A Prospective, Randomized, Double-Blind, Crossover Study to Compare the Efficacy and Safety of Chronic Nifedipine Therapy With That of Isosorbide Dinitrate and Their Combination in the Treatment of Chronic Congestive Heart Failure

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We performed a prospective, randomized, double-blind, crossover study to compare the efficacy and safety of vasodilation with the calcium entry blocker nifedipine with that of isosorbide dinitrate (ISDN) and their combination as treatment for heart failure. Twenty-eight patients with New York Heart Association Functional class II or III chronic heart failure due to left ventricular systolic dysfunction were studied. All patients were maintained on a constant dose of digitalis and diuretics throughout the study. Eight weeks of therapy with nifedipine alone or in combination with ISDN resulted in a significantly higher incidence of heart failure deterioration necessitating hospitalizations and/or additional diuretics. Twenty-four percent of patients required hospitalization during nifedipine therapy and 26% required hospitalization during nifedipine-ISDN combination therapy in comparison to 0% requiring hospitalization during ISDN therapy alone. The total number of heart failure–worsening episodes was nine among patients on nifedipine, three among patients on ISDN (p<0.001 versus nifedipine), and 21 among patients on nifedipine-ISDN combination (p<0.001 versus nifedipine, p<0.0001 versus ISDN). Premature discontinuation of drug administration due to clinical deterioration or other side effects occurred in 29% of patients during nifedipine therapy, 5% of patients during ISDN therapy (p=0.05 versus nifedipine), and 19% of patients during the combination therapy. A comparison of eight patients who demonstrated clinical deterioration on nifedipine with the remainder of the patients demonstrated no significant difference in left ventricular ejection fraction (0.24±0.06 versus 0.23±0.07) or maximal oxygen uptake during exercise (13±3 versus 14±2 ml/kg/min). A significant reduction in diastolic blood pressure was noted during therapy with nifedipine alone or in combination with ISDN (71±10 and 72±11 versus 80±12 mm Hg at baseline, both p<0.05) but not with ISDN alone (80±12 mm Hg). No significant change from baseline was noted in systolic blood pressure and heart rate during treatment with all three drug regimens. Treadmill exercise time demonstrated a comparable improvement on all three drug regimens 2 and 4 hours after drug administration (316±87 and 324±88 seconds at baseline, 398±118 and 413±121 seconds on ISDN, 389±87 and 411±109 seconds on nifedipine, and 372±92 and 384±100 seconds on nifedipine-ISDN combination therapy; p<0.05 versus baseline). These changes in exercise time, however, were not associated with a significant change in maximal oxygen uptake. We conclude that the administration of nifedipine alone or in combination with ISDN in patients with chronic heart failure due to left ventricular systolic dysfunction who demonstrate relative stability during ISDN therapy results in frequent clinical deterioration necessitating treatment. Worsening heart failure cannot be predicted by resting left ventricular ejection fraction or functional capacity as measured by maximal oxygen uptake. These findings demonstrate the potential hazard associated with the use of calcium entry blockers with nifedipine for vasodilation in patients with mild to moderate chronic heart failure due to left ventricular systolic dysfunction. (Circulation 1990;82:1954–1961)
The role of vasodilators in the treatment of chronic congestive heart failure (CHF) has been extensively studied during the past two decades. Several drugs with direct arterial vasodilator effects have demonstrated abilities to improve hemodynamic profile. More recently, hydralazine, the most frequently investigated arterial dilator, was used in combination with isosorbide dinitrate (ISDN) in a large, randomized trial and was reported to reduce mortality in patients with mild to moderate CHF. The benefits of these drugs, however, have been limited by a relatively high frequency of side effects, inconsistent response among patients, development of tolerance, and only a slight effect on clinical status and exercise capacity. These limitations and continuing poor prognoses of patients with chronic CHF explain the recommendations for continuing research in this field and the need for investigation of new pharmacological agents. Calcium entry-blocking agents have also been investigated for their potential applications as vasorelaxing drugs in patients with CHF. Nifedipine, a dihydropyridine derivative, has been the calcium entry blocker most extensively investigated in heart failure. This drug has a strong arterial dilatory effect resulting in a marked decrease in peripheral vascular resistance and augmentation of cardiac output and has been suggested by several investigators as an effective treatment for patients with heart failure. However, occasional reports of depression in cardiac performance attributed to the negative inotropic effect of nifedipine have raised concern regarding the usefulness and safety of this therapeutic approach. These conflicting results and the lack of controlled, long-term clinical trials clearly indicate the need for additional studies to further define the potential role of nifedipine in the treatment of patients with chronic heart failure due to left ventricular systolic dysfunction. The present study was therefore designed to evaluate the safety and efficacy of chronic arterial dilation with nifedipine alone and in combination with venodilation with ISDN compared with ISDN alone in patients with mild to moderate heart failure due to left ventricular systolic dysfunction who are treated with digoxin and diuretics.

