Importance of internal controls, statistical methods, and side effects in short-term trials of vasodilators: a study of hydralazine kinetics in patients with aortic regurgitation

Charles R. McKay, M.D., Michele Nana, M.D., David T. Kawanishi, M.D., Uri Elkayam, M.D., P. Anthony N. Chandraratna, M.D., Joyce N. Weiss, Ph.D., and Shahbudin H. Rahimtoola, M.D.

ABSTRACT We determined that the spontaneous changes in cardiac output (CO) over 12 hr in 21 patients with chronic severe aortic regurgitation averaged ±8.9% (p = .03). We then measured changes in CO over time after administering incremental doses of oral hydralazine (50, 100, 150, and 200 mg) every 12 hr and analyzed these changes by several methods. Changes over time of only +14% were highly significant (p < .001) when analyzed by t test, but were not significant by repeated-measures analysis of variance (ANOVA). When changes in CO were compared with internal control values (spontaneous changes over 12 hr), only changes of 20% or more were significant (p < .05). Transient "peak effects" markedly overestimated the maximum effects after all doses. We then compared the incremental doses of hydralazine, given either every 8 or every 12 hr, with respect to (1) the hemodynamic changes induced, and (2) the relative incidence of acute side effects. Maximal increases in CO were similar when hydralazine was given every 8 hr (16 patients) and every 12 hr (21 patients), and ranged from +14% after 50 mg to +61% after 200 mg. After the 150 and 200 mg doses, marked sustained increases in CO were present at 8 hr and mild increases in CO were still present at 12 hr. Hydralazine every 8 hr was associated with side effects in 25% to 86% of patients, but when the drug was given every 12 hr it was associated with side effects in only 5% to 19% of patients (p < .001). We conclude that (1) there are significant variations in control hemodynamics over time, (2) time-related effects should preferably not be compared with a single pretherapy baseline but instead should be compared, by repeated-measures ANOVA, with a value from a control group, (3) transient peak effects should preferably not be used to analyze time-related hemodynamic changes, (4) oral hydralazine given in 150 to 200 mg doses every 12 hr induces marked increases in CO and moderate sustained effects over 12 hr, with a lower incidence of acute side effects. This regimen would be expected to improve patient compliance and long-term benefits.

Circulation 72, No. 4, 865-872, 1985.

HYDRAZINE has beneficial hemodynamic effects in patients with congestive heart failure1-2 and those with valvular regurgitation.3-7 Optimal oral doses of hydralazine have usually been determined by increasing the dose every 3 to 6 hr7-10; however, in some of these studies maximal effects were seen only after 24 hr8,10 and the incidence of side effects was high, ranging from 41% to 50%.7-9 Moreover, the hemodynamic effects of therapy were evaluated by comparing a single "peak effect" to a single pretherapy baseline value rather than to a value from a control group of patients who were not treated.

The present study was undertaken (1) to determine spontaneous changes in values for various hemodynamic parameters in patients with chronic severe aortic regurgitation who were not receiving hydralazine therapy (control group), (2) to determine whether the conclusions regarding optimal hydralazine doses are different if the drug effects are analyzed by comparison with a single baseline determination, a single peak effect, or the values from a control group (spontaneous...
changes), and (3) to determine the optimal effective level and frequency of dose of oral hydralazine that induces sustained beneficial hemodynamic effects with minimal side effects.

Methods

Patient population. Thirty-seven patients (six women and 31 men) with symptomatic, severe, chronic aortic regurgitation were studied. Their mean age was 48 years (range 21 to 70). All patients reported dyspnea (NYHA functional class II or III); other symptoms included occasional chest pains in three patients and palpitations or dizziness after exertion in five patients. All patients had peripheral and cardiac findings of severe aortic regurgitation, and all had 3+ to 4+ aortic regurgitation demonstrated by aortic root cineangiography. The angiographic left ventricular ejection fraction was 0.55 ± 0.15 (mean ± SD) and ranged from 0.26 to 0.80. Five patients had mild mitral regurgitation and none had mitral stenosis. Four had 30% to 50% stenosis in one coronary artery. In one patient who had undergone mitral valve replacement previously, the prosthetic mitral valve function was demonstrated to be normal by clinical findings, hemodynamic data, and angiography. The cause of the aortic regurgitation was judged to be congenital in four, remote endocarditis in four, presumed rheumatic disease in eight, and idiopathic in 21.

