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# Age and gender related changes in stereoselective pharmacokinetics and pharmacodynamics of verapamil and norverapamil

SUNEEL K. GUPTA[1], LINDA ATKINSON[1], TRI TU[1] & JAMES A. LONGSTRETH[2]
[1]ALZA Corporation, Palo Alto, California and [2]G. D. Searle & Co., Skokie, Illinois, USA

1 Pharmacokinetics and pharmacodynamics of R- and S-verapamil and R- and S-norverapamil were studied at steady state following administration of 180 mg verapamil delivered by a controlled-release gastrointestinal therapeutic system (COER-verapamil).

2 Of the 30 young (19 to 43 years) and 30 elderly subjects (65 to 80 years) enrolled, approximately half of each age group were women; all subjects were healthy and none were smokers.

3 Mean R- and S-verapamil and R- and S-norverapamil $C_{max}$, $C_{min}$, and AUC values for elderly subjects were 1.2 to 2.2 times greater than those for young subjects; these differences were statistically significant at $P < 0.05$. Median $t_{max}$ values for young and elderly subjects were not significantly different for any enantiomer. The mean half-life values of R- and S-verapamil for elderly subjects were approximately 20 h compared with approximately 13 h for young subjects, respectively. The mean half-life values of R- and S-norverapamil for elderly subjects were approximately 31 h and 20 h, respectively, compared with approximately 19 h and 21 h for young subjects, respectively.

4 In both age groups, the mean plasma verapamil concentrations of each enantiomer were higher for women than for men at all time points.

5 Mean arterial pressure (MAP) had a significant correlation to R- ($r^2$ = 0.86) and S-verapamil ($r^2$ = 0.87) concentration values that was not influenced by either gender or age of the patient. Change in PR-interval also had a significant correlation to R- and S-verapamil concentration values. However, the sensitivity of the response to changes in R- and S-verapamil concentration values in elderly subjects was about 1/5 of that in younger subjects.

**Keywords** verapamil pharmacokinetics pharmacodynamics elderly young gender

## Introduction

Verapamil is a calcium ion influx inhibitor having antiarrhythmic, antianginal, and antihypertensive properties. The immediate-release dosage form is approved for treatment of angina (including vasospastic angina and unstable angina), atrial arrhythmias, and hypertension. Controlled onset extended release (COER)-verapamil, an osmotically-controlled, sustained-release dosage form [1], is designed to delay the delivery and absorption of verapamil for 5 h after ingestion, then deliver drug continuously for about 10 h.

Age-related differences in stereoselective drug clearance have been demonstrated for drugs such as hexobarbitone [2], mephobarbitone [3], and propranolol [4]. For mephobarbitone and propranolol, both age-related and gender-related differences in clearance have been reported. Prolonged verapamil elimination half-life, decreased drug clearance, increased drug

Correspondence: Dr Suneel K. Gupta, Clinical Pharmacology, ALZA Corporation, P.O. Box 10950, Palo Alto, CA 94303-0802, USA

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distribution, and no effect on bioavailability have been reported previously to occur with increasing age [5–7].

Schwartz *et al.* [6, 8, 9] reported a decreased clearance of S-verapamil but not R-verapamil in elderly subjects as compared with young subjects following single intravenous infusions. There was no apparent age related change in volume of distribution or protein binding. Verapamil potency for lowering blood pressure and prolongation of PR-intervals were also less in the elderly [6]. When the data from these studies [8, 9] were pooled and analyzed for gender related differences, S-verapamil clearance was reported to be significantly higher in elderly women compared with elderly men although the number of older subjects was small. Gender-related differences were not detected in the larger group of young subjects. Since the clearance of verapamil also decreases with attainment of steady state [10], these differences are difficult to interpret for dosing recommendations. In addition, these investigators did not correlate the pharmacokinetic differences to other demographic differences, such as gender, lean body mass, etc. In this study, we investigated the effects of age and gender on the pharmacokinetics and pharmacodynamics of verapamil at steady state when delivered from the COER oral sustained-release formulation.

## Methods

### *Subjects*

Sixty healthy subjects were enrolled in this study: 30 subjects (16 male and 14 female) between the ages of 19 and 43 years (young) and 30 subjects (14 male and 16 female) between the ages of 65 and 80 years (elderly); none were smokers. With the exception of two Hispanic subjects in the young group, all subjects were Caucasian. When these age groups were divided into subgroups by gender, the mean height (164 cm) and weight (61 kg) of the young women were similar to those (160 cm and 65 kg) of the elderly women, while the mean weights of the young and elderly men were similar (76 kg and 79 kg, respectively) and the mean heights were different (180 cm and 174 cm, respectively).

