Appropriateness of Nitrate Use in a General Medicine Population

Lotan Shilo, Ruth Hadari, Susy Kovatz, Mahmud Qasim, and Louis Shenkman

BACKGROUND: Nitrates are one of the most commonly prescribed drug groups for cardiac disease, especially for angina pectoris and congestive heart failure. The chronic efficacy of nitrates is limited by the development of tolerance, which can be attenuated by use of sustained-release preparations or administration of regular-release preparations asymmetrically.

OBJECTIVE: To determine whether patients receiving isosorbide 5-mononitrate (ISMN) use the drug in a pharmacologically appropriate manner and whether they had been instructed in the prophylactic use of sublingual nitrates prior to effort.

METHODS: We administered a questionnaire regarding details of nitrate use to 229 patients with ischemic heart disease using oral ISMN, prescribed prior to their current admission. The study was conducted in a 600-bed university-affiliated hospital.

RESULTS: We found that only 15% of patients receiving regular-release ISMN were taking the drug asymmetrically. In contrast, 82.6% of the patients receiving sustained-release ISMN were using the drug properly. Only 38.1% of the patients treated with regular-release ISMN were treated with the dose recommended in the literature. Furthermore, of the 190 patients who reported experiencing effort angina, only 17.9% had been instructed in the prophylactic use of nitrates prior to effort.

CONCLUSIONS: The majority of patients (85%) using regular-release ISMN were taking the medication in an inappropriate fashion, while most patients taking sustained-release preparations were using them properly. More than half the patients treated with regular-release ISMN were treated with doses exceeding the recommended dose. In addition, most patients experiencing effort angina had not been instructed regarding the prophylactic use of nitrates. These findings suggest that both physicians and pharmacists must be reminded of the continuing need to properly counsel patients regarding appropriate drug use.

KEY WORDS: isosorbide mononitrate, patient education.

lease oral nitrate preparations. For example, regular-release ISMN should be dosed in an asymmetric manner (taking the drug twice daily with an interval of 6–7 h between doses), or sustained-release preparations should be administered once daily. In addition, nitrates in doses higher than those recommended have been shown to be associated with rebound ischemia and the zero-hour effect (i.e., increased frequency of ischemic episodes prior to the morning dose). Therefore, dosage escalation is usually not recommended in most patients.

In this study, we evaluated whether oral nitrate preparations were being used correctly, patients treated with these drugs were instructed in the proper use of oral nitrate preparations, and the patients were instructed that sublingual nitrates can be used prophylactically before effort.

Methods

During a two-month period we administered a questionnaire to patients with ischemic heart disease who were receiving nitrate preparations that were prescribed prior to their current admission to the medical or surgical departments and to patients visiting the emergency department. All patients admitted during the hours of 0800–1800 who were receiving ISMN and were able to complete the questionnaire were interviewed. Patients who were admitted or seen in the emergency department because of an acute cardiovascular diagnosis (e.g., acute myocardial infarction, unstable angina, pulmonary edema) were excluded, as were patients who were treated with dinitrates. These patients were excluded to prevent the possible selection bias of including patients whose inappropriate use or dosing of nitrates contributed to their clinical deterioration. Patients treated with dinitrates were excluded because of the large number of preparations in use and the limited data regarding appropriate dosage. The study was conducted in a 600-bed university-affiliated hospital and was approved by the hospital’s ethics committee.

In addition to age, diseases, and indication for admission, the questionnaire included questions regarding nitrate use. The questions, which were asked by one of the physicians participating in the study, included:

1. type of nitrate preparation(s), dose, and duration of treatment;
2. time of day nitrates were taken, to determine whether the drug was taken asymmetrically;
3. if the nitrate preparation was changed, when, and why;
4. other medications used;
5. if the patient experienced anginal attacks — if yes, frequency, time of day, and the effort that usually causes angina;
6. if the patient was ever told that sublingual nitrates can be used prophylactically;
7. name and specialty of the physician who prescribed nitrates, to examine whether physician specialization affected the level of care (names of the physicians were included in the questionnaire to verify specialty and board certification);
8. whether the physician or the pharmacist instructed the patient in the use of the drug.

In addition, we interviewed eight pharmacists in four community pharmacies in the hospital’s catchment area and asked whether they instructed patients in the proper use of nitrates. We also interviewed five cardiologists, seven general internists, and seven family physicians and asked if they instructed their patients on the prophylactic use of nitrates and on asymmetric dosing. Finally, we examined written instructions and package inserts in the drug packages of 70 patients included in the study who entered the hospital with their medications.

