Pharmacokinetics and Pharmacodynamics of Intravenous Diltiazem in Patients With Atrial Fibrillation or Atrial Flutter

Virgil C. Dias, PharmD; Scott J. Weir, PharmD, PhD; and Kenneth A. Ellenbogen, MD

Background. Diltiazem, a calcium channel blocker, has been shown to be safe and effective in the treatment of patients in atrial fibrillation and/or atrial flutter. However, there have been no pharmacokinetic/pharmacodynamic studies of diltiazem in these patients.

Methods and Results. The pharmacokinetics and pharmacodynamics of intravenous diltiazem were determined in 32 patients with atrial fibrillation or atrial flutter (mean±SD age, 66±7 years; mean baseline heart rate, 131±10 beats per minute) after 20 mg or 20 mg followed by 25-mg bolus doses and a 10 and 15 mg/hr infusion for 24 hours. After the 10 and 15 mg/hr infusions of diltiazem, mean±SD elimination half-life was 6.8±1.8 and 6.9±1.5 hours, volume of distribution was 411±151.8 and 299±70.8 l, and systemic clearance was 42±12.4 and 31±8.3 l/hr, respectively. Percentages of the plasma concentrations of the principal metabolites desacetyldiltiazem and N-desmethyldiltiazem to diltiazem were <15% and <10%, respectively. Thirty of 32 patients maintained response throughout the 24-hour infusion of diltiazem. Using a sigmoidal E\text{max} pharmacodynamic model, a strong relation (mean±SD r\textsuperscript{2}, 0.78±0.2) was observed between plasma diltiazem concentration and percent heart rate reduction. Mean±SD E\text{max} (maximum percent reduction in heart rate from baseline) and E\text{50} (plasma diltiazem concentration that achieves half E\text{max}) were 52±17% and 110±84 ng/ml, respectively. The model predicts that mean plasma diltiazem concentration of 79, 172, and 294 ng/ml are required to produce a 20%, 30%, and 40% reduction in heart rate, respectively. A relation between plasma diltiazem concentration and percent change in systolic blood pressure (SBP) or diastolic blood pressure (DBP) from baseline was not observed (mean±SD r\textsuperscript{2}, SBP/DBP: 0.35±0.24/0.36±0.2). There were no untoward side effects observed.

Conclusions. First, the pharmacokinetics of diltiazem in patients with atrial fibrillation or atrial flutter is nonlinear with an apparent dose-dependent decrease in systemic clearance with increasing infusion rate. Second, using a sigmoidal E\text{max} model, there is a strong relation between plasma diltiazem concentration and percent heart rate reduction. Third, the plasma concentrations of the principal metabolites desacetyldiltiazem and N-desmethyldiltiazem are low and are not expected to contribute significantly to the pharmacodynamics of intravenous diltiazem in these patients. (Circulation 1992;86:1421–1428)

Key Words • diltiazem • atrial fibrillation • atrial flutter • supraventricular tachyarrhythmias

Diltiazem hydrochloride is a calcium channel blocker that exhibits frequency-dependent effects at the atrioventricular (AV) node such that it markedly slows AV nodal conduction and prolongs AV nodal refractoriness when conduction through the AV node is rapid, e.g., during atrial fibrillation or atrial flutter. Diltiazem has been shown to be safe and effective in slowing a rapid ventricular rate in patients with atrial fibrillation or atrial flutter\textsuperscript{2–8} and converting paroxysmal supraventricular tachycardia (PSVT) to sinus rhythm.\textsuperscript{9,10}

A few studies have examined the pharmacokinetics and pharmacodynamics of intravenous diltiazem. These studies have been conducted in healthy volunteers,\textsuperscript{11,12} patients with hypertension (without significant cardiac or pulmonary disease),\textsuperscript{13,14} and patients with a history of PSVT.\textsuperscript{15} There have been no pharmacokinetic/pharmacodynamic studies of diltiazem in patients with atrial fibrillation or atrial flutter, who generally are older and have significant underlying cardiac and/or pulmonary disease.\textsuperscript{16}

The objective of this study was to characterize the pharmacokinetics and pharmacodynamics of intravenous diltiazem in patients with atrial fibrillation or atrial flutter.