Methods

Patient Selection

The present study was designed to include male or female patients between 18 and 75 years old who had a well-documented history of congestive heart failure of at least 1 month’s duration with symptoms consistent with New York Heart Association (NYHA) functional class II or III and left ventricular ejection fraction of less than 40%. All patients had to be capable of performing treadmill exercise testing and of remaining clinically stable on a constant maintenance dose of digitalis and diuretics during an initial stabilization period of at least 2 weeks. Exercise testing had to be limited by symptoms of congestive heart failure such as dyspnea or exhaustion.

Criteria for exclusion from the study were being pregnant, being of childbearing potential, or currently nursing; history of acute myocardial infarction within the first month before study entry; primary valvular disease as a reason for symptoms; angina pectoris; cardiomyopathy other than dilated congestive cardiomyopathy; significant primary pulmonary, hepatic, renal, or hematological disease; and inability to give informed consent.

Study Protocol

The study consisted of the following four phases (Figure 1).

Phase 1—Stabilization period. This phase consisted of a single-blinded, placebo, baseline period lasting for at least 2 weeks during which all patients continued to take digoxin and diuretics at their usual established dosage. All other vasodilators were discontinued, and each patient was instructed to take one nifedipine placebo capsule q.i.d. plus one ISDN placebo tablet q.i.d. Exercise treadmill test (ETT) was given to all patients at the end of the first and second weeks at 2 and 4 hours after dose administration with determination of maximal oxygen consumption (V̇O₂max). These two ETTS had to demonstrate a less-than-20% difference in exercise time at both 2 and 4 hours. When there was a more-than-20% difference between tests, the ETT was repeated within 3–6 days until two consecutive ETTS with exercise times of 20% or less were achieved.

After successful completion of phase 1, all patients were randomized to one of three possible double-blinded study drug regimens: 1) active nifedipine plus ISDN placebo, 2) active ISDN plus nifedipine placebo, and 3) active nifedipine plus active ISDN. Randomization was conducted according to a Latin square design by the use of a computer-generated randomization code. Dosage of study medications was titrated on a patient-by-patient basis according to the safety titration procedure outlined below.

Phases 2, 3, and 4—Efficacy periods. Phases 2–4 consisted of three identical double-blinded, study drug administration periods lasting for 8 weeks each. The study was designed for each patient to cross over to a different study drug treatment regimen every 8 weeks so that by the end of the study, all patients would have received all three treatment regimens in a random fashion. ETTS and V̇O₂max determinations were repeated at the end of each 8-week efficacy period at 2 and 4 hours after the dose.

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**Drug Safety Titration Procedure**

During all study phases, patients were taking a combination of capsules (either nifedipine or placebo) and tablets (either ISDN or placebo). The maximum dosage of study medications was two capsules (i.e., 2×10 mg) q.i.d. and two tablets (i.e., 2×20 mg) q.i.d. Dosage of study medications was titrated at the start of each 2-month efficacy period as follows: one capsule plus one tablet q.i.d. given for 3 days. If tolerated by the patient without significant adverse effects, dosage was increased to two capsules plus two tablets q.i.d. for the remainder of the 2-month efficacy period.

