Sublingual Nitroglycerin: Improving Patient Compliance With A Demonstration Dose

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Abstract: Forty-four patients were studied for compliance in the use of their first prescription for sublingual nitroglycerin. Fourteen HMO physicians participated in this randomized, prospective study by administering the first dose to half the patients during the office visit in which the diagnosis of angina pectoris was made. No other changes were made in the physicians' customary methods of diagnosing and treating angina pectoris. Patients who received the demonstration dose were significantly more likely to have used the sublingual nitroglycerin at least once before their second visit (75 percent of the study group compared with 44 percent of the control group). There was no difference between the groups in having the drug with them at the second visit. While serious reactions to sublingual nitroglycerin are rare, 6 patients experienced symptoms from the first dose, including 1 patient who fainted. The results suggest that compliance in using the initial prescription for sublingual nitroglycerin can be improved when the physician supervises the first dose. (J Am Bd Fam Pract 1988; 1:251-4.)

Sublingual nitroglycerin (NTG) has been widely accepted as safe and effective therapy for angina pectoris,[1,2] since it was first recommended for use more than 100 years ago.[3] It is effective not only for the acute anginal attack but also as a prophylaxis before such activities as vacuuming or mowing the lawn or before emotionally stressful situations that are known or expected by the patient to induce angina.[4] NTG is rapidly absorbed from the sublingual mucosa, having its maximal effect at 3 to 15 minutes.[5] It is believed that NTG lowers myocardial oxygen demand through venodilation and a decline in systemic vascular resistance, thus reducing blood pressure, intracardiac pressures, and left ventricular size.[6]

NTG has proved to be remarkably free of serious side effects or complications. Common side effects include headache, flushing, palpitation, nausea, postural hypotension, and reflex tachycardia.[7] The individual response to nitrates is, however, quite unpredictable. Blood pressure usually falls slightly, but it may drop considerably when the patient is upright. The resulting hypotension and reflex tachycardia may be hazardous to patients with severe coronary disease. Severe bradycardia with profound hypotension has been reported after sublingual NTG administration.[8,9] Because potentially serious reactions occurred in 4 of 110 patients studied, Prodger recommended that the first dose of sublingual NTG should be given under physician supervision and that the dose should be low (0.15 to 0.3 mg).[10] The doses producing those reactions were higher (0.6 to 1.3 mg) than are commonly used today.

There have been no patient compliance studies of sublingual NTG use, although experience suggests that compliance is less than ideal. Despite presumably clear patient instruction and education about the need for and use of NTG, patients frequently report continued anginal symptoms without using a single tablet as prescribed. Commonly given reasons are that the angina was brief or not severe. There may be other significant emotional reasons for this failure in compliance, such as fear of taking the drug or reluctance to accept the diagnosis of heart disease.

This study was undertaken to determine whether the initial patient compliance in the use of sublingual NTG could be improved by giving the first dose under the physician's direct supervision. This demonstration dose would be given when the diagnosis of angina was first made, but not while the patient was having acute symptoms. The physician's presence might be reassuring and help overcome possible psychological barriers. The patient could become familiar with any side effects and discuss them immediately with the

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physician, who would also be able to provide care in the unlikely event of a serious reaction.

Methods

Fourteen family physicians participated in the study and each treated from 1 to 6 patients. All physicians and patients were members of a large health maintenance organization, and the study was conducted in an outpatient setting. Physicians were asked to include all patients with a new diagnosis of angina pectoris. Those with suspected acute myocardial infarction or unstable angina requiring hospitalization were excluded, as were patients who had previously taken NTG or any other antianginal medications. No other selection criteria were used. Neither a firm diagnosis nor any testing was required, because a clinical diagnosis of angina based on history alone is commonly the sole basis for the initial prescription of sublingual NTG. Physicians followed their usual practices in evaluating the symptoms, diagnostic workup, and educating the patient about angina and the use of NTG. There was no limitation on the concomitant use of other antianginal agents after the initial visit. These methods were the same for both the control and study groups. Because this study dealt with patient compliance, patients were not made aware of the nature of the study, and patient permission was not sought or believed to be required ethically because no unusual treatment was involved. Patients are commonly instructed to take sublingual NTG prophylactically in the absence of symptoms before exertion. The only difference here was the added medical supervision of the first dose.

Each physician was given several sealed envelopes, one of which was opened at random after identifying a patient who fit study guidelines. The instructions assigned the patient to the test group or control group. For both groups, there was the same brief data summary sheet on which the physician noted the character and frequency of the angina. If a demonstration dose of sublingual NTG was to be given, it was given with the patient seated and any side effects were recorded. The demonstration was usually sublingual nitroglycerin (Nitrostat™) 0.4 mg. One patient received 0.15 mg. Information was gathered during two office visits—first at the time the diagnosis was made and again at the subsequent return visit, generally between 2–5 weeks, at which time patients were asked whether they had taken the sublingual NTG since the previous visit and whether it relieved their symptoms. Patients were also asked whether they had the NTG tablets with them at the time of that return visit, another important aspect of NTG compliance.

