The interaction between propranolol and the novel antimigraine agent zolmitriptan (311C90)

Richard W. Peck, Emma J. Seaber, Ruth Dixon,* Catherine G. Gillotin,† Barry C. Weatherley, Gary Layton & John Posner††**

Glaxo Wellcome R&D Ltd, Greenford Road, Greenford, Middlesex UB6 0HE

Aims Zolmitriptan (Zomig, formerly known as 311C90), a selective $5HT_{1B/1D}$ agonist is under development as an acute oral treatment for migraine. Despite the use of prophylactic medication, such as propranolol, breakthrough attacks often occur in patients. Consequently we investigated the effects of propranolol on the pharmacokinetics of, and cardiovascular responses to, zolmitriptan.

Methods A double-blind, randomized, crossover study of the effects of pre-treatment with propranolol 160 mg daily for 7 days or placebo on the pharmacokinetics and effects on blood pressure of a single 10 mg dose of zolmitriptan in 12 healthy volunteers.

Results Propranolol increased mean zolmitriptan C_{max} and AUC by 56% and 37% respectively; mean $t_{1/2}$ was prolonged from 3.1 to 4.0 h. Mean C_{max} and AUC of the pharmacologically active *N*-desmethyl metabolite were reduced by 24% and 11% respectively and the metabolite : parent AUC ratio (AUC_m/AUC_p) fell from 0.46 to 0.26. Mean C_{max} and AUC for the inactive indole acetic acid metabolite were both reduced by 13% and AUC_m/AUC_p from 1.04 to 0.59. A small pressor effect of short duration was observed following zolmitriptan with mean peak rises of 13 and 11 mmHg in systolic and diastolic pressures respectively; propranolol had no effect on the pressor response.

Conclusions The results suggest that propranolol inhibits biotransformation of zolmitriptan but with no change in the small pressor response to zolmitriptan. It is therefore unlikely that the pharmacokinetic changes will lead to clinically important changes in pharmacological effects and dosage adjustment of zolmitriptan is not required in patients taking propranolol for migraine prophylaxis.

Keywords: propranolol, zolmitriptan, interaction, migraine

Introduction

Zolmitriptan, (311C90, (S)-4[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-2-oxazolidinone), is a selective $5HT_{1B/1D}$ receptor agonist in late stage clinical development for the acute, oral treatment of migraine [1]. Two hours after oral doses of 2.5 mg or above, headache severity is reduced from moderate or severe to mild or none in 65–81% of patients compared with improvement in only 15–34% after placebo [2]. After oral dosing up to 50 mg, zolmitriptan produces transient increases in blood pressure, its plasma concentrations are dose-proportional with peak values at 2–4 h after dosing and elimination half-life is 2.5–3.0 h [3–5]. It is principally eliminated by metabolism [4]; three metabolites are detected in man: 183C91 (*N*-desmethyl) is a $5HT_{1B/1D}$ receptor agonist at least twice as potent as zolmitriptan; 1652W92 (*N*-oxide) and 2161W92 (indoleacetic acid) are inactive. The involvement of cytochrome P450 enzymes in zolmitriptan metabolism has been demonstrated *in vitro* but the rates of reaction have been too slow to characterize individual enzymes.

Propranolol is a first-line drug for the prophylaxis of frequent migraine attacks, at an average daily dose of 120–160 mg [6]. However, it is not completely effective, consequently patients taking propranolol may also wish to take zolmitriptan to treat breakthrough attacks. Therefore, in this study, we investigated the impact of pre-treatment with propranolol on the pharmacokinetics and effects on blood pressure of a single dose of zolmitriptan in healthy volunteers.

Methods

Subjects

Fourteen healthy volunteers (8M, 6F, age 20–39 years, weight 55–89 kg) were recruited. All were in good general health, non-smokers, taking no regular medication except the oral contraceptive pill 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

Correspondence: Dr Richard Peck, Glaxo Wellcome R&D Ltd, Greenford Road, Greenford, Middlesex UB6 0HE.

Current addresses: *Zeneca Pharmaceuticals, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG; †Laboratoires Glaxo Wellcome, 20 rue Rouget de Lisle, 92442 Issy les Moulineaux, Paris, France; **Pfizer Central Research Ltd, Sandwich, Kent CT13 9NJ; ††Bios Ltd, Pinewood College Ride, Bagshot, Surrey GU19 5ER.

