Cardiovascular effects of verapamil in patients with essential hypertension

ROLAND E. SCHMIEDER, M.D., FRANZ H. MESSERLI, M.D., GUILLERMO E. GARAVAGLIA, M.D., AND BORIS D. NUNEZ, M.D.

ABSTRACT The cardiovascular effects of intravenous verapamil and 3 months of oral administration of a slow-release form of verapamil (verapamil-SR) were studied in 10 patients with mild-to-moderate essential hypertension. Intravenous verapamil reduced arterial pressure by 15% (p < .01) through a fall in total peripheral resistance of 29% (p < .01); provoked a reflexive rise in heart rate (by 19%, p < .02), cardiac output (by 74%, p < .01), and plasma catecholamines; and shifted intravascular volume toward the cardiopulmonary circulation indicating peripheral venoconstriction. Quite in contrast to the immediate effects of the intravenous drug, oral therapy with verapamil-SR for 2 to 3 months lowered arterial pressure effectively (by 15%, p < .01) by inducing vasodilation of 15% (p < .02), but without causing reflex tachycardia, activation of the sympathetic-adrenergic or renin-angiotensin systems, or volume expansion. Oral therapy with verapamil-SR preserved systemic and renal blood flow and slightly reduced cardiac mass (by 6%, p < .05) and renal vascular resistance (by 25%, p < .05). Whereas intravenous verapamil tended to depress myocardial contractility or left ventricular function. These cardiovascular effects make verapamil-SR an excellent agent for long-term antihypertensive therapy.


THE HEMODYNAMIC HALLMARK of established essential hypertension is an increased total peripheral resistance that is caused by functional and structural changes in the arterial vascular beds. An antihypertensive agent should therefore be used to reduce the elevated total peripheral resistance and by such means lower arterial pressure. Apart from reducing total peripheral resistance, an ideal antihypertensive agent should also maintain systemic and regional blood flow, preserve cardiac performance, prevent fluid and salt retention, and not produce reflexive stimulation of the sympathetic adrenergic or the renin angiotensin system. Moreover, in patients with left ventricular hypertrophy and renal impairment the drug should allow left ventricular hypertrophy to regress and renal function to improve. Because calcium-entry blockers have the potential to fulfill some of the above criteria, they are evolving as attractive antihypertensive agents.

Indeed, in several therapeutic trials verapamil has been documented to control arterial hypertension effectively and safely. Its potential to lower blood pressure has been found to be equivalent to that of other antihypertensive agents. The present study was designed to analyze the complete antihypertensive cardiovascular profile of verapamil.

Methods

Therapeutic protocol. Ten patients (seven men and three women; six whites and four blacks) with mild-to-moderate essential hypertension (World Health Organization stage I to II) were included in the therapeutic trial. The mean age was 49 ± 10 years, the average body weight 81 ± 13 kg, and body surface area 1.9 ± 0.19 m². Secondary causes of arterial hypertension, as well as congestive heart failure (NYHA class II to IV), myocardial infarction within the last 6 months, impairment due to valvular or congenital cardiac lesions, and clinically significant hepatic or renal insufficiency, were ruled out by routine clinical examinations, as previously outlined. In particular, a 12-lead electrocardiogram and a 2 min rhythm strip were recorded in each patient to detect cardiac arrhythmias. Additional criteria for exclusion of patients from the study were bradycardia of less than 50 beats/min, sick sinus syndrome, second or third-degree of atrioventricular block, left bundle branch block, atrial flutter, or fibrillation associated with preexcitation syndromes. Women included in the study were neither pregnant nor lactating and were following a medically recog-
nized contraceptive program. The protocol for the study was approved by the Institutional Clinical Investigation Committee, and informed consent was obtained from each patient.

Patients had either never been treated in the past or had all antihypertensive medication discontinued for at least 4 weeks before entry in the study. Each was included in the study only if his or her diastolic pressure was equal to or higher than 90 mm Hg and less than 115 mm Hg on at least two consecutive outpatient visits during the 4 weeks before the hemodynamic baseline evaluation. Patient enrollment was a randomized process and not related to previous antihypertensive therapy. For the last 2 weeks of this washout phase, the patients received a placebo identical to the verapamil tablet.

