Verapamil Pharmacodynamics and Disposition in Young and Elderly Hypertensive Patients

Altered Electrocardiographic and Hypotensive Responses

DARRELL R. ABERNETHY, M.D., Ph.D.; JANICE B. SCHWARTZ, M.D.; ELIZABETH L. TODD, Ph.D.; ROBERT LUCHI, M.D.; and ELEANOR SNOW, P.A.; Houston, Texas

We studied verapamil pharmacodynamics and disposition in seven young, ten elderly, and seven very elderly hypertensive males. Maximal decrease in mean (± SD) blood pressure tended to be greater in the elderly (−13.5 ± 5.9 mm Hg) and the very elderly patients (−15.9 ± 9.6 mm Hg) compared with that in young patients (−7.3 ± 4.2 mm Hg). Disparate effects on heart rate responses were noted with reflex tachycardia in young patients compared with decreases in heart rate among the elderly and very elderly. Sensitivity to verapamil-induced prolongation in electrocardiographic P-R interval was less in the very elderly, and maximal prolongation in P-R interval induced by verapamil was less in the elderly and very elderly. Verapamil disposition was also age related. Total verapamil clearance was decreased in elderly (10.5 ± 3.5 mL/min · kg; p < 0.05) and very elderly (8.0 ± 4.1 mL/min · kg; p < 0.01) when compared with that in young patients (15.5 ± 4.5 mL/min · kg). Elimination half-life was prolonged in the elderly (7.4 ± 3.3 h; p < 0.01) and very elderly (8.0 ± 1.2 h; p < 0.01) compared with that in young patients (3.8 ± 1.1 h). Our data indicate age- and hypertension-related physiologic changes result in predictable pharmacokinetic changes. However, the complex alterations in verapamil pharmacodynamic responses indicate an interaction between direct drug effects and age- and disease-related changes in hemodynamic and autonomic nervous system function.

Calcium antagonists are being advocated for use in the treatment of geriatric hypertensive patients. Unfortunately, few data are available to assist the clinician in predicting therapeutic or toxic effects of these drugs in the geriatric patient.

Understanding drug effect and toxicity in elderly patients is of increasing importance as the proportion of elderly in the general population increases (1). Some drug groups—for example, oral anticoagulants and benzodiazepines—show increased activity in the elderly when pharmacodynamic measures such as prolongation of prothrombin time (2) or sedation (3, 4) are evaluated. Increased sensitivity to such drug effects has been explained in part by pharmacokinetic changes associated with aging such that decreased drug clearance and increased accumulation in elderly patients are reported for many oxidized drugs (5) and some drugs that undergo extensive first-pass hepatic extraction (high clearance drugs) (6, 7). However, these observations do not explain pharmacodynamic effects of some cardiovascular drugs such as beta-adrenergic agonists and antagonists in the elderly.

Alterations in adrenergic physiology that occur with increasing age include decreased baroreflex sensitivity (8), decreased chronotropic response to beta1-adrenergic agonists, and decreased sensitivity to beta-adrenergic blockade (9). In contrast, pharmacokinetic studies of beta-adrenergic antagonists in aged patients have shown decreased clearance of propranolol, associated with higher steady-state concentrations during multiple-dose therapy (10-12). Partial explanation for the mechanism of this discrepancy between pharmacodynamic and clinical observation and pharmacokinetic evaluation in aged patients may be due to decreases in beta-adrenergic receptor number or affinity (13).

Hemodynamic effects of aging include decreased compliance of large vessels in the arterial tree (14), increased left ventricular afterload, a longer time required for cardiac contraction and relaxation, and a greater dependence on the Frank-Starling mechanism to increase cardiac output due to the diminished heart rate response during exercise or stress (15, 16). There are conflicting data regarding impairment in net cardiac function associ-
ated with advanced age (15, 16). Cardiac electrophysio-
logic alterations in elderly humans include a decrease in
the intrinsic heart rate after autonomic blockade with
atropine and propranolol (17), a decrease in the maxi-
mum achievable heart rate (18, 19), and a prolongation of
the P-R interval on the surface electrocardiogram due
to a delay in cardiac conduction proximal to His bundle
(20, 21). In addition to the slowing and decreased re-
sponsiveness of the sinus node with aging, symptomatic
sinus node dysfunction is commoner in the geriatric popu-
lation (22). These changes in resting and exercise heart
rate and atrial conduction may reflect age-related chang-
es in adrenergic responsiveness and sinus automaticity
(23).

