Intravenous Nitroglycerin in the Treatment of Spontaneous Angina Pectoris: A Prospective, Randomized Trial

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SUMMARY A prospective, randomized study of i.v. nitroglycerin (TNG) in the management of repetitive spontaneous angina pectoris was undertaken in 40 consecutive patients. The clinical effectiveness of i.v. TNG (group A) was compared with that of oral isosorbide dinitrate (ISDN) and topical 2% nitroglycerin ointment (NO) in combination (group B) during a 72-hour treatment period. The doses of both nitrate regimens were adjusted so that the mean arterial pressure in the two groups was reduced by 15 ± 3% of control values to the same level (77 mm Hg). The i.v. TNG dose of 10–200 μg/min yielded arterial plasma TNG levels of 1.2–65.3 ng/ml and estimated plasma (arterial) clearance of 106 ± 55 ml/min/kg of body weight (mean ± SD). In group B, the doses were 20–60 mg (oral ISDN) and ½–2 inches (NO) every 6 hours. Intravenous TNG reduced the number of spontaneous ischemic episodes from 3.3 ± 0.8 per 24 hours during the control period to 1.0 ± 0.3 per 24 hours during the treatment period (p < 0.01), while the ISDN/NO combination reduced the number of episodes from 3.1 ± 0.4 to 1.4 ± 0.3 (p < 0.01). Overall, the magnitude of the therapeutic effect of i.v. TNG was statistically indistinguishable from that of ISDN/NO, although i.v. TNG did have somewhat greater clinical benefit on day 2 of the 3-day treatment period. Furthermore, the data suggested more consistent control of ischemic episodes with i.v. TNG during the first 24 hours of the trial. Although both regimens markedly reduced the frequency of spontaneous ischemic episodes, only 36% of patients in group A and 17% in group B experienced no ischemic episodes during the study period (NS). Forty-three percent of patients in group A and 61% in group B (NS) required early coronary artery bypass surgery to control recurrent ischemic episodes refractory to medical therapy.

We conclude that i.v. TNG and ISDN/NO, when administered in doses adjusted to produce similar effects on systemic arterial pressure, have nearly equivalent clinical effects in the management of patients with frequent episodes of spontaneous angina pectoris. Intravenous TNG offers the advantage of more consistent control of ischemic episodes during the first 24 hours of treatment. Nevertheless, the recurrence rate of spontaneous ischemic episodes during medical therapy is high with both regimens, and early coronary artery bypass surgery may be required for long-term management.

SUBLINGUAL NITROGLYCERIN (TNG) has been used for over a century in the treatment of ischemic heart disease, but the use of i.v. TNG is a more recent therapeutic approach. Information indicating a beneficial effect of i.v. TNG has been reported for patients with acute myocardial infarction, left ventricular failure, and intraoperative hypertension. However, i.v. TNG is being used more frequently in hospitalized patients with unstable angina pectoris, especially those with recurrent episodes of spontaneous (rest) angina. Recent studies suggest that periodic reductions in regional coronary perfusion, mediated at least in part by coronary artery spasm, may trigger episodes of spontaneous angina. Maintenance of sustained plasma levels of a coronary vasodilator such as TNG by continuous infusion therefore might prevent spontaneous ischemic episodes. In support of this contention, several studies have suggested a significant and sometimes dramatic therapeutic effect of i.v. TNG in this clinical setting. Unfortunately, none of these studies included a randomized control, which is especially important in assessing the therapeutic efficacy of antianginal agents because of the spontaneous variability in the occurrence of ischemic episodes.

We therefore performed a prospective, randomized trial comparing the therapeutic effect of i.v. TNG with that of oral isosorbide dinitrate (ISDN) in combination with 2% nitroglycerin ointment (NO) in patients with repetitive episodes of spontaneous angina. Although we might have chosen other regimens, we studied these two long-acting agents because they are commonly used together to manage refractory unstable angina.

