A CONTROLLED PHARMACOKINETIC EVALUATION OF TIZANIDINE AND BACLOFEN AT STEADY STATE

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ABSTRACT:
Clinical trials with tizanidine when administered alone have shown that 5-chloro-4-(2-imidazolin-2-ylamino)-2,1,3-benzothiadiazole (tizanidine) is safe and effective for spasticity control. However, given its mechanism of action and requirement for titration, clinical experience suggests that tizanidine is likely to be used in combination with other antispastic agents with different mechanisms of action, such as baclofen. The objective of this study was to examine the pharmacokinetics of both tizanidine and baclofen under steady-state conditions when administered alone or concomitantly. This was a randomized, three-period, multiple-dose, Latin Square design study consisting of tizanidine HCl, 4 mg t.i.d. for seven consecutive doses; baclofen, 10 mg t.i.d. for seven consecutive doses; and both regimens simultaneously for seven consecutive doses.

Drug administration was performed every 8 h, three times daily. Fifteen normal men served as study subjects. A priori, a clinically significant difference was set as 30%. Concentrations of tizanidine and baclofen were nearly identical during the single and concomitant dosing periods. All of the calculated steady-state pharmacokinetic parameter changes for baclofen, tizanidine, and its major metabolites were within the 30% criterion. Small differences in renal clearance were observed when the two drugs were coadministered, but these changes are unlikely to be clinically important. Thus, it is unlikely that coadministration of tizanidine and baclofen during dose-titration of the former will result in a pharmacokinetic interaction.

5-Chloro-4-(2-imidazolin-2-ylamino)-2,1,3-benzothiazdiazole (tizanidine) is an alpha-2 adrenergic agonist that diminishes spasticity by depressing polysynaptic reflexes and by increasing presynaptic inhibitory actions of spinal interneurons. Its adrenoceptor agonism has been shown to directly impair excitatory amino acid release from spinal interneurons and to inhibit facilitatory coeruleospinal pathways (Collingridge and Davies, 1982; Davies, 1982).

In two double-blind, placebo-controlled studies, tizanidine provided statistically and clinically significant reduction in muscle tone in patients with spasticity of spinal cord origin (Nance et al., 1994; United Kingdom Tizanidane Trial Group, 1994). In active-controlled studies, tizanidine was found effective, and of at least similar anti-spastic efficacy to diazepam and baclofen. Tizanidine was also rated as better tolerated than these active controls as judged by investigators (Lataste et al., 1994; Wallace, 1994).

In both patients and healthy volunteers, tizanidine is rapidly absorbed after oral administration. The absolute oral bioavailability is ~20 to 34%, reflecting a large, first-pass hepatic metabolism. Tizanidine exhibits linear pharmacokinetic behavior with an elimination half-life of ~2 to 4 h. Steady-state conditions of tizanidine are typically achieved within 24 to 48 h after institution of therapy. There is no apparent change in pharmacokinetic parameters with repeated administration (Tse et al., 1987). Tizanidine is extensively metabolized, with the two major metabolites of tizanidine having been identified as DS-200-717 (metabolite 3, guanidine, [(5-chloro-4-(2-imidazolin-4-ylamino)-2,1,3-benzothiazdiazole] and DS-201-341 (metabolite 4, amide, [5-chloro-4-(guanidino)-2,1,3-benzothiazdiazole]). Based on total recovery analysis, renal excretion is apparently the major excretory route for tizanidine and its metabolites accounting for ~65% of the administered i.v. dose. These metabolites have very little pharmacological activity (Heazlewood et al., 1983; Koch et al., 1989; Wagstaff and Bryson, 1997).

Baclofen, like tizanidine, is also used in the management of patients with spastic disorders. Baclofen decreases the frequency and amplitude of muscle spasms (tonic reflexes) that arise in response to muscle stretching in patients with various spinal cord lesions. The drug simultaneously and equally suppresses cutaneous reflexes and muscle tone but only slightly depresses the amplitude of tendon jerks (phasic reflexes). Baclofen appears to act primarily at the spinal cord level by inhibiting spinal polysynaptic afferent pathways but may also inhibit...
monosynaptic afferent pathways (Sayers et al., 1980; Novack et al., 1983; Chen et al., 1987; Standaert and Young, 1996).