Verapamil and other calcium channel blockers are
used in the treatment of angina and cardiac arrhythmias
and are being evaluated for use as antihypertensive
agents. Therefore, these agents have enormous potential
for use in the elderly patient. Advantages may include
peripheral vasodilatory effects without significant fluid
retention (24), bronchiolar relaxation (25), low inci-
dence of central nervous system depression, and single-
drug treatment of both hypertension and coronary artery
disease. However, potentially deleterious effects of calci-
um channel blockade in the elderly patient include sinus
node dysfunction, prolongation of atrioventricular con-
duction, and negative inotropism (26, 27) which may act
in synergism with the impairments in cardiovascular homeo-
ostasis associated with aging. We compare the phar-
macodynamics and disposition of verapamil in young
versus elderly and very elderly hypertensive men.

Methods

SUBJECTS

Twenty-four male patients with essential hypertension, ages
23 to 102 years, were stratified into three groups. Group 1 in-
cluded seven men 23 to 36 years of age and group 2, ten men 61
to 74 years of age. Both groups included hypertensive outpa-
tients receiving no medication for at least 1 week before the
study; none had evidence of other medical illness as assessed
by history and physical examination, electrocardiogram, complete
blood count, SMA-20, and urinalysis. Group 3, seven inpatients
from the Houston Veterans Administration Medical Center
Geriatrics Ward, were 75 to 102 years of age. None of these
patients had an acute medical illness at the time of the study.
All seven patients were living independently or with family
members before and after this period of hospitalization, were
ambulatory, and had normal cognitive function. Three of the
seven patients were hospitalized specifically to participate in the
study and four were in the final stages of convalescence from an
illness that had resulted in their hospitalization. These illnesses
were urosepsis, unstable angina pectoris, congestive heart fail-
ure, and immobility due to degenerative joint disease. Medi-
tations included digoxin (two patients), furosemide (one pa-
tient), nitroglycerin (two patients), ibuprofen (one patient),
theophylline (one patient), and amitriptyline (two patients).
Patients taking other medications were excluded. The attending
physician in each case thought that discontinuing the medica-
tion of the study participant would not be in the best clinical
interest of the patient. Subjects in all three groups were mental-
ly competent and participated after giving written informed
consent. All patients were within 25% of their ideal body
weight (Table 1).

STUDY PROTOCOL

All patients received verapamil hydrochloride, 10 mg, admin-
istered by continuous intravenous infusion over 10 minutes.

Seventeen patients (five from group 1, eight from group 2, and
four from group 3) also received oral verapamil hydrochloride,
120 mg, after an overnight fast. Patients who did not receive
oral verapamil were either unwilling to participate or impos-
sible to contact (groups 1 and 2) or had been discharged from
the hospital (group 3). Intravenous and oral studies were sepa-
ated by at least 48 hours.

Before each dose, at the end of drug administration (time 0),
and at 5, 15, 30, and 45 minutes, and 1, 1.25, 1.50, 1.75, 2, 2.25,
2.5, 3, 4, 6, 8, 10, and 24 hours after the dose, venous blood
samples were drawn into heparinized tubes. Along with each
blood sample, blood pressure measurement, heart rate measure-
ment, and lead II electrocardiographic strips were recorded at
25 and 50 mm/s paper speed. An indwelling 20-g venous cathe-
ter, kept patent by 1-mL irrigation with a dilute heparin solu-
tion (10 U/mL) after each sample, was used to draw blood
samples during the first 10 hours after the verapamil dose. The
24-hour sample was obtained by venipuncture. Blood specimens
were centrifuged and the plasma separated and stored at
-20 °C until analyzed.

SAMPLE ANALYSIS

Concentration of verapamil and norverapamil was analyzed by
liquid chromatography using nitrophenyl-phosphorl-
detector (28). The extent of verapamil binding to plasma protein
was determined from single samples obtained in the nonfasting
state at least 8 hours after the verapamil dose by equilibrium
dialysis using duplicate 1-mL plasma samples after spiking plas-
ma values with 150 ng/mL of verapamil. Dialysis was done at
37 °C for 5 hours. Recovery of verapamil from the dialysis sys-
tem was complete. Equilibrium between bound and unbound
verapamil was complete at 5 hours and verapamil binding was
concentration-independent to 500 ng/mL.