Hemodynamics. Diagnostic cardiac catheterization studies were performed in all patients, after which the right heart balloon flotation catheter used for the diagnostic study was left in place. Patients were monitored for 18 to 24 hr in the intensive cardiac care unit. After this observation period, recordings were made of the following at predetermined intervals: (1) heart rate (HR) and blood pressure, (2) right atrial, pulmonary arterial, and pulmonary arterial wedge (PAW) pressures by use of the Statham P23Db transducer with the zero level at the midsternal position, and (3) cardiac output (CO) by the thermodilution method and with use of an average of three determinations. The usual calculations were made for derived hemodynamic parameters.11

Spontaneous changes. Spontaneous changes in all hemodynamic parameters were determined, without intervention, in 21 patients with chronic aortic regurgitation. There were 18 men and three women with a mean age of 48 years (range 21 to 62). With the patient resting supine in bed, hemodynamic data were collected at an index time (0 hr) and then 1, 2, 4, 6, 8, 10, and 12 hr later. The average value for each parameter for each patient was calculated over the 12 hr observation period. The spontaneous change for each patient was then calculated as the coefficient of variation (CV% = standard deviation SD/mean × 100).12 The average of these coefficients of variation for all 21 patients is reported as the spontaneous change in each parameter. The mean baseline value without intervention was also used to calculate percent changes in each parameter after intervention. Since the coefficient of variation has the same denominator, it can be directly compared with the percent change in each parameter after each dose of hydralazine.

Hydralazine dose schedules. Incremental doses of hydralazine (50, 100, 150, and 200 mg doses) were given to determine dose-response relationships. Because the clinical goal is to maintain a therapeutically significant increase in CO without a return to the control value and without side effects, there was no washout period between doses.

In 16 patients, the doses of hydralazine listed above were given every 8 hr. There were 13 men and three women with a mean age of 52 years (range 23 to 70). Hemodynamic data were collected just before each dose was administered and 1, 2, 4, 6, and 8 hr later. End points that precluded further increases in dose were an increase in CO of 50% or more for 8 hr; adverse effects, including tachycardia of 140/min or more for 1 hr; or symptoms of intolerable palpitations, flushing, or dizziness.

In 21 patients, the same incremental doses were given every 12 hr. There were 18 men and three women with a mean age of 48 years (range 21 to 62). Hemodynamic data were collected just before each dose was administered and 1, 2, 4, 6, 8, 10, and 12 hr later. The same end points were used to preclude further increases in dose.

Statistical analysis. Hemodynamic data were analyzed by one-way repeated-measures analysis of variance (ANOVA) and by the Student-Newman-Keuls multiple-range tests when overall statistical significance was achieved.13,14 Single comparisons were performed with Student’s t test for paired data. Analyses were performed with the use of the CLINFO system and the SAS statistical package on the IBM 370 system at the University of Southern California. The proportion of patients who experienced side effects on either regimen was compared with the Mantel-Haenszel chi-square statistic.15 Here death was the side effect and time was dose; this approach seemed best for the analysis of data in a situation in which there was patient attrition.

Results

Group comparison. Baseline characteristics were compared in 21 patients receiving hydralazine every 12 hr and the 16 patients receiving hydralazine every 8 hr. There were no significant differences with respect to age, functional class, Estes left ventricular hypertrophy score on the electrocardiogram, resting left ventricular ejection fraction, or resting CO between these two groups.