Methods

Patient Population

Forty consecutive patients of both sexes admitted to the coronary care units of the Dartmouth-Hitchcock Medical Center with a diagnosis of unstable angina pectoris who satisfied the following entry criteria were prospectively enrolled in this investigation. All patients had sustained at least two episodes of spontaneous myocardial ischemia during a 48-hour pretreatment control period. In 38 of 40 patients, ischemic episodes were accompanied by typical cardiac pain or discomfort; in two patients, some ischemic episodes were reflected only by spontaneous electrocardiographic changes not accompanied by symptoms. To confirm that symptoms were related to myocardial ischemia, we required that chest pain last less than 15
minutes in duration and be associated with reversible ischemic electrocardiographic changes, consisting of ST-segment elevation or depression $\geq 1$ mm or pseudonormalization of T waves in one or more leads. Because chest pain due to myocardial ischemia is not always accompanied by electrocardiographic changes, typical symptoms associated with no or minimal ECG changes were acceptable criteria if the pain lasted at least 15 minutes and if the patient had other objective evidence of coronary artery disease (e.g., history of typical exertional angina, positive exercise stress test, or documented myocardial infarction). Thus, patients selected for this study had repetitive spontaneous ischemic episodes and would be classified as having type IB or C or type II (severe) unstable angina according to the criteria of Chahine. All patients gave written informed consent.

Patients were excluded from the investigation if the initial systolic arterial pressure was less than 90 mm Hg, if the patient had known intolerance to nitrates, or if angina developed in relation to valvular heart disease, cardiomyopathy, or significant anemia (hematocrit $< 30\%$). Patients with other serious intercurrent illnesses or a medical condition that might militate against aggressive antianginal therapy (e.g., advanced malignancy, multiorgan failure) were also excluded.

In all patients, plasma samples for creatine kinase and its myocardial-specific fraction (CK-MB) were drawn immediately and every 8 hours for a total of four determinations. Twelve-lead ECGs were performed with each blood sampling. In seven patients, these studies indicated that a myocardial infarction had occurred before entry into the study (elevation of CK to twice the normal level with 4% or greater MB fraction) and that the presumptive diagnosis of unstable angina was in error. These patients were excluded from further study according to criteria established before the investigation. One additional patient withdrew himself before completion of the 3-day drug trial. Thus, 32 patients who had spontaneous angina and no evidence of acute infarction were included in the final analysis.

Drug Administration

Patients fulfilling these criteria were randomized to treatment for a 72-hour study period with i.v. TNG (group A) or with a combination of ISDN and 2% NO (group B). TNG solutions were prepared by the hospital pharmacy by dissolving 30 mg of TNG tablets (Lilly) in 30 ml of sterile water. The resulting solution was filtered through a 0.22-$\mu$ Millipore filter and further diluted in sterile 5% dextrose in water to a final concentration of 120 $\mu$g/ml. Because TNG in solution can be adsorbed by plastic bags and tubing, solutions were prepared in glass bottles and infused through a standardized 252-cm length of polyvinylchloride tubing. TNG infusions were initiated at a rate of 5 $\mu$g/min using a constant-volume infusion pump. Infusion rates were increased by 5 $\mu$g/min every 5 minutes until the systolic arterial pressure was reduced by 20% of its control value (but in no case $< 90$ mm Hg) or until an infusion rate of 200 $\mu$g/min had been reached. Arterial pressure was monitored continuously in both treatment groups with an indwelling 18-gauge radial artery cannula connected to a Hewlett-Packard 78304A bedside monitor. The initial oral dose of ISDN (Ives) in group B patients was 20 mg and the initial dose of 2% NO (Kremers-Urban) was 0.5 inch (5.8 mg nitroglycerin) applied over a standardized surface area of 54 cm2. Doses of both ISDN and NO were repeated every 6 hours in a staggered fashion so that each patient received one drug or the other every 3 hours. Doses of ISDN were increased by 20 mg every 6 hours and doses of 2% NO were increased in 1-inch increments every 6 hours to reduce the systolic arterial pressure by 20% of control, but not below 90 mm Hg. The maximal dose of ISDN was 60 mg every 6 hours and the maximal dose of 2% NO was 2 inches every 6 hours. Thus, drug doses in both treatment groups were adjusted to achieve the same magnitude of reduction of systemic arterial pressure. This approach allowed valid comparison of the clinical effects of the different drugs used in this investigation.