PHARMACOKINETIC DATA ANALYSIS

After intravenous verapamil doses, plasma drug concen-
trations after the infusion were fitted to equations formed by a
linear sum of exponential terms with iterative weighted nonlinear
least-squares regression analysis (29, 30). After correction of the
coefficients for the infusion time (31), the derived func-
tions were used to calculate the elimination half-life, total ap-
parent volume of distribution using the steady-state and the
area method, and total clearance (32). Area under the plasma
concentration-time curve from time zero was determined by the
trapezoidal method. To this result was added the residual area
extrapolated to infinity, calculated as the final concentration
denoted by the slope of the terminal phase of the plasma concen-
tration-time curve to give the total area under the curve. The
area under the curve was used to calculate model-independent
parameters for volume of distribution and total clearance, and
also used for estimation of verapamil absolute bioavailability
(33).

After oral doses of verapamil, the area under the curve was
determined as described above, and elimination half-life was
determined by linear regression analysis of the terminal log lin-
ear phase of the plasma concentration-time curve. Absolute
bioavailability of verapamil was determined using the dose-nor-
malized ratio of oral and intravenous areas under the curve in
the same patient during the two trials.

PHARMACODYNAMIC DATA ANALYSIS

After each verapamil dose, three pharmacodynamic parame-
ters (electrocardiographic P-R interval, blood pressure, and
tachycardia rate) were determined at the time each blood sample was
obtained for analysis of verapamil concentration. Electrocardio-
graphic P-R interval was measured for ten successive cardiac
cycles, and the mean used for that individual data point. Blood
pressure was obtained by cuff plethysmography with each pa-
cient in the same position throughout the study (sitting or su-
pine) and expressed as mean arterial pressure: (systolic-diastol-
ic pressure) / 3 + diastolic pressure = mean blood pressure.

Heart rate was determined as the mean of five cardiac cycles by
measurement of the R-R interval on the surface electrocardi-
ogram. The P-R interval was related to verapamil plasma con-
centration after intravenous doses by a sigmoid E_{max} pharaco-
Table 1. Patient Characteristics, Pharmacodynamic Values, and Pharmacokinetic Values for Verapamil in Male Hypertensive Patients*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Young</th>
<th>Elderly</th>
<th>Very Elderly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>7</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>29 ± 5†</td>
<td>68 ± 4†</td>
<td>84 ± 9†</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>76 ± 11</td>
<td>88 ± 13†</td>
<td>60 ± 12‡</td>
</tr>
<tr>
<td>Cigarette smoking (yes/no), u</td>
<td>1/6</td>
<td>2/8</td>
<td>0/7</td>
</tr>
<tr>
<td>Baseline mean blood pressure, mm Hg</td>
<td>108 ± 16</td>
<td>114 ± 12</td>
<td>100 ± 11</td>
</tr>
<tr>
<td>Baseline heart rate, beats/min</td>
<td>71 ± 11‡</td>
<td>69 ± 9‡</td>
<td>84 ± 11†</td>
</tr>
<tr>
<td>Baseline P-R interval, ms</td>
<td>164 ± 22</td>
<td>190 ± 39</td>
<td>164 ± 23</td>
</tr>
</tbody>
</table>

Pharmacodynamic values

| Change in mean blood pressure, mm Hg     | -7.3 ± 4.2     | -13.5 ± 5.9    | -15.9 ± 9.6  |
| Change in heart rate, beats/min          | +8 ± 5‡        | -1 ± 10‡       | -6 ± 8‡      |
| EC₅₀, ng/mL                              | 22.2 ± 3.8‡    | 26.3 ± 15.2‡   | 103 ± 68†    |
| E₅₀, ms                                  | 43.8 ± 14.8‡   | 19.9 ± 5.2‡    | 11.7 ± 5.1†  |
| Oral doses (linear model)                |                |                |              |
| Slope, ms/ng . mL⁻¹                      | 0.671 ± 0.497  | 0.592 ± 0.410  | ...          |
| Intercept, ms                            | 33.1 ± 37.6    | 22.1 ± 11.2    | ...          |