Subjects were considered healthy on the basis of medical history, physical examination, and results from blood chemistry, haematology, urinalysis, and electrocardiogram. All volunteers gave written informed consent. The protocol was approved by the Institutional Review Board of Harris Laboratories, Lincoln, Nebraska, where the study was conducted.

One COER-verapamil 180 mg was administered at 22.00 h on 5 consecutive days. Pre-dose blood samples were taken on days 2, 3, and 4; blood samples were taken 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 14, 16, 20, 24, 30, and 36 h following administration of the fifth dose. Blood pressure was monitored every 15 min using noninvasive ambulatory blood pressure monitoring (Ambumed) before and after the fifth dose.

### *Plasma analysis*

A validated stereospecific, high performance, capillary electrophoretic method [11] was used to determine simultaneously the plasma concentrations of R-verapamil, S-verapamil, R-norverapamil, and S-norverapamil. The concentration *vs* response curve was linear from 2.5 ng $ml^{-1}$ to 250 ng $ml^{-1}$. The between-day precision ranged from 5.7% to 10.6%; the lower limit of quantification was 2.5 ng $ml^{-1}$ for each analyte. Concentrations ranging from 2.5 ng $ml^{-1}$ to 250 ng $ml^{-1}$ were analyzed with mean relative standard deviations of 6.3% for R-verapamil, 7.0% for S-verapamil, 9.3% for R-norverapamil, and 9.3% for S-norverapamil.

### *Pharmacokinetic analysis*

The maximum observed plasma R- and S-verapamil and R- and S-norverapamil concentrations ($C_{max}$) and corresponding times ($t_{max}$) were expressed in ng $ml^{-1}$ and hours after dosing, respectively. Following the fifth dose of COER-verapamil 180 mg, $C_{max}$, $t_{max}$, and the minimum observed plasma verapamil and norverapamil concentrations ($C_{min}$) were determined. The AUC was determined by the linear trapezoidal method for 24 h following administration of the fifth dose. The half-life ($t_{1/2}$) was estimated by linear regression of log-transformed (natural log) plasma concentration values of R- and S-verapamil and R- and S-norverapamil during the terminal log-linear decline phase of the data after $t_{max}$ of the fifth dose.

The following demographic variables were calculated to examine their influence on verapamil pharmacokinetic parameters:

Body surface area (SA), using the following equation [12]:

$$SA\ (cm^2) = 71.84 \cdot Weight^{0.425} \cdot Height^{0.725}$$

Lean body mass, using the following equations [13]:

$$\text{For men: LBM (kg)} = 2.04 \cdot 10^{-3} \cdot Height^2$$
$$\text{For women: LBM (kg)} = 1.75 \cdot 10^{-3} \cdot Height^2$$

Ideal body weight (IBW), using the following equations [14]:

$$\text{For men: IBW (kg)} = 48.18 + (Height - 150) \cdot 1.0737$$
$$\text{For women: IBW (kg)} = 45.45 + (Height - 150) \cdot 0.8948$$

### *Pharmacodynamics*

The average heart rate time profiles were analyzed during the steady-state nighttime hours (from 23.00 h to 06.00 h) and steady-state daytime hours (07.00 h to 22.00 h). The average heart rate values were computed by first calculating the heart rate area under the curve (AUHRC) using the linear trapezoidal rule and dividing the AUHRC by the number of hours in the time interval. Mean arterial pressure (MAP) was calculated as

$$MAP = \frac{Diastolic - Systolic}{3} + Diastolic$$

PR-interval measurements were taken every hour 1 day before verapamil treatment (baseline) and following the fifth administration of COER-verapamil 180 mg. The change in PR-interval was calculated by subtracting, at any given time, the baseline value from the corresponding PR-interval.

*Statistical analysis*

Analysis of variance model was used to evaluate the influence of age and gender on $C_{max}$, $t_{max}$, $C_{min}$, AUC(0,24h), $t_{1/2}$, and ratios of AUC(0,24h) R- to S-verapamil, R-verapamil to R-norverapamil, S-verapamil to S-norverapamil and R-norverapamil to S-norverapamil values. The level of significance was set at $\alpha = 0.05$.