After evaluation of the baseline measurements in the hemodynamic laboratory, verapamil was given intravenously over 2 min (0.15 mg/kg body weight up to a maximum dose of 10 mg). The hemodynamic and echocardiographic evaluations were repeated 2 to 5 min after the injection of drug. Patients completing the acute dosing phase received 240 mg verapamil daily in slow-release form (Isotrol-SR 240 mg). If the patient’s diastolic pressure was still greater than 90 mm Hg after 1 week, the dose was increased to 240 mg in the morning and 120 mg in the evening. If the therapeutic goal (diastolic pressure less than 90 mm Hg) was still not achieved after 2 weeks, the patient received 240 mg verapamil-SR for the remainder of the study period. Each patient had to complete at least 8 weeks of effective therapy before the second set of measurements was obtained (after 8 to 12 weeks of short-term therapy). The second hemodynamic study was done 12 to 24 hr after the last oral dose of verapamil-SR. The final dose of verapamil-SR was 240 mg a day in three patients, 240 mg in the morning and 120 mg in the evening in three patients, and 240 mg twice a day in four patients.

Laboratory examinations. At the end of the 4 week washout phase, patients were studied in the hemodynamic laboratory after an overnight fast, as previously described. Briefly, catheters were inserted into a brachial artery and an antecubital vein by a modified Seldinger technique and advanced to the ascending aorta just proximal to the subclavian artery and superior vena cava, respectively. Continuous recording of arterial pressure was obtained simultaneously with the electrocardiogram (lead III). Cardiac output was measured in triplicate with the indocyanine green dye technique. Stroke volume and total peripheral resistance were calculated by standard formulas. The ratio of pulse pressure to stroke volume was calculated as an estimate of the distensibility of large arteries. Resting supine hemodynamic measurements were performed before (baseline) and after intravenous administration of verapamil (acute dosing phase). In addition, the same hemodynamic measurements were repeated after 8 to 12 weeks of oral therapy with verapamil.

Plasma volume was measured during the hemodynamic study with 131I-labeled plasma serum albumin. Total blood volume and red cell mass were estimated from the plasma volume and hematocrit (total blood volume = plasma volume/(100 – hematocrit); red cell mass = total blood volume – plasma volume; hematocrit was adjusted by the correction factor 0.91 for total body hematocrit). Central blood volume was assessed from the indocyanine green dye dilution curve by calculating the product of mean transit time and blood flow per second. Since the catheters were not placed in the pulmonary artery and right atrium, the central blood volume calculated from our curves overestimates the "true" central blood volume. Nevertheless, our values do provide a good estimate of the portion of the total blood volume distributed to the cardiopulmonary system. In particular, the values reliably indicate changes within the same patient.

Renal blood flow was determined by measuring the clearance of 131I para-aminohippuric acid and glomerular filtration rate by calculating the 24 hr creatinine clearance. Sodium excretion was measured in the 24 hr urine sample as well. The 24 hr samples were carefully controlled for incomplete collected specimens. Samples with a urine volume of less than 600 ml and a urinary creatinine excretion below the expected value were discarded. Filtration fraction and fractional sodium excretion were calculated by standard formulas. Splanchnic blood flow was obtained from the plasma clearance of injected indocyanine green dye (50 mg). Distensibility of large arteries was estimated by dividing pulse pressure by stroke volume.

Plasma renin activity and aldosterone and catecholamine plasma levels were determined by radioimmunoassay and radioenzymatic assay, respectively, after patients had been recumbent for 1 hr on an ad libitum sodium diet.

In seven patients, a good M mode echocardiographic tracing was obtained before and after therapy by use of an ultrasonicoscope (Smith-Kline Echoline 28) interfaced with a strip-chart recorder (Honeywell) and a probe measuring 1.27 cm in diameter. The techniques for left ventricular visualization have been described previously. All echocardiograms were read by two independent investigators according to standard measurement convention. Variables of left ventricular structure were septal wall thickness, posterior wall thickness, relative wall thickness (posterior wall thickness divided by left ventricular radius), and left ventricular mass index calculated according to the formulas of Bennett and Evans.