Methods

Patients

Thirty-two patients with established atrial fibrillation or atrial flutter (duration, >24 hours) were included in
FIGURE 1. Characteristics of Patients With Atrial Fibrillation or Atrial Flutter

<table>
<thead>
<tr>
<th>Diagnosis (%)*</th>
<th>Cardiovascular</th>
<th>Hypertension</th>
<th>Valvular heart disease</th>
<th>Coronary artery disease</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>11 (34)</td>
<td>6 (19)</td>
<td>8 (25)</td>
<td>6 (19)</td>
<td>14 (44)</td>
</tr>
</tbody>
</table>

*One patient may have more than one diagnosis.

This pharmacokinetic and pharmacodynamic study (Table 1). On entry into the study, all patients had a ventricular rate (documented electrocardiographically) ≥120 beats per minute for at least 15 minutes before receiving study drug. Atrial fibrillation was diagnosed by the absence of discrete, regular atrial activity. Atrial flutter was diagnosed by the presence of discrete flutter waves typically noted in limb leads II, III, and aVF at a rate of 250–350 min⁻¹. None of the patients were hypertensive (systolic blood pressure, <90 mm Hg); in severe congestive heart failure (New York Heart Association functional class III or IV); had a history of sinus node dysfunction, second- or third-degree AV block, or Wolff-Parkinson-White syndrome; or had a known allergy to diltiazem. In 30 of 32 patients, no calcium channel blocker, class Ia or Ic antiarrhythmic agent (e.g., quinidine, procainamide, flecainide, or encaïnide), amiodarone, or β-blocker had been administered for at least five elimination half-lives before administration of diltiazem. One patient received verapamil and one patient received propranolol within five elimination half-lives of entry into the study. Twenty-two of the 32 patients had received digoxin before entry into the study. Only two patients received digoxin during the study. One patient received one dose of 0.25 mg at hour 0.5 of the infusion, and one patient received one dose of 0.125 mg at hour 1.5 of the infusion. None of the other patients received digoxin during the bolus or infusion parts of the study. Mean±SD digoxin plasma concentrations before and after the study were 0.69±0.3 ng/ml (range, 0.2–1.2 ng/ml) and 0.63±0.23 ng/ml (range, 0.3–1.2 ng/ml) (therapeutic range, 0.9–2.1 ng/ml), respectively.

Study Design

The patients included in this study were part of a double-blind, randomized, placebo-controlled study. Patients were enrolled at five participating study centers (see “Appendix”) after the protocol was approved by the investigational review board at each center. The study design is illustrated in Figure 1. Before entry into the study, each patient had signed an informed consent. On entry into the study, a medical history was obtained, and a physical examination was performed. If the presence of a persistent atrial fibrillation or atrial flutter (ventricular rate, ≥120 beats per minute for at least 15 minutes) was confirmed at baseline, the patient was given a 20-mg intravenous bolus dose of open-label diltiazem over 2 minutes (drug period I). Patients who did not achieve a therapeutic response (defined as heart rate <100 beats per minute, ≥20% decrease in heart rate from baseline, or conversion to sinus rhythm) within 15 minutes of the 20-mg dose were given a 25-mg bolus followed by 15 min observation.
intravenous bolus dose of diltiazem over 2 minutes and monitored again for a therapeutic response over the next 15 minutes (drug period 1). If the patient did not achieve a satisfactory therapeutic response to either dose, the patient was withdrawn from the study.

Patients who achieved a therapeutic response during drug period 1 received a double-blind continuous intravenous infusion of diltiazem or placebo beginning at an infusion rate of 10 mg/hr and increasing to 15 mg/hr if response was lost while on the 10-mg/hr infusion rate (drug period 2). An increase in the infusion rate from 10 to 15 mg/hr was permitted at hour 4 if response was maintained but further heart rate reduction was desired. Patients were observed every 30 minutes during the infusion for a therapeutic response while at rest for at least 5 minutes. Placebo and diltiazem intravenous infusion solutions were prepared by adding 100 ml of study drug (5 mg/ml) to flexible polyvinyl chloride infusion bags containing 400 ml of D,W, resulting in a concentration of 1 mg/ml. The infusion solution was administered intravenously beginning at a rate of 10 ml/hr and increased as needed to 15 ml/hr via a previously calibrated infusion pump.

