



THERAPEUTICS INITIATIVE

Evidence Based Drug Therapy

MEDICAL MANAGEMENT OF ISCHEMIC HEART DISEASE: THE OPTIMAL USE OF NITRATES

There are 3 classes of drugs which are effective in the symptomatic management of angina pectoris. These 3 classes are nitrates, beta-blockers, and Ca channel blockers. In addition to the pharmacologic management advise your patients about lifestyle changes: cessation of smoking, low saturated fat diet, and regular low intensity cardiovascular exercise. Do not forget the proven benefits of acetylsalicylic acid (ASA), 80-325 mg daily, in decreasing the risk of myocardial infarction.¹

• What is the drug of choice for prevention of stable angina pectoris?

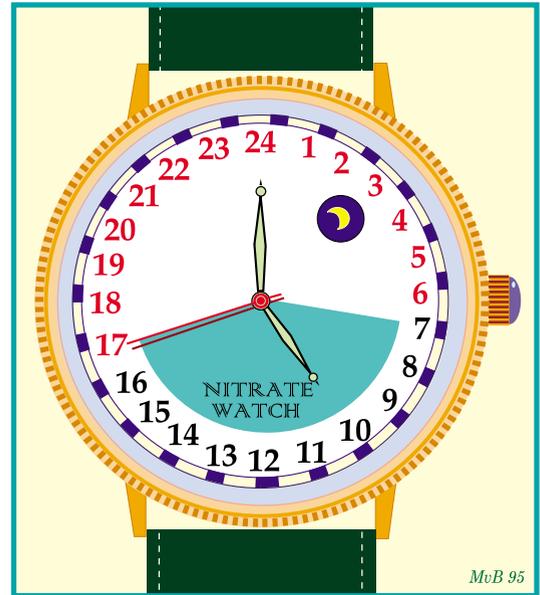
There is increasing evidence that beta-blockers are the drug of first choice in the management of angina. Beta blockers are at least as effective as the other two classes in controlling symptoms. Beta blockers have also been shown to decrease the risk of adverse cardiac events in patients with angina and silent ischemia.² Nitrates and Ca channel blockers have not been shown to have this added beneficial effect.

• What about the patient who is not controlled or intolerant to beta blockers?

Long acting nitrates work well in combination with beta blockers and are the obvious second choice. Start with isosorbide dinitrate (ISDN) in a low dose of 10 mg at 0800 and 1400h and titrate to effect. The other nitrate preparations have either not been compared or not been shown to be more effective than ISDN.³ Daily doses may be timed according to the patient's symptoms. For daytime dosing no ISDN or any other long acting nitrate should be given after 5 pm.⁴ (See picture)

• How does one prevent the development of nitrate tolerance?

If nitrates are administered around the clock, tolerance to their effects develops rapidly.^{3,4} Once tolerance has developed the drug is probably not having any beneficial effect. The drug must be taken such that therapeutic serum concentrations are only present for 12-14 hours of the day. Physicians should

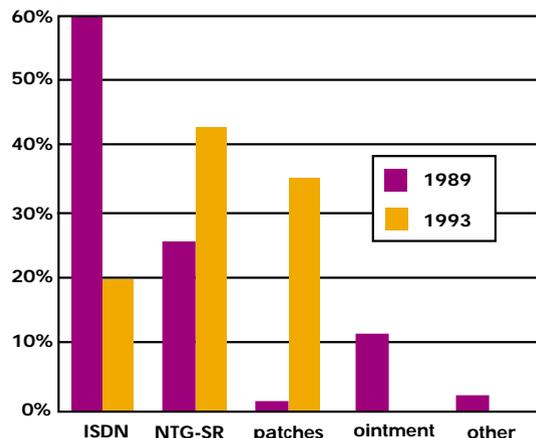


be aware that the CPS recommends around the clock dosing for most nitrate preparations and that this is **never** appropriate.

• How does isosorbide dinitrate work?

ISDN works directly on the vascular smooth muscle in an identical manner to the natural endothelium derived relaxing factor, nitric oxide. ISDN has a short half-life and is primarily effective clinically by metabolism to the active metabolite isosorbide-5-mononitrate, which has an average half-life of 5 hours. This is the active ingredient in the two new nitrate preparations Imdur and Ismo. These two preparations are no more effective than ISDN and the serum concentrations of isosorbide-5-mononitrate are similar for the three preparations. The duration of ISDN's antianginal effect is approximately 6 hours, which is similar to most sustained release preparations.

