311C90 (Zolmitriptan), a novel centrally and peripheral acting oral 5-hydroxytryptamine-1D agonist: a comparison of its absorption during a migraine attack and in a migraine-free period

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The oral absorption of a 10-m. oral dose of the novel 5-hydroxytryptamine (5HT\textsubscript{1D}) agonist, 311C90, was compared during a moderate or severe migraine headache and in a migraine-free period in an open, two-period study. The safety and efficacy of 311C90 in acute migraine were also assessed. Twenty patients attended the clinics during a moderate or severe migraine attack and 18 patients returned for a second dose in a migraine-free period 311C90 was less rapidly absorbed during a migraine attack compared to the migraine-free period, consistent with gastric stasis during a migraine attack. The median area under the curve (AUC) was 15.7 ng/ml at lower during a migraine (median AUC: 18.4ng/ml h, range: 0–60.8 ng/ml h) compared to the migraine-free period (median AUC: 33.4 ng/ml h, range 9.4–79.5 ng/ml h) (95% confidence interval: 6.9,25.3) and the time to reach maximum plasma concentration was delayed (n = 18). Eleven out of 20 patients experienced a significant improvement in migraine headache intensity at 2 h post-dose. Plasma 311C90 concentrations were generally higher in those patients who responded to treatment with 311C90 in the plasma, but there was one patient with no quantifiable 311C90 in the plasma whose headache improved. Minor adverse experiences were reported in 11 out of 20 patients during a migraine attack and in 11 out of 18 patients outside an attack. They occurred shortly following drug administration and were of short duration, but their occurrence did not appear to be related to plasma 311C90 concentration. There were no clinically significant changes in blood pressure or 12-lead ECG during the assessment period. 311C90 efficacy, migraine, oral absorption, safety

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311C90 is a novel, selective 5-hydroxytryptamine-1D (5HT\textsubscript{1D}) agonist in development for the acute oral treatment of migraine headache. It has high affinity.
for 5HT_1D and 5HT_1D subtypes, modest affinity for 5HT_1A receptors but lacks significant affinity for other 5HT and monoamine receptors (1). In isolated human and animal vasculature, it acts via 5HT_1D-like receptors to produce vasoconstriction and interacts with the trigeminovascular system to inhibit neurogenic inflammation provoked by trigeminal stimulation. In these properties, 311C90 displays two to three times greater potency than sumatriptan. However, the additional ability to modulate the central components of the trigeminovascular system (2) differentiates it from other currently used, selective 5HT_1D agonists. In healthy subjects three principal metabolites have been detected in plasma: the N-desmethyl metabolite, the N-oxide and indole acetic acid metabolites. Of these the N-desmethyl metabolite has agonist activity at 5HT_1D receptors and therefore is an active metabolite (3).

In clinical trials, 311C90 has shown efficacy rates of 66-77% with doses of 5–20 mg (n = 1181) in the acute treatment of migraine headache (4). This compares favorably with efficacy rates obtained with a 100-mg oral dose of the 5HT_1D agonist, sumatriptan, which range between 50% and 67% (5, 6).

In healthy subjects, 311C90 was rapidly absorbed following oral administration with the maximum plasma concentrations (C_{max}) occurring at 2–4 h post-dose but with significant plasma concentrations being achieved within 20 min (3). However, migraine may be associated with delayed gastric emptying, which may lead to impairment and delay in drug absorption (7). In the case of sumatriptan, there was a small reduction in the extent of absorption over the first 4 h after a 25-mg oral dose and a delay in absorption reflected in a longer time to reach maximum plasma concentrations (8).

This study was conducted to compare the absorption of 311C90 during a migraine attack and in a migraine-free period to examine the tolerability and efficacy of 311C90 in the acute treatment of migraine and to investigate the relationships between plasma 311C90 concentrations, efficacy and adverse experiences.