## Results

Postanalysis comparison of estimated AUC values showed that we had at least 70% power to detect at least 30% difference between the AUC values of the two age groups for all four analytes. Steady state plasma concentrations were adequately quantifiable in all subjects for all analytes. However, S-verapamil concentrations for some young subjects declined to below the quantification limit too soon to quantify the half-life value.

*Pharmacokinetics*

The plasma R- and S-verapamil and R- and S-norverapamil concentrations immediately prior to dosing on days 1 to 5 indicated that steady state was reached by administration of the third dose for all four enantiomers. The R- and S-verapamil plasma concentration profiles were lower for young subjects than for elderly subjects but were similarly shaped (Figure 1). Mean concentrations for both groups declined for about 3 h, then increased for about 6 h, reached maximum levels about 9 h post dose, and then declined slowly. As observed for R- and S-verapamil, the R- and S-norverapamil plasma concentration profiles were also lower for young subjects than for elderly subjects and were similarly shaped (Figure 1).

The young and elderly subjects were further subclassified by gender. The mean R- and S-verapamil and R- and S-norverapamil plasma concentration-time profiles for women in the elderly and young groups were higher than those for males (Figure 1). Elderly women had the highest and young males the lowest concentrations of all four analytes.

The steady-state pharmacokinetic parameters for both verapamil and norverapamil obtained following the fifth dose of 180 mg COER-verapamil are summarized in Table 1. Elderly subjects had higher mean $C_{max}$, $C_{min}$, and AUC(0,24h) values than young subjects for all enantiomers. The mean AUC(0,24h) values of the elderly subjects for R- and S-verapamil were 1.65 times higher (90% CI = 1.4–2.0) and 2.04 times higher (90% CI = 1.6–2.7) than that of the young subjects, respectively. Elderly females had the highest and young males had the lowest AUC(0,24h) values for all enantiomers. AUC(0,24h) values of all enantiomers for young females and elderly males were similar. Elderly subjects had a higher verapamil to norverapamil AUC(0,24h) ratio for both enantiomers compared with young subjects. There was no significant difference between the mean $t_{max}$ values of young and elderly subjects for any enantiomer. The