End-systolic wall stress was regarded as the most appropriate indicator for assessment of afterload. Left ventricular function was estimated by calculating ejection fraction, fractional fiber shortening, and velocity of circumferential fiber shortening. Since these three variables of cardiac performance are highly dependent on cardiac loading conditions, they may not accurately reflect myocardial contractility. Thus, the ratio of end-systolic wall stress to end-systolic volume index was used to assess the inotropic cardiac state since this index is independent of preload and accounts for afterload.

Ambulatory blood pressure. Ambulatory arterial blood pressure was recorded every 7.5 min by indirect measurement and simultaneously with a continuously recorded electrocardiogram (Delmar Avionics Pressure Meter II) over one 24 hr period beginning at 9:00 a.m. Data from the printouts of blood pressure and heart rate obtained over a 24 hr period were averaged for each 2 hr period and aberrant readings were excluded by criteria described previously. Daily life activity was defined as the time period from 8:00 a.m. to 10:00 p.m. and sleep hours from 10:00 p.m. to 8:00 a.m. Daily life activity measurements were averaged, and these as well as averages of measurements taken during sleep hours were analyzed by one-way analysis of variance with repeated measurements before and after oral therapy.

Statistics. One-way analysis of variance with repeated measurements was used to compare baseline value changes to the effects of intravenous and oral administration of verapamil. Linear correlation coefficients (Pearson) were calculated when indicated. Group data are expressed as the mean plus or minus standard deviation in the text and as the mean plus or minus standard error of the mean in the figures.

Results

Effects of intravenous drug. Intravenous administration of verapamil resulted in a marked drop in systolic, diastolic, and mean arterial pressure due to a reduction in total peripheral resistance, whereas cardiac output increased (table 1). The rise in cardiac output was predominantly produced by an increase in heart rate.
and left ventricular ejection rate. Plasma norepinephrine and epinephrine levels increased in parallel (table 2), pointing to a reflexive stimulation of the sympathetic adrenergic system. Intravascular volume was consistently shifted to the cardiopulmonary system, most likely by peripheral venoconstriction, as indicated by an increase of the total to central blood volume ratio (table 3). The echocardiographic data revealed a tendency toward depressed myocardial contractility after intravenous administration of verapamil, as suggested by a declining ratio of end-systolic wall stress to end-systolic volume index (table 4). However, preload assessed by end-diastolic volume index tended to increase, and therefore preload-dependent variables of left ventricular function (ejection fraction, fractional fiber shortening, velocity of circumferential fiber shortening) remained unchanged (table 4). Despite the

and left ventricular ejection rate. Plasma norepinephrine and epinephrine levels increased in parallel (table 2), pointing to a reflexive stimulation of the sympathetic adrenergic system. Intravascular volume was consistently shifted to the cardiopulmonary system, most likely by peripheral venoconstriction, as indicated by an increase of the total to central blood volume ratio (table 3). The echocardiographic data revealed a tendency toward depressed myocardial contractility after intravenous administration of verapamil, as suggested by a declining ratio of end-systolic wall stress to end-systolic volume index (table 4). However, preload assessed by end-diastolic volume index tended to increase, and therefore preload-dependent variables of left ventricular function (ejection fraction, fractional fiber shortening, velocity of circumferential fiber shortening) remained unchanged (table 4). Despite the

and left ventricular ejection rate. Plasma norepinephrine and epinephrine levels increased in parallel (table 2), pointing to a reflexive stimulation of the sympathetic adrenergic system. Intravascular volume was consistently shifted to the cardiopulmonary system, most likely by peripheral venoconstriction, as indicated by an increase of the total to central blood volume ratio (table 3). The echocardiographic data revealed a tendency toward depressed myocardial contractility after intravenous administration of verapamil, as suggested by a declining ratio of end-systolic wall stress to end-systolic volume index (table 4). However, preload assessed by end-diastolic volume index tended to increase, and therefore preload-dependent variables of left ventricular function (ejection fraction, fractional fiber shortening, velocity of circumferential fiber shortening) remained unchanged (table 4). Despite the