**Methods**

**Patients**

Female and male migraine patients aged 18–55 years were recruited from the outpatient population of the Departments of Neurology, Gentofo and Glostrup Hospitals, Copenhagen, Denmark. Patients were eligible if they suffered one to six episodes per month of migraine with or without aura as defined by the International Headache Society (1988) (9). They were excluded if they were taking any regular medication (excluding oral contraceptives and hormone replacement therapy), if they had a history of hypertension, coronary artery, or peripheral vascular disease, hypercholesterolemia (> 6.5 mmol/l), renal, hepatic, or psychiatric disorder, or a family history of premature coronary artery disease. Women who were pregnant, breastfeeding or not using adequate contraception were excluded, as were patients who had participated in more than two therapeutic trials of antimigraine treatment or who had migraine which consistently failed to respond to treatment. On the study days, patients were excluded if they had experienced a previous migraine attack in
the last 48 h or had taken ergot-containing drugs within 48 h, sumatriptan or
narcotic analgesics within 24 h or non-steroidal analgesics within the last 6h.
Patients were not treated during a migraine aura.

Study design and treatments

This was an open, two-period study in which patients received a 10-mg oral dose
of 311C90 for treatment of a migraine headache and on a second occasion received
the same dose in the migraine-free period. 311C90 tablets (each 5 mg) were
supplied by The Wellcome Foundation Ltd, Dartford, UK. Following approval of the
study from the Ethics Committee of the Copenhagen County and the Danish Health
Board, patients attended the clinic for a screening procedure which included
medical history and examinations, hematology and clinical chemistry profiles,
12-lead ECG, urinalysis and, for women of childbearing potential, a urinary
pregnancy test. Provided there was no clinically significant abnormality, patients
were asked to return to the clinic with their next migraine headache of moderate or
severe intensity. On arrival at the clinic, female patients were questioned as to the
chance of pregnancy and a urinary pregnancy test was performed where possible.
The pretreatment duration of headache was recorded and in order to assess the
effect of food on 311C90 absorption, the time the patient last ate was recorded.
Following baseline measurements, patients were treated with a single 10-mg dose
(two 5-mg tablets) of oral 311C90. Headache severity and accompanying symptoms,
blood pressure and heart rate were assessed predose (time 0) and at 15, 30, 45,
60, 90, 120, 180 and 240 min post-dose. Twelve-lead ECGs were recorded predose
and at 30, 60 and 240 min post-dose. Patients still experiencing headache at 2 h
were offered escape medication (not sumatriptan or ergotamine). Patients remained
at the clinic for at least 4 h post-dose and were contacted by the investigator at 24 h
post-dose for a follow-up telephone conversation to record adverse experiences and
any headache recurrence occurring after they had left the clinic.

On a second occasion, patients returned to the clinic after having been
migraine-free for at least 48 h and again received a single 10-mg dose of 311C90.
Study procedures were identical to the previous occasion, with the omission of
migraine assessments.

Plasma concentrations and pharmacokinetics

Venous blood samples were taken via an indwelling cannula at the following
times; predose, 15, 30, 45, 60, 90, 120 and 240 min post-dose. The plasma was
separated by centrifugation and frozen until assay. Concentrations of 311C90 and
its three principal metabolites—the N-desmethyl, N-oxide and indole acetic acid
metabolites—were determined by solid phase extraction followed by reverse phase
high pressure liquid chromatography with fluorescence detection. The lower limit of
quantification was 2 ng/ml for each analyte.

From individual plasma concentration-time profiles, the maximum plasma
concentration (C_{max}) and the time associated with it (t_{max}) were observed. The area
under the curve (AUC) was estimated over 0–4 h (AUC_{0–4}) and 0–2 h (AUC_{0–2}) using
the trapezoida method. Median differences between the first (migraine) and second
(migraine-free) dosing occasions were estimated for pharmacokinetic parameters for
each analyte and 95% confidence intervals were calculated using a method based on the Wilcoxon signed rank test. The maximum plasma concentration of 311C90 and its active N-desmethyl metabolite over the first 2 h \( (C_{\text{max}0-2}) \) and AUC\(_{0-2} \) were summarized for patients who were classified as responders and non-responders at 2 h. Scatter plots were constructed to examine the relationship between 311C90 AUC\(_{0-4} \) and the occurrence of the most common adverse experiences.