**Exercise Test**

A modified Naughton protocol was used for exercise testing. This protocol had 2-minute stages, beginning at a speed of 2 mph and 0% slope (2 mets) with incremental increases in speed and/or slope to achieve approximately 1 additional mets per stage. Respiratory measurements during treadmill exercise were taken with the use of a metabolic cart (Sensormedic MMC Horizon System). Respiratory response measurements and computations included VO₂ (ml/kg/min) and carbon dioxide production (VCO₂; ml/kg/min). Exercise testing was continued to achieve anaerobic threshold, which was determined by a respiratory gas exchange ratio (VCO₂/VO₂) exceeding 1.0 or 0.15 more than its resting value. All ETTs were performed after the second daily drug dose at approximately 2:00 and 4:00 PM.

**Data Analysis**

Five parameters were analyzed. First, exercise time to exhaustion was analyzed. Second, VO₂ max during exercise was analyzed, and the results of these evaluations were assessed at 2 and 4 hours after drug administration to evaluate the duration of effect in addition to its magnitude. Third, standing values of heart rate and systemic blood pressure were measured at 2 hours after drug administration and immediately before ETT. Fourth, clinical worsening of heart failure requiring hospitalization or temporary increase in diuretics was determined. Because initial diuretic dosage was maintained at a constant level during the study, a single dose of intravenous furosemide or oral hydrochlorothiazide (50 mg) or metolazone (5 mg) o.d. for 3 days was given to treat episodes of CHF worsening. Finally, side effects were analyzed. Patients who dropped out of the study due to symptomatic side effects or recurrent episodes of worsening heart failure were crossed over prematurely to the next treatment sequence as soon as they were stabilized. Diuretic dose was restored to the level of the baseline period in such cases before the crossover.

Analysis of variance for Latin square design and Newman-Keuls test were used to compare the effects of all three drug regimens on exercise time, VO₂ max, and upright heart rate and blood pressure. Differences in incidence of worsening CHF and other side effects were analyzed by χ² test. 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. Values are given as mean±SD. A probability value of less than 0.05 was considered statistically significant.

**Results**

**Patient Population**

Fifty-one patients with a history of heart failure entered the stabilization period. Twenty-three patients were excluded before randomization for non-compliance (eight patients), NYHA functional class I as determined by symptoms and VO₂ max of 20 ml/kg/min or more (six patients), worsening of heart failure (four patients), chronic obstructive pulmonary disease (two patients), angina-limiting ETT (two patients), and inability to walk on the treadmill (one patient). Twenty-eight patients were randomized and entered phase 2 of the study. There were 25 men and three women ranging in age from 35 to 71 years (mean±SD age, 55±10 years). The cause of CHF was coronary artery disease in nine patients and congestive cardiomyopathy in 19 patients. Eight of the patients were classified into NYHA functional class II and 20 into class III. Using the metabolic classification, 11 patients were in class B (VO₂ max,
16–20 ml/kg/min), and 17 patients were in class C (VO\textsubscript{max}, 10–15 ml/kg/min). The diagnosis of left ventricular systolic dysfunction was confirmed by radionuclide ventriculography in all patients. Left ventricular ejection fraction ranged from 0.08 to 0.35 (mean ejection fraction, 0.23±0.07).

Five randomized patients were excluded from the study due to noncompliance (two patients), psychiatric disorder (one patient), and loss to follow-up after the initiation of the study (two patients). Therefore, data analysis comprises the remaining 23 patients.

**Treadmill Exercise Time**

Two patients were discontinued from the study due to worsening of heart failure, and one patient died during phase 2; therefore, 20 of the 23 remaining patients completed at least phase 2 of the study and were included in the analysis of treadmill exercise time (Figure 2). Nineteen patients completed 8 weeks of ISDN therapy and had an ETT at the end of their treatment period, 15 patients completed nifedipine treatment, and 17 patients completed their treatment period with combination therapy. Baseline exercise time at 2 hours after placebo administration was 316±87 seconds and increased to 398±118 seconds after 8 weeks of ISDN therapy, to 389±97 seconds after nifedipine therapy, and to 372±92 seconds after ISDN-nifedipine combination therapy. ETT time values as measured on all three drug regimens did not differ among each other but were significantly longer than baseline ($p<0.05$). A similar significant increase in exercise time was seen at 4 hours after drug administration: 324±88 seconds at baseline, 413±121 seconds on ISDN, 411±109 seconds on nifedipine, and 384±100 seconds on their combination ($p<0.05$ versus baseline). No significant difference was noted between exercise time values obtained at 2 and 4 hours. Analysis of treadmill exercise time in 14 patients who completed all three treatment periods demonstrated similar values on ISDN, nifedipine, and their combination at 2 hours (405±133, 378±90, and 383±93 seconds, respectively) and at 4 hours (410±135, 401±106, and 396±103 seconds, respectively).