and left ventricular ejection rate. Plasma norepinephrine and epinephrine levels increased in parallel (table 2), pointing to a reflexive stimulation of the sympathetic adrenergic system. Intravascular volume was consistently shifted to the cardiopulmonary system, most likely by peripheral venoconstriction, as indicated by an increase of the total to central blood volume ratio (table 3). The echocardiographic data revealed a tendency toward depressed myocardial contractility after intravenous administration of verapamil, as suggested by a declining ratio of end-systolic wall stress to end-systolic volume index (table 4). However, preload assessed by end-diastolic volume index tended to increase, and therefore preload-dependent variables of left ventricular function (ejection fraction, fractional fiber shortening, velocity of circumferential fiber shortening) remained unchanged (table 4). Despite the

and left ventricular ejection rate. Plasma norepinephrine and epinephrine levels increased in parallel (table 2), pointing to a reflexive stimulation of the sympathetic adrenergic system. Intravascular volume was consistently shifted to the cardiopulmonary system, most likely by peripheral venoconstriction, as indicated by an increase of the total to central blood volume ratio (table 3). The echocardiographic data revealed a tendency toward depressed myocardial contractility after intravenous administration of verapamil, as suggested by a declining ratio of end-systolic wall stress to end-systolic volume index (table 4). However, preload assessed by end-diastolic volume index tended to increase, and therefore preload-dependent variables of left ventricular function (ejection fraction, fractional fiber shortening, velocity of circumferential fiber shortening) remained unchanged (table 4). Despite the

and left ventricular ejection rate. Plasma norepinephrine and epinephrine levels increased in parallel (table 2), pointing to a reflexive stimulation of the sympathetic adrenergic system. Intravascular volume was consistently shifted to the cardiopulmonary system, most likely by peripheral venoconstriction, as indicated by an increase of the total to central blood volume ratio (table 3). The echocardiographic data revealed a tendency toward depressed myocardial contractility after intravenous administration of verapamil, as suggested by a declining ratio of end-systolic wall stress to end-systolic volume index (table 4). However, preload assessed by end-diastolic volume index tended to increase, and therefore preload-dependent variables of left ventricular function (ejection fraction, fractional fiber shortening, velocity of circumferential fiber shortening) remained unchanged (table 4). Despite the

and left ventricular ejection rate. Plasma norepinephrine and epinephrine levels increased in parallel (table 2), pointing to a reflexive stimulation of the sympathetic adrenergic system. Intravascular volume was consistently shifted to the cardiopulmonary system, most likely by peripheral venoconstriction, as indicated by an increase of the total to central blood volume ratio (table 3). The echocardiographic data revealed a tendency toward depressed myocardial contractility after intravenous administration of verapamil, as suggested by a declining ratio of end-systolic wall stress to end-systolic volume index (table 4). However, preload assessed by end-diastolic volume index tended to increase, and therefore preload-dependent variables of left ventricular function (ejection fraction, fractional fiber shortening, velocity of circumferential fiber shortening) remained unchanged (table 4). Despite the
also well controlled during sleep in all three patients who received a 240 mg dose of verapamil-SR once a day in the morning. Heart rate remained unchanged during daily life activities, but it did fall significantly (but less than 7%) at night (figure 1). No rates consistently below 60 beats/min were seen during verapamil-SR medication in any of the 10 patients.

After 3 months of oral treatment with verapamil-SR, mean arterial pressure was lowered in all 10 patients to the same extent as after intravenous administration (table 1). However, the drop in mean arterial pressure after the intravenously given dose was only modestly linked to the fall in mean arterial pressure after oral therapy (r = .61 p < .05) and was not clearly related to plasma renin activity or age.

The decline in arterial pressure was caused by a significant reduction in total peripheral resistance. Cardiac output was preserved despite a slight, but significant, deceleration of heart rate (figure 2). In contrast to the findings after intravenous administration of verapamil, variables of preload (end-diastolic volume index), myocardial contractility (end-systolic wall stress/end-systolic volume index), and left ventricular function (ejection fraction, fractional fiber shortening, velocity of circumferential fiber shortening) were nearly identical before treatment and after oral therapy (table 4).