A patient was considered to have maintained therapeutic response (infusion responder) if response was not lost during the continuous 24-hour double-blind infusion. A patient was considered to have failed to maintain therapeutic response to the continuous infusion (infusion nonresponder) if response was lost over two consecutive evaluations spaced 30 minutes apart while receiving the 15-mg/hr infusion in drug period 2. Infusion nonresponders in drug period 2 were rebolused with an intravenous 20-mg dose (or 20 mg followed by 25 mg) of diltiazem (drug period 3). Responders in drug period 3 received an open-label continuous 10–15 mg/hr infusion of intravenous diltiazem (drug period 4). The open-label infusion of diltiazem was prepared and administered as previously described in drug period 2. Nonresponders in drug period 3 were withdrawn from the study. Response to open-label infusion of intravenous diltiazem in drug period 4 was similarly defined as in drug period 2.

If response was not lost at the end of the 24 hours in drug periods 2 or 4, the infusion was stopped and patients were entered into a 10-hour washout period. Subsequent therapy for atrial fibrillation or atrial flutter was at the discretion of the patient’s physician.

Heart rate and blood pressure were obtained before administration of intravenous diltiazem, immediately after the 2-minute injection of intravenous diltiazem, and every 5 minutes until response was achieved in the 17-minute observation period (drug periods 1 and 3). Blood (plasma) samples, blood pressure, and heart rate measurements were obtained at 1, 3, 5, 10, 15, 20, and 24 hours during the continuous double-blind and open-label infusions (drug periods 2 and 4, respectively) and at 1, 3, 5, and 10 hours during the washout. Heart rate and rhythm were obtained from 1-minute ECG rhythm strips (lead II), and blood pressure was obtained from a standard sphygmomanometer.

Of the 32 patients included in the pharmacokinetic/pharmacodynamic analysis, 31 patients (16 in drug period 2 and 15 in drug period 4) received a 24-hour infusion of intravenous diltiazem. One patient received a 16-hour infusion of intravenous diltiazem in drug period 4. Seventeen patients received the 10-mg/hr infusion only; in 15 other patients, the infusion of 10 mg/hr was increased to 15 mg/hr. Adequate washout data were obtained in all 32 patients. Five other patients who received a 24-hour intravenous infusion of diltiazem were not included in the pharmacokinetic/pharmacodynamic analysis because their plasma concentrations of diltiazem could not be obtained due to assay interference (four patients) and lost plasma samples (one patient).

**Plasma Sample Collection, Assay, and Data Analysis**

Blood samples were drawn into plastic syringes and transferred to silanized glass tubes with 10 units/ml heparin. Plasma was separated by centrifugation and frozen at −20°C. Plasma diltiazem and primary metabolite—desacetyldiltiazem and N-desmethyldiltiazem—concentrations were determined by high-performance liquid chromatography with ultraviolet detection. The lower limits of quantitation for diltiazem, desacetyldiltiazem, and N-desmethyldiltiazem were 6.25, 3.12, and 3.12 ng/ml, respectively. Over a plasma concentration range of 6.25–200 ng/ml for diltiazem and 3.12–200 ng/ml for the metabolites, the daily reproducibility for the

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**Figure 2.** Plots of plasma diltiazem concentration–time and percent heart rate reduction–time profiles for patients 45-003, 46-003, and 45-009. *Heart rate obtained at the 15th minute of the baseline period before administration of intravenous diltiazem.
method was 5.6%, 6.9%, and 5.5% for diltiazem, desacetyldiltiazem, and N-desmethyldiltiazem, respectively.18