**Maximal Oxygen Uptake**

VO\textsubscript{max} during exercise changed from baseline values of 14.0±2.6 and 14.9±3.6 at 2 and 4 hours, respectively ($n=20$), to 15.5±4.1 on ISDN at both 2 and 4 hours ($n=18$), 15.8±2.5 and 16.1±2.8 ml/kg/min on nifedipine ($n=14$), and 15.2±2.5 and 13.9±3.9 ml/kg/min on ISDN-nifedipine combination ($n=15$) (Figure 3). No significant differences were found between measurements performed at 2 and 4 hours during baseline or after each drug treatment.

**Heart Rate and Blood Pressure**

A significant reduction in diastolic blood pressure was noted during therapy with nifedipine alone or in combination with ISDN (71±10 and 72±11 versus 80±12 mm Hg during baseline; both $p<0.05$) (Figure 4). In contrast, no change in diastolic blood pressure was noted on ISDN alone (80±12 mm Hg). Systolic blood pressure was 118±15 mm Hg at baseline, 109±18 mm Hg on nifedipine, 118±15 mm Hg on ISDN, and 115±20 mm Hg on the combination. No significant differences were found among these values. Similarly, there were no significant differences among heart rate values at baseline (90±12 beats/min) and on nifedipine (87±11 beats/min), ISDN (87±13 beats/min), or their combination (86±11 beats/min).

**Hospitalizations and Need for Additional Diuretics**

Five of 21 patients (24%) who received nifedipine were hospitalized for worsening CHF (Table 1). This number of patients was comparable to the number of patients hospitalized for the same indication during therapy with nifedipine and ISDN in combination (six of 23, or 26%) but significantly higher than that...
seen during therapy with ISDN alone (none of 20, or 0%). In addition, three patients required additional
doses of diuretics for worsening CHF symptoms
when on nifedipine. Similar therapy was required in
two patients during nifedipine-ISDN therapy
\((p=NS)\) and in three patients during ISDN therapy
\((p=NS)\). The total number of heart failure–worsening
episodes requiring therapy was nine on nifedi-
pine, three on ISDN \((p<0.09\) versus nifedipine), and
21 on nifedipine-ISDN combination \((p<0.001\) versus
nifedipine and \(p<0.0001\) versus ISDN).

Analysis of the results during the first study period
showed four CHF-worsening episodes on nifedipine,
two on ISDN, and nine on nifedipine-ISDN combi-
nation \((p<0.05\) versus ISDN). Only one such event
was recorded within the first week after drug cross-
over in a patient who was switched from ISDN to
nifedipine-ISDN combination. A comparison of
the eight patients who demonstrated clinical deterio-
ration on nifedipine with the remainder of the patients
showed no significant differences in left ventricular
ejection fraction \((0.24\pm0.06\) versus \(0.23\pm0.07\)) or
\(\text{Vo}_{\text{O}}_2\) max \((13\pm3\) versus \(14\pm2\) \text{ml/kg/min}).

Other Side Effects

Sixty-eight percent of the patients had new adverse
signs or symptoms during treatment with nifedipine.

Table 1. Episodes of Hospitalizations and Increase in Diuretics for Worsening Congestive Heart Failure

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients (n)</th>
<th>Hospitalizations</th>
<th>Increase in diuretics dose</th>
<th>Total</th>
<th>CHF episodes (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nifedipine (NIF) (n=21)</td>
<td></td>
<td>5*</td>
<td>3</td>
<td>8</td>
<td>9†</td>
</tr>
<tr>
<td>Isosorbide dinitrate (ISDN) (n=20)</td>
<td></td>
<td>0</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>NIF+ISDN (n=23)</td>
<td></td>
<td>6*</td>
<td>2</td>
<td>8</td>
<td>21‡‡‡</td>
</tr>
</tbody>
</table>

CHF, congestive heart failure.