Figure: Prescription of prophylactic nitrate products; 1989 as compared to 1993



• What is the role of sustained release preparations, ointment and patches?

These alternate forms of delivery have not been shown to be more effective than oral ISDN.⁴ The ointment and patches offer a longer duration of action, but this has little advantage given the necessity for an 8-10 hour drug free period to prevent tolerance.

• How do I switch from one preparation to another?

If your patient is receiving a long acting nitrate for 24h switch to appropriate daytime dosing, and continue for one week. Then switch to an approximate equivalent dose of ISDN given 2 or 3 times daily. (see below)

• What prophylactic nitrate products are used in British Columbia?

As can be seen from the Figure and Table the most commonly prescribed preparations are also the most expensive. This is not the same pattern as in other provinces: in Ontario and Saskatchewan where NTG-SR (Nitrong) and patches are not a benefit the primary products prescribed are ISDN and NTG ointment.

• How does one treat acute angina?

Nitrates in the form of sublingual tablets or oral spray can be used for acute angina at any time of the day or night. There is no evidence of any difference in the effectiveness of these two preparations. Since the sublingual tablets are half the price they are the most cost-effective, except in the patient who seldom uses the medication, in which case the spray, with its 3 year shelf-life, may be less costly.

Table: Dosing and Cost for Prophylactic Nitrate Therapy

Drug	Usual Dosage Range	Daily Ingredient Cost*
Nitrate patches Nitro-Dur® (0.2, 0.4, 0.6, 0.8 mg/hr) Transderm-Nitro® (0.2, 0.4, 0.6, mg/hr)	Apply 1 patch daily (Remove 12 hours later)	\$1.26 - \$1.91 \$1.38 - \$1.81
Isosorbide dinitrate generic (regular release 10 & 30 mg) Coronex® Isordil®	10 - 30 mg (0800, 1400h) or (0700, 1200, 1700h)	\$0.04 - \$0.13 \$0.20 - \$0.90 \$0.11 - \$0.37
Isosorbide dinitrate (sustained release 20 mg) Cedocard-SR® Coradur®	20 - 60 mg (0800, 1400h)	\$0.74 - \$2.21 \$0.74 - \$2.21
Nitroglycerin Sublingual tablets Nitrolingual spray Nitrogard-SR® (buccal tablet) Nitrong SR®	0.3 - 0.6 mg prn 0.4 mg prn 1-5 mg (0700, 1200, 1700h) 2.6 - 5.2 mg (2-3 doses, see ISDN for times)	\$0.09 (3 doses) \$0.20 (3 doses) \$0.59 - \$1.06 \$0.93 - \$2.78
Isosorbide-5-mononitrate Ismo® Imdur®	20 mg (0800, 1500h) 60 mg (0800)	\$1.12 \$0.64

* Based upon average 1993 Pharmacare price.

References

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2. Pepine CJ, Cohn PF, Deedwania PC et al. Effects of treatment on outcome in mildly symptomatic patients with ischemia during daily life: the Atenolol Silent Ischemia Study (ASIST). *Circulation*. 1994 Aug; 90:762-8.
3. Bassett K, Rhone ML. The efficacy and effectiveness of sustained release oral nitroglycerin in comparison to regular delivery isosorbide dinitrate for the prophylactic treatment of stable angina pectoris. *Health Technology Review*. BCOHTA 94:1T, September 1994.
4. Rudolph W, Dirschinger J, Reiniger G, Beyerle A, Hall D. When does nitrate tolerance develop? What dosages and which intervals are necessary to ensure maintained effectiveness? *European Heart Journal*. 1988; 9(Suppl. A):63-72.

The Therapeutics Initiative was established to disseminate up to date evidence based drug therapy information to physicians and pharmacists. We are also committed to evaluating the effectiveness of all our educational activities using the Pharmacare data base. The data will be in a form such that individual physicians, pharmacies or patients will not be identified. If you do not wish to be part of this evaluation process, please notify us and you will be excluded from the evaluation.