

Knowledge, Attitude and Practice of Physicians in Appropriate Prescription of Organic Nitrates in Iran

H. MIRKHANI and P. FADAKAR

For author affiliations, see end of text.

Received November 30, 2008; Revised January 21, 2009; Accepted February 26, 2009

This paper is available online at <http://ijpt.iums.ac.ir>

ABSTRACT

Organic nitrates are commonly used in angina pectoris and ischemic cardiomyopathy. In order to optimize their effectiveness and patient convenience, several aspects must be observed. Adequate doses, suitable dosage forms and asymmetric pattern of usage to prevent the nitrate tolerance are some factors that a physician must be familiar with. The objective of the present study was to define the pattern of organic nitrates administration by Iranian physicians. To investigate the pattern of organic nitrates prescription, 42000 written prescriptions by physicians were reviewed and 345 of those which had at least one nitrate drug in, were considered. Also, a questionnaire was designed and the responses of 54 physicians were collected. Results showed that nitroglycerine 6.4 mg was the most and isosorbide dinitrate 40 mg was the least prescribed oral forms. No spray and topical forms had been prescribed. The most written dosing frequency was three times a day. Asymmetric pattern of usage had not been observed in prescriptions. Results of questionnaires showed that about 80% of physicians were familiar with nitrate tolerance phenomenon but only about 20% of them knew the appropriate way to prevent it. More than half of the respondents believed that the appropriate dose for ischemic heart disease was higher than that in congestive heart failure while it was claimed that the opposite was right. These findings suggest that more efforts must be carried out to increase the knowledge, attitude and practice of Iranian physicians regarding the appropriate dosing and administration of organic nitrates.

Keywords: *Organic nitrates, Drug prescription, Administration, Dosage*

Organic nitrates are one of the most prescribed agents in ischemic heart disease (IHD). They are also used in congestive heart failure (CHF) especially of ischemic origin. In Iran, several agents and dosage forms of organic nitrates are available (Table 1). The main aim of their administration is maximal efficacy (relieving ischemia, reducing preload and afterload) in association with the ease of use and minimal side effects. For obtaining maximal efficacy, right dosing (right dose, right time) must be observed. Nitrate tolerance (loss of beneficial response despite continued therapy and presence of therapeutic level in the blood) complicates nitrate dosing. In spite of extensive research, the exact cause of nitrate tolerance is still unknown. Several theories have been proposed in this regard [1]. It is claimed that excess organic nitrate administration lead to superoxide and peroxynitrite production and the latter compounds can reduce guanylyl cyclase activity (the enzyme responsible for cGMP production) and aldehyde dehydrogenase activity (the enzyme responsible for organic nitrates activation

in vessels) and impair endothelial function [1, 2]. Some experts believe that the vasodilating effect of organic nitrates result in neurohumoral activation and angiotensin-II formation. It is a potent vasoconstrictor.

Moreover, it can produce vasoconstrictive free radicals [1, 3]. Although in some studies, interventions such as using antioxidants, ACE inhibitors, folic acid, L-arginine and hydralazine have showed positive results [1, 2], at present time the only accepted way to prevent nitrate tolerance is asymmetric nitrate administration, i.e. nil or low level of nitrate in the blood for about 10-12 h [3, 4]. For patient convenience and improving compliance using appropriate dosage form must also be considered. To our knowledge, no study which considers knowledge, attitude and practice of Iranian physicians in the administration of organic nitrates, has been conducted so far. The objective of the present study was to define the pattern of organic nitrates administration by Iranian general practitioners (GPs) and specialists.

Table 1. Organic nitrates available in Iran

Agent	Dosage forms
Nitroglycerine	Sublingual capsule and tablet: 0.4 mg Spray: 0.4 mg/dose Extended release tablet and capsule: 2.6 & 6.4 mg Ointment: 2% Dermal patch: 5 mg/24h, 10 mg/24
Isosorbide mononitrate	Ampoule: 1 mg/ml & 2 mg/ml Tablet (extended release): 60 mg
Isosorbide dinitrate	Sublingual tablet: 5 mg Oral tablet: 10 mg Extended release tablet: 40 mg

Table 2. Frequency of oral nitrate administration in reviewed prescriptions*

Total prescriptions		GTN N (%)		ISDN N (%)	
		6.4 mg	2.6 mg	10 mg	40 mg
GP	143	97 (67.8%)	31 (21.7%)	14 (9.8%)	1 (0.7%)
Specialist	162	126 (77.8%)	28 (17.3%)	7 (4.3%)	1 (0.6%)
Total	305	223 (73.1%)	59 (19.3%)	21 (6.9%)	2 (0.7%)

*No isosorbide mononitrate tablet and other suitable dosage forms for prevention of ischemic attack (e.g. dermal patch and ointment) had been prescribed.