Evaluation of efficacy, safety and tolerability

The principal measure of efficacy was headache relief. Headache severity was assessed using a four-point verbal scale (0 = no headache, 1 = mild headache, 2 = moderate headache, 3 = severe headache). Headache response was defined as an improvement from moderate or severe headache to mild or no headache at 2 h. The presence or absence of accompanying symptoms (nausea, vomiting, photophobia and phonophobia) was also recorded. Recurrence of headache was defined as a moderate or severe headache which returned within 24 h of an initial response at 2 h.

Pulse, blood pressure and 12-lead ECGs were recorded at baseline and at intervals up to 4 h post-dose. Hematology and clinical chemistry profiles were performed at predose and at 4 h post-dose. Adverse experiences, defined as any undesirable medical events whether or not related to the study drug, were recorded in response to a standard question at intervals for 4 h post-dose and at a follow-up telephone conversation at 24 h.

Results

Patients

Twenty patients (16F, 4M) attended the clinics during a moderate or severe migraine attack and all were treated with a 10-mg dose of 311C90. Eighteen patients returned for a second dose in a migraine-free period, two being unable to return for personal reasons. The patients had a mean age of 38 years (range 22–50 years). Body weights ranged from 50 to 102 kg with a mean of 69 kg. One patient had a brief aura prior to the onset of the headache. At baseline, 14 patients had severe headache and I had moderate headache, 18 had nausea, 15 phonophobia and 18 photophobia. The median pretreatment curation of headache was 5 h (range 2–29 h).

Plasma concentrations and pharmacokinetics

Plasma 311C90 concentrations (Fig. 1) showed considerable between-subject variability on both dosing occasions. \( C_{\text{max}} \) and AUC\(_{0-4} \) values ranged from 0 to 27.9 ng/ml and 0 to 60.8 ng/ml.h, respectively during a migraine attack and from 3.5 to 26.3 ng/ml
and 9.4 to 79.5 ng/ml.h, respectively in the migraine-free period. All three metabolites were detected in the plasma. Plasma concentrations of the active, N-desmethyl metabolite and of the inactive, N-oxide metabolite were approximately one-half to one-third of those of the parent compound whilst concentrations of the inactive, indole acetic acid metabolite were similar to those of the parent (Table 1). Most patients (14 out of 18) had higher concentrations of 311C90 and metabolites on the second, migraine-free occasion, thus median 311C90 $C_{\text{max0-4}}$ and AUC$_{0-4}$ values were higher on this occasion than on the first, migraine occasion (Table 1). The median difference between dosing occasions in $C_{\text{max0-4}}$ was 5.4 ng/ml and the median difference in AUC$_{0-4}$ was 15.7ng/ml.h ($n = 18$). On the first occasion, 11 out of 20 patients had a $C_{\text{max0-4}}$ value at 4 h or later, whilst on the second occasion the median $t_{\text{max}}$ value was 2.5 h and 7 out of 18 patients had a $C_{\text{max}}$ value at 4 h or later. There was no apparent relationship between drug absorption and time from drug administration to last meal (median time from last meal: 4 h, range: 1.7–19.8 h occasion 1). Three patients who vomited within 2 h of drug ingestion had very low or unquantifiable 311C90 concentrations at 120 min post-dose. Plasma 311C90 concentrations and plasma concentrations of the active N-desmethyl metabolite were generally higher in those patients who responded to treatment with 311C90 (Table 2), but there was one patient with no quantifiable 311C90 in the plasma whose headache improved. Three out of 4 patients with detectable plasma concentrations of 311C90 at 30 min were responders and 9 out of 11 patients with detectable concentrations at 60 min were responders whilst 7 out of 9 with non-quantifiable concentrations at 60 min were non-responders.
Efficacy

Eleven patients experienced a headache response (improvement from moderate or severe to mild or no headache) at 2 h. Nausea, photophobia and phonophobia had resolved in 13, 8 and 5 patients, respectively by 2 h. Eight patients required escape medication. Four patients reported recurrence of moderate or severe headache following an initial reduction of headache severity from moderate or severe to mild or none at 2 h. The median time to recurrence was 20.5 h (range 17.75–21.75 h). There was no apparent relationship between pretreatment duration of headache and response.