Committee and the King's Healthcare Research Ethics Committee. All volunteers gave written informed consent.

Study design

The study was of a randomized, balanced, crossover design and double-blind with respect to propranolol. On the two occasions, which were at least 1 week apart, subjects received either propranolol 160 mg (Inderal-LA, Zeneca Pharmaceuticals, Macclesfield) or an identical placebo once daily for 7 days. A 10 mg dose of zolmitriptan was taken with the last dose of propranolol or placebo. All doses were given under supervision, with 200 ml water. For the first 6 days of each occasion, subjects were dosed on an out-patient basis but they were admitted to the study unit 2 h before the doses of zolmitriptan and stayed for 24 h afterwards. Subjects were required to fast and abstain from caffeine overnight, and from alcohol for 24 h, before admission to the unit. Based on data from a previous study [5] it was estimated that 12 subjects would give 80% power to detect a 20% change in zolmitriptan AUC and a 7 mmHg change in diastolic blood pressure after zolmitriptan and propranolol compared with zolmitriptan and placebo, using 2-sided, 5% level tests.

Blood samples for assay of zolmitriptan and its metabolites 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, 9, 11, 13, 15 and 24 h after each dose of zolmitriptan and all urine was collected for 24 h. Pulse, and blood pressure were recorded before each dose of propranolol/placebo. Blood pressure was also recorded 30 and 5 min before zolmitriptan and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 13 and 24 h afterwards. For all measurements until 4 h post-zolmitriptan subjects were on strict bed rest; subsequent measurements were after at least 10 min resting supine. Twelve-lead ECGs were recorded before and after zolmitriptan and a 2-lead ECG was recorded by Holter tape throughout each subject's days in the unit.

Drug assay and pharmacokinetic methods

Plasma was separated and the volume of each urine collection was determined and a 20 ml aliquot taken. Samples were stored at -20° C or below. Plasma and urine concentrations of zolmitriptan and metabolites were determined by h.p.l.c. [5]. The calibration range was 2–200 ng ml^{-1} for all analytes in plasma and 100–2000 ng ml^{-1} in urine. Pharmacokinetic analyses were performed using SIPHAR 4.0b (Simed, 9–11 rue G. Enesco, Crêteil, France). 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 calculated by the linear trapezoidal rule and extrapolated to infinity by the addition of C_t/λ_z, where C_t was the last measured concentration and λ_z the terminal phase elimination rate constant obtained by log-linear regression. The elimination half-life, $t_{1/2}$, was calculated as $\ln(2)/\lambda_z$. Apparent clearance, CL/F, and volume of distribution, V_z/F, were calculated as Dose/AUC and $\lambda_z CL/F$ respectively. Renal clearance (CL_R) was calculated as Ae/AUC(0, 24 h) where Ae, calculated as the product of urine volume and concentration, was the amount excreted in urine for 24 h after the zolmitriptan dose and AUC(0, 24 h) was determined as AUC$-(C_t/\lambda_z)\, e^{-\lambda z(24-t)}$. Mean residence time (MRT) for zolmitriptan was calculated using statistical moments [7]. For the metabolites, the ratio of metabolite : parent AUC, AUC_m/AUC_p, was calculated.

Statistical methods

Comparisons of pharmacokinetic parameters, except t_{max}, after zolmitriptan and propranolol compared with zolmitriptan and placebo were performed using ANOVA. All parameters, except Ae, were log-transformed prior to analysis. The geometric mean ratio and its 95% confidence interval (CI) were determined for each comparison. For t_{max}, differences between median values, and their 95% CIs, were estimated using the Wilcoxon Rank Sum test in the manner suggested for taking account of any occasion effect [8]. Baseline blood pressure was taken as the mean of the two measurements recorded 30 and 5 min before zolmitriptan. Baseline values and the peak post-zolmitriptan increases in blood pressures were compared between the propranolol and placebo occasions by ANOVA and the 95% CIs calculated for the differences between occasions.