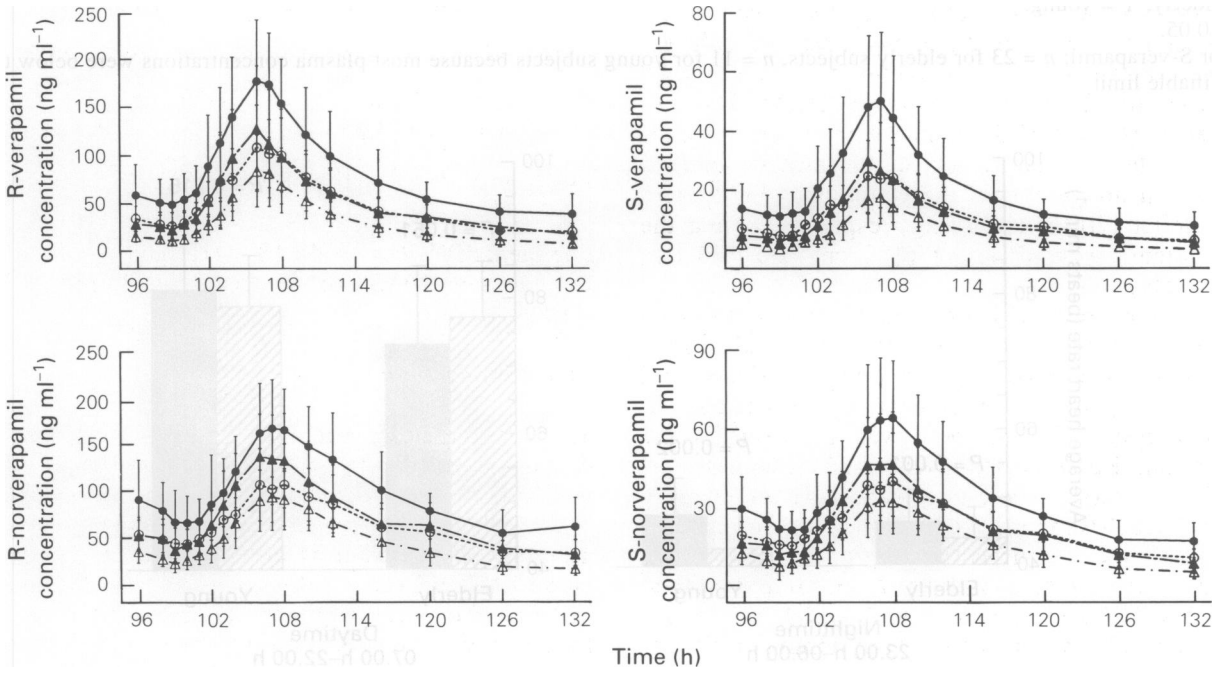


**Figure 1** Mean plasma R-verapamil, S-verapamil, R-norverapamil, S-norverapamil concentration-time profiles at steady state in young and elderly subjects (men and women) following COER-verapamil 180 mg. △ young male, ○ elderly male, ▲ young female, ● elderly female.

mean R-verapamil $t_{1/2}$ value for the elderly group was 1.5 times higher (90% CI = 1.22–1.85) than that for the young group and the difference was statistically significant ($P$ = 0.002). The mean $t_{1/2}$ of S-verapamil for elderly subjects was 1.4 times as long (90% CI = 1.03–1.89) as that for young subjects; however, only 11 young subjects and 23 elderly subjects had enough quantifiable plasma S-verapamil concentrations to calculate this value. The mean $t_{1/2}$ of elderly subjects was 1.61 times longer than that of young subjects for R- (90% CI = 1.2–2.2) and 1.43 times longer than S-norverapamil (90% CI = 1.1–1.8); the differences were statistically significant ($P$ = 0.016 and $P$ = 0.020, respectively).

*Pharmacodynamics*

Haemodynamic data (blood pressure and PR-interval) were calculated on 2 days: at baseline and at steady state (day 5).

*Heart rate* The mean heart rate from Holter recordings showed the usual circadian rhythms for both groups (Figure 2). Average heart rate was lower during nighttime hours than during the daytime hours with similar patterns for all treatments and baseline. The elderly group showed a small (<10%) decrease in heart rate following the fifth dose during daytime hours (Figure 2), whereas the young group showed no change. Following administration of the fifth dose, both age groups showed a small (<10%) but statistically significant increase in heart rate during nighttime hours compared with baseline values (Figure 2).

*Blood pressure* The mean arterial pressure (MAP) of young subjects was lower than that of elderly subjects and that of women was lower than that of men in both age groups ($n$ = 30 for each group). This ranking was consistent at all time points before (17.00 h to 20.00 h) and after COER-verapamil administration. Observed MAP was significantly correlated with verapamil concentration as shown by similar slope for all treatment groups ($P$ = 0.982); however, the intercepts were significantly different ($P$ < 0.01) (Figure 3).

*PR interval* Mean PR-intervals and the change in the PR-interval from the baseline values for both age groups are displayed in Figure 4. The PR-interval values at both baseline and during treatment were

**Table 1** Effect of age on mean ($n$ = 30 for each group) R-, S-verapamil and R-, S-norverapamil pharmacokinetic parameters following COER-verapamil 180 mg

| | *R-verapamil* | | | *S-verapamil* | | | *R-norverapamil* | | | *S-norverapamil* | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Parameter* | *E* | *Y* | *E/Y* | *E* | *Y* | *E/Y* | *E* | *Y* | *E/Y* | *E* | *Y* | *E/Y* |
| $C_{max}$ (ng ml$^{-1}$) | 155.0 | 108.6 | 1.45* | 40.9 | 24.2 | 1.71* | 150.3 | 121.3 | 1.23* | 56.9 | 43.2 | 1.32* |
| $t_{max}$ (h) | 10.0 | 10.0 | 0.96 | 10.2 | 10.0 | 0.96 | 11.2 | 10.9 | 1.02 | 11.0 | 11.0 | 0.99 |
| $C_{min}$ (ng ml$^{-1}$) | 34.1 | 15.6 | 2.15* | 6.2 | 1.2 | 1.67* | 47.6 | 27.9 | 1.70* | 15.8 | 8.8 | 1.71* |
| $t_{1/2}$ (h) | 19.7 | 12.6 | 1.50* | 20.4 | 12.6 | 1.40[a] | 31.3 | 19.3 | 1.61* | 20.0 | 12.4 | 1.43* |
| AUC(0,24h) (ng ml$^{-1}$ h) | 1885 | 1143 | 1.65* | 452 | 222 | 2.04* | 2223 | 1633 | 1.36* | 799 | 549 | 1.46* |

E = elderly, Y = young.
*$P$ < 0.05.
[a]$t_{1/2}$ for S-verapamil: $n$ = 23 for elderly subjects, $n$ = 11 for young subjects because most plasma concentrations were below the quantifiable limit.