Spontaneous changes. Spontaneous changes in CO over 12 hr without intervention are shown in figure 1. Mean COs ranged from 4.9 to 5.4 liters/min (p = .03).

Spontaneous changes in hemodynamic parameters over 12 hr as measured by the coefficients of variation are listed in table 1. The spontaneous changes in CO (8.9%), mean arterial pressure (6.3%), and HR (7.1%) were relatively small; larger variations were encountered in other parameters, for example, mean PAW (18.4%) and right atrial pressure (37.8%).

Comparison of dose effects. We analyzed changes in CO over 12 hr by the four following methods after administration of incremental doses of hydralazine: (1) by determining changes at single times after each dose by Student’s t test for paired data, (2) by determining changes over time by repeated-measures ANOVA and comparing them with a single baseline CO, (3) by determining changes over time by ANOVA and comparing them with internal control values, and (4) by determining peak effect CO retrospectively and applying the paired t test.

Changes at single times by t test. Figures 2 and 3 (middle panels) show the mean CO for 21 patients over the 12 hr after the 50 and 100 mg doses of hydralazine were
Changes in CO at each time are compared with a baseline determination obtained before the 50 mg dose by paired t test. Probability values, listed at the bottom of each figure, show "significant" changes even for very small increases from baseline.

Changes over time compared with a single baseline value. Changes over time were also analyzed by repeated-measures ANOVA and compared with a single baseline value. Probability values are listed at the bottom of figures 2 and 3. None of these changes were significant after the 50 mg dose (p < .07), while changes of +16% above the baseline CO were significant after 100 mg of hydralazine.

Changes compared with internal control values. Changes over time were also compared with internal control values (spontaneous changes) over 12 hr. Probability values are listed at the bottom of figures 2 and 3. No changes were significant after the 50 mg dose, and increases in CO of +20% were significant after 100

mg of the drug. Thus, after low doses of hydralazine, the importance of small-to-moderate changes in CO and the duration of effects were overestimated unless internal controls were incorporated into the analysis.

Changes over time or transient peak effect. Table 2 compares two methods of determining maximal effects of oral hydralazine on CO. Peak effect CO is the maximum CO determined for a patient after each dose, regardless of time after dose. It occurred from 2 to 6 hr after the dose and most often occurred 2 hr after the higher doses. Peak effects were compared with baseline values by paired t test. The mean effects at 2, 4, and 6 hr after each dose were compared with the same baseline values by repeated-measures ANOVA.

For all doses, the peak effect COs were uniformly higher than those obtained over time. After the 50 mg dose, the transient peak effect CO was much higher than any average CO 2 to 6 hr after the dose. This peak effect was statistically significant while none of the changes in CO over time were significant at p < .05 (figure 2). After higher doses, the p values for the peak

Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean value</th>
<th>Average coefficient of variation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>74</td>
<td>7.1</td>
</tr>
<tr>
<td>CO</td>
<td>5.2</td>
<td>8.9</td>
</tr>
<tr>
<td>Stroke volume index</td>
<td>39.8</td>
<td>12.0</td>
</tr>
<tr>
<td>Mean right atrial pressure</td>
<td>4.5</td>
<td>37.8</td>
</tr>
<tr>
<td>Mean pulmonary artery pressure</td>
<td>20.9</td>
<td>13.2</td>
</tr>
<tr>
<td>Mean PAW pressure</td>
<td>12.1</td>
<td>18.4</td>
</tr>
<tr>
<td>Mean systemic arterial pressure</td>
<td>82.3</td>
<td>6.3</td>
</tr>
<tr>
<td>Systemic vascular resistance</td>
<td>1250</td>
<td>11.1</td>
</tr>
<tr>
<td>Pulmonary vascular resistance</td>
<td>115</td>
<td>33.6</td>
</tr>
</tbody>
</table>

FIGURE 1. Spontaneous changes in CO over 12 hr in 21 patients with chronic severe aortic regurgitation. Changes were statistically significant by repeated-measures ANOVA (p = .032). The means for hour 2 and hour 10 were significantly different (p < .05) by the Student-Newman-Keuls multiple-range test.