"Standard" antianginal therapy, which was received by patients in both treatment groups A and B, consisted of bedrest in the coronary care unit, supplemental oxygen, and sedation with oral diazepam. Beta-adrenergic blocking agents (propranolol or metoprolol) were administered every 6 hours to reduce the resting heart rate to 45–60 beats/min. An increase in heart rate by more than 25% above control during an ischemic episode was also an indication for increasing the dose of $\beta$ blocker. Spontaneous ischemic episodes during the study period were managed with sublingual TNG or i.v. morphine sulfate or (in group A patients) by transiently increasing the i.v. TNG infusion rate.

Clinical Data

The number of spontaneous ischemic episodes experienced by each patient was quantitated daily by the investigators using specially designed data collection sheets. In addition to noting episodes of chest discomfort and obtaining 12-lead ECGs during these episodes, the investigators identified ischemic events by observing spontaneous shifts in the ST segments of a centrally monitored electrocardiographic lead. The electrocardiographic lead that demonstrated the most marked change during ischemic episodes was monitored. Two patients had ST-segment deviation without associated symptoms. Patients who experienced two or more episodes of spontaneous ischemia while receiving doses of organic nitrates sufficient to reduce systolic arterial pressure by 20% of its control value and a $\beta$ blocker sufficient to lower the heart rate to 45–60 beats/min were considered candidates for early coronary angiography and coronary artery bypass surgery if appropriate coronary lesions were identified. Based on previous data, these patients were considered to have a high risk of progressing to acute myocardial infarction with medical therapy alone. Patients who had a particularly high frequency of spontaneous ischemic attacks (at least four per 24 hours) while receiving the antianginal therapy described...
above were considered candidates for intraaortic balloon counterpulsation before coronary angiography. Thus, the criteria for coronary angiography, bypass surgery, and intraaortic balloon counterpulsation were standardized for both treatment groups.

Coronary angiography was performed percutaneously from the femoral artery. Cineangiograms were filmed at a speed of 64 frames/sec. Sublingual TNG was used during the angiograms only to treat episodes of spontaneous angina or to investigate the possibility of coronary artery spasm. Procedures to provoke coronary artery spasm were not used routinely. Coronary angiograms were reviewed independently by two of the investigators. Interpretations were subsequently compared and cases of disagreement were resolved by consensus.

Nitrate Plasma Levels

Blood samples for determination of plasma TNG and ISDN levels were drawn when a maximal stable drug dose had been reached. In group A, samples were drawn at least 2 hours after the optimal infusion rate was achieved. In group B, samples were drawn 6 hours after the previous dose of ISDN and 3 hours after the previous dose of NO. Samples were obtained from arterial lines in 15 patients and by venipuncture in two patients. Blood samples were drawn into tubes containing EDTA and immediately placed on ice. Plasma was separated by centrifugation at 3000 rpm and 4°C, and was frozen at −20°C until assay. TNG and ISDN assays were performed by gas chromatography, as previously described and validated.25,26

Statistical Methods

Data are expressed as the mean ± SD. The significance of change in the frequency of ischemic episodes with treatment within groups was evaluated both by paired t test and by analysis of variance. The significance of differences in frequency of ischemic episodes between groups was evaluated by the t test for unpaired data. Clinical outcomes of different treatment groups (i.e., need for coronary artery bypass surgery) were compared by chi-square test. Differences were considered significant if p < 0.05.

Results

Patient Profiles

Clinical profiles of patients in groups A and B are shown in table 1. The groups were similar with respect to age, sex, angina pattern, history of myocardial infarction, pattern of electrocardiographic changes with angina, prevalence of congestive heart failure and prior antianginal therapy. Although patients in group B tended to receive higher prestudy doses of ISDN than patients in group A, the differences between mean doses of ISDN were not statistically significant because of scatter in the data. No patient had received long-acting nitrates for at least 6 hours before the study, but 23 of 32 patients had received long-acting nitrates as part of their previous antianginal therapy. Because patients in group B tended to receive higher doses of ISDN before entry into the study, they might have developed greater tolerance to ISDN than patients in group A. This possibility cannot be proved or disproved from our data. These data generally support the adequacy of the randomization process, although more patients in group B than in group A had no ECG changes during angina.

