The pharmacokinetics and effects on blood pressure of multiple doses of the novel anti-migraine drug zolmitriptan (311C90) in healthy volunteers

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Aims Zolmitriptan (311C90), a novel, selective, centrally and peripherally acting 5-HT_{1D}-receptor agonist is under development as an acute treatment for migraine. The tolerability, pharmacokinetics and effects on blood pressure and heart rate of multiple doses of 5 or 10 mg (5 doses administered over 24 h) were compared, in healthy adult volunteers, with those after placebo and single doses of zolmitriptan.

Methods Twelve subjects participated in a randomized, balanced, crossover comparison. Plasma and urine concentrations of zolmitriptan and its metabolites, pulse rate and blood pressure were measured at intervals after drug. Ten volunteers completed the study.

Results Zolmitriptan was well tolerated after single and multiple doses throughout the study. There was no evidence of significant changes in the pharmacokinetic parameters of zomitriptan or its metabolites after the last dose compared to the first, except for an expected rise in peak concentrations and a small, apparent increase in the amount of drug excreted in urine and hence in CL_R. After the last 10 mg dose, mean dosing interval zolmitriptan AUC was 80.3 ng ml^{-1} h compared with 86.5 ng ml^{-1} h after the single 10 mg dose (95% CI for ratio 0.76–1.13). There was no evidence of changes in the pharmacokinetic parameters of zolmitriptan and its metabolites after 10 mg compared with 5 mg, except a small increase in zolmitriptan CL_R. There were no statistically significant increases in peak systolic or diastolic blood pressure after the last doses of zolmitriptan compared to placebo or in peak blood pressure after the last dose compared to the first. There were no significant differences between blood pressure immediately before the first and last doses of each multiple dose regimen. Peak erect systolic blood pressure after the last 10 mg dose (137 mmHg) was significantly lower than that after placebo (147 mmHg, 95% CI for difference −18, −2) and that after the last 5 mg dose (148 mmHg, 95% CI −19, −3).

Conclusions Repeated doses of 5 or 10 mg zolmitriptan are well tolerated despite higher plasma concentrations than expected from single doses.

Keywords: volunteers, pharmacokinetics, multiple dosing, blood pressure, 311C90, zolmitriptan

Introduction

Migraine is a debilitating and recurring disease affecting 9–16% of the population [1]. 5-$HT_{1B/D}$ receptors are present in the cranial circulation and agonists at these receptors, including sumatriptan and the ergot alkaloids, are believed to act by causing cranial vasoconstriction and by inhibiting the release of calcitonin gene-related peptide (CGRP) and substance P from perivascular trigeminal sensory neurones [2, 3]. More recently, 5-$HT_{1B/D}$ 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]. 311C90, (zolmitriptan, (S)-4[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-2-oxazolidinone), is a novel and selective, centrally and peripherally acting 5-$HT_{1B/D}$ receptor agonist in development for the acute treatment of migraine [5]. In animal models, zolmitriptan has been shown to act at these central sites in addition to its vascular effects [6] and, in this way, differs from sumatriptan which does not appear to cross the blood brain barrier [4].

Single, oral doses of 1–50 mg zolmitriptan were generally well tolerated in healthy volunteers except for some sedation after 50 mg [7]. Plasma concentrations were proportional to dose with peak values at 2–4 h after dosing and elimination half-life was 2.5–3.0 h. Three metabolites were detected in man: 183C91 (*N*-desmethyl) is a 5$HT_{1B/D}$ agonist approximately twice as potent as zolmitriptan; 1652W92 (*N*-oxide) and 2161W92 (indoleacetic acid) are inactive. Commensurate with changes in its plasma concentrations, zolmitriptan

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produced a modest, transient increase in blood pressure. Maximum mean rises in systolic/diastolic blood pressure after single doses of 12, 25 and 50 mg were 4/8, 9/12 and 15/15 mmHg [7]. Single, oral doses of 5 and 25 mg zolmitriptan produced a significant reduction in headache from moderate/severe to mild/none in 62 and 81% of patients respectively 2 h after dosing compared with 15% improvement in placebo recipients [8]. However, up to 36% of patients who initially responded had a recurrence of headache in this study [8]. Patients with an incomplete response after the first dose, or whose headache recurs, may wish to take additional doses of zolmitriptan. Therefore, in this study, we have investigated the tolerability to, pharmacokinetics and effects on blood pressure of five doses of zolmitriptan administered at intervals of 6 h over 24 h.