Results

The questionnaire was administered to 229 patients (161 men) during the study period. The mean ± SD age of the patients was 64 ± 10.7 years. The details regarding nitrate use are presented in Table 1. One hundred sixty patients were treated with regular-release ISMN. One hundred thirty-six patients (85.0%) took the drug approximately 12 hours apart; only 24 patients (15.0%) took the drug asymmetrically, with an interval of 6–7 hours as recommended in the literature and product information. In contrast, 69 patients were treated with sustained-release ISMN; 57 (82.6%) were receiving the drug in an appropriate once-daily fashion (p < 0.001 between the two groups).

One hundred ninety patients (82.9%) experienced symptoms of chest pain during effort or emotional stress. One hundred fifty-seven (82.6%) of these patients were prescribed sublingual nitrate preparation. Sixty-five of these patients had symptoms during mild to moderate effort (climbing 1 flight of stairs or walking 50 m at a regular pace). Only 34 (17.9%) of all of these patients were instructed to use sublingual nitrate preparations prophylactically before effort; only 16 (24.6%) of the 65 patients with moderate to severe angina were given such instructions.

None of the eight pharmacists interviewed instructed patients on asymmetric dosing of nitrates, and the package label indicated only that the drugs should be taken once or twice daily, without referring to timing. Three of the eight pharmacists informed patients on the prophylactic use of nitrates before effort. Of the physicians interviewed, one of five cardiologists, one of seven general internists, and two of seven family physicians instructed their patients on asymmetric use of nitrates and on prophylactic use of the drug.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ISMN</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>regular-release</td>
<td>68</td>
<td>160 (69.9)</td>
<td>61 (38.1)</td>
<td>24 (15)</td>
</tr>
<tr>
<td>sustained-release</td>
<td>51.4</td>
<td>69 (30.1)</td>
<td>NR</td>
<td>57 (82.6)</td>
</tr>
<tr>
<td>Prophylactic sublingual nitrates</td>
<td>NR</td>
<td>190b</td>
<td>NR</td>
<td>34 (17.9)</td>
</tr>
</tbody>
</table>

ISMN = isosorbide 5-mononitrate; NR = not relevant.

*Asymmetric dosing for regular-release ISMN and once daily for sustained-release ISMN.

bTotal number of patients experiencing chest pain during effort or emotional stress.
Discussion

Organic nitrates are a group of widely used drugs, especially for the treatment of ischemic heart disease and congestive heart failure. Nitrates are useful as therapy for symptoms, but no study has shown effects on prolongation of survival in patients with ischemic heart disease. Combined treatment with nitrates and hydralazine can prolong survival in patients with congestive heart failure. Maintaining long-term efficacy can be problematic because of the rapid development of tolerance when dosed inappropriately. The aim of our study was to examine whether these drugs are used in an appropriate manner according to recommended guidelines in order to achieve the desired therapeutic effects. We found that only 15% of the patients treated with regular-release ISMN take their medication properly using an asymmetric dosing interval. On the other hand, 82.6% of the patients treated with sustained-release ISMN were using the drugs in an appropriate fashion. More than half of the patients taking the regular-release drug were taking mean doses that exceeded literature recommendations. In addition, only 17.9% of patients experiencing chest pain or shortness of breath during effort or emotional stress were instructed regarding the prophylactic use of sublingual nitrates. Although the guidelines for the management of patients with chronic stable angina do not list prophylactic use of sublingual nitrates as a requirement, it is clear that sublingual therapy is effective when taken as prophylaxis prior to effort.

We verified that in most cases the cause of improper nitrate use was lack of explanation by the physician or pharmacist, although in some cases patients did not take the drugs properly because of other reasons, such as forgetting the instructions or experiencing adverse effects. Verification of the results of the patient questionnaire was performed by interviewing physicians and pharmacists who prescribed and dispensed the drugs to the patients in the study. The finding that most of the patients questioned did not know about the possibility of using sublingual nitrates prophylactically strengthens the assumption that patients were not instructed properly by physicians and pharmacists. The specialty of the prescribing physician did not have any effect on the treatment.

The high percentage of patients using nitrates in an inappropriate fashion observed in this study population suggests the need for continuing professional education and quality improvement activities regarding the use of nitrates. The most effective manner in which to conduct this education is still not clear. One approach, the use of local medical opinion leaders, was shown to increase the appropriate use of oral aspirin and β-blockers in patients hospitalized with acute myocardial infarction. However, a systematic review by Thomson et al. of the effectiveness of opinion leaders in eight randomized trials in changing physicians’ behavior gave inconclusive results. Our study is limited by the fact that we examined drug use in only one community. While it may be that medical personnel in another geographic area behave differently, we believe that these findings are generally applicable. A question that can be asked is whether inappropriate use of nitrates translates into actual negative clinical outcome. While this is certainly an important issue, our study was not designed to answer it, and we intentionally excluded patients with acute cardiovascular disease to prevent selection bias.