Pharmacokinetic values

| Intravenous doses                        |                |                |              |
| Elimination half-life, h                 | 3.8 ± 1.1†     | 7.4 ± 3.3†     | 8.0 ± 1.2‡   |
| Volume of distribution at steady-state, L/kg | 4.3 ± 1.1     | 4.9 ± 1.6     | 6.1 ± 2.9    |
| Volume of distribution by area, L/kg     | 4.9 ± 1.2      | 7.4 ± 3.9     | 5.7 ± 3.4    |
| Total clearance, mL/min · kg             | 15.5 ± 4.5†    | 10.5 ± 3.4‡   | 8.0 ± 4.1‡   |
| Plasma protein binding, % unbound        | 5.1 ± 1.2      | 6.5 ± 2.0     | 5.3 ± 1.6    |
| Area under the curve, ng/mL · h⁻¹        | 142 ± 38‡      | 180 ± 52      | 372 ± 177†   |
| Oral doses                               |                |                |              |
| Elimination half-life, h                 | 4.8 ± 1.5†     | 5.8 ± 1.9†     | 10.7 ± 1.8‡  |
| Time to peak concentration, h            | 0.9 ± 0.3      | 1.1 ± 0.6     | 4.1 ± 3.6‡   |
| Peak concentration, ng/mL                | 190 ± 55       | 196 ± 152     | 202 ± 209‡   |
| Bioavailability, %                       | 34.1 ± 11.1    | 28.9 ± 16.8   | ...          |

* Values expressed as mean ± SD
† p < 0.01
‡ p < 0.001 by Newman-Keuls multiple range comparison.

Results

Comparison of patient groups for cigarette smoking, baseline mean blood pressure, and baseline electrocardiographic P-R interval showed no significant differences between groups. Elderly patients weighed more than young or very elderly groups, and baseline heart rate was higher in the very elderly than in young or elderly (Table 1).

Figure 1 shows verapamil-induced prolongation of electrocardiographic P-R interval as a function of plasma concentration after intravenous verapamil administration for one member of each patient group. The sensitivity of the atrioventricular node to verapamil as indicated by P-R prolongation (determined as verapamil plasma concentration associated with 50% maximal prolongation in P-R interval, C₅₀) is a "sigmoidity" factor that introduces curvature into the concentration-response curve and permits fitting with less residual error at concentrations approaching no effect and maximal effect (34, 35). Data fitting was done using unweighted iterative nonlinear least-squares regression analysis and iterating the variables E₅₀, C₅₀, and n. Data were graphically examined before fitting.

After intravenous doses, maximum effect always occurred at the end of infusion, which was the time of maximal plasma concentration as well. However, after oral doses in some patients, a definite hysteresis occurred suggesting a lag time between change in plasma compartment concentration and effect. Therefore, after oral verapamil doses, we used a linear pharmacodynamic model of the form: E = (E₅₀ • Cⁿ) / (EC₅₀ⁿ + Cⁿ), where E is prolongation of P-R interval from baseline, E₅₀ is the maximal prolongation in P-R interval, C is drug concentration at the measured effect E, EC₅₀ is the verapamil plasma concentration associated with 50% maximal prolongation in P-R interval, and n is a "sigmoidity" factor that introduces curvature into the concentration-response curve and permits fitting with less residual error at concentrations approaching no effect and maximal effect (34, 35). Data fitting was done using unweighted iterative nonlinear least-squares regression analysis and iterating the variables E₅₀, EC₅₀, and n. Data were graphically examined before fitting.

After intravenous doses, maximum effect always occurred at the end of infusion, which was the time of maximal plasma concentration as well. However, after oral doses in some patients, a definite hysteresis occurred suggesting a lag time between change in plasma compartment concentration and effect. Therefore, after oral verapamil doses, we used a linear pharmacodynamic model of the form: (E - E₀) = S • C, where E is measured P-R interval, E₀ is baseline P-R interval, S is slope, and C is verapamil concentration at the measured effect (E - E₀). Only effect-concentration data after the appearance of peak effect until disappearance of effect were used to minimize the influence of the apparent initial delay in equilibration between the plasma compartment and the effector site (36).