Methods

Subjects

Twelve healthy volunteers (10 men, 2 women; age 23–43 years; weight 58–95 kg; height 160–184 cm) were recruited from the Wellcome Employee Healthy Volunteer Panel. All volunteers were required to be in good general health, non-smokers, taking no regular medication and with no significant past medical history or abnormal findings on physical examination, full blood count, biochemical profile, urinalysis, 12 lead ECG or 24 h Holter monitoring. The study 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, 4-period crossover design with at least 1 week between occasions. On one occasion, subjects received a single, open, fasting, 10 mg oral dose of zolmitriptan. On the remaining occasions, which were double-blind, subjects received five oral doses of either 5 or 10 mg zolmitriptan or an identical placebo with an interval of 6 h between doses. The first and last doses were administered after an overnight fast, at approximately 08.00 h; other doses were taken at least 2 h after food and subjects fasted for a further 2 h after each dose. All doses were given with 200 ml water. Subjects were admitted to the study unit on the morning of dosing and stayed for 12 h after the single dose and for 24 h after the last of the multiple doses. They were required to remain on bedrest for 4 h after the single dose and the first and last of the multiple doses. Caffeine or alcohol-containing drinks were not permitted whilst in the study unit and alcohol was not permitted for 24 h before each occasion. Based on data from a previous study [7], it was estimated that 12 subjects would give 80% power to detect a 20% change in AUC at steady state compared to the single dose (two sided test at 5% level) and that five doses would be sufficient to achieve kinetic steady state.

Blood samples for assay of zolmitriptan and its metabolites 183C91 (*N*-desmethyl), 1652W92 (*N*-oxide) and 2161W92 (indoleacetic acid) were taken pre-dose on each occasion and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10 and 12 h after the single dose and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 12, 18, 24, 24.25, 24.5, 24.75, 25, 25.5, 26, 26.5, 27, 27.5, 28, 29, 30, 31, 32, 34, 36 and 39 h after the first of the multiple doses. All urine was collected for 12 h after the single dose and 6 h after the last of the multiple doses. Pulse and blood pressure were measured and adverse events recorded pre-dose on each occasion and at intervals up to 12 h after the single dose, throughout the period of multiple dosing and for 15 h after the last dose. All supine pulse and BP measurements were made after at least 10 min bed rest using a semi-automatic oscillometric method (Hewlett Packard 70354A), erect blood pressure was measured after 1 min sitting followed by 2 min standing upright. Twelve-lead ECGs were recorded and blood taken for biochemical profile and full blood count pre-dose, 12 h after the single dose and 15 h after the last of the multiple doses. ECGs were also recorded continuously, by Holter monitoring, throughout each subject's time in the study unit.

Drug assay

Plasma was separated by centrifugation of blood samples at 3000 *g* for 10 min and stored at -20° C or below until assay. Plasma concentrations of zolmitriptan and metabolites 183C91, 1652W92 and 2161W92 were determined using a manual solid phase extraction method followed by an ion-exchange reverse phase h.p.l.c. system with fluorescence detection. C_{18} Bond-Eluts extraction cartridges (Anachem) were pre-washed with 1 ml acetonitrile, 0.5 ml water and 1 ml 0.01 M sodium formate buffer (pH 4.0). A 0.2 ml aliquot of plasma and 100 μl internal standard (890W92, 4S-4-[3-(1-methyl-4-piperidyl)-1H-indol-5-yl]2-oxazolidinthione) in 0.5 ml water was applied to the cartridge and drawn through under low vacuum. The cartridge was then washed with 1 ml sodium formate buffer, 0.75 ml water and 0.5 ml of 0.5% acetonitrile in water (v/v). Elution of the analytes of interest from the cartridge was achieved by washing the cartridge with 0.3 ml of 30% acetonitrile: 70% 0.015 M di-ammonium hydrogen orthophosphate (pH 3.5) (v/v). This was then transferred to an h.p.l.c. system for injection. The system comprised a Zorbax TMS column (25 cm × 4.6 mm i.d.), a mobile phase of 15% acetonitrile:85% 0.014 M di-ammonium hydrogen orthophosphate (pH 3.0) (v/v) and an injection volume of 200 μl with a 1 ml min^{-1} flow rate. Fluorescence detection was at 350 nm using a VG Multichrom data system.

The volume of each urine collection was determined and a 20 ml aliquot taken and frozen at -20° C or below until assay. 0.4 ml of each urine sample was shaken for 10 min with 0.4 ml 1 M formic acid and 10 ml chloroform. The sample was then centrifuged at 3000 *g* for 10 min and 20 μl of the urine/formic acid mixture (equivalent to 10 μl of urine) drawn through a Bond Eluts cartridge prepared as described above. The cartridge was washed and eluted as above except that 2% acetonitrile was used in washing and elution was with 0.06 ml 40% acetonitrile in 0.01 M sodium dihydrogen orthophosphate. The h.p.l.c. consisted of a Zorbax SIL column (8 cm × 4 mm) + guard cartridge followed by Supelcosil LC-ABZ (25 cm × 4.6 mm) with a mobile phase of (A) 5% (v/v) acetonitrile in 0.04 M sodium

dihydrogen orthophosphate and (B) 60% (v/v) acetonotrile in 0.04 M sodium dihydrogen orthophosphate in the ratios 0 min: A = 100%, 10 min: A = 80%, 15 min: A = 0%, 25 min: A = 100%. Fluorescence detection was at 350 nm.

