The pharmacodynamics and pharmacokinetics of the $5HT_{1B/1D}$-agonist zolmitriptan in healthy young and elderly men and women

Objective: Zolmitriptan is a selective $5HT_{1B/1D}$-agonist for the treatment of migraine. In this study we investigated the cardiovascular and central nervous system effects and the pharmacokinetics of zolmitriptan in young and elderly adults.

Methods: Twelve young adult and 12 elderly volunteers received single doses of 5, 10, and 15 mg zolmitriptan during a randomizd, double-blind, placebo-controlled study. Blood pressure, heart rate, ECG, and central nervous system effects were monitored, and pharmacokinetic parameters of zolmitriptan and its metabolites calculated.

Results: Zolmitriptan did not affect heart rate and had little effect on systolic blood pressure in the young adults. In the elderly, mean peak supine systolic blood pressure values were 9 to 16 mm Hg higher after zolmitriptan than after placebo. Mean peak diastolic pressure was 6 to 10 mm Hg higher in both age groups. These changes were transient. Postural changes in blood pressure were unaffected. There was a dose-related increase in sedation, but the magnitude of the effects was small. Mean observed peak plasma concentration (C_{max}) and area under the plasma concentration–time profile [AUC(0-∞)] for zolmitriptan and its active *N*-desmethyl metabolite were similar in both age groups but higher in young women than in young men. Metabolite/parent ratios were higher in young men. No such differences were apparent in the elderly. The gender-related difference is probably the result of greater first-pass metabolism in young men. Zolmitriptan half-life was 2.8 to 3.6 hours in the elderly compared with 2.7 to 2.9 hours in young adults. Mean C_{max} and AUC(0-∞) for the inactive, *N*-oxide, and the indole acetic acid metabolites were higher in the elderly, associated with lower renal clearance.

Conclusions: Zolmitriptan was well tolerated, with an effect of age on its effects on blood pressure and the pharmacokinetics of its metabolites. The data suggest no need for dose adjustment for age. In young subjects, concentrations were higher in women than in men, but the differences were insufficient to justify dosage adjustment. (Clin Pharmacol Ther 1998;63:342-53.)

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Migraine is a debilitating and recurring disease that affects 9% to 16% of the population.[1] "$5HT_{1D}$-like" receptors are present in the cranial circulation, and the antimigraine action of agonists at these receptors, including sumatriptan and the ergot alkaloids, is believed to be caused by cranial vasoconstriction and inhibition of the release of calcitonin gene-related peptide and substance P from perivascular trigeminal sensory neurones.[2,3] More recently, $5HT_{1B/1D}$-receptors have been shown to modulate nociceptive input at the level of the trigeminal nucleus caudalis, suggesting that central sites may represent an important additional target for migraine treatment.[4] Zolmitriptan, (Zomig; formerly known as 311C90; (*S*)-4[[3-[2-(dimethylamino)ethyl]-1*H*-

indol-5-yl]methyl]-2-oxazolidinone), is a novel and selective $5HT_{1B/1D}$-receptor agonist for the short-term treatment of migraine.[5] In animal models, zolmitriptan has been shown to act at these central sites, in addition to its vascular effects[6]; in this way, zolmitriptan differs from sumatriptan, which does not appear to cross the intact blood-brain barrier.[4]

Zolmitriptan is highly effective in the short-term treatment of migraine. Two hours after oral doses of 2.5 mg or more, headache severity was reduced from moderate/severe to mild/none in 65% to 81% of patients, compared with improvement in only 15% to 34% after placebo.[7] As expected from the pharmacology of serotonin and the effects of sumatriptan in humans,[8-10] there is a small dose-related increase in blood pressure after dosing with zolmitriptan.[11,12] Single oral doses of 1 to 50 mg zolmitriptan are generally well tolerated by healthy volunteers except for sedation at doses 10 to 20 times the likely therapeutic dose.[11] There is no impairment of objective performance of psychomotor tasks after doses of less than 20 mg zolmitriptan in young adult volunteers, although subjective ratings of sedation on visual analog scales (VAS) after zolmitriptan were slightly higher than those after placebo.[13]

Zolmitriptan is rapidly absorbed after oral administration but as plasma profiles show multiple peaks in some subjects, individual time to reach the peak concentration (t_{max}) values may vary from ½ to 5 hours.[11] It is eliminated mainly by metabolism followed by urinary excretion of the metabolites.[14] There are three major metabolites; the active *N*-desmethyl metabolite, 183C91, which is an agonist at $5\text{-}HT_{1B/1D}$-receptors with at least twice the potency of zolmitriptan,[15] and the *N*-oxide and indole acetic acid metabolites, both of which are pharmacologically inactive. The half-life ($t_{1/2}$) values of zolmitriptan and its metabolites are similar at 2½ to 3 hours.[11,12,14] The incidence of migraine is greatest in young women and declines with age but it also occurs commonly in young men and affects up to 3% of the population older than 65 years.[1,16] Therefore information on pharmacodynamic effects and pharmacokinetics of zolmitriptan is required in both sexes and in the elderly, as well as young adults. In this study we investigated the pharmacodynamic effects of single doses of 5, 10, and 15 mg zolmitriptan on heart rate and its variability, supine and erect blood pressure, and subjective assessments of central activity using VAS in healthy young and elderly men and women. We also examined the pharmacokinetics of zolmitriptan and its major metabolites in these subjects.