FIGURE 2. Change in CO over 12 hr after 50 mg oral hydralazine in patients with aortic regurgitation. Top, Individual baseline and peak effect CO. Middle, Mean changes over time. Bottom, Analyses of changes over time by t test, ANOVA compared with a single baseline value (B), and ANOVA compared with spontaneous changes (SC).
TABLE 2
Maximal effects of oral hydralazine given every 12 hr on CO: comparison of changes over time and transient peak effect

<table>
<thead>
<tr>
<th></th>
<th>50 mg dose</th>
<th>100 mg dose</th>
<th>150 mg dose</th>
<th>200 mg dose</th>
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<tr>
<td></td>
<td>CO</td>
<td>p value</td>
<td>CO</td>
<td>p value</td>
</tr>
<tr>
<td>Baseline</td>
<td>5.1 ± 1.0</td>
<td>—</td>
<td>5.4 ± 1.3</td>
<td>—</td>
</tr>
<tr>
<td>Peak effecta</td>
<td>6.3 ± 0.8</td>
<td>.001</td>
<td>7.2 ± 1.8</td>
<td>.001</td>
</tr>
<tr>
<td>Mean effect atb:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 hr</td>
<td>5.5 ± 1.2</td>
<td>NS</td>
<td>6.2 ± 1.9</td>
<td>.05</td>
</tr>
<tr>
<td>4 hr</td>
<td>5.7 ± 1.0</td>
<td>NS</td>
<td>6.7 ± 1.3</td>
<td>.01</td>
</tr>
<tr>
<td>6 hr</td>
<td>5.8 ± 0.8</td>
<td>NS</td>
<td>6.1 ± 1.1</td>
<td>.05</td>
</tr>
</tbody>
</table>

NS = p > .05.

aBaseline vs a retrospectively determined peak effect CO evaluated by paired t test.

bBaseline vs mean CO 2, 4, and 6 hr after each dose analyzed by repeated-measures ANOVA and Student-Newman-Keuls multiple-range tests.

Effect COs were uniformly smaller than those for the COs over time. Thus, retrospectively selecting the peak effect markedly overestimates the maximal response to hydralazine and may lead to a likely erroneous conclusion that the lower doses of hydralazine are "effective.”

Dose response

Response to dosing every 8 hr. When hydralazine was given every 8 hr, the maximal changes in CO were seen 2 to 6 hr after each dose (figure 4). The maximal increase after the 50 mg dose was 17% (p = NS). CO increased +32% 2 hr after the 100 mg dose (p < .01), +47% 2 hr after the 150 mg dose (p < .01), and +53% 2 hr after the 200 mg dose (p < .01). However, with doses above 100 mg, CO did not return toward the range of spontaneous changes (baseline ± 8.9%) at 8 hr, but remained 27% (p < .05) to 42% (p < .01) above the baseline value.

Changes in values for other hemodynamic parameters at the time of these maximal effects on CO showed that the 53% increase in CO after the 200 mg dose was associated with an increase in HR of 20% (p < .05), an increase in stroke volume index of 36% (p < .01), a decrease in mean arterial pressure of −9% (p = NS), and a decrease in systemic vascular resistance of −49% (p < .01). PAW pressure remained within the range of spontaneous changes.

The magnitude of each response in each individual patient was also evaluated (figure 5). After 50 mg of hydralazine increases in CO of 10% to 29% were seen only on one or two determinations in 57% of patients, increases of 30% to 49% were seen only on one or two determinations in 44% of patients, and increases of 50% or more on one or two occasions or increases of 30% to 49% on three or more determinations were rare. However, after 150 mg of the drug, increases in CO of 50% or more and increases of 30% to 40% on
three or more determinations were seen in approximately one-third of the patients. Increases in CO of 50% or more persisted at 8 hr in 25% of patients after the 150 mg and in 43% of patients after the 200 mg dose.