A calibration curve for each analyte was constructed from the calibration sample included in the assay using 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 1/concentration weighting. The calibration range was 2–200 ng ml^{-1} for all analytes in plasma and 100–5000 ng ml^{-1} in urine and the assay precision and bias were $<20\%$ at the limit of quantification (2 ng ml^{-1}) and $<15\%$ at concentrations ≥ 10 ng ml^{-1} in plasma and ≥ 200 ng ml^{-1} in urine.

Pharmacokinetic methods

Pharmacokinetic analyses were performed for the single dose profile and after the last of the multiple doses using Microsoft Excel v 4.0®. The observed peak plasma concentration, C_{max}, and the time to reach the peak concentration, t_{max}, were taken directly from the plasma profiles. The area under the plasma concentration-time profile (AUC) was estimated using the linear trapezoidal rule. After the single dose, AUC was determined up to the last measured concentration, C_t, using the linear trapezoidal rule and extrapolated to infinity by the addition of C_t/λ_z, where λ_z was the terminal phase elimination rate constant obtained by log-linear regression. After the last of the multiple doses, linear trapezoidal AUC was determined for 6 h (AUC(24, 30 h)). Elimination half-life, $t_{1/2,z}$, was calculated as $\ln(2)/\lambda_z$. Apparent clearance, CL/F, and volume of distribution, V_z/F, were calculated as Dose/AUC and λ_z.CL/F respectively. Renal clearance (CL_R) was calculated as Ae/AUC where Ae, calculated as the product of urine volume and concentration, was the amount excreted in urine for 12 h after the single dose and 6 h after the last of the multiple doses and AUC was determined for the same time intervals.

Statistical methods

Comparisons of pharmacokinetic parameters, except t_{max}, after the last of the multiple 10 mg doses with those after the single dose and between the two multiple dosing regimens were performed using ANOVA taking into account sources of variation due to subject, occasion, dose, and the dose–occasion interaction. All parameters, except Ae, were log-transformed prior to analysis and for the comparison of 5 and 10 mg doses, AUC(0, 6 h) and C_{max} were normalised to a 10 mg dose. The geometric mean ratio and its 95% confidence interval (CI) were determined for each comparison. For t_{max}, differences between median values, and the 95% CI, were estimated for the 5 and 10 mg multiple doses using a method based on the Wilcoxon signed rank test.

Differences between peak blood pressures after the last of the multiple doses were analysed by ANOVA using the factors subject, occasion and dose and the interaction term dose.occasion. The measurement recorded before the first dose was used as a covariate. The differences 10 mg—placebo, 5 mg—placebo and 10—5 mg were estimated and their 95% CIs calculated. The differences between the pre-last-dose and pre-first-dose blood pressures were compared for each multiple dose and the differences between the peak blood pressure recorded 0–6 h after the last dose with that recorded 0–6 h after the first dose were also compared for each formulation. For these comparisons a pooled estimate of variation was used to produce the 95% CIs.

Results

Ten subjects completed the study. One withdrew for personal reasons unrelated to the study having completed three occasions; he did not receive the 10 mg multiple dose. The other subject was withdrawn after his second occasion (5 mg multiple dose) when analysis of the Holter tape showed an episode of non-sustained ventricular tachycardia lasting 5 beats, occurring just before his third dose of zolmitriptan (i.e. almost 6 h since the previous dose). He was asymptomatic throughout. The randomization code was not broken for these subjects, or any others, during the study which remained blind until all data had been captured. Other adverse events were all reported as mild or moderate in severity and none was considered serious. The most common adverse events were headaches which generally occurred on the afternoon of the first day of multiple dosing and the morning of the second. Two subjects reported headaches on the first day of zolmitriptan multiple dosing, both on 5 mg, whilst six subjects reported headaches after the last dose of zolmitriptan, one on 5 mg, 3 on 10 mg and two on both doses. Headaches were reported by four subjects on the first day of placebo and by two subjects after the last placebo dose. Only six subjects reported other adverse events throughout the multiple dosing occasions, usually occurring after the first or second doses; two subjects reported abnormal sensations of tightness or discomfort in the face, neck or trunk after the single dose.

Pharmacokinetic parameters

As expected, peak concentrations of zolmitriptan and its metabolites increased by approximately 50% after the last 10 mg dose compared with the single dose (Table 1). There were no differences between dosing interval AUCs for zolmitriptan or its metabolites after the last dose and AUC after the single dose; consequently the ratios of zolmitriptan AUC to metabolite AUCs were unchanged except for an increase for 1652W92 (mean ratio 1.24, 95% CI 1.06, 1.46). There were no differences between zolmitriptan apparent clearance and volume of distribution after five doses compared with those after the single dose (Table 1). Urinary recoveries of zolmitriptan and its metabolites were greater after the last dose than after the single dose with a corresponding increase in renal clearance. For urinary recovery, the mean (95% CI) increases were 3.3% (1.4, 5.2), 1.3% (0.4, 2.1), 1.5% (0.3, 2.8) and 3.3% (−2.8, 9.3) for zolmitriptan, 183C91, 1652W92 and 2161W92 respectively. The corresponding mean ratios (95% CI) for renal clearance after the last dose compared to the first were 1.29 (1.12, 1.49), 1.21 (0.84, 1.76), 1.19 (0.91, 1.56) and 1.20 (0.91,

Table 1 Geometric mean (range) pharmacokinetic parameters for zolmitriptan, 183C91, 1652W92 and 2161W92 with mean ratios and 95% CIs for ratios of parameters between steady state and single doses and between doses at steady state. Statistically significant comparisons are shown in bold for ease of reading.