Baclofen is rapidly absorbed after oral administration. It is largely excreted unchanged by the kidney, and has a mean elimination half-life of 3–4 h. Renal clearance of baclofen (121 ± 39 ml/min) is similar to creatinine clearance suggesting that glomerular filtration is apparently the dominant renal excretory mechanism. About 15% of a dose of baclofen is metabolized in the liver, mostly by deamination (Wuis et al., 1989; Cederbaum and Schleifer, 1990).

Clinical trials with tizanidine have shown the efficacy and safety profile when administered alone. However, clinical experience suggests that, given its mechanism of action and requirement for titration, tizanidine is likely to be used in combination with other antispastic agents with different mechanisms of action, such as baclofen. Because renal excretion is the predominant excretory route for both agents, concomitant use of both agents may alter the renal excretion or other pharmacokinetic parameters of one or both agents. This study was conducted to determine whether pharmacokinetic changes occur for either tizanidine or baclofen when the agents are administered concomitantly.

Patients and Methods

This was a randomized, three-period, multiple-dose, Latin Square design study consisting of: (a) tizanidine HCl (Zanaflex; Athena Neurosciences, Inc., South San Francisco, CA), 4 mg t.i.d.; seven consecutive doses; (b) baclofen (Lioresal; Geigy Pharmaceuticals, Ardsley, NY), 10 mg t.i.d.; and (c) both regimens simultaneously for seven consecutive doses. Dosing was performed every 8 h, three times daily. These doses were selected to be in the therapeutic range (Standaert and Young, 1996; Wagstaff and Bryson, 1997). Thus, subjects received a total of 14 doses each of tizanidine and baclofen. The subjects fasted for 10 h before the first dose, and for 2 h before each subsequent dose. Subjects fasted for 2 h after each dose. Drug administration was performed under the supervision of clinic personnel.

In order to assure that at least 12 subjects completed the study, 15 were enrolled. Subjects were healthy, nonsmoking men, 19 to 30 years of age. Subjects’ weight was within ± 15% for height and body frame (1983 Metropolitan Height and Weight Table). Excluded from the study were individuals with a recent history of drug or alcohol addiction or abuse; clinically significant medical disorder, especially those that might impair drug disposition; a positive hepatitis B surface antigen screen or a reactive human immunodeficiency virus type I antibody screen; or a history of frequent nausea or emesis regardless of etiology. Also excluded were those individuals with history of allergic response(s) to tizanidine or baclofen; who had used any drug known to induce or inhibit hepatic drug metabolism or investigational drug use within 60 days of study entry; who had used a prescription medication within 14 days before entry or an over-the-counter medication within 7 days before entry (except acetaminophen). This study was approved by an Institutional Review Board, and all subjects provided written informed consent.

Up to 14 days before the first dosing period, subjects underwent a screening examination that consisted of a physical examination with electrocardiogram, hematology, clinical chemistry, and a urinalysis for both clinical evaluation and for drugs of abuse.

Subjects reported to the study site by 2000 h on the evening before dosing of period 1, and were confined to the study unit until the last collection of each period. Period 2 h after the end of dosing. At the check-in for each treatment period subjects provided a urine sample for a drug screen. There was a minimum interperiod washout of 4 days.

During each study period, subjects were continuously monitored by the clinical study staff throughout the confinement portion of the study. This included measurement of sitting blood pressure and radial heart rate within 1 h before each dose and 1–2 h after the morning and afternoon dose. Subjects were instructed to abstain from consuming caffeine and/or xanthine-containing products, alcohol, or grapefruit juice for at least 48 h before days on which dosing was scheduled and during the periods when blood samples were being collected.