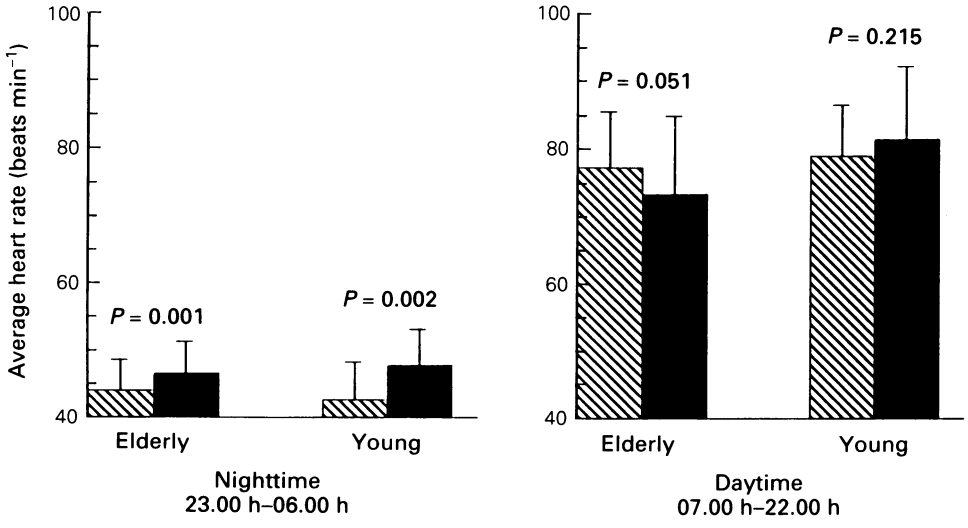


**Figure 2** Comparison of mean heart rate values between elderly and young both at baseline (▨) and following the fifth dose (■) of verapamil.

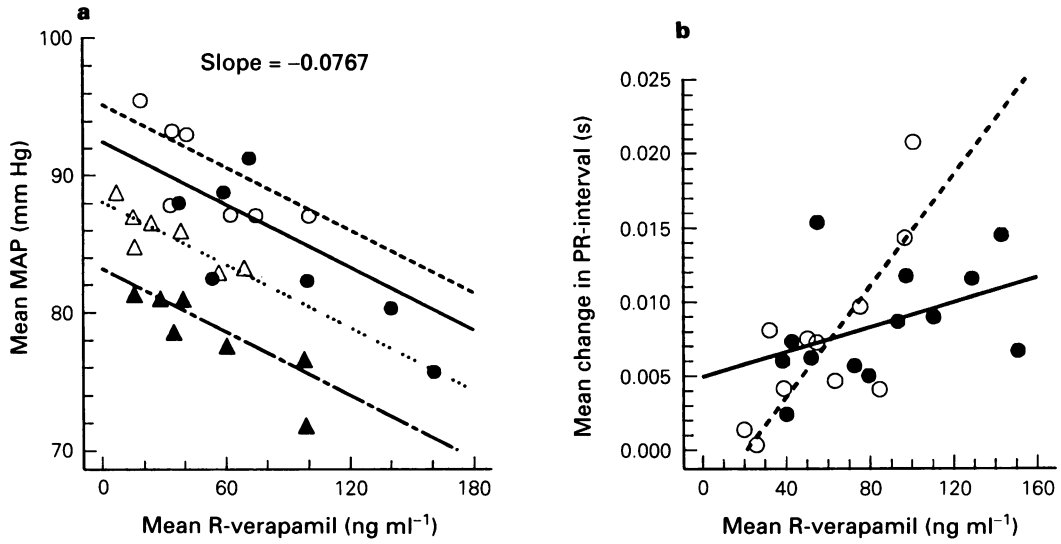


**Figure 3** Relationship of changes in a) mean arterial pressure and b) mean PR-interval to R-verapamil concentrations in young and elderly subjects. a) △ young male, ○ elderly male, ▲ young female, ● elderly female; b) ○ young, ● elderly.