		C_{max} (ng ml^{-1})	AUC (ng ml^{-1} h)	AUC_m:AUC_p	t_{max}† (h)	$t_{\frac{1}{2}}$ (h)	CL/F (ml min^{-1})	CL_R (ml min^{-1})	Ae** (%)	V_z/F (l kg^{-1})
Zolmitriptan	10 mg single dose	13.4	86.6		2.50	2.8	1880	179	9.2	442
		(9.6–19.8)	(67–126)		(0.75–5.0)	(1.6–3.8)	(1270–2390)	(124–276)	(5.0–15.4)	(252–683)
	5 mg steady state	10.0	84.0		1.50	3.0	1920	193	10.6	316
		(6.7–17.5)	(26.9–53.6)		(0.75–4.0)	(1.7–4.9)	(1510–3010)	(128–297)	(6.0–16.0)	(252–831)
	10 mg steady state	19.6	80.3		2.00	3.7	2060	231	12.4	402
		(12.7–30.5)	(48.5–127)		(1.0–3.0)	(2.1–5.4)	(1260–3300)	(160–269)	(5.9–19.0)	(389–894)
	10 mg steady state:	**1.46**	0.93		0.25	**1.31**		**1.29**	**3.3**	0.91
	single 10 mg dose	**1.14, 1.87**	0.76, 1.13		−0.13, 0.75	**1.04, 1.65**		**1.12, 1.49**	**1.4, 5.2**	0.68, 1.22
	10 mg:5 mg	0.98★	0.95★		0.00	1.22		**1.20**	1.9	1.27
		0.77, 1.25	0.78, 1.16		−1.50, 0.21	0.96, 1.53		**1.03, 1.39**	−0.1, 3.8	0.95, 1.71
183C91	10 mg single dose	6.6	42.5	0.56	3.0	3.1		146	4.0	
		(3.5–10.0)	(25.7–58.6)	(0.33–0.74)	(1.5–5.0)	(2.5–4.6)		(105–279)	(2.8–4.8)	
	5 mg steady state	6.2	41.4	0.62	1.25	2.9		151	5.2	
		(3.6–10.4)	(15.4–47.4)	(0.41–0.98)	(0.75–6.0)	(1.4–5.4)		(93–241)	(2.9–7.1)	
	10 mg steady state	10.5	67.2	0.64	2.00	3.0		177	5.3	
		(8.1–19.5)	(35.2–94.1)	(0.32–0.93)	(1.0–4.0)	(1.8–4.1)		(91–221)	(4.0–6.2)	
	10 mg steady state:	**1.60**	1.05	1.05	0.38	0.96		1.21	**1.3**	
	single 10 mg dose	**1.25, 2.05**	0.86, 1.28	0.86, 1.28	−0.75, 1.00	0.70, 1.32		0.84, 1.76	**0.4, 2.1**	
	10 mg: 5 mg	0.85★	0.90★	0.90	0.75	1.02		1.17	0.0	
		0.67, 1.09	0.74, 1.09	0.74, 1.09	0.00, 2.00	0.74, 1.40		0.79, 1.74	−0.8, 0.9	
1652W92	10 mg single dose	5.3	33.2	0.40	3.50	2.7		320	5.6	
		(2.6–8.5)	(27.4–44.5)	(0.29–0.65)	(1.5–5.0)	(1.4–4.7)		(223–327)	(3.6–7.3)	
	5 mg steady state	4.6	25.7	0.38	1.75	3.14		362	7.1	
		(3.1–7.6)	(6.0–31.4)	(0.15–0.63)	(0.75–4.0)	(2.1–13.6)		(240–835)	(3.4–8.8)	
	10 mg steady state	8.5	62.6	0.48	2.25	3.74		382	7.1	
		(5.9–12.1)	(27.2–58.6)	(0.24–0.76)	(1.0–4.0)	(1.9–5.8)		(256–488)	(6.0–8.9)	
	10 mg steady state:	**1.58**	1.13	**1.24**	0.0	1.40		1.19	**1.5**	
	single 10 mg dose	**1.30, 1.93**	0.85, 1.49	**1.06, 1.46**	−0.25, 0.75	0.88, 2.21		0.91, 1.56	**0.3, 2.8**	
	10 mg: 5 mg	0.92★	1.06★	1.13	0.25	1.19		1.05	0.0	
		0.75, 1.12	0.84, 1.33	0.99, 1.30	−0.25, 2.0	0.77, 1.84		0.83, 1.34	−1.3, 1.3	
2161W92	10 mg single dose	15.3	102	1.23	3.50	2.9		426	27.0	
		(8.3–27.2)	(61–169)	(0.78–2.15)	(1.5–5.0)	(2.0–4.7)		(279–638)	(17.2–39.5)	
	5 mg steady state	11.2	99.1	1.24	2.25	3.2		483	31.9	
		(6.0–19.9)	(54.0–134)	(0.77–2.72)	(0.5–4.0)	(1.4–6.9)		(178–949)	(15.9–43.1)	
	10 mg steady state	20.5	178	1.33	3.25	3.4		512	30.3	
		(15.4–39.6)	(129–263)	(0.78–2.44)	(1.5–4.0)	(2.4–4.8)		(246–378)	(24.4–38.1)	
	10 mg steady state:	**1.35**	0.87	1.04	0.00	1.19		1.20	3.3	
	single 10 mg dose	**1.06, 1.71**	0.72, 1.05	0.83, 1.21	−0.25, 0.75	0.82, 1.72		0.91, 1.59	−2.8, 9.3	
	10 mg: 5 mg	0.92★	0.90★	0.99	0.00	1.05		1.06	−1.7	
		0.73, 1.51	0.74, 1.09	0.84, 1.07	−0.50, 1.50	0.73, 1.51		0.78, 1.43	−7.8, 4.5	