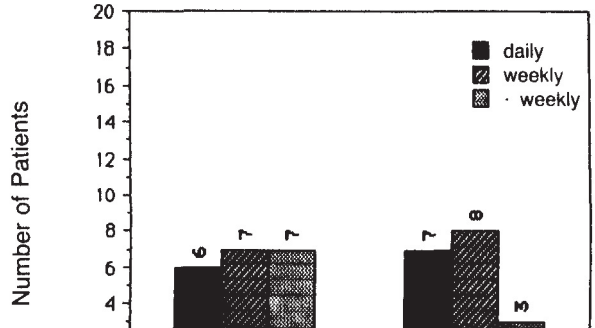

Figure 1. Frequency of angina.

Forty-four patients (21 men, 23 women) completed the second visit, but 6 were excluded from the study. Two were hospitalized before the second office visit, and 4 others were excluded because physicians had not followed the study protocol. Specifically included, however, were patients who claimed to have had no further anginal symptoms, because this could be a manifestation of denial and noncompliance.

Results

Frequency of angina at the time of diagnosis was similar in both groups (Figure 1) and ranged from a single episode (2 patients) to daily attacks.

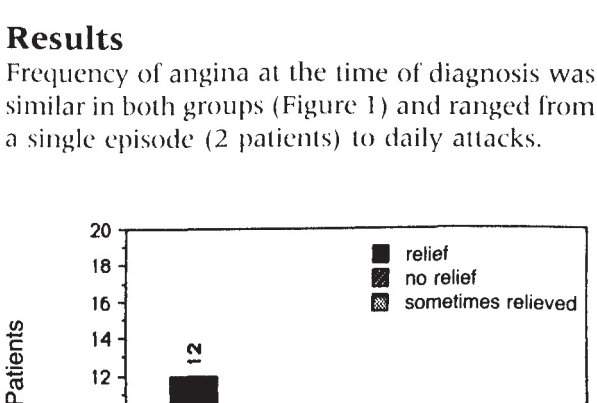

Figure 2. Reported relief of anginal symptoms.

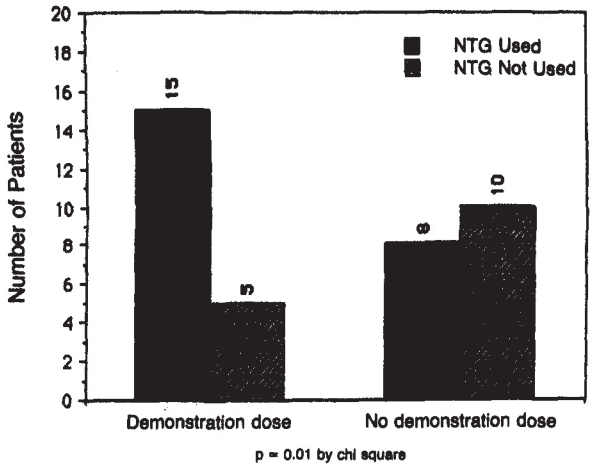

Figure 3. Patients using NTG at least once since prior visit.

The demonstration dose of NTG was given to 20 patients at the initial visit; 18 did not receive it. Both groups were managed in the physician's usual fashion, and physicians were asked to note any unexpected or untoward reactions. Six of the patients who received the test dose experienced reactions. None of these reactions proved to be serious, although the 1 patient who fainted serves to demonstrate a potentially significant problem.

In both groups, patients who used their NTG between visits reported similar relief of their symptoms (Figure 2).

The most notable finding was that patients who received the demonstration dose were significantly more likely to have used the sublingual NTG at least once before their return visit (Figure 3). The association between the demonstration dose and compliance in taking NTG at least once was significant using the chi-square test ($P = 0.01$).

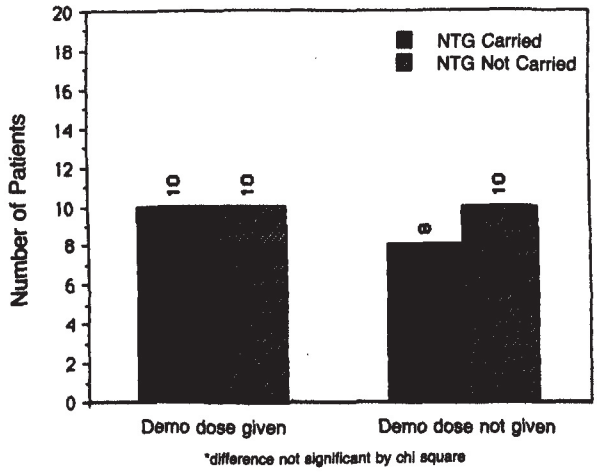

Figure 4. Patients carrying NTG at time of return visit.