Blood specimens were obtained in each period immediately before doses 1, 4, 5, 6, and 7 and after dose 7 at 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, and 24 h. Urine specimens were obtained in each period within 1 h before dose 1 and after dose 7 over the study hours of 0 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 16, and 16 to 24. After recording the volume of the urine voided in the interval, aliquots of the samples were stored for later analysis. The pH of the urine was not measured. Volunteers were instructed to void their bladders immediately before receiving the seventh dose and discard the urine.

Tizanidine and its two metabolites were analyzed by a liquid chromatographic/mass spectrometric/mass spectrometric procedure. The mass spectrometric detection was performed with a sample inlet by heated nebulizer, positive ionization by atmospheric pressure chemical ionization and mass scanning by multiple reaction monitoring analysis. The inter- and intraday assay variability was ≪<10 to 12% for each drug and tizanidine metabolites analyzed with the method. The limit of quantitation for tizanidine, metabolite 3, metabolite 4, and baclofen was 0.2, 0.2, 0.2, and 2 ng/ml in blood and 0.5, 0.5, 50, and 1 ng/ml in urine, respectively. Values lower than the limit of quantitation were assigned the value of zero for calculations of AUCs Pharmacokinetic measures were calculated as shown in the list of nonstandard abbreviations.

Analyses of variance (ANOVA) of pharmacokinetic parameters were performed with the General Linear Model procedure of SAS (version 6.09, Cary, NC). The model included sequence, subject within sequence, and treatment. A test for sequence effects was conducted by the subject within sequence error mean square from the ANOVA as the error term. Treatment related tests were conducted with the residual error (mean square error) from the ANOVA. The drug–drug interaction between tizanidine and baclofen was assessed by testing the difference in the mean pharmacokinetic parameter value when each treatment was given alone to when the two drugs were coadministered. A priori, a clinically significant difference was set as 30%. This hypothesis was tested with two one-sided hypotheses. A 0.05 level of significance was used to determine statistical significance for all hypotheses tested.

Results

Fifteen subjects entered the study and all completed all three periods. The mean age of the subjects was 23.5 ± 2.6 (mean ± S.D.; range 19–27 years). The mean height of the subjects was 71.1 ± 2.7 inches (± S.D.; range, 67–75) and mean weight was 180 ± 19.2 pounds (range, 153–215). Fourteen of the subjects were Caucasian and one was Asian.

Tizanidine. Mean plasma concentrations of tizanidine with and without concomitant baclofen are shown in Fig. 1. These concentrations were nearly identical when administered alone or as concomitant dosing. Pharmacokinetic parameters for tizanidine and its major metabolites are shown in Table 1 and Table 2. All of the calculated
steady-state pharmacokinetic parameter changes were within the 30% criterion. Mean renal clearance (CL\(_r\)) for tizanidine decreased 21% during concomitant administration relative to sole administration. The mean half-life of tizanidine was 1.21 and 1.18 h when administered alone and in combination with baclofen, respectively. The maximum observed plasma concentration (C\(_{\text{max}}\)) of metabolite 3 was 16% greater during coadministration, which is consistent with the 11% smaller CL\(_r\) during coadministration. Conversely, the CL\(_r\) for metabolite 4 was 27% greater during coadministration. Of the 12 possible between treatment statistical comparisons, only one, CL\(_r\) for metabolite 4, was statistically significant.

**Baclofen.** Mean plasma concentrations of baclofen with and without concomitant tizanidine are shown in Fig. 2. As with tizanidine, these concentrations were nearly identical when administered alone as or as concomitant dosing. Each of the mean plasma pharmacokinetic parameters was <10% different between treatments (Table 3). The mean elimination half-life of baclofen was 6.7 and 6.4 h when administered alone and in combination with tizanidine, respectively. The mean CL\(_r\) for baclofen was 11% greater when tizanidine and baclofen were coadministered. None of the pharmacokinetic parameters between the treatment regimens reached the level of statistical significance.