★Dose normalized for 10 mg:5 mg comparison. **Arithmetic mean and 95% CI for differences. †Medians and mean difference between medians.

1.59) respectively. The elimination half-life of zolmitriptan was almost 1 h longer after the last dose (Table 1).

Steady state zolmitriptan concentrations were proportional to dose with no significant dose-related changes in pharmacokinetic parameters except for a slightly higher CL_R after 10 mg compared to 5 mg (Table 1). There were no dose-related changes in pharmacokinetic parameters for any of the metabolites with a dose-proportional increase in plasma concentrations (Tables 1).

Pharmacodynamic effects

Compared with placebo, there were no statistically significant increases in mean peak supine SBP after each of the multiple dose occasions (Table 2, Figure 2). Erect SBP was lower after the last 10 mg dose of zolmitriptan than after placebo or 5 mg with mean (95% CI) differences of −10 mmHg (−18, −2) and −11 mmHg (−19, −3) for peak supine SBP after the last 10 mg dose compared with placebo and 5 mg respectively (Table 2). There was no evidence of a postural drop in blood pressure after zolmitriptan (Table 2). There were no significant differences in mean peak SBP recorded for 6 h after the first dose (i.e. between the first and second doses) compared with that recorded in the same period after the last dose (Table 3). Compared with placebo, diastolic blood pressure (DBP) was higher after the first and last doses of zolmitriptan (Figure 2). However, there were no statistically significant increases in mean peak DBP after the last dose of each multiple dose occasion (Table 2) or between the peak values after the first and last dose of each occasion (Table 3). There were no differences in supine or erect heart rate between occasions (Figure 2). There were no differences in the maximum individual peak changes in SBP, DBP or postural drop after the first or last doses of zolmitriptan compared with those after placebo (Table 4).

Discussion

Plasma concentrations of zolmitriptan and its metabolites were similar to those reported previously [7]. Dose-proportionality of plasma concentrations and dose-independence of pharmacokinetic parameters is in accord with this earlier study, which suggested dose-proportionality of plasma concentrations after single doses up to 50 mg. With a half-life of 2.5 to 3.5 h it is likely that pharmacokinetic steady state has been reached after 24 h; the increase in C_{max} is expected for 6 hourly dosing of a drug with a half-life approximately 3 h. The lack of change in steady state dosing interval AUC compared with that after a single dose suggest that pharmacokinetics of zolmitriptan and its metabolites are unchanged on repeat dosing, despite the small apparent prolongation of the terminal half-life for zolmitriptan.

Total urinary recovery of zolmitriptan and metabolites increased on repeat dosing. It is unlikely this represents a true increase in recovery as that implies an increase in absorption of zolmitriptan which would give higher than expected plasma concentrations on repeat dosing. It is more likely to be due to an underestimate in recoveries after the single dose since urine was only collected for 12 h after the single dose, when parent drug and metabolites were sometimes still quantifiable in plasma and still being excreted in urine. Even if the collection period were longer, some of the parent drug and metabolites in urine would not be quantifiable due to concentrations eventually falling below the assay quantification limit. Drug-related material continues to be excreted in urine beyond this time but it cannot be measured accurately. This unquantified drug/metabolites can represent a few percent of the administered dose. After repeat dosing, plasma and urine concentrations do not fall to near the detection limit during a dosing interval, hence estimates of total recovery will be more accurate and greater than those after single doses. This apparent increase in urinary recovery after the last dose compared with the first also explains the apparent increase in renal clearance, particularly in the case of zolmitriptan.