Patients given a demonstration dose were somewhat more likely to have their NTG with them at the time of their return visit, though this difference was not statistically significant (Figure 4). Whether patients had complied in using their NTG one or more times was not correlated with their compliance in having the NTG with them at the return visit. Among patients who used their NTG at least once, there was no correlation between relief of their anginal symptoms and carrying NTG with them at their second visit. It is of particular note that in the entire study group fewer than half of the patients had their NTG with them at the time of the second visit.

Discussion

This prospective study shows that patient compliance in using the initial prescription of sublingual NTG for angina is improved when patients are given a demonstration dose in addition to the physician's usual instructions and patient education.

Table 1. *Side Effects from the Demonstration Dose of NTG.*

1 Fainted*
1 Dizzy, like tranquilizer
1 Warm face, tight head
1 Mild headache*
1 Minimal lightheadedness
1 Headache, blurred vision

*Patient excluded from original sample.

In this study, only 1 patient experienced a significant reaction (i.e., fainting) from the demonstration dose. Clearly, this type of reaction can be dealt with better in the physician's office than at home or elsewhere. While the previously reported frequency of serious reactions to NTG may not seem to warrant a demonstration dose on the basis of safety alone, the supervision is a distinct advantage in instances when reactions occur. Having the physician available to discuss even minor side effects after the initial dose offers immediate feedback as well as providing reassurance. With the hope of avoiding any serious reactions and to minimize first dose side effects, it might be reasonable to consider using a lower demonstration dose of sublingual NTG.

One potential source of error in the study is that the patient population was not homogeneous, even with clear study guidelines; but this is precisely the mixed group of patients with whom physicians must deal in their practices. Some patients had more serious coronary disease than others, although the reported frequency of angina was similar in the two groups (Figure 1), and some might later prove not to have angina at all. Another potential for error is that after randomly assigning patients to either the control or study groups, physicians were not blinded and could have unintentionally instructed the two groups differently. The fact there was a significant difference in NTG use (Figure 3) but not in carrying NTG (Figure 4) suggests that this source of bias did not occur. The two measures of compliance were chosen because they showed: (1) whether the NTG was used at all between the two visits, and (2) whether patients brought their NTG with them at the time of the return visit. Using the NTG at least once suggests that the patient overcame any psychological barrier, and carrying the drug on one's person is another form of compliance especially appropriate to sublingual NTG. It is similar to epinephrine for beesting anaphylaxis and inhaled bronchodilators for asthma; the drugs are of no use if they are not immediately available. Interestingly, physicians commonly use a demonstration dose in teaching the use of inhalers and encourage practice injection with normal saline. The surprisingly low number of patients (47 percent) who had their NTG with them at the return visit suggests a need for better techniques for educating new angina patients.

References

1. Goldstein RE, Epstein SE. Medical management of patients with angina pectoris. Prog Cardiovasc Dis 1972; 14:360-98.
2. Riseman J, Altman G, Koretsky S. Nitroglycerin and other nitrites in the treatment of angina pectoris. Comparison of 6 preparations and 4 routes of administration. Circulation 1958; 17:22-39.
3. Murrell W. Nitroglycerin as a remedy for angina pectoris. Lancet 1879; 1:80.
4. Winsor T, Berger HJ. Oral nitroglycerin as a prophylactic antianginal drug: clinical, physiologic, and statistical evidence of efficacy based on a three-phase experimental design. Am Heart J 1975; 90:611-26.
5. Abrams J. Nitroglycerin and long-acting nitrates. N Eng J Med 1980; 302:1234-7.
6. Epstein S, Redwood D, Goldstein R, et al. Angina pectoris: pathophysiology, evaluation, and treatment. Ann Intern Med 1971; 75:263-96.
7. Frishman W. Pharmacology of the nitrates in angina pectoris. Am J Cardiol 1985; 56:81-131.
8. Nemerovski M, Shah PK. Syndrome of severe bradycardia and hypotension following sublingual nitroglycerin administration. Cardiology 1981; 67:180-9.
9. Khan A, Carleton R. Nitroglycerin-induced hypotension and bradycardia. Arch Intern Med 1981; 141:984.
10. Prodger SH, Ayman D. Harmful effects of nitroglycerin. Am J Med 1932; 184:480-91.