\*\(p<0.05\) versus ISDN; \#\(p<0.09\) versus ISDN; \$\(p<0.0001\) versus ISDN; \$\(p<0.001\) versus NIF.
severe worsening of CHF and cardiopulmonary arrest (one patient).

Discussion

The present study demonstrates an increased incidence of cardiovascular morbidity during 8 weeks of therapy with nifedipine in patients with heart failure who demonstrate relative stability during ISDN therapy. The use of nifedipine resulted in worsening CHF and hospitalization or intensive diuretic therapy in 38% of the patients. In 32% of the patients, dose reduction or premature discontinuation of therapy were necessary mainly due to worsening CHF, fatigue, or symptomatic hypotension. The clinical deterioration during nifedipine therapy seen in the present study was probably caused by previously demonstrated concomitant arterial dilatory and myocardial depressant effects of nifedipine in patients with CHF due to inhibition of intracellular calcium influx. Although nifedipine-mediated reduction in cardiac muscle force development in patients with normal left ventricular systolic function is usually offset by the vasorelaxing effect of the drug and its consequent reflex augmentation of β-adrenergic activity, this protective mechanism often fails in patients with chronic CHF in whom baroreceptor sensitivity is known to be markedly attenuated. Such a depression in baroreceptor responsiveness may explain the lack of change in heart rate in the present study and in sympathetic response to nifedipine in previous studies despite a significant decrease in systemic blood pressure. Although direct depression of myocardial contractility is the most likely mechanism of clinical deterioration during nifedipine therapy, a previously reported increase in plasma renin activity with nifedipine may lead to an increased angiotensin II level and thus to worsening of CHF due to its vasoconstrictive action as well as its stimulation of sodium and water retention.

The findings of clinical deterioration secondary to nifedipine therapy are in accordance with previous reports from our group and others demonstrating hemodynamic and clinical worsening after nifedipine administration in patients with CHF. Agostoni et al compared the effects of captopril with those of nifedipine in a double-blind, placebo-controlled, crossover fashion. Although a significant improvement was reported by these investigators with captopril, nifedipine therapy resulted in increased body weight and worsening of symptoms in many of the patients. Similarly, a preliminary report by Packer et al described symptomatic deterioration in 29% of CHF patients after a single dose of nifedipine.

A previous report by our group on the spectrum of hemodynamic response to nifedipine described deterioration in 19% of 31 patients with severe chronic CHF. Hemodynamic deterioration could not be predicted by any baseline hemodynamic value or left ventricular function. Similarly, analysis of left ventricular function or VO₂max obtained at baseline in the present study revealed no difference between eight patients demonstrating clinical worsening of CHF on nifedipine and the remainder of the patients. These findings suggest that clinical deterioration during nifedipine therapy cannot be predicted.

In contrast to ISDN, nifedipine resulted in a significant decrease in diastolic systemic blood pressure. Similar findings have been previously described with acute administration of the drug to similar patient populations. Although initial therapy with nitrates has also been reported to reduce blood pressure in patients with CHF, this response has been shown to be significantly attenuated with chronic therapy.

Despite a higher incidence of clinical deterioration with nifedipine and the combination therapy in comparison to ISDN alone, no difference was noted in change in exercise time and VO₂max during treatment with the three drug regimens studied. These findings may seem paradoxical and are probably explained by intensive use of additional diuretic agents for worsening heart failure in some patients during nifedipine therapy and by the exclusion of others who demonstrated clinical deterioration during therapy, thus biasing the data in favor of the drug. In addition, previous studies of vasodilator therapy for heart failure have shown that effective therapy exhibits a progressive improvement in exercise time that may take 12 weeks or longer to reach its maximum; thus, the study period may not have been long enough to separate the effect of ISDN from that of nifedipine. Total exercise time on all three drug regimens was significantly longer than the time recorded during prerandomization baseline evaluation. Because the study was designed to compare the effects of all three regimens with each other rather than with that of placebo, the analysis of changes in exercise performance within each group may not be valid, and it is therefore unclear whether this improvement can be attributed to the drugs. Similar improvement in exercise performance was reported during placebo therapy in patients with heart failure and may be attributed to training effect, improvement of overall patient care, and increased motivation during the trial. Despite the increase in exercise time seen with all three treatments, no significant change was noted in VO₂max, demonstrating failure to increase capacity of oxygen transport to exercising muscles. A similar discrepancy between changes in exercise duration and VO₂max was reported by Wilson et al to be associated with increased levels of lactate, and these changes have been attributed to increased motivation to perform. Another potential explanation of our findings, however, may be a delay in the onset of anaerobic metabolism and lactate accumulation due to drug-mediated increased blood flow to exercising muscles at submaximal load, resulting in prolongation of total exercise duration without change in VO₂max.