After intravenous verapamil doses, changes in mean arterial pressure were transient and maximal in all patients at the end of drug infusion or 5 minutes after. Therefore, only the maximal decrease from baseline level before infusion was used for statistical analysis. Change in heart rate was also transient and, after intravenous doses, again only maximal changes were used. After single oral doses, both change in mean arterial pressure and heart rate were highly variable and inconsistent and, therefore, were not formally evaluated. Differences in patient characteristics and pharmacodynamic and pharmacokinetic parameters among patient groups were evaluated using analysis of variance (Newman-Keuls). All results are expressed as mean ± SD.

Abemethy et al. • Verapamil Pharmacodynamics
Verapamil Concentration (ng/ml)

Figure 1. Relationship of verapamil-induced prolongation in electrocardiographic P-R interval and verapamil plasma concentration using a sigmoid \( E_{\text{max}} \) model after intravenous verapamil.

seen in young patients and decreases in heart rate were seen in both elderly and very elderly patients (Figure 3). Mean arterial blood pressure tended to decrease more in elderly and very elderly patients, although this difference did not reach statistical significance (Figure 3, Table 1).

Pharmacodynamic parameters using the linear pharmacodynamic model derived from the P-R interval-concentration relationship after oral verapamil were similar in young and elderly patients. This finding is shown by the similarity in the slope and intercept of the linear regression of verapamil concentration and prolongation of P-R interval (Table 1) for these two patient groups. The sample size in the very elderly (four patients) was inadequate for evaluation (Table 1). No significant trends were detected in heart rate or blood pressure response in young, elderly, or very elderly patients.

Figure 4 shows verapamil plasma concentrations and pharmacokinetic functions after intravenous administration from a representative member of each patient group. Verapamil total clearance was decreased in the elderly and very elderly patients, resulting in prolongation of the elimination half-life in these groups (Figure 5; Table 1). Volume of distribution was no different among patient groups (Table 1).

After oral doses, bioavailability and peak concentration were similar among age groups. However, time to peak concentration was longer in the very elderly (Table 1). Similarly, plasma protein binding of verapamil was not age-related (Table 1).

Discussion

Verapamil cardiovascular pharmacodynamics are the result of its calcium slow-channel blocking properties, which result in suppression of atrioventricular conduction, suppression of sinoatrial node automaticity, impairment in myocardial contractility, and peripheral vascular relaxation (26). However, the clinical effects seen after verapamil administration are the summation of these direct drug effects and the responses of cardiovascular reflexes. One important reflex contributor is the baroreceptor-mediated increase in beta-adrenergic tone in response to peripheral vasodilation (27).

The interpretation of verapamil pharmacodynamics are further complicated by the presence of optically active stereoisomers. The racemates are different both in pharmacodynamic effect and pharmacokinetic properties in healthy humans. Use of L-verapamil delays atrioventricular nodal conduction much more potently (37); however, it also may have more extensive first-pass hepatic extraction after oral administration, and is less extensively bound to plasma proteins than D-verapamil (38, 39). The racemic mixture is used clinically, and the differential first-pass clearance has been invoked as the explanation for increased drug potency after intravenous as compared to oral administration (40).

We have used the sigmoid \( E_{\text{max}} \) pharmacodynamic model to compare the delay in atrioventricular nodal conduction induced by verapamil in very elderly and elderly with that in young hypertensive men. This com-

Figure 2. Effect of age on intravenous verapamil pharmacodynamics. The concentration required for 50% maximal prolongation of P-R interval is shown on the left. Individual and mean (± SD) values are shown.
Figure 3. Effect of age on intravenous verapamil pharmacodynamics. Change in mean blood pressure (left) and heart rate (right) are the maximum changes that occurred after a 10-minute intravenous verapamil (10 mg) infusion. Individual and mean (± SD) values are shown.