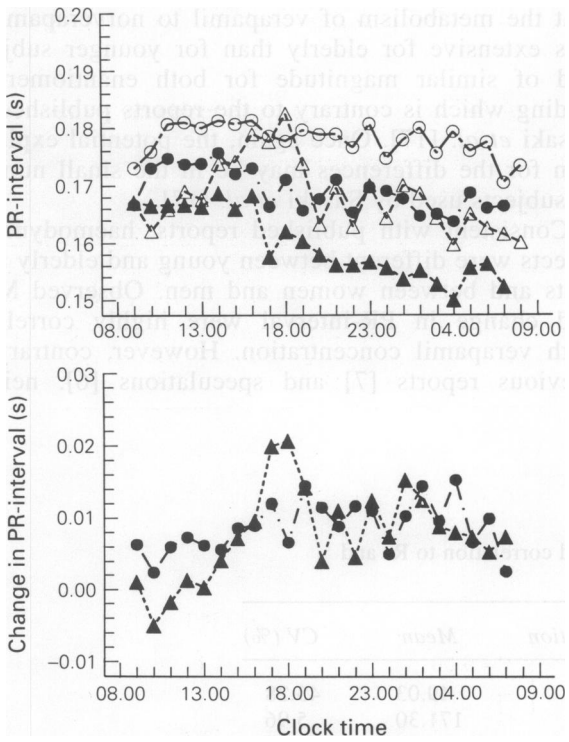


**Figure 4** Mean PR-interval and change in PR-interval from baseline in young and elderly subjects. △ young male, ○ elderly male, ▲ young female, ● elderly female.

higher for the elderly group ($n$ = 30) compared with those for the young group ($n$ = 30). For the elderly group, the PR-interval during the baseline period declined parallel to that after the fifth dose relative to time after treatment began. After treatment, both groups had lower PR-interval values compared with baseline. However, the change in PR-interval from baseline for both the young and elderly groups was similar between 18.00 h and 08.00 h and was not affected by gender. The change in PR-interval was highly correlated to R- ($r^2$ = 0.86) and S-verapamil ($r^2$ = 0.87) concentrations (Figure 3); the slopes were different for the young and elderly groups for each enantiomer (R-verapamil: 0.000188 *vs* 0.0000416, respectively; S-verapamil: 0.00803 *vs* 0.000167, respectively) which shows that the sensitivity of the response to changes in R- and S-verapamil concentration values in elderly subjects was about 1/5 of that in younger subjects.

## Discussion

Both ageing and gender are associated with physiological and metabolic differences for several drugs. Age-dependent and gender-dependent differences occur in both hepatic and renal elimination of drugs [15, 16]. Stereospecific differences in metabolism of mephobarbitone [3] between men and women have also been reported. Sasaki *et al.* [17] reported that, following 80 mg oral administration, the effect of age on metabolism may be greater for S-verapamil than for R-verapamil, but they did not find any gender-related differences. Abernethy *et al.* [7] noted that older subjects were less sensitive than younger subjects to the verapamil concentration-and-effect relationship. However, these conclusions are confounded by the lack of a stereospecific assay method and age-dependent stereoselective pharmacokinetic and protein binding differences [18, 19].

In this study, we investigated the effects of age and gender on the stereoselective pharmacokinetics and pharmacodynamics of verapamil at steady state. Most of the previously reported studies were conducted in small groups of subjects and following a single dose. The verapamil $C_{max}$, $C_{min}$, and AUC values were higher for elderly subjects compared with young subjects. These findings are consistent with those

reported by Sasaki *et al.* [17]. Increase in AUC values with age is in agreement with the reduced clearance of S-verapamil reported by Schwartz *et al.* [6, 8, 9]. However, contrary to our results of elderly females having the lowest clearance, Schwartz *et al.* [9] reported the clearance of S-verapamil to be higher in elderly women as compared with elderly men. They also did not find any age-related changes in R-verapamil clearance. Potential explanations for the differences in the two studies include the much smaller study populations and the use of an intravenous infusion of verapamil by Schwartz *et al.* [6, 9]. Unlike Sasaki *et al.* [17], we found gender-related differences in the pharmacokinetic parameters. The disagreement between the two studies may be related to the small number of subjects ($n$ = 6) used by Sasaki *et al.* [17], despite well-known, large intra-subject variability with verapamil.