METHODS

Subjects. Twelve healthy young adult volunteers (mean age, 29 years; age range, 18 to 39 years) were recruited from the Wellcome healthy volunteer panel, and 12 healthy elderly volunteers (mean age, 69 years; age range, 65 to 76 years) were recruited from the Clinical Age Research Unit volunteer panel, King's College Hospital. There were six men and six women in each age group. The mean body weights in the young and elderly men were 88 kg (weight range, 68 to 99 kg) and 77 kg (weight range, 70 to 86 kg), respectively; mean body weights in the young and elderly women were 63 kg (weight range, 54 to 72 kg) and 65 kg (weight range, 57 to 74 kg), respectively. All volunteers were required to be nonsmokers in good general health who were taking no regular medication, except the oral contraceptive pills in young women or hormone replacement therapy in the elderly women. Volunteers had no history of cardiovascular disease or other significant medical conditions and no abnormalities shown by physical examination, full blood count, biochemical profile, urinalysis, 12-lead ECG, or 24-hour Holter tape. Elderly volunteers were required to have a 24-hour urinary creatinine clearance >40 ml/min. The protocol was approved by the independent Wellcome Protocol Review Committee and the King's Healthcare Research Ethics Committee, and all volunteers gave written informed consent.

Study design. The study was of a randomized, balanced, double-blind, placebo-controlled, four-period crossover design. Each subject received placebo and 5, 10, and 15 mg zolmitriptan in random order on separate occasions, at least a week apart. Subjects were admitted to the study unit on the morning of dosing and remained there for 24 hours. All doses were given with 200 ml water after an overnight fast. Alcohol was not permitted for 24 hours before and after dosing, and caffeine was not permitted for 24 hours after dosing. Subjects were kept on bed rest for the first 4 hours; thereafter they were permitted to move around the study unit, but activity was kept to a minimum.

Supine heart rate and both supine and erect blood pressures were measured twice before dosing and at frequent intervals afterward. All supine heart rate and blood pressure measurements were made after at least 10 minutes bed rest with use of a semiautomatic oscillometric method (Hewlett-Packard

Table I. Mean peak blood pressures, changes with posture, and age differences after 5, 10, and 15 mg zolmitriptan

			Placebo	*5 mg*	*10 mg*	*15 mg*
Supine SBP						
Peak	Absolute value (mm Hg)	Y	135	134	138	137
		E	147	156	157	163
	Mean (95% CI) difference form placebo	Y		−1 (−7, 6)	3 (−3, 10)	2 (−4, 9)
		E		9 (2, 15)	10 (4, 16)	16 (10, 22)
Peak change from baseline	Absolute value (mm Hg)	Y	13	12	16	15
		E	15	22	24	31
	Mean (95% CI) age difference	E-Y	2 (−5, 9)	10 (3, 18)	7 (−2, 17)	16 (8, 23)
Erect SBP						
Peak	Absolute value (mm Hg)	Y	137	138	141	142
		E	151	164	168	167
	Mean (95% CI) difference from placebo	Y		1 (−4, 7)	5 (−1, 10)	6 (0, 11)
		E		13 (7, 19)	17 (11, 23)	16 (10, 22)
Peak change from baseline	Absolute value (mm Hg)	Y	13	12	17	20
		E	13	25	29	28
	Mean (95% CI) age difference	E-Y	1 (−6, 8)	13 (5, 21)	13 (5, 21)	9 (1, 17)
Postural change in SBP						
Peak	Absolute value (mm Hg)	Y	−12	−13	−15	−15
		E	−13	−19	−14	−19
	Mean (95% CI) difference from placebo	Y		−1 (−6, 4)	−3 (−8, 3)	−3 (−8, 3)
		E		−6 (−15, 4)	−1 (−11, 8)	−6 (−15, 3)
Peak change from baseline	Absolute value (mm Hg)	Y	−14	−17	−18	−14
		E	−19	−24	−19	−26
	Mean (95% CI) age difference	E-Y	−5 (−12, 2)	−6 (−13, 1)	−1 (−10, 9)	−11 (−22, 0)
Supine DBP						
Peak	Absolute value (mm Hg)	Y and E	79	85	87	87
	Mean (95% CI) difference from placebo	Y and E		6 (2, 10)	8 (4, 12)	8 (4, 13)
Peak change from baseline	Absolute value (mm Hg)	Y		10		
		E		15		
	Age difference	E-Y		5 (2, 8)		
Erect DBP						
Peak	Peak	Y and E	86	93	96	96
	Mean (95% CI) difference from placebo	Y and E		7 (3, 10)	10 (6, 13)	10 (7, 14)
Peak change from baseline	Change from baseline	Y		12		
		E		14		
	Age difference	E-Y		2 (−1, 6)		
Postural change in DBP						
Peak	Peak	Y and E	−2	−3	−3	−5
	Mean (95% CI) difference from placebo	Y and E		−1 (−5, 3)	−1 (−4, 3)	−3 (−6, 1)
Peak change from baseline	Change from baseline	Y		−10		
		E		−12		
	Age difference	E-Y		−2 (−5, 1)		

SBP, Systolic blood pressure; DBP, diastolic blood pressure; CI, confidence interval; Y, young adults; E, elderly adults.
See text for explanation of why DBP data are pooled across age groups for the comparisons of each dose to placebo and across doses for the comparison of effects in the elderly to those in young adults.

70354A). Before measurement of erect blood pressure, subjects were required to sit for 1 minute and then stand for 2 minutes. Twelve-lead ECGs were recorded and blood was taken for blood count and plasma biochemical profile before and 24 hours after each dose. ECGs were also recorded continuously by Holter monitoring for 24 hours after each dose with computerized quantitative analysis of

rhythm and RR intervals performed with use of dedicated equipment and software of Hertford Medical Limited, Hertford, England. Analysis of the RR intervals gave the number of interbeat intervals that deviated by more than 50 msec from the previous interbeat interval during a specified time (NN_{50} score). This is an index of heart rate variability and therefore cardiac parasympathetic function.[17]

On each occasion, subjects were required to complete a set of 16 VAS for assessment of sedation and mood before and 2, 4, 6, 8, and 24 hours after dosing.[18] The horizontal lines were presented one at a time on a touch-sensitive computer screen and the subject was required to place his or her finger on the screen at a point on the line where he or she rated his or her feeling at the time. A vertical red line appeared at this point and the subjects were free to move this marker until they were satisfied they had chosen the correct position on the scale. Once satisfied, the subject touched a box on the screen to record this position. This method of analyzing volunteers' subjective responses to psychoactive compounds is sensitive to the effects of a variety of drugs.[19] Adverse experiences were recorded before dosing and at intervals up to 24 hours after each dose.