Safety and tolerability

Eleven out of 20 patients reported one or more adverse experience on the first dosing occasion during a migraine attack and 11 out of 18 patients

Table 1. Estimated differences in median AUC\textsubscript{0–4} and C\textsubscript{max 0–4} values for 311C90 and its major metabolites during a migraine (first dosing occasion) and in the migraine-free period (second occasion) (n = 18).

<table>
<thead>
<tr>
<th>Compound</th>
<th>Parameter</th>
<th>Migraine (1)</th>
<th>Migraine-free (2)</th>
<th>Median difference (2-1)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>311C90</td>
<td>AUC\textsubscript{0–4} (ng/ml h)</td>
<td>18.4</td>
<td>33.4</td>
<td>15.7</td>
<td>6.9, 25.3</td>
</tr>
<tr>
<td></td>
<td>C\textsubscript{max 0–4} (ng/ml)</td>
<td>7.9</td>
<td>12.6</td>
<td>5.4</td>
<td>2.0, 7.4</td>
</tr>
<tr>
<td>N-desmethyl metabolite</td>
<td>AUC\textsubscript{0–4} (ng/ml h)</td>
<td>7.6</td>
<td>12.2</td>
<td>4.6</td>
<td>1.7, 7.6</td>
</tr>
<tr>
<td></td>
<td>C\textsubscript{max 0–4} (ng/ml)</td>
<td>3.4</td>
<td>4.8</td>
<td>1.7</td>
<td>0.4, 3.0</td>
</tr>
<tr>
<td>N-oxide metabolite</td>
<td>AUC\textsubscript{0–4} (ng/ml h)</td>
<td>5.9</td>
<td>8.6</td>
<td>4.2</td>
<td>1.8, 7.2</td>
</tr>
<tr>
<td></td>
<td>C\textsubscript{max 0–4} (ng/ml)</td>
<td>2.7</td>
<td>4.0</td>
<td>1.6</td>
<td>0.4, 2.6</td>
</tr>
<tr>
<td>Indole acetic acid</td>
<td>AUC\textsubscript{0–4} (ng/ml h)</td>
<td>12.9</td>
<td>27.7</td>
<td>15.5</td>
<td>7.1, 24.1</td>
</tr>
<tr>
<td>metabolite</td>
<td>C\textsubscript{max 0–4} (ng/ml)</td>
<td>7.7</td>
<td>12.2</td>
<td>4.6</td>
<td>1.5, 7.6</td>
</tr>
</tbody>
</table>
Table 2. Summary of AUC0-2 and Cmax0-2 values for 311C90 and its active N-desmethyl metabolite in patients who were classified as responders (n = 11) and non-responders (n = 9) at 2 h.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Statistic</th>
<th>Cmax0-2 (ng/ml)</th>
<th>AUC0-2 (ng/ml h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Responders</td>
<td>Non-responders</td>
</tr>
<tr>
<td>311C90</td>
<td>maximum</td>
<td>14.4</td>
<td>5.9</td>
</tr>
<tr>
<td></td>
<td>median</td>
<td>7.5</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>minimum</td>
<td>NQ</td>
<td>NQ</td>
</tr>
<tr>
<td>N-desmethyl</td>
<td>maximum</td>
<td>5.8</td>
<td>3.2</td>
</tr>
<tr>
<td>metabolite</td>
<td>median</td>
<td>2.4</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>minimum</td>
<td>NQ</td>
<td>NQ</td>
</tr>
</tbody>
</table>

NQ, not quantifiable.

reported one or more adverse experience on the second, migraine-free occasion (Table 3). The most commonly reported adverse experiences were somnolence, parasthesia, sensations of pain, tightness, pressure or heaviness in the limbs, throat or neck and dry mouth. With the exception of one report of severe nausea, adverse experiences were of mild or moderate intensity. They occurred shortly following drug administration and were of short duration but their occurrence did not appear to be related to plasma 311C90 concentration (Fig. 2). There was no trend for mean blood pressure or heart rate to change post-dose and no clinically significant individual change. There were no clinically significant ECG abnormalities following administration of 311C90.