Model-independent techniques were used to determine diltiazem pharmacokinetic parameters.19 Area under the plasma diltiazem concentration–time curve from zero to infinity (AUCI) was calculated by the sum of the area under the plasma diltiazem concentration–time curve from zero to the last measurable time point (determined by the trapezoidal rule) and the extrapolated area under the plasma diltiazem concentration–time curve from the last measurable time point to infinity (determined by plasma diltiazem concentration at the last measurable time point divided by the terminal first-order elimination rate constant). The last measurable time point varied from patient to patient due to the flexibility in dosing. The maximum plasma concentration and time to reach maximum plasma concentration were obtained from actual plasma diltiazem, desacetyldiltiazem, and N-desmethyldiltiazem–time data. Apparent systemic clearance of diltiazem was determined by dose divided by AUCI. Volume of distribution of diltiazem was determined by systemic clearance divided by terminal first-order elimination rate constant. The relation between plasma diltiazem concentration and percent change in heart rate from baseline and between percent change in systolic blood pressure (SBP) and diastolic blood pressure (DBP) from baseline were examined by fitting individual patient data to linear, loglinear, $E_{\text{max}}$, and sigmoidal $E_{\text{max}}$ pharmacodynamic models20 using a least-squares nonlinear regression analysis.21 A strong pharmacodynamic relation was defined as $r^2 > 0.6$ for individual patient data. The model of best-fit was identified by comparing Akaike and $r^2$ values. The presence or absence of hysteresis was determined in each patient by examining the degree of overlap of the ascending and descending limbs of the percent heart rate reduction versus plasma diltiazem concentration plot. A two-sample $t$ test was used to compare the pharmacokinetic and pharmacodynamic variables between the two different infusion rates of diltiazem and two types of arrhythmias (atrial fibrillation and atrial flutter). Statistical summary data are described as mean±SD.

### Results

**Pharmacokinetics**

**Diltiazem.** Plasma diltiazem concentration–time profiles for three patients are illustrated in Figure 2. Pharmacokinetic parameters were obtained in 31 of 32 patients (one patient had insufficient plasma data to characterize AUCI) as summarized in Table 2. Because diltiazem exhibits nonlinear disposition during continuous intravenous infusion,12 pharmacokinetic parameters are summarized separately for patients receiving the 10- and 15-mg/hr infusions. Due to the flexibility in dosing provided by the study protocol, patients received different total doses of diltiazem. Mean maximum plasma concentration of diltiazem of 242±84 and 470±111 ng/ml were observed generally at the time the 10- and 15-mg/hr infusions, respectively, were discontinued. The mean apparent elimination half-lives of diltiazem were similar following both the 10-mg/hr (6.8±1.8 hr) and the 15-mg/hr (6.9±1.5 hr) infusion rates. Mean systemic clearance of diltiazem was significantly lower in patients receiving the 15-mg/hr infusion (30.7±6.3 l/hr) compared with those receiving the 10-mg/hr infusion (42.0±12.4 l/hr) ($p=0.007$), representing a difference of 27%. The mean volume of distribution of diltiazem was also significantly lower in patients receiving the 15-mg/hr infusion (299±71 l) compared with those receiving the 10-mg/hr infusion (411±152 l) ($p=0.017$), representing a difference of 27%. For the majority of the pharmacokinetic parameters calculated, the intersubject variability was similar for both infusion rates.

**Metabolites.** Pharmacokinetic parameters for the two principal plasma metabolites of diltiazem—desacetyldiltiazem and N-desmethyldiltiazem—following the 10- and 15-mg/hr infusions are summarized in Table 3. The mean maximum plasma concentration for desacetyldiltiazem following the 10- and 15-mg/hr infusions were 30±14 and 68±25 ng/ml, respectively. N-Desmethyldiltiazem achieved slightly lower maximum plasma concentrations of 23±6 and 45±13 ng/ml after 10- and 15-mg/hr infusions, respectively. The times to reach maximum plasma concentration for desacetyldiltiazem were similar to diltiazem. The time to reach maximum plasma concentration for N-desmethyldiltiazem were slightly longer than times for diltiazem and desacetyl-