Blood samples for assay of zolmitriptan and its metabolites 183C91 (*N*-desmethyl), 1652W92 (*N*-oxide), and 2161W92 (indole acetic acid) were taken before dosing on each occasion and ¼, ½, ¾, 1, 1½, 2, 2½, 3, 3½, 4, 5, 6, 7, 8, 9, 10, 12, and 24 hours afterward and all urine was collected for 24 hours after dosing.

Drug assay. Plasma was separated by centrifugation of blood samples at 3000*g* for 10 minutes and stored at −20° C or below until assay. Plasma concentrations of zolmitriptan and metabolites 183C91, 1652W92, and 2161W92 were determined by use of a manual solid-phase extraction method, followed by an ion-exchange reversed-phase HPLC system with fluorescence detection.[12] The volume of each urine collection was determined, and a 20 ml aliquot taken and frozen at −20° C or below until assay as described previously.[12]

A calibration curve for each analyte was constructed from the calibration sample included in the assay with use of the peak height ratio of analyte/internal standard. Sample peak height ratios were then calculated and concentrations determined from the appropriate curve. The standard curve was a linear fit with a 1/concentration weighting. The calibration range was 2 to 200 ng/ml for all analytes in plasma and 100 to 5000 ng/ml in urine; the assay precision and bias were <20% at the limit of quantification and <15% at concentrations ≥10 ng/ml in plasma and ≥200 ng/ml in urine.

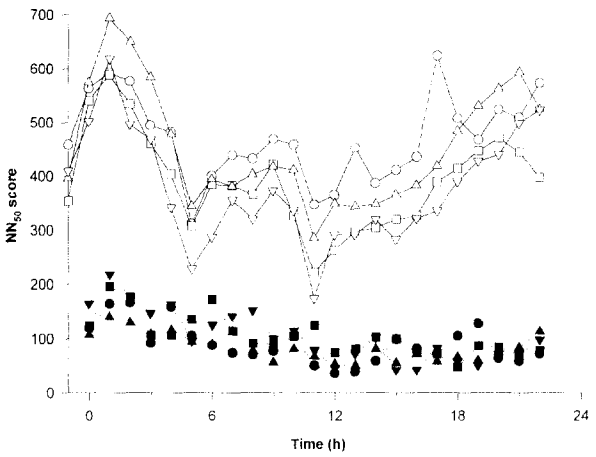

Fig. 1. Mean NN_{50} scores in young *(open symbols)* and elderly *(solid symbols)* volunteers after placebo *(circles)*, 5 mg *(squares)*, 10 mg *(triangles)*, or 15 mg *(inverted triangles)* 311C90.

Pharmacokinetic methods. Pharmacokinetic analyses were performed with use of Microsoft Excel, version 4.0 (Microsoft Corp., Redmond, Wash.). The observed peak plasma concentration (C_{max}) and t_{max} values were taken directly from the plasma profiles. The area under the plasma concentration–time profile [AUC(0-∞)] was estimated up to the last measured concentration (C_t) with use of the linear trapezoidal rule and extrapolated to infinity by the addition of C_t/λ_Z, in which λ_Z is the terminal phase elimination rate constant obtained by log-linear regression. Elimination $t_{1/2}$ was calculated as $\ln(2)/\lambda_Z$. Apparent clearance (CL/F) and volume of distribution (V_Z/F) were calculated as Dose/AUC(0-∞) and $CL/F \cdot \lambda_Z$, respectively. Renal clearance (CL_R) was calculated as Ae/AUC(0-24), in which Ae is the amount excreted in urine for 24 hours after each dose, calculated as the product of urine volume and concentration.

Statistical methods. With 12 subjects in each group, it was estimated that it would be possible to detect a 7 mm Hg difference in diastolic blood pressure between doses within each group, with a power of 80% (two-sided test at 5% level). On the basis of data from a previous study,[11] it was also estimated that with 12 subjects in each group it would be possible to detect a 50% increase in mean values of

Table II. Mean VAS mood factor scores with mean differences from placebo and between age groups after 5, 10, and 15 mg zolmitriptan

Mood group	Mean VAS Norris factor scores				5 mg–placebo*	10 mg–placebo*	15 mg–placebo*	Young	Elderly	Elderly–Young*
	Placebo	5mg	10mg	15mg						
Mental sedation	46.0	55.1	58.2	63.7	9.1 (1.9, 16.2)	12.2 (5.0, 19.4)	17.7 (10.6, 24.8)	58.4	53.2	−5.2 (−18.5, 8.1)
Physical sedation	48.5	56.0	56.0	63.2	7.6 (0.6, 14.6)	7.5 (0.5, 14.5)	14.7 (7.8, 21.7)	59.2	52.6	−6.6 (−20.2, 7.0)
Tranquilization	43.9	43.6	48.7	51.7	−0.3 (−11.0, 10.5)	4.8 (−6.0, 15.5)	7.8 (−2.9, 18.5)	52.5	41.4	−11.1 (−23.4, 1.1)
Other	40.7	47.1	45.6	49.4	6.4 (0.7, 12.2)	5.0 (−0.8, 10.7)	8.7 (3.0, 14.4)	47.4	44.1	−3.3 (−13.8, 7.2)

VAS, Visual analog scale.
* Mean differences; 95% confidence intervals are given in parentheses.

AUC(0-∞) with a power of 80% (two-sided test at 5% level).