Pharmacologic and Hemodynamic Data

The mean i.v. TNG infusion rate at steady state for the 14 patients in group A was 82 ± 98 µg/min (range 10–200 µg/min). The mean maximal daily doses of ISDN and 2% NO for the 18 patients in group B were 187 ± 121 mg/day (range 80–240 mg/day) and 5.6 ± 3.4 inches (65 ± 39 mg TNG) (range 2–8 inches/day). The mean daily doses of β blockers in group A were: propranolol 336 ± 234 mg (n = 10) and metoprolol 200 ± 200 mg (n = 4). In group B the doses of propranolol were 262 ± 184 mg (n = 12) and of metoprolol 213 ± 118 mg (n = 4). Metoprolol was used in place of propranolol in the eight patients who had a history of chronic obstructive pulmonary disease.

*Mean ± SD.
†More than 8 weeks before entry into study.
‡Within 8 weeks of entry into study.
Abbreviations: ST † = ST segment elevation; MI = myocardial infarction; ST ‡ = ST segment depression; TW ‡ = T-wave inversion; CHF = congestive heart failure; IVTNG = intravenous nitroglycerin; ISDN/NO = isosorbide dinitrate/nitroglycerin ointment.
or heavy cigarette smoking. There were no significant differences between the final doses of propranolol or metoprolol in the two treatment groups. Doses of β blockers were titrated during the 72-hour study period to maintain a resting heart rate of 60 beats/min or less. Increasing doses of β blockers were required to achieve this target heart rate during the study period, presumably because of reflex increases in heart rate in response to increasing doses of nitrates. The magnitude of the dose increases were similar in the two patient groups (table 1). Because doses of β blockers increased during the study period, at least some of the clinical improvement in the two treatment groups might have been due to β-blocker therapy.

Nitrate plasma levels drawn during periods of optimal dosing were available in seven patients in group A and 10 patients in group B. Plasma TNG concentration for patients in group A ranged from 1.2 to 65.3 ng/ml (mean 18.4 ± 24.3 ng/ml). If it is assumed that steady-state drug concentration was achieved, the arterial plasma clearance of TNG can be estimated (infusion rate ÷ steady-state concentration) to be 7.9 ± 4.6 l/min (range 2.7–16.7 l/min) or, when corrected for body weight, 106 ± 55 ml/min/kg (range 36–190 ml/min/kg). In group B, plasma ISDN concentrations measured 6 hours after dosing were 0.1–42.5 ng/ml (mean 15.9 ± 12.9 ng/ml), and plasma TNG levels measured 3 hours after NO administration were 0.1–2.4 ng/ml (mean 1.3 ± 0.5 ng/ml). Eight of 10 patients in group B received a final dose of 60 mg of ISDN and 2 inches of NO; in this subgroup, the mean plasma ISDN and TNG concentration at the specified times were 16.4 ± 12.1 ng/ml and 1.7 ± 0.5 ng/ml, respectively.

Figure 1 presents data on systemic arterial pressure during the control and treatment periods for groups A and B. The control systolic, diastolic and mean arterial pressures of the two groups were statistically indistinguishable. During the treatment period, systolic, diastolic and mean pressures declined significantly (p < 0.001), by 22%, 17% and 18%, respectively, in group A and by 12%, 14% and 13%, respectively, in group B. The resulting levels of systolic (107 mm Hg), diastolic (62 mm Hg) and mean (77 mm Hg) arterial pressure were identical in the two groups. Thus, the doses of i.v. TNG and ISDN/NO were appropriately adjusted to result in equivalent systemic arterial pressures. Although the control mean systolic arterial pressures in the two groups were not statistically different, the mean systolic pressure in group A was 13 mm Hg higher than that in group B (fig. 1). Therefore, it is possible that afterload reduction contributed more to the clinical efficacy of nitrate treatment in group A than in group B.

Clinical Data

The 32 patients had 203 episodes of spontaneous ischemia during the 48-hour control period. Figure 2 shows individual patient data on the frequency of ischemic episodes during the control and treatment periods for the two groups. Patients in group A experienced an average of 3.3 ± 0.8 ischemic episodes per 24 hours during the control period, and patients in group B experienced 3.1 ± 0.4 episodes (NS). During treatment, the frequency of ischemic episodes declined by 70%, to 1.0 ± 0.3 per day in group A (p < 0.01), and by 55%, to 1.4 ± 0.3 per day in group B (p < 0.01). These data were virtually identical when the seven patients who did not have ECG changes during chest pain were omitted from the analysis. Thus, both i.v. TNG and ISDN/NO effectively reduced the frequency of spontaneous ischemic episodes. The reductions in the number of ischemic episodes in the two treatment groups were not significantly different when assessed by analysis of variance or by comparing the means before and after treatment by the t test for independent samples. The frequency of ischemic episodes actually increased during the treatment period in one patient in group A (7%) and in three patients in group B (17%) (NS).