### Table 2. Pharmacokinetic Parameters of Intravenous Diltiazem

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>10 mg/hr Infusion (n=17)</th>
<th>15 mg/hr Infusion (n=14)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg)</td>
<td>259.5±33.9 (13.0)</td>
<td>341.2±32.0 (9.4)</td>
<td>. . .</td>
</tr>
<tr>
<td>Cmax (ng/ml)</td>
<td>242.0±84.4 (34.9)</td>
<td>469.9±110.7 (23.6)</td>
<td>.0001</td>
</tr>
<tr>
<td>tmax (hr)</td>
<td>23.0±7.3 (31.9)</td>
<td>26.1±4.1 (15.7)</td>
<td>.173</td>
</tr>
<tr>
<td>AUCt, (ng/ml × hr)</td>
<td>6,436.9±1,699.9 (26.4)</td>
<td>11,858.4±3,271.9 (27.6)</td>
<td>.0001</td>
</tr>
<tr>
<td>Kel (hr⁻¹)</td>
<td>0.110±0.03 (28.5)</td>
<td>0.105±0.03 (23.6)</td>
<td>.640</td>
</tr>
<tr>
<td>t1/2 (hr)</td>
<td>6.8±1.8 (26.0)</td>
<td>6.9±1.5 (21.4)</td>
<td>.780</td>
</tr>
<tr>
<td>CL (l/hr)</td>
<td>42.0±12.4 (29.5)</td>
<td>30.7±8.3 (27.2)</td>
<td>.007</td>
</tr>
<tr>
<td>Vd (l)</td>
<td>411.2±151.8 (36.9)</td>
<td>299.1±70.8 (23.7)</td>
<td>.017</td>
</tr>
</tbody>
</table>

Dose, total intravenous dose administered; Cmax, maximum plasma concentration; tmax, time to reach maximum plasma concentration; AUCt, area under the plasma diltiazem concentration–time curve from zero to infinity; Kel, apparent terminal first-order disposition rate constant; t1/2, apparent elimination half-life; CL, systemic clearance; Vd, apparent volume of distribution; CV, coefficient of variation.

*p value resulting from a two-sample t test comparing the 10-mg/hr with the 15-mg/hr infusion. Values are mean±SD (CV%).
diltiazem. Mean ratios for the area under the plasma concentration–time curve of the metabolites desacetyl-
diltiazem and N-desmethyldiltilazem to diltiazem, were 12% and 14% and 9% and 9% following the 10- and
15-mg/hr infusions, respectively. The area under the plasma concentration–time curve ratios were not sig-
nificantly different for desacetyltilrazem or N-desmethyldiltilazem after the 10- and 15-mg/hr infusions.
There were insufficient data to determine apparent elimination half-life for either desacetyltilrazem or
N-desmethyldiltilazem.

Pharmacodynamics

**Bolus and infusion.** All 32 patients responded to bolus
dose(s) of intravenous diltiazem during drug periods 1
or 3. Thirty of the 32 patients maintained response
throughout the 24-hour infusion of intravenous dilti-
zem in drug periods 2 or 4. Mean baseline heart rate in
the 32 patients was 131±10 beats per minute. After the
intravenous bolus dose of diltiazem, there was a mean
decrease in heart rate of 28% from baseline. Response
to the bolus occurred within a mean time of 4.2±3.6
minutes timed from the beginning of the 2-minute dose.
During the 24-hour infusion, heart rate decreased from
baseline by a mean of 33% at hour 1, 37% at hour 5,
39% at hour 10, 42% at hour 15, and 38% at hour 24
(Table 4). All patients who responded to the bolus and
infusion of diltiazem had a ≥20% decrease in heart rate
from baseline. The majority of infusion responders also
had a heart rate <100 beats per minute. None of the
patients converted to sinus rhythm.

The time course profiles for plasma diltiazem concen-
tration and percent heart rate reduction paralleled each
other as illustrated for three patients in Figure 2. Peak
heart rate reduction was generally observed at the time
of maximal plasma diltiazem concentration. When per-
cent heart rate reduction was plotted as a function of
plasma diltiazem concentration, hysteresis was not ob-
served in 27 of 32 patients.

A strong pharmacodynamic relation (defined as
$r^2>0.6$ for model of best-fit) between plasma diltiazem
concentration and percent reduction in heart rate was
observed in 84% (27/32) of the patients. Percent heart
rate reduction–plasma diltiazem concentration profiles
with model-predicted line of best-fit are illustrated in
Figure 3 for these same three patients. Data for one
patient represent some of the best data to model, data
for another patient represent the most difficult data to
model, and data for a third patient represent a middle
case. The relation between plasma diltiazem concen-
tration and percent heart rate reduction for each of the 32
patients was described by a sigmoidal $E_{\text{max}}$ pharma-
dynamic model: percent heart rate reduction = $E_{\text{max}}$ ×
(plasma diltiazem concentration)$^N$/EC$_{50}^N$ + (plasma
diltiazem concentration)$^N$, where $E_{\text{max}}$ is the max-
imal percent reduction in heart rate, EC$_{50}$ is the plasma
diltiazem concentration at half-maximal effect, and N is
a sigmoidicity parameter. The estimated pharmacody-
namic parameters from these models are summarized in
Table 5. The mean $E_{\text{max}}$ was 52% with a mean EC$_{50}$ of
110 ng/ml. The $E_{\text{max}}$ and EC$_{50}$ were not significantly
different ($p>0.05$) for patients receiving the 10- and