Results

Twelve subjects entered the study initially; one withdrew due to poor tolerance of the intravenous cannula and another withdrew after a brief, entirely asymptomatic, episode of non-sustained ventricular tachycardia, 4 h after dosing, was detected on review of his Holter tape from the first occasion (zolmitriptan and propranolol). The rest of the tape was unremarkable as were his pre- and post-dose 12-lead ECGs. The background incidence of non-sustained ventricular tachycardia is 1–2% in healthy subjects [9] and the event was not considered drug-related. The comparisons of blood pressure and pharmacokinetic data are from the 12 subjects completing both occasions but adverse experiences

Table 1 Comparison of blood pressures (mmHg) before and after 10 mg zolmitriptan in the presence and absence of propranolol.

		Zolmitriptan + propranolol	*Zolmitriptan + placebo*	*Mean difference (95% CI)*
	Before propranolol/placebo	119	119	
Systolic	Before zolmitriptan	117	121	3 (−2, 9)
	After zolmitriptan peak change	13	13	0 (−4, 4)
	Before propranolol/placebo	68	68	
Diastolic	Before zolmitriptan	61	68	7 (4, 10)
	After zolmitriptan peak change	11	11	0 (−4, 4)

Table 2 Comparison of pharmacokinetic parameters of zolmitriptan and its metabolites in the presence and absence of propranolol. Parameter values are geometric means (ranges) with mean ratios (95% CIs for ratio propranolol present : absent).

	Zolmitriptan + propranolol	*Zolmitriptan + placebo*	*Ratio (95% CI)*	*183C91 + propranolol*	*183C91 + placebo*	*Ratio (95% CI)*
C_{max} (ng ml^{-1})	20.1 (12.2–47.0)	14.6 (6.3–34.8)	1.37 (1.16, 1.62)	4.8 (3.1–6.6)	6.3 (3.1–10.7)	0.76 (0.66, 0.87)
AUC (ng ml^{-1}h)	147.9 (94.3–313.2)	94.9 (52.8–170.5)	1.56 (1.37, 1.77)	38.8 (28.5–56.6)	43.8 (26.9–70.6)	0.89 (0.79, 0.99)
AUC_m/AUC_p				0.26 (0.12–0.45)	0.46 (0.21–0.80)	0.56 (0.49, 0.65)
t_{max} (h)[a]	3.0 (1.0–6.0)	3.0 (1.5–5.0)	0.25 (−1.0, 1.75)	3.5 (1.0–6.0)	3.0 (1.5–6.0)	0.0 (−1.5, 1.25)
$t_{\frac{1}{2}}$ (h)	4.0 (2.5–5.8)	3.1 (2.0–3.9)	1.32 (1.14, 1.53)	4.5 (2.6–8.7)	3.0 (2.1–4.0)	1.50 (1.28, 1.77)
V_z/F (l)	380 (170–662)	445 (313–632)	0.85 (0.70, 1.03)			
CL_R (ml min^{-1})	237 (168–317)	244 (197–354)	0.97 (0.82, 1.15)	193 (127–260)	192 (160–253)	1.01 (0.87, 1.17)
MRT (h)	7.3 (6.1–8.4)	5.9 (4.7–7.1)	1.4 (0.9, 2.0)			
Ae (% dose)[b]	22.2 (14.6–32.4)	15.6 (7.7–27.3)	6.7 (4.5, 8.9)	5.0 (3.1–6.3)	5.6 (3.9–8.2)	−0.6 (−1.5, 0.2)
	1652W92 + propranolol	*1652W92 + placebo*	*Ratio (95% CI)*	*2161W92 + propranolol*	*2161W92 + placebo*	*Ratio (95% CI)*
C_{max} (ng ml^{-1})	3.6 (2.0–8.3)	4.0 (2.6–6.2)	0.90 (0.7, 1.12)	11.1 (7.2–17.2)	12.7 (9.2–16.2)	0.87 (0.78, 0.98)
AUC (ng ml^{-1} h)				86.5 (54.7–124.8)	98.9 (76.8–128.2)	0.87 (0.76, 1.00)
AUC_m/AUC_p				0.59 (0.19–1.29)	1.04 (0.51–1.94)	0.56 (0.48, 0.67)
t_{max} (h)[a]	2.5 (1.5–5.0)	3.0 (1.5–6.0)	−0.375 (−1.75, 1.50)	4.0 (1.6–5.0)	2.75 (1.5–6.0)	1.0 (−0.475, 1.75)
$t_{\frac{1}{2}}$ (h)				4.0 (2.8–7.1)	4.5 (2.9–11.7)	0.88 (0.63, 1.25)
CL_R (ml min^{-1})				455 (276–537)	497 (335–708)	0.92 (0.78, 1.08)
Ae (% dose)[b]	5.8 (1.9–8.0)	6.8 (4.6–9.3)	−1.1 (−2.3, 0.2)	26.4 (12.3–41.8)	31.2 (22.1–40.3)	−4.8 (−9.9, 0.3)

[a]Medians and 95% CI for median difference; [b]Arithmetic means and 95% CI for mean difference.

are reported from all 14 subjects. The randomization code was not broken until the study had been completed.