The peak blood pressure and postural changes after each dose of zolmitriptan, compared with placebo, were analyzed by ANOVA, taking into account sources of variation attributable to age group, subject, dose, occasion, gender, and appropriate interactions (subject was fitted as a random effect). The average of the two baseline values was used as a covariate in the analysis. The dose level versus placebo comparisons presented depended on the presence or absence of an age group times dose interaction. To compare age groups, the peak changes from baseline were analyzed. The total NN_{50} scores were compared across doses by ANOVA.

The 16 VAS were grouped into four mood factors that represented mental sedation, physical sedation, tranquilization, and other types of feelings. For each mood factor the average score across scales was were analyzed in the same way as that described for blood pressure.

Pharmacokinetic parameters were analyzed by ANOVA, taking into account sources of variations attributable to subject, occasion, age group, dose level, gender, and appropriate interactions. Except for Ae, parameters were log-transformed before analysis. Differences in log-transformed parameters and their associated 95% confidence intervals (CIs) were estimated between age groups and genders and back-transformed to take the form of ratios on a linear scale. Analyte concentrations were often too low for reliable calculation of pharmacokinetic parameters, especially for 183C91 and 1652W92; mean or median data, ratios, and CIs are only presented if the parameter could be estimated in at least nine subjects from each group; for gender comparisons, data from the young and elderly volunteers were combined because there were only six of each gender in each age group.

RESULTS

As expected, baseline predose blood pressure recordings were higher in the elderly than in the young adults. Mean peak supine and erect systolic blood pressure were higher after all doses of zolmitriptan than after placebo in the elderly, with a trend to greater increases at higher doses (Table I). Mean peak supine systolic blood pressure was –1, 3, and 2 mm Hg higher after 5, 10, and 15 mg zolmitriptan, respectively, than that after placebo in the young adults, whereas it was 9, 10, and 16 mm Hg higher in the elderly. In the young volunteers the 95% CIs for the differences in systolic blood pressure, compared with placebo, always included zero.

For diastolic blood pressure, the differences between doses were consistent between age groups and the increase in diastolic blood pressure in the elderly was consistently higher than that in young adults across all doses. Data from both age groups were therefore combined for the dose comparison with placebo, and data from all doses were combined for the comparison between age groups. Compared with placebo, there was an increase of 6 to 10 mm Hg in mean peak diastolic blood pressure after zolmitriptan, and the increase in peak supine diastolic blood pressure was 5 mm Hg higher in the elderly than in the young adults across all doses (Table I).

There was no evidence of any effect of zolmitriptan on postural changes in blood pressure (Table I) or heart rate and no evidence of an effect of zolmitriptan on heart rate variability as measured by the NN_{50} score (Fig. 1). NN_{50} scores were lower in

Table III. Mean ± SD pharmacokinetic parameters of zolmitriptan and its *N*-desmethyl (183C91), *N*-oxide (1652W92), and indole acetic acid (2161W92) metabolites in healthy young and elderly subjects

	Dose	*Zolmitriptan*		*183C91*		*1652W92*		*2161W92*	
	(mg)	*Young*	*Elderly*	*Young*	*Elderly*	*Young*	*Elderly*	*Young*	*Elderly*
AUC (hr · ng/ml)	5	65.3 ± 29.7	62.8 ± 31.3	—	—	—	—	65.4 ± 19.9	97.7 ± 41.5
	10	124.3 ± 70.9	112.9 ± 39.7	—	54.0 ± 12.9	—	—	99.7 ± 27.1	213.5 ± 100.2
	15	160.4 ± 115.8	164.0 ± 76.6	75.6 ± 26.3	78.3 ± 18.9	53.1 ± 11.4	83.3 ± 29.2	162.0 ± 57.3	283.1 ± 115.6
C_{max} (ng/ml)	5	9.1 ± 3.8	9.9 ± 3.7	4.2 ± 1.3	4.5 ± 0.9	3.4 ± 1.1	4.4 ± 1.5	8.6 ± 3.0	14.3 ± 5.7
	10	18.9 ± 13.1	18.6 ± 6.5	6.8 ± 2.8	8.7 ± 2.5	4.6 ± 1.5	8.5 ± 4.0	14.7 ± 4.9	28.3 ± 14.7
	15	23.3 ± 13.8	22.7 ± 8.1	10.5 ± 4.0	10.5 ± 2.6	6.8 ± 2.4	10.4 ± 4.2	21.0 ± 8.5	34.0 ± 15.4
$t_{1/2}$ (hr)	5	2.67 ± 0.69	2.77 ± 0.80	—	—	—	—	3.16 ± 0.62	3.43 ± 0.93
	10	2.75 ± 0.17	3.17 ± 0.89	—	2.77 ± 0.99	—	—	3.09 ± 0.70	4.02 ± 1.02
	15	2.92 ± 0.69	3.56 ± 0.75	3.02 ± 0.74	3.32 ± 1.00	2.73 ± 0.62	3.53 ± 0.93	3.50 ± 1.00	4.34 ± 1.84
t_{max} (hr)*	5	1.5	1.5	3.5	2.5	3.25	2.25	3.5	2.5
	10	3.5	1.75	3.5	2.75	3.75	3.5	4.0	3.5
	15	3.75	3.25	5.0	4.0	4.0	4.0	4.0	4.5
CL/F (ml/min)	5	1392 ± 424	1589 ± 741	—	—	—	—	—	—
	10	1667 ± 866	1561 ± 480	—	—	—	—	—	—
	15	2050 ± 1076	1709 ± 569	—	—	—	—	—	—
CL_R (ml/min)	5	204 ± 62	127 ± 45	—	—	—	—	522 ± 190	297 ± 123
	10	222 ± 68	129 ± 30	—	117 ± 48	—	—	521 ± 174	268 ± 46
	15	223 ± 71	136 ± 44	167 ± 54	116 ± 51	369 ± 147	219 ± 87	431 ± 107	273 ± 109
V_Z/F (L)	5	311 ± 101	348 ± 112	—	—	—	—	—	—
	10	389 ± 188	405 ± 113	—	—	—	—	—	—
	15	483 ± 202	523 ± 205	—	—	—	—	—	—
Ae (% dose)	5	14.7 ± 9.2	9.9 ± 5.3	6.5 ± 1.9	4.7 ± 2.4	7.9 ± 2.1	7.6 ± 1.7	37.7 ± 9.1	32.9 ± 6.0
	10	16.0 ± 9.7	8.4 ± 3.4	5.4 ± 2.2	3.7 ± 1.3	6.8 ± 2.4	6.6 ± 1.2	30.5 ± 5.3	28.3 ± 5.0
	15	12.9 ± 5.5	8.8 ± 4.6	4.8 ± 1.3	3.6 ± 1.3	6.5 ± 2.6	6.5 ± 1.5	29.1 ± 8.1	28.7 ± 6.5
AUC_m/AUC_p	5	—	—	—	—	—	—	1.25 ± 0.41	2.05 ± 1.15
	10	—	—	0.53 ± 0.27	0.51 ± 0.16	—	—	1.01 ± 0.45	2.01 ± 0.88
	15	—	—	0.56 ± 0.22	0.53 ± 0.16	0.35 ± 0.09	0.56 ± 0.21	1.23 ± 0.44	1.89 ± 0.70