### Table 3. Pharmacokinetic Parameters of Desacetyltilrazem and N-Desmethyldiltilazem

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Desacetyltilrazem</th>
<th>N-Desmethyldiltilazem</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 mg/hr (n=16)</td>
<td>15 mg/hr (n=14)</td>
</tr>
<tr>
<td></td>
<td>15 mg/hr (n=17)</td>
<td>15 mg/hr (n=12)</td>
</tr>
<tr>
<td>C$_{\text{max}}$ (ng/ml)</td>
<td>30.2±14.1 (46.6)</td>
<td>68.4±24.8 (36.3)</td>
</tr>
<tr>
<td></td>
<td>23.3±6.5 (28.0)</td>
<td>45.0±12.7 (28.3)</td>
</tr>
<tr>
<td>$t_{\text{max}}$ (hr)</td>
<td>25.9±5.2 (19.9)</td>
<td>25.5±8.5 (33.5)</td>
</tr>
<tr>
<td></td>
<td>28.7±3.8 (13.4)</td>
<td>27.4±2.7 (9.8)</td>
</tr>
<tr>
<td>AUC$_{0\to\infty}$ (ng/ml × hr)</td>
<td>675.7±287.1 (42.5)</td>
<td>1,383.7±530.5 (38.3)</td>
</tr>
<tr>
<td></td>
<td>498.4±144.7 (29.0)</td>
<td>898.5±255.9 (28.5)</td>
</tr>
<tr>
<td>AUC ratio</td>
<td>0.12±0.02 (19.2)</td>
<td>0.14±0.1 (33.0)</td>
</tr>
<tr>
<td></td>
<td>0.09±0.02 (27.6)</td>
<td>0.09±0.02 (23.5)</td>
</tr>
</tbody>
</table>

C$_{\text{max}}$, maximum plasma concentration; $t_{\text{max}}$, time to reach maximum plasma concentration; AUC$_{0\to\infty}$, area under the plasma concentration–time curve from zero to the last measurable time point; AUC ratio, ratio of AUC$_{0\to\infty}$ for desacetyltilrazem and N-desmethyldiltilazem to AUC$_{0\to\infty}$ for diltiazem; CV, coefficient of variation.

Values are mean±SD (CV%).

* $p$ value resulting from a two-sample $t$ test comparing the 10-mg/hr and 15-mg/hr infusions.

### Table 4. Heart Rate and Systolic and Diastolic Blood Pressures in Response to Bolus, During Infusion, and During Washout of Intravenous Diltiazem

<table>
<thead>
<tr>
<th>Percent change from baseline</th>
<th>At response to bolus</th>
<th>Infusion hour</th>
<th>Washout hour</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>131±10</td>
<td>-28±8</td>
<td>-33±9</td>
</tr>
<tr>
<td></td>
<td>-37±10</td>
<td>-39±8</td>
<td>-42±11</td>
</tr>
<tr>
<td></td>
<td>-38±10</td>
<td>-39±12</td>
<td>-42±11</td>
</tr>
<tr>
<td></td>
<td>-38±12</td>
<td>-40±12</td>
<td>-42±11</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>132±22</td>
<td>-13±12</td>
<td>-9±11</td>
</tr>
<tr>
<td></td>
<td>-9±11</td>
<td>-11±12</td>
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<td>-7±11</td>
<td>-5±12</td>
<td>-3±11</td>
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<tr>
<td>DBP (mm Hg)</td>
<td>85±12</td>
<td>-12±14</td>
<td>-12±13</td>
</tr>
<tr>
<td></td>
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<td>-10±13</td>
</tr>
<tr>
<td></td>
<td>-6±12</td>
<td>-6±12</td>
<td>-6±12</td>
</tr>
</tbody>
</table>

bpm, Beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure.