GTN: glyceryl trinitrate, nitroglycerine; ISDN: isosorbide dinitrate; GP: general practitioner

METHODS

Prescriptions and questionnaires review

In order to investigate the pattern of organic nitrate prescription, 42000 written prescriptions of GPs and specialists in Fars province, Iran, in 2002 were reviewed and 345 of those which had at least one type of nitrate drug in, were considered. These prescription orders ordinarily and randomly are collected by the local Rational Drug Prescription Committee. Dosage form, type of nitrate, usage order and dosage including asymmetrical pattern of use were the main considered items in each prescription.

In addition to orders review, a questionnaire was designed and distributed in a continuous medical education conference which was held for GPs of Fars province (attendance= 87 GPs) and their responses were collected. Also, 15 cardiologists of Shiraz city (capital city of the Fars province) were contacted directly and received questionnaires. Criteria for choosing the dose, equivalent doses of nitroglycerine (GTN) and isosorbide dinitrate (ISDN), the appropriate dose in the coronary heart disease and congestive heart failure, knowledge about the nitrate tolerance and the way to prevent it were the main questions. The structural and scientific validity of questions have been discussed with a community medicine specialist and a medical internist, respectively.

Obtained results were analysed and compared with standard pharmacological texts and published review articles regarding the rational prescription of drugs, in general and organic nitrates administration, in particular.

Statistical analysis

Descriptive statistical methods were used to summarise the obtained results of prescriptions and questionnaires. To interpret the differences, chi-square test was used. The *p* values less than 0.05 were considered significant.

RESULTS

Of about 42000 considered prescriptions, 345 (0.82 %) had at least one type of nitrates listed. Of these, 168 (48.7 %) had been written by GPs and 177 (51.3%) by specialists (50.8% by internists and cardiologists and 0.5% by other specialists). The prescriptions had been written by 151 physicians (115 GPs, 36 specialists). Of 345 prescriptions, 305 had oral forms in it and no one contained sprays, patches and ointments and also isosorbide mononitrate (ISMN). Forty prescriptions had only sublingual dosage forms.

GTN 6.4 mg was the most and ISDN 40 mg (sustained release) was the least prescribed oral nitrates (Table 2). One prescription had both GTN and ISDN. The most prescribed doses were 3.2 and 6.4 mg of GTN and 10 and 20 mg of ISDN, three times daily for both agents (Table 3). Prescriptions without using direction were more prevalent (*p*<0.01) among GPs compared to specialists (Table 3). Asymmetric pattern of usage had been considered in none of the prescriptions.

The questionnaires were collected from 39 GPs and 15 cardiologists. The responding rate of GPs was about 45%. The cardiologists were contacted directly and all of them filled the questionnaires. The results of questionnaire analyses showed that the type and severity of disease were the main factors for chosen dose among 69.2% of GPs and 80% of specialists. More than half of both groups believed that the nitrate dose in IHD must

Table 3. Frequency of daily usage times in reviewed prescriptions

	Number of pre- scriptions	No order	GTN				ISDN			
			QD	BID	TID	QID	QD	BID	TID	QID
GP	143 (100 %)	38 (26.6 %)	8 (5.6 %)	33 (23.1%)	49 (34.3%)	1 (1.0%)	-	1 (1.0%)	12 (8.4 %)	1 (1.0%)
Specialist	162 (100 %)	22 (13.6%)*	1 (1.0%)	44 (27.2%)	86 (53.1%)	2 (1.2 %)	-	7 (4.3 %)	-	-
Total	305	60 (19.7%)	9 (3.0%)	77 (25.2 %)	135 (44.3%)	3 (1.0 %)	-	1 (0.0%)	19 (6.2%)	1 (0.0%)

The values are expressed as n (%) of prescriptions.