Previous data on the pharmacokinetics of the metabolites of zolmitriptan were limited as assay sensitivity was less than in this study [7]. The data now suggest that, similar to sumatriptan [9], the major metabolite is the indole-acetic acid (2161W92). However concentrations of 183C91, the *N*-desmethyl metabolite, are approximately half those of zolmitriptan. 183C91 is a $5HT_{1B/D}$ agonist with a potency twice that of zolmitriptan. It is therefore likely it will contribute to the therapeutic effect of zolmitriptan. The similarity of the apparent elimination half-lives of the metabolites to that of parent drug suggest their kinetics are formation-rate limited. Renal clearance values for

Table 2 Mean peak blood pressures and maximum postural drops (mmHg) after the last dose of zolmitriptan or placebo with mean (95% CI) differences between doses.

			5 mg zolmitriptan		*10 mg zolmitriptan*		
		Placebo	*Mean*	*Difference from placebo*	*Mean*	*Difference from placebo*	*Difference from 5 mg*
Systolic	Supine	137	139	2 (−3, 6)	138	1 (−4, 7)	−1 (−6, 5)
	Erect	147	148	1 (−6, 8)	137	−10 (−18, −2)	−11 (−19, −3)
	Postural drop	−12	−9	3 (−2, 8)	−8	4 (−2, 9)	1 (−5, 6)
Diastolic	Supine	79	80	1 (−5, 7)	78	−1 (−8, 6)	−2 (−9, 5)
	Erect	88	93	5 (−1, 11)	93	5 (−2, 12)	0 (−7, 7)
	Postural drop*	1	2	1 (−4, 6)	5	4 (−1, 9)	3 (−2, 8)

*Positive values indicate that many subjects did not have a fall in diastolic blood pressure at any timepoint; the maximum 'drop' for these subjects was taken as the smallest increase.