AUC, area under the plasma concentration-time curve; C_{max}, peak plasma concentration; $t_{1/2}$, half-life; t_{max}, time to reach C_{max}; CL/F, apparent clearance; CL_R, renal clearance; V_Z/F, volume of distribution; Ae, amount of unchanged drug excreted in urine; AUC_m/AUC_p, metabolite/parent ratios.
* Median.

the elderly than the young subjects, were more variable with time in the young subjects, and increased during periods of inactivity. There were no drug-related ST segment or rhythm abnormalities on the 12-lead ECGs or Holter recordings.

Peak VAS scores were higher after all doses of zolmitriptan than after placebo for mental and physical sedation, generally increasing with dose (Table II). The incremental changes in VAS scores with increasing dose were independent of age, and the effects of age were consistently present at all doses. Data were therefore combined across ages for each dose and across doses for each age group. Scores were slightly lower in the elderly than in the young subjects, but the 95% CIs for the differences were wide (Table II).

Pharmacokinetic parameters of zolmitriptan and its metabolites are presented in Table III. Plasma concentrations of zolmitriptan, 183C91, and 1652W92 generally showed more than one peak (Fig. 2). Mean C_{max} and AUC(0-∞) for zolmitriptan increased approximately in proportion to dose in both age groups (Table III and Fig. 2), and the ratio of AUC of each metabolite to that of zolmitriptan was independent of dose. Other pharmacokinetic parameters of zolmitriptan and its metabolites were also independent of dose except for small decreases in the percentage of the dose recovered as metabolites after the 15 mg dose (Table III).

Mean values of C_{max} and AUC(0-∞) for zolmitriptan and 183C91 were similar in the young and elderly subjects (Table IV and Fig. 2). However, the C_{max} of 1652W92 and the C_{max} and AUC(0-∞) of values 2161W92 were significantly increased in the elderly, associated with lower CL_R values for both and a longer $t_{1/2}$ for 2161W92. The CL_R values for zolmitriptan and 183C91 were also lower in the elderly and zolmitriptan $t_{1/2}$ was slightly longer in the elderly, particularly after the 15 mg dose.

Mean values of C_{max} and AUC(0-∞) for zolmi-

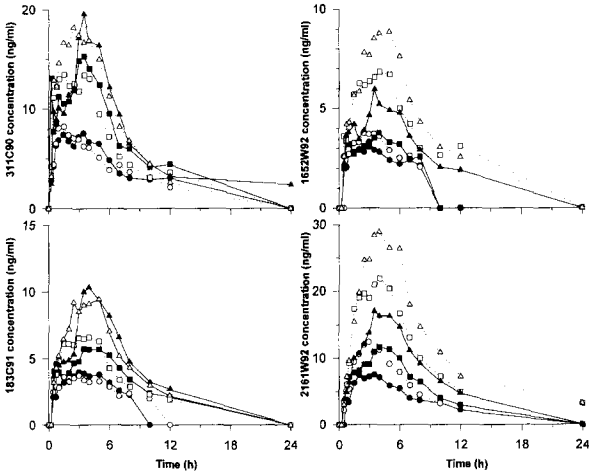

Fig. 2. Median plasma concentrations of zolmitriptan and its major metabolites after 5 mg *(circles),* 10 mg *(squares),* and 15 mg *(triangles)* in young *(closed symbols)* and elderly *(open symbols)* volunteers.

triptan were higher in women than in men (Table V). This was entirely attributable to differences in the young subjects (Fig. 3); in young men the mean ± SD AUC(0-∞) after 10 mg was 66.1 ± 24.0, whereas in young women it was 168 ± 68.7 hr · ng/ml. Corresponding values in elderly men and women were 112.5 ± 33.5 and 114 ± 48.1 hr · ng/ml, respectively (n = 6 in all groups). Mean zolmitriptan CL_R was usually lower in women than in men, particularly after the 15 mg dose; in young women, 14.5% to 21% of the dose was recovered unchanged in urine, compared with 6.4% to 10.7% in young men and in the elderly subjects.

For 183C91, combining data from all dose levels, metabolite/parent AUC ratio was higher in young men, 0.65, compared to young women, 0.40 (ratio, 1.62; 95% CI, 1.05, 2.50; n = 6) with no gender-related differences in the elderly. There was no evidence of other gender-related differences in 183C91 pharmacokinetic parameters.