*$n=32$.

*Obtained at the 15th minute of the baseline period before administration of intravenous diltiazem.
patients were similar (52±17% versus 50±16%, respectively). The mean EC50 was higher for atrial flutter patients than for atrial fibrillation patients (160±117 versus 101±76 ng/ml, respectively); however, the difference was not statistically significant (p=0.15). As summarized in Table 6, the model predicts that mean plasma diltiazem concentrations of 79, 172, and 294 ng/ml produce a 20%, 30%, and 40% reduction in heart rate, respectively.

A relation between plasma diltiazem concentration and percent reduction in SBP and DBP from baseline was not observed in the majority of patients (mean r2: SBP, 0.35±0.24; DBP, 0.36±0.2). A strong relation (r2>0.6) between plasma diltiazem concentration and percent reduction in SBP and DBP was seen in only four and three patients, respectively. Mean baseline SBP of 132 mm Hg was reduced by 13% in response to the bolus and by 9% at hour 1 and hour 5, 8% at hour 10, and 7% at hour 20 and hour 24 of the infusion. Mean baseline DBP of 85 mm Hg was reduced by 12% in response to the bolus and by 12% at hour 1 and hour 5, 9% at hour 10, and 10% at hour 20 and hour 24 of the infusion (Table 4).

**Washout.** After the 24-hour infusion, there was a gradual and steady return of heart rate and blood pressure toward baseline (Table 4). Over the 10-hour washout period, mean percent reduction in heart rate from baseline ranged from 38% at washout hour 1 to 16% at washout hour 10. The mean percent reduction in SBP and DBP ranged from 7% and 10%, respectively, at washout hour 1 to 1% and 1%, respectively, at washout hour 10. During the 10-hour washout period, 13 patients maintained response, and eight other patients had received additional antiarrhythmic therapy.

**Adverse Events**

There were no deaths, prolonged hospitalizations, permanent disabilities, or dosage reductions as a result of an adverse event. Of the 32 patients, five had adverse events that were related to diltiazem: Three experienced a transient injection site reaction, one experienced a warm sensation lasting 3 minutes, and one had asymptomatic ventricular pauses lasting as long as 4.2 seconds.

**Discussion**

The pharmacokinetics of intravenous diltiazem in patients with atrial fibrillation or atrial flutter have not been previously reported. In this study, the mean maximum plasma concentration of diltiazem was 242 and 470 ng/ml following the 10- and 15-mg/hr infusions, respectively. The apparent elimination half-life of diltiazem was 6.9 hours. There was a nonlinear dose-

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**TABLE 6. Pharmacodynamic Model-Predicted Plasma Diltiazem Concentration Required to Produce a Given Heart Rate Reduction**

<table>
<thead>
<tr>
<th>Percent heart rate reduction</th>
<th>n</th>
<th>Predicted plasma diltiazem concentration required (ng/ml) (mean±SD) (CV%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>31</td>
<td>78.8±72.8 (92.3)</td>
</tr>
<tr>
<td>30</td>
<td>29</td>
<td>171.5±241.2 (140.6)</td>
</tr>
<tr>
<td>40</td>
<td>24</td>
<td>294.4±243.6 (143.9)</td>
</tr>
</tbody>
</table>

CV, coefficient of variation.

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**FIGURE 3. Plots of percent heart rate reduction–plasma diltiazem concentration plots for three patients (45-003, 46-003, and 45-009). The solid line represents the least-squares fit of the sigmoidal Emax model. Patients 45-003, 46-003, and 45-009 represent good (r2=0.97), median (r2=0.78), and poor (r2=0.49) pharmacodynamic relations, respectively. Patient 45-009 exhibited clockwise hysteresis.**
dependent decrease in systemic clearance from 42 to 31 l/hr after the 10- and 15-mg/hr infusions of diltiazem, respectively. Steady-state conditions for diltiazem were not attained during the 24-hour infusion. The elimination half-life of 6.9 hours of diltiazem in these patients suggests steady-state conditions would be achieved after 32 hours of continuous infusion.