Adverse events were all mild or moderate in intensity and none was serious. Eleven of the twelve subjects reported adverse events on the placebo treatment arm and ten of fourteen reported them on the propranolol arm. Most occurred after the dose of zolmitriptan with the most common events being headache, probably related to caffeine restriction, and symptoms of tightness, pressure or discomfort in the face, neck, throat or jaw, typical of this drug class.

Blood pressure and pulse both fell during propranolol dosing. After 7 days propranolol, the mean systolic blood pressure was 3 mmHg lower than after placebo (95% CI −2, 9) and diastolic pressure was 7 mmHg lower (95% CI 4, 10) (Table 1). There was a transient increase in blood pressure after zolmitriptan on both occasions with no differences between zolmitriptan and propranolol compared with zolmitriptan and placebo (Table 1). The post dose changes in heart rate were also similar on the two occasions.

In the presence of propranolol, there were 56% and 37% increases in mean zolmitriptan C_{max} and AUC respectively and 24% and 11% falls in mean 183C91 C_{max} and AUC respectively (Table 2). 2161W92 C_{max} and AUC were both 13% lower. Mean zolmitriptan half-life increased from 3.1 to 4.0 h and that of 183C91 increased from 3.0 to 4.5 h. Urinary recovery of unchanged drug increased from 15.6% to 22.2% of the administered dose, with a corresponding decrease in recovery of 2161W92 from 31.2% to 26.4%. Plasma 1652W92 concentrations were low and generally it was not possible to characterize the elimination phase (Table 2). There was no obvious effect of propranolol on 1652W92 concentrations.

Discussion

The principle effect of propranolol was to increase plasma zolmitriptan concentrations with a corresponding decrease in the concentrations of metabolites 183C91 and 2161W92. There was an increase in urinary recovery of unchanged zolmitriptan with a fall in recovery of 2161W92. The half-lives of zolmitriptan and 183C91 were longer in the presence of propranolol. There was no obvious effect on concentrations of 1652W92 but the data were limited. The pattern of concentration changes suggests that propranolol reduces metabolism of zolmitriptan to 183C91 and 2161W92. The effects of propranolol on the concentrations of zolmitriptan and 183C91 were small in comparison with the between-subject variability in their concentrations.

After oral dosing, zolmitriptan undergoes first-pass metabolism [4]; a reduction in its metabolism would increase concentrations by increasing oral bioavailability and by reducing systemic clearance. Reduced first-pass metabolism of zolmitriptan when dosed with propranolol would explain the increase in urinary zolmitriptan and reduced systemic clearance could also explain the small increase in half-life. The extraction ratio and intrinsic clearance of zolmitriptan are not known. However, pharmacokinetic theory predicts that changes in hepatic blood flow do not affect AUC of low extraction drugs. For high extraction drugs, after oral dosing, a decrease in hepatic blood flow simultaneously reduces oral bioavailability and decreases oral clearance with no net change in AUC [ref 7, page 191]. Thus, although propranolol reduces hepatic blood flow in healthy subjects [10] this cannot explain its effects on zolmitriptan pharmacokinetics.

Propranolol inhibits CYP2D6 [11] CYP3A4 [12] and CYP1A2 [13]. In addition, it is a substrate for CYP2D6, CYP1A2 and probably also CYP2C19 [14] suggesting the additional possibility of competitive effects for this isozyme. It is not clear which of these actions are responsible for the effects seen in this study. The formation of 183C91, an *N*-desmethyl metabolite is probably mediated by cytochrome P450. However, similarly to sumatriptan [15] the indole-acetic acid, 2161W92, is most likely formed by the action of monoamine oxidase (MAO). Although a substrate for MAO [16], there is no evidence that propranolol is an MAO inhibitor thus the parallel change in 183C91 and 2161W92 concentrations in this study suggests that 2161W92 may be formed by further metabolism of 183C91.