*Response to dosing every 12 hr.* When hydralazine was given every 12 hr maximal changes in CO were also seen 2 to 6 hr after each dose and were similar to those seen with the 8 hr schedule (figure 6). The increases in CO after 50 mg ranged from 11% to 14% (p = NS). CO increased +32% 2 hr after the 100 mg dose (p < .01), +45% 2 hr after the 150 mg dose (p < .01), and +61% 2 hr after the 200 mg dose (p < .01). Mild-to-moderate increases in CO persisted at 12 hr. For example, after the 150 mg dose, CO remained 18% (p < .01) above the baseline value; after the 200 mg dose, the CO remained 30% (p < .01) above baseline.

Changes in values for other hemodynamic parameters at the time of these maximal effects on CO showed that the 61% increase in CO after the 200 mg dose was associated with an increase in HR of 24% (p < .01), an increase in stroke volume index of +32% (p < .01), a decrease in mean arterial pressure of −4% (p = NS), and a decrease in systemic vascular resistance of −33% (p < .01). PAW pressure remained within the range of spontaneous changes.

The magnitude of each response in each individual patient was also evaluated (figure 5). Patient responses after the 50 and 100 mg doses given every 12 hr were similar to responses in those given the same doses every 8 hr. After 150 mg, however, increases in CO of 30% to 49% persisted over three or more determinations, or to 8 hr after dosing, in 25% of patients. Increases in CO of 50% or more persisted for three or more determinations, or to 8 hr, in 20% to 38% of patients. After 200 mg of drug increases in CO of 30% to 49% were seen on three or more determinations in 33% of patients and at 8 hr in 44% of patients. Increases in CO of 50% or more that persisted for three or more determinations were seen in 33% of patients. Note that at 12 hr increases in CO of 30% to 49% were seen after both the 150 and 200 mg doses in 30% of patients, but increases of 50% or more were seen in only 10% to 19% of patients.

*Side effects.* When hydralazine was given every 8 hr,
the incidence of acute side effects with each successive dose increased from 25% at 100 mg to 86% at 200 mg (table 3). Twelve patients experience palpitations, two had dizziness, and one had tachycardia. However, when hydralazine was given every 12 hr, the incidence of acute side effects with each dose ranged from 5% at the 100 mg dose to 19% at the 200 mg dose. Four patients experienced palpitations; four had dizziness. Tachycardia, hypotension, and flushing were not observed. The chi-squared test revealed that the increased incidence of side effects with the 8 hr dosage schedule was significant ($\chi^2 = 10.0, p < .001$, table 3).

**Discussion**

**Spontaneous changes in hemodynamic parameters.** Our data show that for patients with severe aortic regurgitation, spontaneous changes in various hemodynamic parameters range from 7% to 37% (table 1); moreover, these changes over time can reach statistical significance without intervention (figure 1). Therefore, the magnitude of spontaneous changes should be assessed to determine statistical and clinical importance of hemodynamic changes observed after therapeutic interventions.

**Importance of internal controls and statistical methods.** Our data demonstrate that changes in CO over time after hydralazine are best analyzed by repeated-measures ANOVA. Moreover, small changes in CO may reach statistical significance, even by ANOVA, when an arbitrary baseline CO is used for comparison (figure 3). We have shown that analyses that compare a single baseline determination and a retrospectively determined peak effect overestimate the statistical and clinical importance of effects of small and moderate doses (table 2). A comparison of changes over time after intervention with internal control values yields better statistical and clinical interpretations of the maximal effects and the duration of effects. Recently, Bailar et al. have emphasized that a study incorporating internal controls will support substantially stronger inferences than a study without internal controls; our present study demonstrates that for hemodynamic studies, internal controls that include spontaneous changes over time are important.