Data on 1652W92 were generally too sparse to make any reliable comparisons between genders. Plasma 2161W92 concentrations were higher in women than in men (Table V). This was associated with lower CL_R. As with the other metabolites, because of the more marked differences in concentrations of zolmitriptan than of 2161W92 between men and women, the metabolite/parent AUC ratio was generally higher in men than in women, especially in the young subjects. Combining data from all dose groups, mean metabolite/parent AUC ratios were 1.42 and 0.88 in young men and women, respectively (ratio, 1.63; 95% CI, 0.95, 2.78). Other 2161W92 pharmacokinetic parameters were unrelated to gender.

For all metabolites, t_{max} was similar and usually slightly later than that of zolmitriptan (Table III). Apparent $t_{1/2}$ values of 183C91 and 1652W92 were similar to those of zolmitriptan, but that of 2161W92 was usually about 30 minutes longer (Table III).

Adverse events were typical of $5HT_{1B/1D}$-agonist drugs, namely, sensations of tightness, heaviness, or pressure in any part of the body but particularly the jaw, throat, and neck unaccompanied by ECG changes; paresthesia; and sedation. There were no differences in the spectrum, severity, or incidence of adverse effects between the age groups. There were three withdrawals from the study. Two volunteers had syncopal episodes on their first study occasions; one young subject fainted while standing for a blood pressure reading 6 hours after 5 mg zolmitriptan, and an elderly subject fainted while standing after discharge from the unit more than 24 hours after receiving the 10 mg dose. A third subject had adverse events typical of $5HT_{1B/1D}$-agonists during her first occasion; although these were not severe she withdrew from the study. The blind was maintained, but all three withdrawn subjects were replaced and the data presented are from the 12 subjects who completed the study.

DISCUSSION

The mild pressor effect of zolmitriptan is the result of vasoconstriction, which is a well-recognized effect of drugs in this class.[8-10] Consistent with previous studies,[11,12,14,20] there was minimal effect of zolmitriptan on systolic blood pressure in the young with a small increase in diastolic blood pressure at the doses used in this study. There was a trend toward these changes being dose-related, but the relationship was inconsistent and the slope was shallow, especially in the young adults. In an analysis of results from all double-blind placebo-controlled studies in healthy young adults, the mean peak increases in systolic and diastolic blood pressure after 20 mg zolmitriptan compared with placebo were only 5 and 8 mm Hg (G.R. Layton, personal communication, August 1996), suggesting that the effects of zolmitriptan are small, even with doses manyfold higher than those likely to be used therapeutically.

In the elderly, baseline blood pressure was higher

Table IV. Mean (95% CIs) ratios (elderly/young) for pharmacokinetic parameters of zolmitriptan and its major metabolites

	Dose (mg)	*Zolmitriptan*	*183C91*	*1652W92*	*2161W92*
AUC (hr · ng/ml)	5	1.01 (0.67, 1.50)	—	—	2.06 (1.55, 2.73)
	10	1.05 (0.71, 1.56)	—	—	1.73 (1.31, 2.30)
	15	1.12 (0.76, 1.64)	—	—	1.89 (1.45, 2.46)
C_{max} (ng/ml)	5	1.11 (0.78, 1.58)	1.10 (0.85, 1.43)	1.30 (0.97, 1.74)	1.66 (1.22, 2.26)
	10	1.10 (0.77, 1.57)	1.34 (1.03, 1.75)	1.78 (1.33, 2.37)	1.86 (1.37, 2.53)
	15	1.05 (0.74, 1.50)	1.05 (0.80, 1.36)	1.51 (1.13, 2.02)	1.60 (1.18, 2.18)
$t_{1/2}$ (hr)	5	1.04 (0.84, 1.29)	—	—	1.30 (1.03, 1.64)
	10	1.12 (0.91, 1.37)	—	—	1.20 (0.95, 1.52)
	15	1.23 (1.00, 1.50)	—	—	1.25 (1.01, 1.55)
CL_R (ml/min)	5	0.61 (0.45, 0.82)	—	—	0.48 (0.35, 0.67)
	10	0.55 (0.41, 0.73)	—	—	0.59 (0.43, 0.80)
	15	0.61 (0.46, 0.79)	—	—	0.53 (0.40, 0.71)
Ae (% dose)*	5	−4.3 (−10.0, 1.4)	−1.8 (−3.3, −0.3)	−0.3 (−2.0, 1.3)	−4.9 (−10.7, 0.9)
	10	−8.1 (−14.0, −2.3)	−1.8 (−3.4, −0.2)	−0.2 (−1.9, 1.6)	−2.4 (−8.9, 4.1)
	15	−4.1 (−9.7, 1.6)	−1.2 (−2.7, 0.3)	0.0 (−1.7, 1.6)	−1.0 (−7.0, 5.0)
AUC_m/AUC_p	5	—	—	—	1.92 (1.28, 2.90)
	10	—	—	—	1.55 (1.03, 2.33)
	15	—	—	—	1.73 (1.17, 2.55)

* Mean difference.

than in young adults and there was a statistically significant increase in systolic and diastolic blood pressure measurements after all doses of zolmitriptan. The dose relationship of the increase in diastolic blood pressure was the same in both age groups, whereas for systolic blood pressure, the effect of increasing dose was greater in the elderly than the young subjects. For diastolic blood pressure, especially supine, in the elderly the increase after zolmitriptan was consistently slightly greater than that in the young after all doses studied, whereas the changes in systolic blood pressure were more variable.