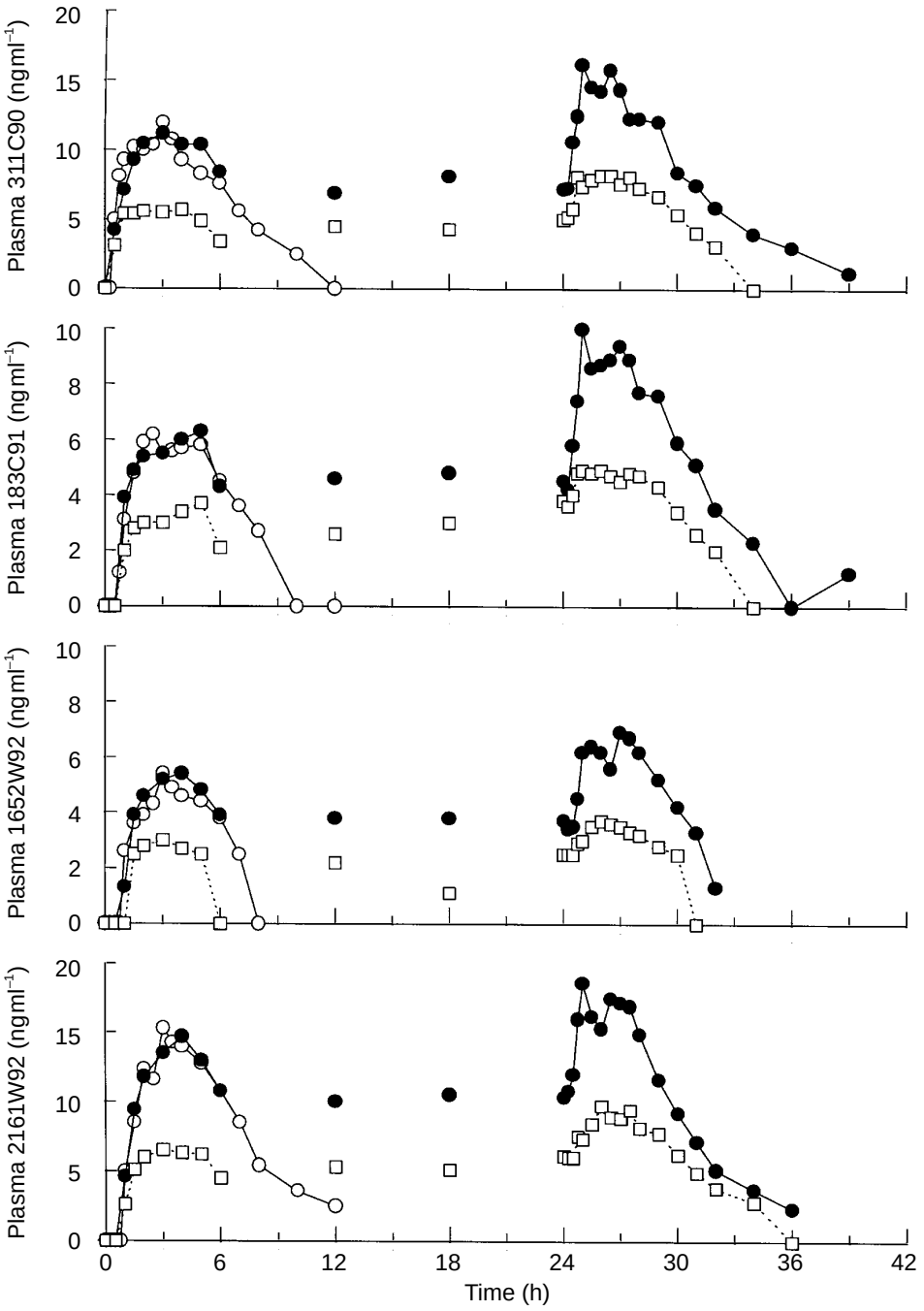

Figure 1 Median plasma concentrations of zolmitriptan and its major metabolites after a single 10 mg dose of zolmitriptan (○) and repeat dosing with 5 mg (□) or 10 mg (●). Zolmitriptan doses given at 0, 6, 12, 18 and 24 h.

zolmitriptan and the three metabolites generally exceed glomerular filtration rate suggesting active secretion into the renal tubule. However, the difference from glomerular filtration rate is small for zolmitriptan and 183C91 suggesting they undergo only limited secretion whereas this would appear more important for 1652W92 and 2161W92.

It has been reported that tolerance develops to the cardiovascular effects of sumatriptan during a second intravenous infusion given at least 45 min after the end of an initial 15 min dose-escalating infusion [10]. If tolerance to the cardiovascular effects of zolmitriptan were to develop during 24 h dosing, its adverse effects and effects on blood pressure might decrease. On the other hand, increased peak concentrations after the last dose compared to the first might increase blood pressure effects. Adverse effects tended to decrease on repeat dosing but were uncommon throughout the study. Similarly, the effects of zolmitriptan on blood pressure were mild. There was a small increase in blood pressure, particularly diastolic, after the first and last doses; blood pressure was not recorded frequently after the other doses. However the differences in peak blood pressure after the last dose of each repeat dosing occasion were not statistically significant nor was there, in general, any significant difference between pre- and post-dose readings after the first and last dose of each occasion. Thus there is no evidence of a significant attenuation or enhancement of cardiovascular effects on repeat dosing, even taking into account the accumulation of zolmitriptan, although it must