There were a total of 19 adverse events reported by 7 subjects during the trial. Headache was the most frequently reported adverse event, with 11 episodes reported by 4 subjects—three each during baclofen and tizanidine treatment periods, and five during combination treatment. Asthenia was the second most commonly reported event, with three episodes reported by three subjects, all after the combination treatment. The remaining five adverse events were all considered “mild” in intensity: dizziness, dyspepsia, and somnolence were each experienced after tizanidine, and two episodes of rhinitis were each experienced after tizanidine, and two episodes of rhinitis considered “mild” in intensity: dizziness, dyspepsia, and somnolence.

**Discussion**

The objective of this study was to investigate the potential drug–drug interaction between tizanidine and baclofen at steady-state conditions. This was accomplished by examining the plasma and urinary pharmacokinetics of baclofen, tizanidine, and its two major metabolites after the repeated administration of tizanidine and baclofen alone or in combination. None of the calculated steady-state pharmacokinetic parameter differences for any of the four compounds was as great as 30%, the a priori criterion for interaction, when tizanidine and baclofen were coadministered compared to when the two drugs were given individually.

The steady-state plasma concentration profiles for tizanidine were very similar when administered alone and when coadministered with baclofen. Of all the main measures, the greatest plasma pharmacokinetic parameter difference was for time of the maximum measured plasma concentration (T\(_{\text{max}}\) (25%)). This is of questionable significance because the percentage difference in T\(_{\text{max}}\) is sensitive to sample collection times. Each of the other plasma pharmacokinetic parameters was <9% different between treatments.

After the coadministration of tizanidine and baclofen, mean CL\(_r\) for tizanidine decreased 21%, which did not reach a statistically significant difference. This difference in tizanidine CL\(_r\) was also of limited significance because <1% of the tizanidine dose was excreted unchanged in the urine over the 24 h period after the last dose. The change in CL\(_r\) amounted to a mean decrease of only 0.010 mg of tizanidine in the urine of the 24 h period.

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**TABLE 1**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Tizanidine Alone</th>
<th>Tizanidine with Baclofen</th>
<th>% Changea</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(_{\text{max}}) (ng/ml)</td>
<td>2.51 (1.12)</td>
<td>2.42 (1.03)</td>
<td>9.7 (61.3)</td>
</tr>
<tr>
<td>T(_{\text{max}}) (h)</td>
<td>0.90 (0.27)</td>
<td>1.10 (0.54)</td>
<td>29.4 (66.4)</td>
</tr>
<tr>
<td>K(_{\text{e}}) (h(^{-1}))</td>
<td>0.60 (0.14)</td>
<td>0.60 (0.11)</td>
<td>8.4 (13.7)</td>
</tr>
<tr>
<td>t(_{1/2}) (h)</td>
<td>1.21 (0.26)</td>
<td>1.18 (0.20)</td>
<td>-6.3 (13.5)</td>
</tr>
<tr>
<td>AUC(_{\text{t}-\text{last}}) (ng ⋅ h/ml)</td>
<td>6.00 (3.75)</td>
<td>5.72 (3.03)</td>
<td>4.6 (46.5)</td>
</tr>
<tr>
<td>CL(_{r}) (ml/min)</td>
<td>74.3 (39.4)</td>
<td>58.9 (24.9)</td>
<td>26.4 (151)</td>
</tr>
</tbody>
</table>

* % Change calculated as: \([100 \cdot (\text{Parameter}_{\text{tizanidine alone}} - \text{Parameter}_{\text{tizanidine plus baclofen}}) / \text{Parameter}_{\text{tizanidine alone}}]\).