The differences in the effects of zolmitriptan on blood pressure between young and elderly adults are not explained by different pharmacokinetics because concentrations of zolmitriptan and its active metabolite were similar in the two age groups (see below). It is more likely that the difference is related to age-associated changes in vascular architecture and compliance. In any case, the magnitude of increases compared with placebo was small in both age groups, and it should be noted that the doses are greater than the therapeutic dose of 2.5 mg that has recently been established.[7] Furthermore, these changes in blood pressure are relatively small compared with the usual daily variability in blood pressure, and no changes in blood pressure were detected in migraine patients treated with zolmitriptan at doses up to 25 mg.[20] Thus we conclude that the pressor effect of zolmitriptan in volunteers is unlikely to be of clinical concern in healthy young or elderly persons aged up to the mid-seventies. The oldest subject in this was study was 76 years old; care should be taken in extrapolating our results to subjects older than 76 years.

It seems to be unlikely that the two syncopal episodes were the result of effects of zolmitriptan on postural changes in blood pressure. One case was a witnessed vasovagal episode related to standing for a blood pressure measurement; the other occurred more than 24 hours after dosing when the drug was unquantifiable in plasma. The absence of any effects on postural changes in blood pressure support this view. There have been no similar episodes in more than 300 administrations of zolmitriptan to healthy volunteers in other studies. The lack of effect of zolmitriptan on heart rate variability (NN_{50} score) suggests no effect of zolmitriptan on the parasympathetic system. Changes in heart rate variability are a sensitive indicator of such effects[17] as shown by the much lower scores and the reduced hour-to-hour variation in the elderly, who are known to have reduced parasympathetic nervous system function.[17,21,22]

It is likely that at least some of the therapeutic effect of zolmitriptan is exerted in the central nervous system, presumably at the central end of the bipolar trigeminal neuron.[3,6] Indeed, neurophysio-

Table V. Geometric mean pharmacokinetic parameters of zolmitriptan and its major metabolites in men and women with mean (95% CIs) ratios for comparisons

		Zolmitriptan			*2161W92*		
	Dose (mg)	*Men*	*Women*	*Ratio (95% CI)*	*Men*	*Women*	*Ratio (95% CI)*
NAUC (hr · ng/ml)*	10	90.9	130.4	0.70 (0.49, 1.00)	129.9	158.4	0.82 (0.61, 1.10)
	15	77.3	125.0	0.62 (0.44, 0.88)	117.7	163.8	0.72 (0.54, 0.96)
NC_{max} (ng/ml)*	5	15.4	21.6	0.71 (0.53, 0.96)	19.2	24.2	0.79 (0.59, 1.07)
	10	13.9	22.2	0.63 (0.46, 0.85)	18.0	21.8	0.82 (0.61, 1.11)
	15	11.4	18.1	0.63 (0.47, 0.85)	14.6	19.9	0.73 (0.54, 0.99)
$t_{1/2}$ (hr)	10	3.0	2.7	1.13 (0.91, 1.40)	3.3	3.6	0.93 (0.72, 1.21)
	15	3.1	3.2	0.97 (0.79, 1.19)	3.7	3.7	0.98 (0.76, 1.27)
CL_R (ml/min)	10	166	157	1.06 (0.81, 1.38)	394	318	1.24 (0.94, 1.64)
	15	201	138	1.46 (1.14, 1.86)	404	284	1.42 (1.08, 1.88)
Ae (% dose)†	5	9.9	14.1	−4.3 (−9.5, 1.0)	36.3	34.3	2.0 (−4.1, 8.0)
	10	9.8	14.7	−4.8 (−10.3, 0.6)	30.7	28.4	2.3 (−4.4, 8.9)
	15	10.1	11.6	−1.5 (−6.7, 3.8)	29.8	28.8	1.0 (−5.4, 7.3)
AUC_m/AUC_p	10	—	—	—	1.50	1.20	1.25 (0.84, 1.84)
	15	—	—	—	1.51	1.32	1.15 (0.79, 1.67)

* Normalized to 10 mg dose.
† Arithmetic mean and mean differences.

logic investigation has shown a central effect of zolmitriptan in humans compatible with a presynaptic autoreceptor–mediated decrease in serotonergic transmission.[23] The subjective effects of zolmitriptan on VAS sedation scores confirm penetration of zolmitriptan across the blood-brain barrier and are consistent with those reported previously.[13] However, the VAS scores and the reports of sedation as an adverse experience show that it is only mild at these doses. Doses up to and including 15 mg are not associated with any objective evidence of clinically important impairment of function,[13] and overall it is unlikely there will be clinically significant sedation after therapeutic doses of zolmitriptan. Scores were actually lower in the elderly than the young adults, indicating that sedation is not greater in the elderly.

In a previous study of single doses across a much wider range of doses (1 to 50 mg), plasma concentrations of zolmitriptan were dose proportional[11] and a study of repeat doses of 5 and 10 mg indicated dose-independent pharmacokinetic parameters at steady state.[12] The results of this study are consistent with those studies. Multiple peaks in the plasma profile of zolmitriptan have been observed previously after oral dosing.[11] Enterohepatic cycling is unlikely because only one peak is observed after intravenous administration.[14] It is more likely that the profile after oral dosing represents continued absorption over much of the upper gastrointestinal tract. Similar multiple peaks have been reported after oral dosing with sumatriptan.[24]

Overall, mean zolmitriptan concentrations and $t_{1/2}$ values were similar in the young and elderly subjects. Zolmitriptan is cleared primarily by metabolism[14] and, in general, metabolic drug clearance does not significantly change with age in adulthood. By contrast, concentrations of the indole acetic acid metabolite 2161W92 were increased in the elderly subjects, associated with the lower CL_R that is to be expected in this age group. However, this metabolite has no pharmacologic activity and an increase in its concentrations after a single dose of zolmitriptan is of no clinical consequence. Therefore we consider there are no pharmacokinetic reasons to adjust the dose of zolmitriptan in the elderly.