Comparison is appropriate because maximal effect is shown (represented by a maximum prolongation of surface electrocardiographic P-R interval before progression to higher degree atrioventricular block); there is time independence of the concentration-effect relationship; no lag time is apparent between plasma compartment and effector compartment; and the pharmacodynamic effect is exclusively related to the parent drug. Fulfillment of these requirements when verapamil is administered intravenously is shown by the following observations. Presence of a maximal effect is shown by observation of a maximum P-R prolongation over a range of verapamil concentrations obtained at different times. Time-independence has been shown by others with the presence of a constant concentration-effect relationship with ascending, descending, or steady-state concentrations in animals (41) and by chronic dosing in humans (36). This result is further supported by documentation of parallel and rapid changes in plasma concentration, cardiac muscle verapamil concentration, and impairment in atrioventricular conduction reported in the animal model (42). Finally, norverapamil, the demethylated metabolite of verapamil, is the only metabolite with pharmacologic activity. Norverapamil has 10% to 20% of the potency of verapamil as a vasodilator in the animal model; however, it is without electrophysiologic effects (43). Furthermore, after intravenous infusion, only very small norverapamil concentrations are found in plasma.

In contrast to the intravenous studies, reverse hysteresis was consistently seen after oral verapamil administration, suggesting a lag time between plasma concentration and effect. Therefore, a linear pharmacodynamic model using only concentration-effect points after maximal effect was used (36) to minimize changes in effect with time and to facilitate comparison with the intravenous data.

The findings that verapamil pharmacodynamic effects are dramatically altered in elderly and very elderly hypertensive men as compared with the effects in young hypertensive men are consistent with several possible mechanisms. The likeliest explanation is the summation of altered direct verapamil effects and indirect cardiovascular reflexes.

The trend toward increased hypotensive effect in the elderly and very elderly hypertensive patients was unexpected. This finding suggests that elderly patients are more sensitive to the vasodilator effects of verapamil or that alterations in verapamil-induced negative inotropic effects were also a factor. Vascular alpha2-adrenergic receptor blockade has been suggested as one of the means by which calcium antagonists mediate vasodilation (44), although this hypothesis has recently been challenged (45, 46). Indirect measures of alpha2 receptor numbers in aging suggest unchanged (47, 48) or decreased receptor numbers (49). The functional significance in vivo of these findings is unknown. Similarly, numbers and function of specific calcium channel antagonist receptors in relation to age are unknown.

In the young patients, hypotension resulted in the expected and previously described reflex tachycardia (26, 27).
27); however, in the elderly and very elderly, no change or decreased heart rate was seen. This finding may be in part the result of impaired baroreflex responses and decreased sensitivity in the elderly to beta-adrenergic activation (8, 9, 13). Another possibility for the lack of change in heart rate is decreased parasympathetic withdrawal in the elderly; however, there is little evidence for such a mechanism. Instead, the available evidence suggests decreased baseline parasympathetic tone in the elderly because atropine does not increase the heart rate in the elderly as much as in younger persons (23). Heart rate variation during deep inspiration with concomitant beta-adrenergic blockade is less in the elderly, and resting heart rate during beta-adrenergic blockade is increased in elderly compared to the rate in young persons (50). In addition, decreased atrial concentrations of acetylcholine have been reported in young rats that have been compared with senescent rats (51). In the absence of beta-adrenergic chronotropic effects, the direct suppressant effect of verapamil on the sinoatrial node (26, 27), in conjunction with mild impairment in sinus node function seen with age (17-23), are therefore the likeliest explanation for the negative chronotropic effect seen with verapamil in the elderly and very elderly patients. This fact may have also contributed to the trend toward increased hypotensive effects seen in the elderly and very elderly patients.

The decreased response and maximal effect of verapamil-induced prolongation of atrioventricular conduction in the elderly and very elderly patients may also be due to both direct drug effect and indirect reflex effects. Baseline P-R interval was not significantly different between patient groups, nor was baseline mean blood pressure. Resting heart rate was somewhat greater in the very elderly patients (Table 1). Direct verapamil effect prolongs P-R interval due to delay in atrioventricular conduction (26, 27). However, heart rate and sympathetic, parasympathetic, and intrinsic baroreflex activity each influence atrioventricular conduction as well. The inhibitory effects of verapamil on the slow inward calcium current in cardiac tissues have been shown to be both use and frequency dependent (52, 53). The use-dependent properties dictate that more depression of atrioventricular nodal transmission is produced by calcium channel blockade as the stimulation rate is increased (52, 53). Therefore, the mild reflex tachycardia we saw in the young patients may have enhanced the verapamil-induced P-R prolongation. Because the heart rates were similar at the time of maximal verapamil concentrations in the very elderly and young patients, yet the effect differed, this mechanism alone cannot explain all of our findings. Although baroreflex activation may enhance atrioventricular conduction due to vagal withdrawal (54), Nakaya and associates (55) have shown that the magnitude in heart rate increase after verapamil in conscious dogs is not affected by pretreatment with atropine.