Figure 3 displays data on the frequency of ischemic episodes during the control period and on each of the three successive days of the treatment period for the two groups. The frequency of ischemic episodes was significantly lower on day 2 in patients receiving i.v. TNG (p < 0.001), but on days 1 and 3 the frequencies
of ischemic events were not different in the two treatment groups (NS). Thus, a breakdown of the data in this fashion revealed somewhat more therapeutic benefit on day 2 with i.v. TNG that was not apparent from the pooled data in figure 2. Nevertheless, this small additional beneficial effect was not evident on days 1 and 3, and its clinical significance is uncertain. Most, if not all, of the therapeutic effects of both treatment regimens were fully expressed within 24 hours, and the therapeutic effects were sustained for the remainder of the 72-hour treatment period.

Despite the significant decline in the frequency of ischemic episodes with both treatment regimens, figures 2 and 3 show that spontaneous ischemic episodes continued to occur in both groups at a lower frequency during therapy. Thus, it proved difficult in these patients with severe recurrent spontaneous angina to control spontaneous ischemic events completely, even with intensive medical therapy. Only five of 14 patients (36%) in group A and three of 18 (17%) in group B became free of ischemic events during treatment (NS). Six of 14 patients (43%) in group A and 11 of 18 patients (61%) in group B required early coronary angiography and coronary artery bypass surgery (NS). Surgery was undertaken in these patients because they had sustained two or more episodes of spontaneous ischemia while receiving optimal doses of their nitrate and β-blocker preparations. These patients were considered candidates for coronary angiography and bypass surgery according to established criteria because of previous data suggesting that they were at high risk for infarction or death with medical therapy alone. Four patients in the series (13%) (two in group A and two in group B) required intracoronary balloon counterpulsation because of a particularly high frequency of ischemic episodes (four or more per 24 hours) while receiving sufficient doses of nitrates and β blockers to achieve the target arterial pressure and heart rate. There were four deaths, two in group A and two in group B. Two patients (one in group A and one in group B) died of extensive acute myocardial infarction during the treatment period. One of these two patients had refused cardiac surgery that was recommended because of persistent rest angina despite medical therapy. Two patients (one in group A and one in group B) died during coronary bypass surgery, one of aortic dissection and the other of perioperative myocardial infarction.
The side effects of nitrate therapy observed in this study included hypotension (systolic arterial pressure < 90 mm Hg requiring temporary discontinuation of nitrates) and headache. The incidence of these side effects in the two patient groups were similar: i.v. TNG caused hypotension in three of 14 and headache in three of 14, and ISDN/NO caused hypotension in six of 18 and headache in one of 18. Hypotensive episodes were more common during sleeping hours in both groups. Methemoglobin levels were not measured in this study.

Although i.v. TNG and ISDN/NO produced nearly equal therapeutic effects in this short-term trial, we wondered whether i.v. TNG might offer the advantage of more immediate or consistent control of ischemia during the initial hours of treatment, for the infusion rate can be titrated rapidly to achieve the desired hemodynamic effect. To address this question the fraction of total ischemic episodes during the first 24 hours of treatment was plotted as a function of time in 6-hour intervals for the two groups (fig. 4). These data show that i.v. TNG produced rapid and sustained control of ischemic episodes during the initial 24 hours of therapy, but patients treated with ISDN/NO demonstrated a recurrence of ischemic episodes between 12 and 18 hours. Systolic blood pressure at 6, 12, 18 and 24 hours of treatment was 125, 119, 108 and 122 mm Hg, respectively, in group A and 113, 112, 112, and 112 mm Hg, respectively, in group B. Thus, the changes in blood pressure and frequency of ischemic episodes during the first 24 hours of treatment (fig. 4) tended to be parallel in the two groups.

Of the 25 patients who underwent coronary angiography, three (12%) had one-vessel disease, seven (28%) two-vessel disease and eight (32%) three-vessel disease. Four patients (16%) had 50% or greater stenosis of the left main coronary artery. Three patients (12%) had normal coronary anatomy. These patients might have had coronary artery spasm, but provocative tests were not performed to establish this diagnosis.