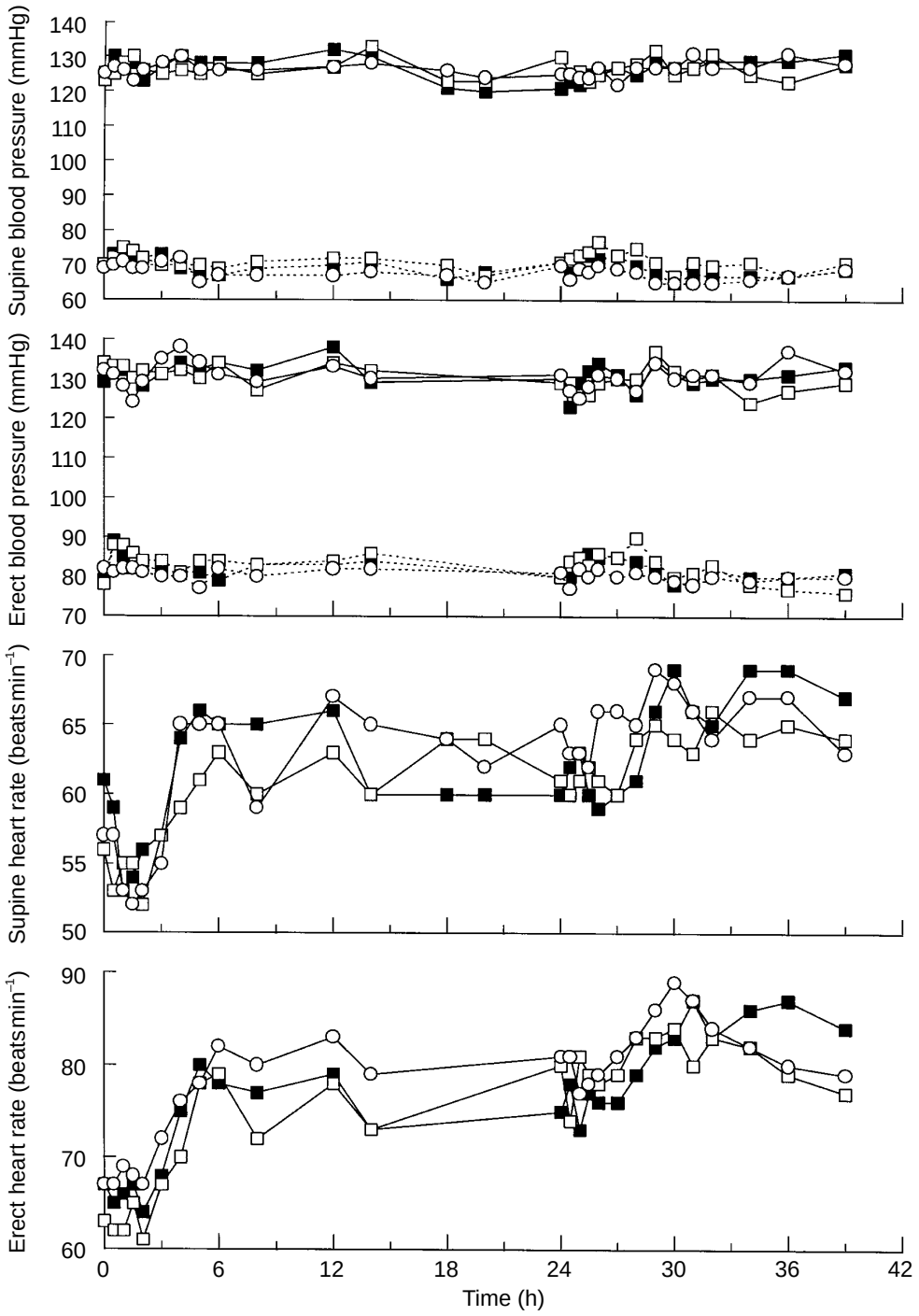

Figure 2 Mean blood pressures and heart rates after repeat dosing with placebo (○), 5 mg (■) or 10 mg (□) zolmitriptan. Zolmitriptan doses given at 0, 6, 12, 18 and 24 h.

be recognised that there is little evidence of any significant impact of zolmitriptan on blood pressure in this study. At higher doses, zolmitriptan has been shown to have a moderate vasoconstrictor effect in healthy volunteers [7, 11] and sumatriptan administration is associated with increases in blood pressure in volunteers [12–16]. Consequently, it is likely that zolmitriptan does lead to a small increase in blood pressure in volunteers. However, both the mean and peak individual effects are very slight at the doses in this study and probably of no clinical significance. Furthermore zolmitriptan did not increase blood pressure in patients being treated for an acute migraine attack [8].

The incidence of asymptomatic, non-sustained ventricular tachycardia on Holter tapes in apparently healthy young adults is 1–2% [17–19]. In this study, the episode which occurred about 6 h after the second dose of zolmitriptan was identified on analysing the tape after the subject had completed the whole occasion in which he received all five doses of zolmitriptan. The rest of the recording was unremarkable and there was no evidence of ST segment changes or changes in the QT or QT_c intervals before or after the event. It is thought unlikely to have been drug-related.

In conclusion, doses of zolmitriptan up to 10 mg taken 6 hourly for 24 h were tolerated well with no important effects on blood pressure and no other clinically significant

Table 3 Comparison of mean peak blood pressures and maximum postural drops (mmHg) 0–6 h after the first and last doses of zolmitriptan or placebo.

			First dose	*Last dose*	*Mean difference*	*95% CI*
Systolic	Supine	5 mg	137	134	2	−2, 7
		10 mg	134	137	−2	−7, 2
		Placebo	136	137	−2	−5, 3
	Erect	5 mg	143	140	3	−4, 9
		10 mg	140	140	0	−7, 6
		Placebo	145	141	5	−2, 11
	Postural drop	5 mg	−7	−7	−1	−5, 4
		10 mg	−4	−9	5	0, 9
		Placebo	−9	−9	0	−5, 4
Diastolic	Supine	5 mg	81	76	5	2, 8
		10 mg	79	80	−1	−4, 2
		Placebo	78	74	4	1, 7
	Erect	5 mg	91	91	0	−3, 3
		10 mg	92	92	−1	−4, 3
		Placebo	88	88	0	−3, 4
	Postural drop*	5 mg	2	4	−3	−6, 1
		10 mg	5	2	3	−1, 7
		Placebo	2	3	−1	−5, 2

*Positive values for postural drop indicate that many subjects did not have a fall at any timepoint; the maximum 'drop' for these subjects was taken as the smallest increase.

Table 4 Maximum individual peak blood pressures and postural drops in blood pressure (mmHg) after the first and last doses of zolmitriptan or placebo.

		First dose			*Last dose*		
		Placebo	*5 mg*	*10 mg*	*Placebo*	*5 mg*	*10 mg*
Systolic	Supine	152	149	149	152	158	155
	Erect	163	154	152	158	153	155
	Postural drop	−25	−15	−8	−25	−16	−17
Diastolic	Supine	112	96	97	100	94	100
	Erect	107	104	108	103	106	104
	Postural drop	−9	−7	−1	−11	−9	−12

adverse effects. Pharmacokinetic parameters were dose-proportional and did not change on repeated dosing. The results suggest that, in the event of symptom recurrence a few hours after their first dose, patients may take further doses of zolmitriptan without significant risk.

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