The disposition properties of intravenous diltiazem in patients with atrial fibrillation and atrial flutter differ from those in normal volunteers. In the study by Weir et al. in normal volunteers receiving a 10- and 15-mg/hr infusion of diltiazem for 24 hours, the mean maximum plasma concentration of diltiazem was lower (170 and 270 ng/ml after 10- and 15-mg/hr infusions, respectively), the apparent elimination half-life was shorter (4.1-5 hours), and the systemic clearance was greater (52 and 48 l/hr after 10- and 15-mg/hr infusions, respectively) than for patients in atrial fibrillation and atrial flutter. However, the volume of distribution of diltiazem in normal volunteers appeared to be similar to patients in atrial fibrillation and atrial flutter (391 versus 299-411 l). The decreased systemic clearance of diltiazem in patients in atrial fibrillation or atrial flutter noted in this study may be due to the older age of these patients (mean age, 66 years) and to the underlying cardiovascular disease state. In the study by Schwartz et al., the apparent elimination half-life of diltiazem was longer (mean, 4.5 versus 3.3 hours), and the systemic clearance of diltiazem was decreased (mean, 15.5 versus 21.2 l/min/kg) in elderly compared with young hypertensive patients.

Characterization of the relation between plasma diltiazem concentration and heart rate reduction in atrial fibrillation and atrial flutter patients has not been previously reported. We were able to establish this relation in 27 of the 32 patients studied. These 27 patients demonstrated no hysteresis between a change in plasma diltiazem concentration and a corresponding change in heart rate, i.e., little or no delay in response after an adjustment in plasma diltiazem concentration. This finding is of clinical importance because it suggests that heart rate change in atrial fibrillation and atrial flutter patients may be affected fairly rapidly after increasing or decreasing the rate of a continuous infusion of diltiazem. By establishing a pharmacodynamic model in each patient, we were able to predict the therapeutic diltiazem plasma concentration required to produce a given percent reduction in heart rate. The mean therapeutic plasma diltiazem concentrations required to produce 20%, 30%, and 40% reductions in heart rate were 79, 172, and 294 ng/ml, respectively.

Five of the 32 patients studied had relatively poor model fits of the pharmacodynamic data. Each of these patients demonstrated clockwise hysteresis between a change in plasma diltiazem concentration and a corresponding change in heart rate, which could suggest development of tolerance. An explanation for the resultant poor fits of the data in these five patients is not readily apparent and requires further investigation. Two patients had atrial flutter. Three patients had atrial fibrillation, one of whom did not maintain therapeutic response during the infusion.

Five patients in this study had atrial flutter. Atrial flutter patients had similar E_{max} (50% versus 52%) but higher EC_{50} (160 versus 110 ng/ml) values than did atrial fibrillation patients. Although the EC_{50} was not significantly different, possibly because of the small number of atrial flutter patients in the study, these findings suggest atrial flutter patients may require higher diltiazem plasma concentrations than atrial fibrillation patients to achieve the same magnitude of heart rate reduction.

We did not observe a relation between plasma diltiazem concentration and percent reduction in blood pressure from baseline in the majority of our patients. The lack of a correlation may be a result of postprandial effects and diurnal variation on blood pressure. In addition, we cannot rule out a change in hemodynamics secondary to reduction of a rapid ventricular rate after administration of diltiazem.

Plasma concentrations of the principal metabolites desacetyldiltiazem and N-desmethyldiltiazem were low, i.e., <15% and <10% of the plasma concentration of diltiazem, respectively. The relative potencies of desacetyldiltiazem and N-desmethyldiltiazem compared with diltiazem (based on animal studies) ranged from 50% to 100% and from 20% to 30%, respectively (data on file at Marion Merrell Dow Inc.). Thus, in this study, the concentration of these metabolites of diltiazem is expected to contribute little to the pharmacodynamics in patients with atrial fibrillation and atrial flutter.

Conclusions

First, the pharmacokinetics of diltiazem in patients with atrial fibrillation and atrial flutter are nonlinear with an apparent dose-dependent decrease in systemic clearance with increasing infusion rate. Second, with a sigmoidal E_{max} model, there is a strong relation between diltiazem plasma concentration and percent heart rate reduction. Third, the plasma concentrations of the principal metabolites desacetyldiltiazem and N-desmethyldiltiazem are low and are not expected to contribute significantly to the pharmacodynamics of intravenous diltiazem in these patients.

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Appendix

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