GTN: glyceryl trinitrate, nitroglycerine; ISDN: isosorbide dinitrate; QD: every day; BID: twice daily; TID: three times daily; QID: four times daily; GP: general practitioner

* $p < 0.01$, in comparison to written prescriptions by GPs

be greater than the used dose in CHF. Eighty two of the GPs and 87% of the specialists were familiar with nitrate tolerance phenomenon but only 15% of the GPs and 27% of the specialists knew the way to prevent it, i.e. asymmetrical dosing. However the difference was not significant. Equivalent doses of GTN and ISDN were answered by 3 GPs (8%) and 7 specialists (47%). Among them, four specialists and 1 GP believed that 6.4 mg of GTN is equivalent to 20 mg of ISDN. The answers of other respondents were quite diverse (6.4 mg of GTN is equivalent to 10, 30, 40 and 50 mg of ISDN).

DISCUSSION

Organic nitrates are widely used in IHD and CHF. They are mixed vasodilators but their venodilator effect is greater than their effect on arteries. They also dilate large coronary arteries and arteriols. These effects redistribute the coronary blood flow from epicardial to endocardial and from non-ischemic to ischemic regions. Organic nitrates can also relax coronary artery spasm. All of these properties lead to relief of ischemia-induced cardiac pain. In CHF, the combination of hydralazine plus ISDN decrease mortality but to a level lower than those obtained with ACE inhibitors use. So, this combination is recommended for patients unable to tolerate ACE inhibitors. No study has shown that organic nitrates can prolong survival when used without hydralazine in patients with heart failure [3, 5, 6]. In spite of this, because of their prominent venodilating effect, they are a good option for CHF patients who suffer from pulmonary symptoms [3, 6]. Unfortunately, tolerance to beneficial effects of nitrates will rapidly occur if an adequate nitrate-free period is not considered in their dosing.

In the present study, the knowledge, attitude and practice of a sample of GPs and specialists of Fars province (south of Iran, 7.4 % of the total area, 6.1% of the total population) in prescription pattern of nitrates were considered. In the reviewed prescriptions oral sustained-release GTN and regular-release ISDN with or without sublingual tablets and capsules were the main prescribed nitrates (Table 2). Considering the advantages of sprays and topical forms for certain groups of patients, it seems that their absence in prescriptions is due to lack of familiarity of physicians, their higher costs or hard accessibility; or a combination of these factors. Abstention to prescribe sustained-release ISDN and ISMN is also questionable. Their

efficacy with double and even single daily dosing [3, 7] makes them attractive agents for improving patient compliance and asymmetric pattern of use [7, 8]. It may be due to the lack of an effective and reliable center which can introduce newer drugs and dosage forms to the physicians. It is worthwhile to note that almost all drugs in Iran are dispensed as generic forms and advertisements on newer drugs or dosage forms are limited (at least in comparison to western countries).

One of the physicians had prescribed both oral GTN and ISDN. There is no rational reason using oral nitrate combination [9]. It is believed that 2.6 mg of GTN and 10 mg of ISDN are the minimal effective doses for prevention of cardiac ischemia [3, 4]. These doses had been selected by 26.2% of physicians (Table 2) and their effectiveness in Iranian patients was unknown to us. At least in CHF patients, it seems that greater doses are required [4].

There were numerous prescriptions without using direction, especially among GPs (Table 3). Although it may be due to chronic use of these drugs by visited patients, writing the using direction is mandatory and cannot be neglected. Among others, three times daily dosing was the most prevalent dosing frequency (Table 3). Limited number of physicians had prescribed the drugs once a day and 4 times daily. Both of these regimens seem irrational. Once daily dosing of GTN and ISDN produce short-live anti-ischemic and vasodilatory effect. Four times daily dosing will induce nitrate tolerance. Although both twice and thrice daily dosing have been proposed, some experts claim that the long-term efficacy of the latter is questionable [3]. The main parameter governing the appropriate dosing frequency is the duration of action of drug and the tolerance phenomenon. Since we have no idea about the duration of action of the available oral nitrates in Iran, it is impossible to judge about the best dosing frequency (twice daily vs. thrice daily) and it is quite advisable to conduct further studies to find the answer to the above question.