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**TABLE 2**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Tizanidine Alone</th>
<th>Tizanidine with Baclofen</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(_{\text{max}}) (ng/ml)</td>
<td>11.6 (2.36)</td>
<td>13.4 (4.68)</td>
</tr>
<tr>
<td>T(_{\text{max}}) (h)</td>
<td>1.3 (0.50)</td>
<td>1.7 (0.80)</td>
</tr>
<tr>
<td>K(_{\text{e}}) (h(^{-1}))</td>
<td>0.14 (0.04)</td>
<td>0.13 (0.04)</td>
</tr>
<tr>
<td>t(_{1/2}) (h)</td>
<td>5.37 (1.27)</td>
<td>6.29 (2.95)</td>
</tr>
<tr>
<td>AUC(_{\text{t}-\text{last}}) (ng ⋅ h/ml)</td>
<td>57.0 (16.4)</td>
<td>58.9 (18.0)</td>
</tr>
<tr>
<td>CL(_{r}) (ml/min)</td>
<td>13.6 (5.61)</td>
<td>12.1 (4.17)</td>
</tr>
</tbody>
</table>

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**TABLE 3**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baclofen Alone</th>
<th>Baclofen with Tizanidine</th>
<th>% Changea</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(_{\text{max}}) (ng/ml)</td>
<td>2.51 (42.8)</td>
<td>208 (27.6)</td>
<td>1.05 (20.1)</td>
</tr>
<tr>
<td>T(_{\text{max}}) (h)</td>
<td>1.2 (0.53)</td>
<td>1.3 (0.52)</td>
<td>21.2 (54.9)</td>
</tr>
<tr>
<td>K(_{\text{e}}) (h(^{-1}))</td>
<td>0.11 (0.02)</td>
<td>0.11 (0.01)</td>
<td>3.9 (12.0)</td>
</tr>
<tr>
<td>t(_{1/2}) (h)</td>
<td>6.67 (0.92)</td>
<td>6.44 (0.73)</td>
<td>-2.5 (11.8)</td>
</tr>
<tr>
<td>AUC(_{\text{t}-\text{last}}) (ng ⋅ h/ml)</td>
<td>874 (136)</td>
<td>891 (136)</td>
<td>2.3 (7.7)</td>
</tr>
<tr>
<td>CL(_{r}) (ml/min)</td>
<td>151 (38.5)</td>
<td>168 (36.7)</td>
<td>23.7 (71.3)</td>
</tr>
</tbody>
</table>

* % Change calculated as: \([100 \cdot (\text{Parameter}_{\text{baclofen alone}} - \text{Parameter}_{\text{baclofen plus tizanidine}}) / \text{Parameter}_{\text{baclofen alone}}]\).
The plasma concentration profiles of metabolite 3 were comparable when tizanidine was administered alone or with baclofen. However, the mean trough concentrations of metabolite 3 from 24 to 48 h, as well as $C_{\text{max}}$, were greater when tizanidine was coadministered with baclofen. The greater mean plasma concentrations were consistent with the 10.9% smaller $CL_r$ for metabolite 3 observed when tizanidine and baclofen were coadministered. Conversely, the mean trough concentrations of metabolite 4 were greater when tizanidine was administered alone. This was consistent with the 23.7% greater $CL_r$ for metabolite 4 when tizanidine and baclofen were coadministered.

The steady-state plasma concentration profiles for baclofen were very similar when administered alone and when coadministered with tizanidine. Each of the mean plasma pharmacokinetic parameters was <10% different between treatments. The mean cumulative amount of baclofen excreted in the urine was greater when baclofen was coadministered with tizanidine. The mean $CL_r$ for baclofen was 11.4% greater when tizanidine and baclofen were coadministered. The change in $CL_r$ amounted to an increase in the mean amount of baclofen excreted in the urine of 1.10 mg (11% of the dose) over the 8 h dosing interval after the last dose. As with tizanidine, this difference is unlikely to be clinically significant because the decrease in mean $T_{1/2}$ for elimination was <14 min (3.4%). Both the separate and coadministrations of tizanidine and baclofen were well tolerated.

In summary, there was no clinically relevant drug-drug interaction in the plasma pharmacokinetics of either tizanidine or baclofen when the two drugs were coadministered. No interaction in renal clearance between the two agents when administered concomitantly would be expected because the clearance mechanisms are quantitatively so different. Thus, it is unlikely that coadministration of tizanidine and baclofen during dose-titration of the former will result in a pharmacokinetic interaction.

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References