Reports of the effects of calcium antagonists on exercise performance in patients with heart failure...
are limited. A previous study by Agostoni et al. demonstrated no significant improvement in exercise time during 2 months of nifedipine therapy. Similarly, the use of felodipine, a new calcium antagonist vasodilator, also failed to improve exercise capacity in patients with CHF of moderate severity.6

Although the present study population is larger than those of previously published trials evaluating long-term effect of calcium entry-blocking agents in patients with CHF, the total number of patients is limited. This limitation is partially corrected by the crossover design of the trial, which allows direct comparison of all three treatments in the same patients. Such an approach eliminates the influence of difference in patient characteristics seen in parallel group design.67 Inability to assess all three treatments in every patient due to death or premature crossover is an inherent weakness of the crossover design and may also limit the results of the present study. A comparison of all three drug regimens when given during the first study period, however, supports the overall results of the study, which demonstrate a higher incidence of CHF-worsening episodes on nifedipine alone and nifedipine-ISDN combination than on ISDN alone.

The conclusions drawn in the present study regarding drug effect on clinical status could have been strengthened if carry-over effects from one agent to the next could be excluded. Because treatments were given consecutively in a crossover fashion, there is no simple way to assess for carry-over effects. A paucity of CHF-worsening episodes within the first week after crossovers, however, suggests a low likelihood of carry-over effects. In addition, the marked contrast in clinical status during the ISDN treatment period and the other two treatment periods using nifedipine should rule out residual effect of ISDN as a cause for clinical deterioration during subsequent treatment. Our findings are also supported by those from previous studies demonstrating either stability or symptomatic improvement with ISDN37,40 or hemodynamic as well as symptomatic deterioration with nifedipine.10,11

ISDN has been widely used for the treatment of chronic CHF and has been served in the present study as a reference treatment for the assessment of the safety and efficacy of arterial dilation with nifedipine. The selection of the 40-mg dose of ISDN given four times daily as a standard treatment in this study was based on reports indicating the long-term efficacy of this drug and dose.3,37,40,48 During the time required to complete the present study, doubt had been raised regarding the real efficacy of nitrates in the treatment of CHF.49 In addition, findings of resistance to the standard ISDN dose in many patients50 and demonstration of early tolerance development to frequent dosing intervals51,52 resulted in recommendations for the use of higher dosages given only twice or thrice daily.40,51 The present study demonstrated a favorable clinical course and side-effect profile during therapy with ISDN alone compared with nifedipine. However, with the lack of a concomitant placebo period, the absolute effect of ISDN cannot be determined. Our study, however, clearly demonstrates that the addition of 40 mg ISDN given four times daily does not prevent nifedipine-mediated clinical deterioration as indicated by a similar number of patients who had worsening of CHF episodes during therapy with this drug combination.

Summary

The present study compared in a prospective, randomized, and double-blind fashion the effect of 8 weeks of vasodilator therapy with nifedipine, ISDN, and their combination in patients with mild to moderate chronic heart failure (NYHA functional classes II and III). The outcome of this trial indicates that despite similar effects of all three drug regimens on exercise performance, the use of nifedipine alone or in combination with ISDN is associated with a significantly higher incidence of clinical deterioration and worsening of CHF. Deterioration in clinical status was not predictable by pretreatment severity of CHF as manifested by ejection fraction or functional classification determined by VO_{2\text{max}}. These findings substantiate previous reports of hemodynamic deterioration with short-term nifedipine therapy and demonstrate the potential hazard associated with the use of this drug in patients without active myocardial ischemia who have chronic CHF due to left ventricular systolic dysfunction.

References


**Key Words**: maximal oxygen consumption • vasodilators • exercise • clinical trials
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