Discussion

Plasma concentrations of 311C90 were lower in the first 4h post-dose and absorption was delayed during a migraine attack compared with during the

Table 3. Summary of adverse experiences (AE) reported, regardless of attributability to 311C90, during a migraine attack or in a migraine-free period.

<table>
<thead>
<tr>
<th>Adverse experience</th>
<th>During migraine (n = 20)</th>
<th>Migraine - free (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Parasthesia</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>pain/pressure in head, neck or throat</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Dry mouth/thirst</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Heaviness in limbs</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Other*</td>
<td>5</td>
<td>7</td>
</tr>
</tbody>
</table>

*Other, AEs reported by two or fewer subjects, including nausea, headache, pain in knees, anorexia, chills, asthenia.
migraine-free period, consistent with delayed gastric emptying. The duration from last eating to closing was similar on both treatment occasions and it is unlikely that food would account for the difference observed. Plasma concentrations of the three major metabolites were also lower during a migraine attack and concentrations of the metabolites relative to parent compound were consistent with those reported in healthy subjects (3), suggesting that it is impaired absorption and not a change in metabolism that accounts for the lower 311C90 concentrations observed. Three patients vomited within 2 h of drug administration but excluding these patients from the calculation of median values and the median difference between occasions did not substantially affect the results. Thus Table 1 includes those who vomited. There was substantial interindividual variation in plasma 311C90 concentrations with C_{max0-4} varying from 0 to 27.9 ng/ml and AUC_{0-4} from 0 to 60.8 ng/ml h during a migraine attack. There appeared to be a relationship between plasma 311C90 concentration and response. Responders had higher median concentration than non-responders, although low or non-quantifiable levels did not always preclude efficacy or the occurrence of adverse experiences. Patients who vomited within 2 h of dosing had very low plasma concentrations and two out of three failed to respond. Speed of absorption may also be a factor governing likelihood of response. Since this study had a small number of patients and was of open design, it is not possible to demonstrate efficacy conclusively. However, despite delayed absorption during migraine attack, 11 out of 20 patients experienced significant headache relief, along with improvement in accompanying symptoms of nausea, photophobia and phonophobia. In addition, previous double-blind placebo-controlled studies with larger sample sizes have shown high efficacy rates of oral 311C90 in the acute treatment of migraine (4, 10). However, the delayed absorption of orally administered 311C90 during a migraine attack (C_{max} at 4 h or later in 11 out of 20 patients treated during an attack) in combination with generally higher and more rapidly detectable plasma 311C90 concentrations in those patients who responded
to treatment within 2 h, suggests that parenteral drug formulation may improve efficacy. In the present study, the duration of headache prior to dosing was highly variable, but there did not appear to be a relationship between pretreatment headache duration and chance of response, suggesting that 311C90 may be an effective treatment at any time after the start of migraine headache. 311C90 was generally well tolerated. The nature and frequency of adverse experiences were similar on both dosing occasions and were consistent with those already reported (4). There was no apparent relationship between plasma 311C90 concentration and the occurrence of the most frequent adverse experiences. There were no clinically important changes in blood pressure and no changes in 12-lead ECGs recorded during the time of peak plasma concentrations of 311C90 and its active metabolite. ECGs taken at the time of adverse experiences, such as tightness, pain or pressure in the upper body, were unchanged, suggesting that these symptoms are not of cardiac origin.

In conclusion, an oral 10-mg dose of 311C90 was less rapidly absorbed during a migraine attack compared to the migraine-free period, consistent with temporary gastric stasis during a migraine attack. However, 11 out of 20 patients experienced significant headache relief when treated during a migraine attack. 311C90 was generally well tolerated and was without significant effects on blood pressure or ECG.

References
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(abstract). Cephalalgia 1991;11 Suppl 11:222


Endnotes

1 (Popup)
  British approved name.