Discussion

The results of this study indicate that both i.v. TNG and ISDN/NO administered concurrently with β-adrenergic blocking agents markedly reduced the frequency of spontaneous ischemic episodes in patients with recurrent episodes of spontaneous angina. When the doses of nitrates are adjusted to produce similar effects on systemic arterial pressure, there appears to be only modest therapeutic advantage derived from i.v. TNG compared with ISDN/NO. The overall frequency of ischemic episodes during the 72-hour treatment period was statistically the same in the two groups, although on day 2 of the trial, patients treated with i.v. TNG had significantly fewer episodes. One special advantage of i.v. TNG was more consistent control of ischemic episodes during the first 24 hours of treatment, presumably due to more effective titration to the optimal nitrate dose. Although both treatment regimens resulted in a significant decline in the frequency of ischemic episodes, neither regimen consistently abolished all ischemic episodes. Only 36% of patients treated with i.v. TNG and 17% of patients treated with ISDN/NO (NS) became free of ischemic events during the treatment period. Approximately half of the patients in both treatment groups required early coronary angiography and subsequent coronary artery bypass surgery because of intractable ischemia not controlled by medical therapy alone. Indications for coronary angiography and bypass surgery were standardized in this study to permit valid comparison of these data for the two treatment groups. Thus, the data suggest that intensive medical therapy with nitrates and β blockers has therapeutic limitations in patients with repetitive episodes of spontaneous angina. Similar results have been reported by others.17

Measurement of plasma concentrations in this study was not intended to allow detailed pharmacokinetic analysis of the treatment regimens, but rather to confirm absorption and systemic availability of nitroglycerin and ISDN from the different routes and dosage forms of administration. The arterial plasma TNG concentrations and clearance values obtained after i.v. TNG were similar to those observed by Armstrong et al.8 in patients with congestive heart failure who responded to TNG treatment. In another study by Armstrong et al.,23 administration of 1–2 inches (12.5–25 mg) of NO to nine patients with congestive heart failure yielded a mean plasma TNG concentration of about 3 ng/ml 3 hours after application, compared with a mean concentration of about 2 ng/ml in our study. Fung et al.26 showed recently that after 1 week of ISDN, 60 mg four times daily, the mean plasma ISDN concentration 6 hours after dosing was about 10 ng/ml,
compared with a concentration of 16.4 ± 12.1 ng/ml in the present study. The results suggest that with the different routes and dosages used here the systemic availability of nitrates was similar to that in other studies.

Several methodologic considerations deserve attention. First, the patient population was relatively small. Nevertheless, the total number of ischemic episodes experienced by the patient population as a whole during the control period was large, and this number was used to determine the clinical efficacy of nitrate therapy. The results of this study are specifically applicable, therefore, to a selected group of patients with unstable angina who experience frequent episodes of spontaneous ischemia, a subpopulation in whom i.v. TNG would probably be selected for therapeutic use. Second, patients in both treatment groups received a β-adrenergic blocking agent in addition to nitrate therapy. Doses of β blockers were titrated during the treatment period to maintain a resting heart rate of 45–60 beats/min. Increasing doses of β blockers were required to achieve this target heart rate during the study period, presumably because of reflex increases in heart rate in response to increasing doses of nitrates. Therefore, at least some of the clinical improvement during the treatment period may have been due to β blockade. However, the doses of β blockers and the magnitudes of the dose increases in the two treatment groups were statistically equivalent. Finally, because an i.v. preparation was being compared with oral and topical agents used together, and because the doses of both drug regimens were individually titrated to produce a specific hemodynamic effect, it was not possible to carry out the study in a blinded fashion.

We conclude that i.v. TNG is a useful agent in the management of patients with repetitive spontaneous angina, but that much of its therapeutic benefit can be reproduced with conventional nitrate therapy using ISDN and 2% NO. Intravenous TNG may be especially useful for consistent control of frequent spontaneous ischemic events during the initial hours of therapy. Despite intensive medical treatment using either nitrate regimen in conjunction with β-blocking agents, a substantial number of patients with recurrent spontaneous angina continue to experience ischemic episodes not controlled by medical therapy, and coronary artery surgery may need to be considered for subsequent management.

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