More than half of both groups (GPs and specialists) believed that the required dose of nitrates in IHD is higher than that in CHF. It is claimed that the opposite was right [4]. It is stated that the required doses of nitrates to achieve desirable hemodynamic effects in CHF must be greater than those needed to relieve stable angina pectoris [4]. A great proportion of both groups had claimed that they were familiar with nitrate tolerance phenomenon but a much smaller proportion

knew the way of its prevention and in none of the reviewed prescriptions, the asymmetric dosing, the only accepted way to prevent nitrate tolerance [3, 4], had been followed. In the scant published studies [6, 8, 10] failure to observe a 10-12 hour nitrate free period has been attributed to lack of patient education or inappropriate pattern of use by patients. However, in the present study the main problem has appeared from the physicians' side to write appropriate order. We have no convincing explanation for the great discrepancy between knowledge and practice of studied physicians in the appropriate nitrate dosing.

Forty seven percent of the specialists and only 8% of GPs, determined the equivalent doses of GTN and ISDN (a dose which produces almost similar effect, irrespective of its duration) based on their opinions and experiments. Since no study considering this subject has been carried out on available oral nitrates in Iran, the judgment about the validity of the answers is impossible. Regarding this problem and considering the fact that a great proportion of the questioned subjects did not reply to the above question, conducting studies on the hemodynamic effect of the available nitrates is advisable.

Although the above-mentioned parameters have been considered in a limited community, we believe that these findings can, more or less, be extended to the whole community because the theoretical and practical medical education in every university in Iran has a similar curriculum and content. In conclusion it seems that interventions to increase the knowledge and change the attitude and practice of Iranian physicians in rational organic nitrates prescription must be considered. In order to determine the intensity and duration of action of available nitrates, performing pharmacokinetics and hemodynamic studies on available organic nitrates are also highly recommended.

ACKNOWLEDGEMENTS

The authors would like to thank Dr. S. Salari, Dr. Z. Agha-Maleki, Dr. M. Ghaemi-Nia and Ms. S. Kamalzadeh for their assistance in reviewing prescriptions and questionnaires. This work was supported by the grant No. 83-2317, Vice-chancellery of Research, Shiraz University of Medical Sciences.

REFERENCES

1. Münzel T, Daiber A, Mülsch A. Explaining the phenomenon of nitrate tolerance. *Circ Res* 2005; 97:618-28.
2. Fayers KE, Cummings MH, Shaw KM, Laight DW. Nitrate tolerance and the links with endothelial dysfunction and oxidative stress. *Br J Clin Pharmacol* 2003; 56:620-8.
3. Opie LH, White HD. Nitrates. In: Opie LH, Gersh BJ, eds. *Drugs for the Heart*. 6th ed. W. B. Saunders Company; 2005. p. 33-49.
4. Abrams J. How to use nitrates. *Cardiovasc Drugs Ther* 2002; 16:511-4.
5. Cheng JW. A review of isosorbide dinitrate and hydralazine in the management of heart failure in black patients, with a focus on a new fixed-dose combination. *Clin Ther* 2006; 28:666-78.
6. Shilo L, Hadari R, Kovatz S, Qasim M, Shenkman L. Appropriateness of nitrate use in a general medicine population. *Ann Pharmacother* 2001; 35:1339-42.
7. Waller DG. Optimal nitrate therapy with a once-daily sustained-release formulation of isosorbide mononitrate. *J Cardiovasc Pharmacol* 1999; 34:S21-7.
8. Straka RJ, Fish JT, Benson SR, Suh JT. Magnitude and nature of noncompliance with treatment using isosorbide dinitrate in patients with ischemic heart disease. *J Clin Pharmacol* 1996; 36:587-94.
9. Reuveni H, Aviram EE, Elhayani A, Lifshitz M, Peled R, Galai N, Sherf M, Paran E. The prescription pattern of oral nitrates in coronary artery disease. Appropriateness and cost considerations. *Eur J Clin Pharmacol* 2001; 57:595-7.
10. Löfdahl P. Compliance as a factor in the development of nitrate tolerance: a patient investigation. *J Int Med Res* 1993; 21:51-7.

CURRENT AUTHOR ADDRESSES

- H. Mirkhani, Department of Pharmacology & Medicinal and Natural Products Chemistry Research Center, Shiraz University of Medical Sciences, Shiraz 71344, Iran. E-mail: mirkhanh@sums.ac.ir (corresponding author)
- P. Fadakar, Department of Pharmacology, Shiraz University of Medical Sciences, Shiraz 71344, Iran.