The elderly and very elderly patients had progressively less verapamil-induced prolongation of the P-R interval when measured by either EC50 or maximal effect (E_max). This finding may be the result of decreased sensitivity of the atrioventricular node to verapamil, some enhancement of atrioventricular conduction due to verapamil-induced suppression of the sinoatrial node with decreased heart rate, decreased sympathetic responsiveness, or, more likely, a combination of all these factors. Verapamil administration may lead to sinus node depression in patients with sinus node disease (56) and sinus node function is altered with aging. In our elderly and very elderly patients with no preexisting history of sinus node dysfunction, small decreases in heart rate were seen after intravenous verapamil doses frequently used clinically. We did not see marked sinus slowing, sinus node pauses, or sinus node exit block. After oral verapamil administration, changes in atrioventricular conduction were similar in young and elderly groups. Therefore, a pharmacokinetic explanation may also contribute to the decreased sensitivity after intravenous verapamil administration. If the difference in clearance between D-verapamil and the more potent L-verapamil (38) become progressively increased with increasing age, an apparent attenuation of
drug effect would appear. However, this action seems unlikely in view of the dramatic decrease in racemic verapamil biotransformation, with total clearance reduced nearly 50% in the very elderly.

Our pharmacokinetic findings are consistent with those reported for other oxidatively biotransformed high-clearance drugs (6, 7, 10). Total clearance is reduced; therefore, in the absence of a significant change in volume of distribution, elimination half-life is prolonged. Similarly, absolute bioavailability is not age related. Appropriate conclusions to be drawn from such pharmacokinetic data are that drug accumulation would be greater in the elderly during chronic dosing, particularly for a drug such as verapamil, which may accumulate more extensively during chronic dosing than is predicted after single doses (57), perhaps due to nonlinear kinetics at higher plasma concentrations (58). However, the conclusion that elderly patients may be more sensitive to a given intravenous verapamil dose is not supported by our pharmacodynamic data.

After oral doses, concern about drug accumulation due to decreased clearance is warranted because the verapamil effect-concentration relationship was similar between young and elderly patients. Furthermore, although we were unable to model blood pressure responses after single oral doses of verapamil, the intravenous data suggest that elderly and very elderly patients may be more sensitive to verapamil-induced hypotension. With appropriate downward dose adjustment, the antihypertensive effects of verapamil can be achieved without increased heart rate. Clinically, this finding may be of particular benefit in the patient with coexisting coronary artery disease.

Concern has been expressed that age-related changes in drug biotransformation and excretion, as well as effect, may not be a linear function with advancing age. Little pharmacokinetic and pharmacodynamic data exist for patients greater than 75 years of age. We were able to evaluate this age group, of considerable importance due to their extensive drug exposure (59). Although statistically significant differences between the elderly and very elderly patients were not seen, there was a trend toward even greater change in the very elderly compared to the young hypertensive patients in both pharmacodynamic and pharmacokinetic data. This finding suggests that for verapamil, the pattern of impaired drug clearance and the pharmacodynamic effects seen continues to increase with advancing age into the eighth and ninth decades of life.

ACKNOWLEDGMENTS: The authors thank Maya Sadubhan for technical assistance, Dr. Jerry R. Mitchell for his support, and Ms. Rebecca Fallon for manuscript preparation.

Grant support: in part by grant AM-33479 from the United States Public Health Service.

Requests for reprints should be addressed to Darrell R. Abernethy, M.D., Ph.D.; Division of Clinical Pharmacology, Department of Medicine, Roger Williams General Hospital, 825 Chalkstone Avenue, Providence, RI 02908.

References


2. Shepard AM, Hewick DS, Moreland TA, Stevenson III. Age as a


31. Loo JC, Riegelman S. Assessment of pharmacokinetic constants from

32. Wagner JG. Linear pharmacokinetic equations allowing direct calculation of many needed pharmacokinetic parameters from the coefficients and exponents of polynomial equations which have been fitted to the data. J Pharmacokinet Biopharm. 1976;4:443-67.