The ratios of $t_{1/2}$ of R-norverapamil to R-verapamil for elderly and young subjects were similar, about 1.5, to each other. The ratios of $t_{1/2}$ of S-norverapamil to S-verapamil for both age groups were similar, about 1.0, to each other. This suggests that age affects the elimination of R- and S-verapamil and R-norverapamil but not S-norverapamil. These observations are also consistent with the AUC ratio of verapamil to norverapamil being greater for the R-enantiomer than for the S-enantiomer. Comparison of verapamil and norverapamil $t_{1/2}$ values suggest that R-norverapamil is elimination-rate limited and S-norverapamil is formation-rate limited.

To evaluate whether demographic variables could explain the observed differences in AUC values for all analytes between elderly and young populations, the following demographic variables were evaluated: age, height, total body weight, lean body mass, body mass index, and body surface area. Based on the linear regression method, verapamil and norverapamil AUC(0,24h) values had an inverse linear relationship with lean body mass, height, and age. The other variables did not show a significant correlation. Lean body mass had the highest correlation ($r^2$ = 0.23, $P <$ 0.05) to AUC for each enantiomer (Table 2). The combined demographic variables of lean body mass and age showed the highest correlation ($r^2$ = 0.34) to AUC for each enantiomer (Table 2). Gender did not affect the total variability once the data was correlated for lean body mass and age. Based on this analysis, dosing recommendations could be based on lean body mass. However, any conclusions may be biased because the relationship was established based on a relatively small number ($n$ = 30) of healthy subjects.

Based on a comparison of R- and S-verapamil AUC values in elderly and young subjects, Sasaki *et al.* [17] concluded that the effect of age on metabolism was greater for S-verapamil than for R-verapamil. This was confirmed in the present study as shown by the larger AUC ratio of elderly to young subjects for S-verapamil (2.0) as compared with R-verapamil (1.7). However, our study also suggests that the metabolism of verapamil to norverapamil is less extensive for elderly than for younger subjects and of similar magnitude for both enantiomers, a finding which is contrary to the reports published by Sasaki *et al.* [17]. Once again, the potential explanation for the differences may be in the small number of subjects used by Sasaki *et al.* [17].

Consistent with published reports, haemodynamic effects were different between young and elderly subjects and between women and men. Observed MAP and change in PR-interval were highly correlated with verapamil concentration. However, contrary to previous reports [7] and speculations [6], neither

**Table 2** Mean demographic variables and correlation to R- and S-verapamil AUC values ($n$ = 60)

| *Variable* | *Abbreviation* | *Mean* | *CV (%)* |
|---|---|---|---|
| Age (years) | AGE | 49.03 | 45.28 |
| Body height (cm) | HT | 171.30 | 5.96 |
| Body weight (kg) | WT | 70.18 | 16.53 |
| Body weight inverse (1/kg) | WT-INV | 0.0146 | 16.74 |
| Body mass index (kg/m$^2$) | BMI | 23.86 | 12.36 |
| Lean body mass (kg) | LBM | 56.18 | 18.34 |

| *Variables in model* | *Correlation ($r^2$)* *R-verapamil* | *S-verapamil* |
|---|---|---|
| Lean body mass | 0.26 | 0.23 |
| Height | 0.22 | 0.20 |
| Age | 0.20 | 0.19 |
| Age, lean body mass | 0.37 | 0.34 |
| Age, height | 0.32 | 0.30 |
| Inverse weight, lean body mass | 0.30 | 0.26 |
| Age, height, lean body mass | 0.39 | 0.36 |
| Age, inverse weight, lean body mass | 0.38 | 0.34 |

gender nor age influenced the correlation between change in MAP and verapamil concentrations. PR-interval was also highly correlated, as hysteresis was observed. A partial explanation of the differences may be the use of baseline correction in this study. The difference in slope between young and elderly (Figure 3) suggests there is a difference in sensivitity. The data from this study support the hypothesis that both ageing and gender affect the clearance of verapamil and stereoselective formation of norverapamil and also suggest that ageing does not affect the sensitivity to verapamil-related haemodynamic effects. The differences seen in this study suggest that age and gender *per se* affect the pharmacokinetics of verapamil, although most of the effect from gender may be related to body size.

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