Since the higher zolmitriptan concentrations in the presence of propranolol were not associated with a greater rise in blood pressure, it is likely the potential affects of the increase in zolmitriptan concentrations were offset by the reduction in concentrations of 183C91 which is also a $5HT_{1B/1D}$ receptor agonist or by the blood pressure lowering effects of propranolol itself.

In conclusion, propranolol was associated with a reduction in the extent of conversion of zolmitriptan to the active metabolite 183C91. However, there were no changes in the pharmacological effects on blood pressure and it is unlikely that the pharmacokinetic changes will lead to clinically important changes in therapeutic effect. Consequently dosage adjustment of zolmitriptan is not required in patients taking propranolol for migraine prophylaxis.

We acknowledge the skilful bioanalytical assistance of John Allanson.

References

1 Martin GR. Pre-clinical profile of the novel $5HT_{1D}$ receptor agonist 311C90. *New Advances Headache Res* 1994; **4**: 3–4.
2 Ferrari MD. The clinical effectiveness of 311C90 in the acute treatment of migraine. *Eur Neurology* 1996; **36** (Suppl 2): 4–7.
3 Seaber E, On N, Phillips S, Churchus R, Posner J, Rolan P. The tolerability and pharmacokinetics of the novel antimigraine compound 311C90 in healthy male volunteers. *Br J Clin Pharmacol* 1996; **41**: 141–147.
4 Seaber E, On N, Dixon RM, *et al.* The absolute bioavailability and metabolic disposition of the novel antimigraine compound zolmitriptan (311C90). *Br J Clin Pharmacol* 1997; **43**: 579–587.
5 Dixon R, Gillotin C, Gibbens M, Posner J, Peck RW. The pharmacokinetics and effects on blood pressure of multiple doses of the novel anti-migraine drug zolmitriptan (311C90) in healthy volunteers. *Br J Clin Pharmacol* 1997; **43**: 273–281.
6 Welch KMA. Drug therapy of migraine. *New Engl J Med* 1993; **329**: 1476–1483.
7 Rowland M, Tozer TN. *Clinical Pharmacokinetics: Concepts and Applications* (3rd edition). Baltimore: Lea & Febiger, 1995.
8 Koch GG. The use of non-parametric methods in the statistical analysis of the two period crossover design. *Biometrics* 1972; **82**: 577–584.
9 Stinson JC, Pears JS, Williams AJ, Campbell RW. Use of

24 h ambulatory ECG recordings in the assessment of new chemical entities in healthy volunteers. *Br J Clin Pharmacol* 1995; **39**: 651–656.

10 Soons PA, DeBoer A, Cohen AF, Breimer D. The assessment of hepatic blood flow in healthy subjects by continuous infusion of indocyanine green. *Br J Clin Pharmacol* 1991; **32**: 697–704.

11 Rowland K, Yeo WW, Ellis SW, *et al*. Inhibition of CYP2D6 activity by treatment with propranolol and the role of 4-hydroxypropranolol. *Br J Clin Pharmacol* 1994; **38**: 9–14.

12 Bax NDS, Tucker GT, Lennard MS, Woods HF. The impairment of lignocaine clearance by propranolol—major contribution from enzyme inhibition. *Br J Clin Pharmacol* 1985; **19**: 597–603.

13 Conrad KA, Nyman DW. Effects of metoprolol and propranolol on theophylline elimination. *Clin Pharmacol Ther* 1980; **28**: 463–467.

14 Walle T, Walle K, Cowart D, Conradi E. Pathway-selective sex differences in the metabolic clearance of propranolol in human subjects. *Clin Pharmacol Ther* 1989; **46**: 257–263.

15 Dixon CM, Park GR, Tarbit MH. Characterisation of the enzyme responsible for the metabolism of sumatriptan in human liver. *Biochem Pharmacol* 1994; **47**: 1253–1257.

16 Walle T, Walle UK, Olanoff LS. Quantitative account of propranolol metabolism in urine of normal man. *Drug Metab Dispos* 1985; **13**: 204–209.

(*Received 20 February 1997, accepted 30 July 1997*)