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 Cmax and AUC by 56% and 37% respectively; mean t1/2 was prolonged from 3.1 to 4.0 h. Mean Cmax and AUC of the pharmacologically active N-desmethyl metabolite were reduced by 24% and 11% respectively and the metabolite:parent AUC ratio (AUCm/AUCp) fell from 0.46 to 0.26. Mean Cmax and AUC for the inactive indole acetic acid metabolite were both reduced by 13% and AUCm/AUCp 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-[2-[(dimethylamino)ethyl]-1H-indol-5-yl]methyl]–2-oxazolidinone), is a selective 5HT1B/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 5HT1B/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 vivo 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 Committee: Dr Richard Peck, Glaxo Wellcome R&D Ltd, Greenford Road, Greenford, Middlesex UB6 0HE. Current addresses: *Zeneca Pharmaceuticals, 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.

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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 at 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 SIPSAR 4.0b (Simed, 9–11 rue G Enesco, Créteil, France). The observed peak plasma concentration, Cmax, the time to reach the peak concentration, tmax, 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 Ct/λz, where Ct was the last measured concentration and λz the terminal phase elimination rate constant obtained by log-linear regression. The elimination half-life, t1/2, was calculated as ln(2)/λz. Apparent clearance, CL/F, and volume of distribution, Vz/F, were calculated as Dose/AUC and VzCL/F respectively. Renal clearance (CLR) 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–(Ct/λz)e−λz(24−t). Mean residence time (MRT) for zolmitriptan was calculated using statistical moments [7]. For the metabolites, the ratio of metabolite/parent AUC, AUCm/AUCp, was calculated.

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>
<thead>
<tr>
<th>Table 1 Comparison of blood pressures (mmHg) before and after 10 mg zolmitriptan in the presence and absence of propranolol.</th>
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</thead>
<tbody>
<tr>
<td><strong>Zolmitriptan + propranolol</strong></td>
</tr>
<tr>
<td>--------------------------------------------------------</td>
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<tr>
<td><strong>Systolic</strong></td>
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</table>

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).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Zolmitriptan + propranolol</th>
<th>Zolmitriptan + placebo</th>
<th>Ratio (95% CI)</th>
<th>1H3C9Y + propranolol</th>
<th>1H3C9Y + placebo</th>
<th>Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C$_{\text{max}}$ (ng ml$^{-1}$)</td>
<td>20.1 (12.2–47.0)</td>
<td>14.6 (6.3–54.8)</td>
<td>1.37 (1.16, 1.62)</td>
<td>4.8 (3.1–6.6)</td>
<td>6.3 (3.1–10.7)</td>
<td>0.76 (0.66, 0.87)</td>
</tr>
<tr>
<td>AUC (ng ml$^{-1}$ h)</td>
<td>147.9 (94.3–313.2)</td>
<td>94.9 (52.6–370.5)</td>
<td>1.56 (1.37, 1.77)</td>
<td>38.8 (28.5–56.6)</td>
<td>43.8 (26.9–70.6)</td>
<td>0.89 (0.79, 0.99)</td>
</tr>
<tr>
<td>AUC$<em>{\text{m}}$/AUC$</em>{\text{p}}$</td>
<td>3.0 (1.5–5.0)</td>
<td>3.0 (1.5–5.0)</td>
<td>0.25 (1.0, 1.75)</td>
<td>3.5 (1.5–6.0)</td>
<td>3.0 (1.5–6.0)</td>
<td>0.0 (1.5, 1.25)</td>
</tr>
<tr>
<td>t$_{\text{max}}$ (h)$^a$</td>
<td>4.0 (2.5–5.9)</td>
<td>5.1 (2.5–5.9)</td>
<td>1.32 (1.14, 1.53)</td>
<td>4.5 (2.6–8.7)</td>
<td>3.0 (2.1–4.0)</td>
<td>1.50 (1.28, 1.77)</td>
</tr>
<tr>
<td>Vz/F (l)</td>
<td>380 (270–662)</td>
<td>448 (313–632)</td>
<td>0.88 (0.70, 1.00)</td>
<td>193 (127–260)</td>
<td>192 (160–253)</td>
<td>1.01 (0.87, 1.17)</td>
</tr>
<tr>
<td>Cl$_{\text{in}}$ (ml min$^{-1}$)</td>
<td>257 (168–317)</td>
<td>244 (197–384)</td>
<td>0.97 (0.82, 1.15)</td>
<td>193 (127–260)</td>
<td>192 (160–253)</td>
<td>1.01 (0.87, 1.17)</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>7.5 (6.1–8.4)</td>
<td>5.9 (4.7–7.1)</td>
<td>1.4 (0.9, 2.0)</td>
<td>6.7 (4.5, 9.9)</td>
<td>5.0 (3.1–6.3)</td>
<td>5.6 (3.9–8.2)</td>
</tr>
<tr>
<td>Ae (% dose)$^b$</td>
<td>22.2 (14.6–32.4)</td>
<td>15.6 (10.7–27.3)</td>
<td>1.32 (0.9, 1.75)</td>
<td>4.0 (2.8–7.1)</td>
<td>4.5 (2.9–11.7)</td>
<td>0.88 (0.63, 1.25)</td>
</tr>
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</table>

$^a$Medians and 95% CI for median difference; $^b$Arithmetic means and 95% CI for mean difference.
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.

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References
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