Summary

Our study suggests that physicians and pharmacists should be reminded of the need to give patients more detailed instructions regarding the use of oral and sublingual nitrates. In addition, the use of sustained-release preparations of these drugs administered once daily should be encouraged, since administration of the drugs in this way will increase patients’ compliance and ensure proper use.

Lotan Shilo MD, Senior Physician, Department of Medicine “C”; Clinical Pharmacology Consultant, Sapir Medical Center, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel
Ruth Hadari MD, Senior Physician, Department of Medicine “C”, Sapir Medical Center, Sackler School of Medicine, Tel Aviv University
Susy Kovatz MD, Senior Physician, Department of Medicine “C”, Sapir Medical Center, Sackler School of Medicine, Tel Aviv University
Mahmud Qasim MD, Resident, Department of Medicine “C”, Sapir Medical Center, Sackler School of Medicine, Tel Aviv University
Louis Shenkman MD, Head, Department of Medicine “C”, Sapir Medical Center; Professor of Medicine, Sackler School of Medicine, Tel Aviv University

Reprints: Lotan Shilo MD, Department of Medicine “C”, Meir Hospital, Sapir Medical Center, Kfar-Saba 44281, Israel, FAX 972-9-741 700, E-mail lotansh@post.tau.ac.il

References

La mayoría de los pacientes (85%) que utilizaban ISMN de liberación regular estaban tomando su medicamento de manera incorrecta, mientras que la mayoría de los pacientes que tomaban ISMN de liberación controlada lo estaban utilizando de manera correcta. Más de la mitad de los pacientes que tomaban ISMN de liberación regular estaban recibiendo dosis más altas que las recomendadas. Además, la mayoría de los pacientes que sufrían de angina por esfuerzo no habían sido instruidos acerca del uso profiláctico de los nitratos. Estos hallazgos sugieren que tanto médicos como farmacéuticos deben tener presente la necesidad de orientar a los pacientes sobre el uso adecuado de sus medicamentos.

Louise Mallet

CONCLUSIONES:
La mayoría de los pacientes (85%) que utilizaban ISMN de liberación regular estaban tomando su medicamento de manera incorrecta, mientras que la mayoría de los pacientes que tomaban ISMN de liberación controlada lo estaban utilizando de manera correcta. Más de la mitad de los pacientes que tomaban ISMN de liberación regular estaban recibiendo dosis más altas que las recomendadas. Además, la mayoría de los pacientes que sufrían de angina por esfuerzo no habían sido instruidos acerca del uso profiláctico de los nitratos. Estos hallazgos sugieren que tanto médicos como farmacéuticos deben tener presente la necesidad de orientar a los pacientes sobre el uso adecuado de sus medicamentos.

Homero A Monsanto

RÉSUMÉ
OBJECTIF: Déterminer si les patients qui reçoivent le 5-mononitrate d’isosorbide, préparation à libération prolongée administrée une fois par jour ou la préparation régulière en prise deux fois par jour, les utilisent de manière appropriée au niveau pharmacologique. Évaluer si les patients ont été informés de l’utilisation de la nitroglycérine par voie sublinguale pour la prophylaxie d’une crise d’angine.

MÉTHODES: L’étude a été conduite dans un hôpital universitaire de 600 lits. Un questionnaire a été administré chez 229 patients avec problèmes cardiaques admis au centre hospitalier afin d’évaluer comment ils utilisaient les préparations de nitrates.

RÉSULTATS: Les auteurs rapportent que seulement 15% des patients recevant la préparation régulière de 5-mononitrate d’isosorbide (administration deux fois par jour) l’utilisaient de façon appropriée. Par ailleurs, chez 82,6% des patients recevant la préparation à action prolongée (administration une fois par jour) de 5-mononitrate d’isosorbide l’utilisaient correctement. Seulement 38,1% des patients traités avec la préparation régulière de 5-mononitrate d’isosorbide recevaient les posologies recommandées dans la littérature. De plus, des 190 patients qui ont présenté de l’angine à l’effort, seulement 17,9% avaient été informés de l’utilisation des nitrates pour la prophylaxie de crises d’angine avant un effort.

CONCLUSIONS: La majorité des patients (85%) utilisant le 5-mononitrate d’isosorbide le prenaient de façon inappropriée tandis que la majorité des patients qui prenaient les préparations à action prolongée l’utilisaient correctement. Plus de la moitié des patients recevant la préparation à action rapide de 5-mononitrate d’isosorbide étaient traités avec des doses excédant les doses recommandées. De plus, la plupart des patients avec de l’angine à l’effort n’avaient pas été informés de l’utilisation des nitrates pour la prophylaxie de crises d’angine avant un effort.

Homero A Monsanto