Previous authors, including ourselves and many others not cited, have reported hemodynamically “effective” doses of hydralazine in patients with heart failure.\(^2, 8-10\) or valvular regurgitation\(^3, 4, 6, 7\) based on an analysis that did not take spontaneous changes into consideration. It is therefore possible that these studies may have yielded overoptimistic and possibly erroneous conclusions regarding the beneficial effects of certain doses, optimal doses, and dosing schedules of hydralazine. This may also apply to the evaluation of effects of other therapeutic agents. Furthermore, it needs to be emphasized that a statistically significant change in parameter value does not necessarily imply the clinical significance of that change.

**Optimal doses of hydralazine in patients with aortic regurgitation**

**Comparison of dose intervals.** Our study demonstrates that higher doses of hydralazine (150 to 200 mg) given every 8 or 12 hr induce significant increases of 40% to 60% in CO in patients with chronic severe aortic regurgitation. These doses may thus induce maximal transient reductions in systemic vascular resistance, regardless of dosing interval. Much higher doses may be needed to induce further changes. These data are consistent with results of previous studies, which show that the peak hemodynamic effect is partially determined by the transient peak plasma level of hydralazine.\(^17\) These high doses, when given every 12 hr, but not when given every 8 hr, were well tolerated without cumulative hemodynamic effects and without a high incidence of acute side effects. The cumulative hemodynamic effects and incidence of side effects after repeated 200 mg doses of hydralazine were not determined in this study.

Over the short term, increases in CO after hydralazine are achieved in patients with aortic regurgitation at the expense of the regurgitant volume.\(^6, 18\) Peak increases in CO of over 50% have been associated with a decrease in regurgitant fraction from 0.64 to 0.48.\(^6\) Thus, only large increases in CO have been associated with significant reductions in regurgitant flow. The effects of lesser increases in CO on reductions in regurgitant fraction are not known. The long-term effects of hydralazine with respect to changes in CO are also unknown and need to be studied.\(^4, 19\) Of interest is the fact that in a previous study, oral doses of hydralazine beginning at 50 mg and increased in small increments

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**TABLE 3**

Hydralazine kinetics: incidence of acute side effects with incremental doses

<table>
<thead>
<tr>
<th>Oral dose of hydralazine (mg)</th>
<th>Incidence of side effects with dosing:</th>
<th>8 hr</th>
<th>12 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Every 8 hr</td>
<td>Every 12 hr</td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>4/16 (25%)</td>
<td>1/21 (5%)</td>
<td></td>
</tr>
<tr>
<td>150</td>
<td>5/12 (42%)</td>
<td>4/20 (20%)</td>
<td></td>
</tr>
<tr>
<td>200</td>
<td>6/7 (86%)</td>
<td>3/16 (19%)</td>
<td></td>
</tr>
</tbody>
</table>

$\chi^2 = 10.0; p < .001.$
every 4 to 6 hr induced transient marked increases in CO in only four of 10 patients with chronic severe aortic regurgitation. In doses of 50 and 100 mg, 5% to 25% of our patients had transient increases in CO; sustained increases in CO were rare. Doses of 150 to 200 mg of hydralazine given every 8 hr induced cumulative effects at 8 hr in 25% to 43% of our patients and the incidence of side effects was 25% to 86%. However, when hydralazine was given in doses of 150 to 200 mg every 12 hr, 30% to 45% of patients had persistent marked increases in CO, only 10% to 19% had cumulative increases at 12 hr, and the incidence of side effects was only 5% to 19%.

The small changes in PAW pressure observed in our patients have been noted previously. Large decreases would not be expected over the short term unless significant mitral regurgitation were present and were concomitantly reduced.

