (0.46 ± 0.03 vs 0.65 ± 0.03, *P* < 0.01). There was an inverse relationship between age and blood DMO/TMO ratio at 4 h (*r* = 0.81, *y* = -0.007*x* + 0.907). Cigarette smoking did not affect serum DMO/TMO ratios (young: non-smoker 0.65 ± 0.03 vs smoker 0.63 ± 0.06, NS; elderly: nonsmoker 0.46 ± 0.03 vs smoker 0.47 ± 0.04, NS).

Discussion

Branch (1982) and Park (1982) have listed the desired properties of model substrates to be used as indicators of hepatic drug metabolizing capacity. Although antipyrine is often used for this purpose (Vestal *et al.*, 1975; Greenblatt *et al.*, 1982, 1983), TMO also has the necessary properties and it has the additional advantage of being metabolized to a single metabolite (DMO) (Withrow, 1982).

Like TMO, antipyrine (Vestal *et al.*, 1975; Greenblatt *et al.*, 1982, 1983), aminopyrine (Piroette & Allaf, 1983) and imipramine (Abernethy *et al.*, 1985) are also metabolized through *N*-demethylation, and their clearance values are also decreased with ageing. The results of this study provide further support for the use of TMO as a marker of hepatic drug oxidation and confirm that some oxidative pathways are impaired in the elderly.

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