Most migraine patients are young women,[1] and the therapeutic dose of zolmitriptan has been established in a largely female clinical trial population. In this study, consistent with previous results,[14] mean plasma concentrations in young men were slightly lower than in women. However, there was a wide range of concentrations within each gender and a substantial overlap between them. Furthermore, the relationship between plasma concentration and therapeutic effect of $5HT_{1B/1D}$-agonists is not well understood. Clinical data suggest similar efficacy in males and females (data on file; Zeneca Pharmaceuticals, Macclesfield, England), therefore the ap-

183C912			*1652W9*		
Men	*Women*	*Ratio (95% CI)*	*Men*	*Women*	*Ratio (95% CI)*
—	—	—	—	—	—
—	—	—	—	—	—
7.5	10.2	0.74 (0.57, 0.96)	7.3	7.8	0.93 (0.69, 1.26)
6.7	8.5	0.79 (0.61, 1.03)	5.6	6.6	0.85 (0.63, 1.15)
6.3	7.4	0.84 (0.65, 1.10)	4.9	6.0	0.83 (0.62, 1.12)
—	—	—	—	—	—
—	—	—	—	—	—
—	—	—	—	—	—
—	—	—	—	—	—
5.3	5.9	−0.5 (−2.1, 1.0)	7.9	7.6	0.3 (−1.4, 2.0)
5.0	4.1	0.9 (−0.7, 2.5)	7.1	6.3	0.7 (−1.0, 2.5)
4.4	4.0	0.5 (−1.1, 2.0)	7.0	6.0	1.1 (−0.6, 2.8)
—	—	—	—	—	—
—	—	—	—	—	—

* Normalized to 10 mg dose.
† Arithmetic mean and mean differences.

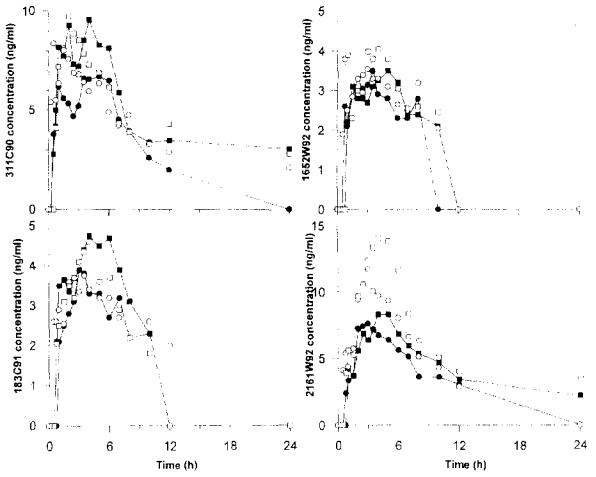

Fig. 3. Median plasma concentrations of zolmitriptan and its major metabolites in young *(closed symbols)* and elderly *(open symbols)* men *(circles)* and women *(squares)* after 15 mg.

proximately 30% lower mean concentrations in men are of no clinical significance.

The most likely explanation for the gender-related differences in young adults is lower bioavailability in men caused by greater first-pass metabolism; after 10 mg, mean oral bioavailability in young men and women was 38% and 60%, respectively.[14] The higher ratios of metabolite AUC values to those of zolmitriptan in young men and the higher recovery of unchanged zolmitriptan in young women in this study support this hypothesis. The difference in first-pass metabolism may be the result of gender-related differences in metabolizing enzymes. The enzymes responsible for the metabolism of zolmitriptan have not been identified, but it is likely that one or more cytochrome P450 (CYP) isozymes are involved in the formation of the *N*-desmethyl (183C91) and the *N*-oxide (1652W92) metabolites. 2161W92 is an indole acetic acid probably formed by the metabolism of zolmitriptan, or one of the other metabolites, by monoamine oxidase. CYP2C19 is thought to have higher activity in men, whereas CYP3A4 is reported to be higher in women; CYP2D6 does not appear to be substantially affected by gender, and the data are conflicting for CYP1A2.[25] Ethinyl steroid–containing oral contraceptive pills are inhibitors of CYP3A4[26] and CYP1A2[27] and have been shown to decrease the clearance of a number of drugs.[25-28] In this study five of the six young women studied were taking oral contraceptives; thus it was not possible to compare users and nonusers in this study. However, in five separate studies performed in the same unit with the same bioanalytical and pharmacokinetic methods mean ± SD zolmitriptan AUC(0-∞) was 143.4 ± 36.7 and 121.7 ± 63.6 hr · ng/ml in 16 oral contraceptive users and 11 nonusers, respectively (E. Seaber and R.W. Peck, unpublished data, 1996), suggesting that oral contraceptive inhibition of CYP1A2 or CYP3A4 does not account for all the gender-related differences reported here. There are no data on the effect of gender on the activity of monoamine oxidase.

Any explanation for the gender-related differences in zolmitriptan first-pass metabolism in young adults must also account for the lack of gender-related differences in the elderly. It is interesting to note that propranolol bioavailability is higher in young women than in men, related to decreased first-pass (probably CYP2C19-mediated) side-chain oxidation[29] and that clearances of both propranolol stereoisomers decrease with age in men and women[30] but with no evidence to suggest that the gender-related difference in bioavailability and first-pass metabolism decreased with age. There is currently insufficient data on the combined effects of gender and age on the activity of the cytochrome P450 isozymes to determine whether there is a single isozyme with the appropriate pattern of activity to explain all of the age- and gender-related differences

in zolmitriptan pharmacokinetics. The gender-related difference in the young subjects suggest that CYP2C19 may be involved, but the expression of 2C protein in human liver is independent of age, although the method used could not distinguish the different 2C subtypes.[31]

In conclusion, zolmitriptan was well tolerated by both young and elderly adults, with minimal effect of age on its pharmacokinetic parameters or effects on blood pressure, heart rate variability, or subjective sedation scores. The data suggest no need for dose adjustment for age. The small gender-related difference in pharmacokinetics in the young is insufficient to justify different dosage requirements.

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