Examination of levels of norepinephrine, epinephrine, plasma renin activity, and aldosterone also did not reveal any significant change from baseline after short-term therapy. Dopamine levels seemed to be lower (table 2). Plasma volume, red cell mass, and total blood volume were not altered by oral administration of verapamil-SR (table 3). Furthermore, verapamil-SR did not provoke sodium excretion or retention. Although intravascular volume shifted toward the cardiopulmonary system after verapamil was given intravenously, a trend in the opposite direction was
found after oral therapy: verapamil-SR induced a slight redistribution of intravascular volume to the periphery when compared with before treatment (table 3).

Finally, we analyzed the effects of verapamil-SR on target organ damage. Septal and posterior wall thickness of the left ventricle did not change significantly; in contrast, relative wall thickness and left ventricular mass decreased significantly, although the decreases were less than 10% from pretreatment values (table 4). Large artery distensibility estimated by the ratio of pulse pressure to stroke volume improved after short-term therapy with verapamil-SR (table 1). After oral therapy renal blood flow, glomerular filtration rate, filtration fraction, and splanchnic blood flow were not different from pretreatment values. However, renal vascular resistance was significantly diminished (table 5), in parallel to the fall in total peripheral resistance.

**Discussion**

Verapamil was the first calcium channel–entry blocker used in the treatment of hypertension, and several trials have attested to the efficacy and safety of this compound. In all 10 patients examined in this study, intravenous and short-term oral administration of verapamil reduced arterial pressure by decreasing total peripheral resistance. Intravenous verapamil led to an increase in cardiac output mainly due to an acceleration of heart rate. Furthermore, although myocardial contractility was slightly attenuated, left ventricular function (and thus stroke volume) was preserved by the Frank-Starling mechanism because, in parallel, preload tended to increase.

In contrast to the findings after intravenous dosing verapamil-SR did not provoke any abnormalities of cardiac output, preload, left ventricular function, or of the inotropic state of the myocardium after short-term oral therapy. This is in agreement with a study by Lund-Johansen examining the long-term effects of verapamil: cardiac output measured after 1 year of medication was nearly identical to pretreatment values, at rest as well as during exercise.

The blood pressure–lowering effect of verapamil has been attributed to relaxation of vascular smooth muscle. Such vasodilation, however, activates compensatory mechanisms in order to maintain pressure level. Thus, calcium-entry blockers (nifedipine, nitrendipine) when given over the short term are prone to provoke reflexive cardiac stimulation. We found that intravenous verapamil also caused reflex tachycardia. This effect is most likely secondary to decreased baroreceptor-mediated vagal activity and/or augmented sympathetic activity. The net activation of the sympathetic-adrenergic system led to a rise in plasma epinephrine and norepinephrine levels, as well as to peripheral vasoconstriction, as indicated by centripetal redistribution of the intravascular volume. Despite these counterregulatory mechanisms, arterial pressure remained lowered — a finding that could be explained by the fact that calcium-entry blockers appeared to attenuate norepinephrine- and angiotensin II–induced vasoconstriction.

No reflexive stimulation of the sympathetic-adrenergic system was evident after oral therapy with verapamil-SR. In the current study, plasma catecholamines returned to baseline values, vasoconstriction no longer occurred, and heart rate at rest was even somewhat lower than before therapy. Some studies have indicated that short-term therapy with verapamil resulted in a decelerated heart rate, whereas others have not. In all of these studies, however, the decrease in heart rate was far less than that observed after β-blockade.

Unlike other vasodilators, verapamil-SR taken orally did not produce sodium retention, volume expansion, or stimulation of the renin-angiotensin system. This agrees with previous reports documenting a lack of significant change in plasma arginine-vasopressin level, serum osmolality, and water clearance. Since calcium inhibits renin secretion by a direct action on the juxtaglomerular cells, one might expect calcium-entry blockers such as verapamil to activate the renin angiotensin cascade. Quite in contrast, no significant differences in plasma renin activity or aldosterone levels were seen in our study, and Leonetti et al. even reported an attenuation of angiotensin-mediated aldosterone secretion, as reflected by a higher ratio of plasma renin activity to aldosterone during verapamil-SR therapy.