Previous optimization procedures. For patients with valve regurgitation and heart failure, hemodynamic monitoring and frequent increases of dose every 4 to 6 hr, with no washout period, have commonly been used to determine optimal doses of oral hydralazine. Some of these protocols have demonstrated further increased effects on CO after 24 hr on the same oral dose and the need to adjust medications over 24 to 72 hr. With usual doses of 300 to 400 mg/day a 21% incidence of early "nonresponders" who had excessive decreases in blood pressure, increases in HR, or adverse symptoms without an increase in stroke volume index has been demonstrated. These studies also noted a high incidence of severe late side effects that precluded further use of hydralazine. On the other hand, some patients may require unusually high doses to achieve beneficial hemodynamic effects. Thus, dose optimization procedures in which dose is increased every 4 or 6 hr may frequently induce acute side effects in individual patients before optimal increases in CO can be achieved with higher doses. Our data suggest that the side effects observed by others may have been due to cumulative biologic effects of the dosing schedules that were used, and could have been reduced by the every-12-hr schedule.

Pharmacokinetics of hydralazine. Pharmacokinetics of hydralazine have been studied previously in patients with systemic hypertension and with congestive heart failure. Small oral doses of about 1 mg/kg in patients with systemic hypertension resulted in decreased mean arterial pressure after 30 min; the peak effect was usually seen at 2 hr, and a sustained effect was seen for 8 to 12 hr. Changes in mean arterial pressure after a single effective dose were similar to changes after five of these low doses when hydralazine was given every 12 hr. Thus, low doses given every 12 hr induce minimal cumulative effects in hypertensive patients. Changes in mean arterial pressure have been related to peak plasma concentrations as determined by a specific assay method. However, sustained arteriolar effects are present at 8 to 12 hr and greatly exceed the plasma half-life of 10 to 15 min.

The major plasma metabolite of hydralazine (hydralazine pyruvic acid hydrzone) has no effect on blood pressure. Direct hydralazine binding to arterial smooth muscle cells, possibly by chelation, appears to be the mechanism of action. Thus, factors that affect first-pass metabolism through the liver will determine bioavailability (peak hydralazine levels) and, therefore, peak biologic effects. Hydralazine bioavailability increases after eating, decreases with hepatic congestion, and increases in patients with a slow-acetylator phenotype. Increased plasma levels after incremental doses are possibly due to saturation of the noninducible n-acetyl transferase system. Acetylator phenotype is a determinant of which patients will experience adverse symptoms. We have demonstrated that increasing maximal effects on CO are seen with incremental oral doses. We have also shown that similar maximal effects are seen after each dose from 50 to 200 mg, whether given every 8 or every 12 hr. Our findings are consistent with the previously demonstrated kinetics of hydralazine in hypertensive patients.

In conclusion, significant spontaneous changes in CO and other hemodynamic parameters occur over 12 hr in patients with severe aortic regurgitation. The statistical and clinical importance of lower doses (50 to 100 mg) of hydralazine are overestimated when single baseline determinations and transient peak effects are used to determine optimal doses. Use of internal controls plus evaluation of time-related effects by repeated-measures ANOVA provide "better" information regarding the effects, optimal dose, and proper dosing intervals for a pharmacologic intervention.

In patients with chronic severe aortic regurgitation, oral hydralazine given in doses of 50 and 100 mg induces transient increases in CO of 50% or more in a small percentage of patients (5% to 25%); however, sustained increases in CO are rare.

In patients with chronic severe aortic regurgitation, oral hydralazine given in doses of 150 to 200 mg induces significant sustained increases in CO, which have previously been demonstrated to be associated with significant decreases in regurgitant flow. Moreover, when these doses are given every 12 hr, they are associated with significantly fewer acute side effects.
than doses every 8 hr. Therefore, hydralazine may be
given in doses of 150 mg or more every 12 hr in these
patients. This regimen would be expected to improve
patient compliance, and thus long-term benefits. Re-
results of this short-term study should not be considered
to indicate benefits of long-term therapy with hydra-
lagen. Studies in progress are intended to provide data
on the long-term effects of this drug in patients with
chronic aortic regurgitation.23

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_Circulation_. 1985;72:865-872
doi: 10.1161/01.CIR.72.4.865

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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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:
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