In the present study verapamil-SR did not significantly change renal function, as judged by analysis of

---

**Table 5**

**Regional hemodynamics before and after short-term therapy with verapamil-SR**

<table>
<thead>
<tr>
<th>Metric</th>
<th>Baseline</th>
<th>After therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal blood flow (ml/min)</td>
<td>749 ± 58</td>
<td>829 ± 56</td>
</tr>
<tr>
<td>Renal/central blood flow (%)</td>
<td>13.7 ± 1.1</td>
<td>15.4 ± 1.4</td>
</tr>
<tr>
<td>Renal vascular resistance (U)</td>
<td>16 ± 2</td>
<td>12 ± 1*</td>
</tr>
<tr>
<td>Glomerula filtration rate (ml/min)</td>
<td>100 ± 5</td>
<td>106 ± 9</td>
</tr>
<tr>
<td>Filtration fraction (%)</td>
<td>22 ± 2</td>
<td>20 ± 1</td>
</tr>
<tr>
<td>Splanchnic blood flow (ml/min)</td>
<td>441 ± 34</td>
<td>658 ± 47</td>
</tr>
<tr>
<td>Splanchnic vascular resistance (U)</td>
<td>18 ± 1</td>
<td>15 ± 11</td>
</tr>
</tbody>
</table>

Results are expressed as the mean ± SEM.

*Ap < .05 vs baseline values.
renal blood flow, glomerular filtration rate, and filtration fraction, and this is in accordance with previous observations.\textsuperscript{53, 54, 58, 59} However, renal vascular resistance was reduced in parallel with the fall of total peripheral resistance. Whether this reduction in renal vascular resistance indicates less vasoconstriction alone or reflects structural changes in the renal vascular bed remains undetermined.\textsuperscript{1, 3} In contrast to diitiazem, which does not seem to affect the distensibility of large arteries,\textsuperscript{60, 61} verapamil-SR acted simultaneously on small and large arteries: both total peripheral resistance and the pulse pressure/stroke volume ratio decreased, the latter suggesting an increase in arterial distensibility.

Antihypertensive therapy with calcium-entry blockers has been shown to allow regression of left ventricular hypertrophy.\textsuperscript{61, 62} We observed (in the seven patients in whom a good tracing was obtained) a decrease in left ventricular mass index as well as relative wall thickness after 8 to 12 weeks of effective antihypertensive therapy with verapamil-SR. This reduction in cardiac mass could be due to either a lowered concentration of intracellular calcium ions, which are necessary for protein synthesis, or a reduced sensitivity to angiotensin II, which initiates protein synthesis in cardiac muscle.\textsuperscript{63, 64}

In conclusion, short-term oral therapy for 2 to 3 months with verapamil-SR lowered arterial pressure by vasodilation without activating counterregulatory mechanisms such as reflexive tachycardia, volume expansion, sodium retention, or activation of the renin-angiotensin or sympathetic-adrenergic system. Systemic and renal blood flow, left ventricular function, and myocardial contractility remained well preserved, whereas target organ damage appeared to improve. These cardiovascular effects make verapamil-SR an excellent agent for oral antihypertensive therapy in established essential hypertension.

References

1. Folkow B: Physiological aspects of primary hypertension. Physiol Rev 62: 347, 1982
32. Reichek N, Devereux RB: Reliable estimation of peak left ventricular systolic pressure by M-mode echocardiographic-determined end-diastolic relative wall thickness: identification of severe valvu-
33. Bennett DH, Evans DW: Correlation of the left ventricular mass determined by echocardiography with vector cardiography and electrocardiographic voltage measurements. Br Heart J 36: 981, 1974


38. Grossmann W, Braunwald E, Mann T, McLauren LP, Green LH: Contractile state of the left ventricle in man as evaluated from end-systolic pressure-volume relations. Circulation 56: 845, 1977


Cardiovascular effects of verapamil in patients with essential hypertension.
R E Schmieder, F H Messerli, G E Garavaglia and B D Nunez

Circulation. 1987;75:1030-1036
doi: 10.1161/01.CIR.75.5.1030
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1987 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/75/5/1030