THE USE OF NITRATES IN CHRONIC STABLE ANGINA

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This overview has been prepared by staff at the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) and is based in part on a study commissioned by CCOHTA: Efficacy, effectiveness, and cost analysis of nitrate therapy for the prevention of angina pectoris conducted by Holbrook AM, Dolovich L, Grootendorst P, Brogran T, Kitching A, Crossley T. Centre for Evaluation of Medicines, St. Joseph’s Hospital (Hamilton, Ontario) and Departments of Medicine, Clinical Epidemiology and Biostatistics, and Economics, McMaster University (Hamilton, Ontario), Brogan Consulting Inc. (Ottawa, Ontario), and the Faculty of Pharmacy, University of Toronto (Toronto, Ontario).

The overview has been reviewed and accepted by CCOHTA's Scientific Advisory Panel. It does not necessarily reflect the opinions of the Panel, the Board of CCOHTA or the investigators.
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Nitrates are one of many agents indicated in the management of angina. For many years, isosorbide dinitrate (ISDN) was widely prescribed in the prevention and treatment of anginal attacks, but its use has declined with the marketing of novel but more costly nitrate delivery systems such as sustained release tablets and patches. Controversies exist as to whether or not these new formulations offer any additional benefits or harm compared to isosorbide dinitrate.

Toward this end, a study commissioned by CCOHTA entitled Efficacy, effectiveness, and cost analysis of nitrate therapy for the prevention of angina pectoris evaluated the use of nitrates in chronic stable angina. Specifically, the study had two objectives: 1) to compare the effectiveness of the different nitrate preparations; 2) to conduct an economic evaluation to determine if the higher cost of the newer nitrates is accompanied by greater clinical benefits. This overview summarizes the findings of the commissioned study.

CONCLUSIONS

A meta-analysis of randomized controlled trials comparing nitrates against other nitrates showed that there were no significant differences between nitrates for the different outcomes evaluated (performance at stress tests, frequencies of anginal attacks, the use of sublingual nitroglycerin, tolerance, and adverse effects). There did not appear to be any differences between nitrates for tolerance, duration of therapy and switching between the different nitrates when analyzing utilization data obtained from a sample of provincial/private drug databases. However, no studies have evaluated the impact of nitrates on important outcomes such as mortality, myocardial infarction, or quality of life.

Given that the evidence did not prove the superiority of one nitrate over another, the economic evaluation conducted was a cost-minimization analysis.

1) In 1995, isosorbide dinitrate had the lowest cost per unit for all provinces. Patches were the most expensive, except in New Brunswick and Quebec with isosorbide dinitrate sustained release tablets (Coradur®, Cedocard-SR®) within the range of cost for patches.

2) In 1995, the use of ISDN varied between provinces, ranging from 13% in Nova Scotia to 81% in Ontario. Differences in usage patterns probably reflected whether or not other nitrates were reimbursed by provincial drug plans.

3) In 1995, more than $45 million were spent by provincial governments on nitrates (dispensing fees not included).

4) Based on 1995 utilization data and 1996 drug prices (the cost of certain nitrate preparations such as nitrate patches decreased in early 1996), it has been projected that total national spending for nitrates will decrease in 1996. However, national savings of $9 million could still be incurred if ISDN replaced other nitrates 50% of the time.

5) Ontario had the highest consumption of ISDN (81% utilization) in 1995. However, based on trends seen in other provinces, it is anticipated that the province’s total spending for nitrates will increase as nitrate patches have recently been approved for reimbursement.

Limitations to the commissioned study included the small number of head to head trials available for the meta-analysis and the use of administrative databases for effectiveness data.

INTRODUCTION
Angina pectoris is a condition characterized by episodic chest discomfort and is usually indicative of coronary artery disease. The chest discomfort is described as heaviness, pressure, squeezing, suffocating or choking. It is precipitated by physical exertion, or strong emotions such as excitement or anger. It is referred to as “stable” when the frequency and precipitants of attacks remain relatively predictable.

Short-acting nitrates such as sublingual nitroglycerin are commonly used in the treatment of acute anginal attacks since they provide immediate relief. The use of a short-acting nitrate alone may be sufficient to manage patients with infrequent symptoms or with mild disease. Prophylactic treatment of stable angina includes the use of long-acting nitrates, beta blockers, calcium channel blockers or a combination of these agents.

The commissioned study compared the different nitrate preparations available for use in chronic stable angina. It did not evaluate the overall management of stable angina nor did it assess the use of nitrates for other indications such as unstable angina, congestive heart failure and acute myocardial infarction.

The primary roles of nitrate therapy are to prevent and relieve anginal symptoms. There is no evidence that nitrates reduce coronary heart disease morbidity or mortality. In comparative studies, nitrates appear as effective as beta blockers or calcium channel blockers. The use of a nitrate instead of another agent will depend on patient factors such as the presence of co-morbid conditions. Combination therapies are commonly used. However, incremental benefits of adding a nitrate to another agent are not known.

Nitrates have few side effects. The two most common ones are headache and hypotension. Although nitrate headaches affect quality of life, they are usually treatable with mild analgesics and often disappear with prolonged nitrate use. Hypotension may occur with the first dose. Initiation of treatment with small doses is effective in reducing the likelihood of developing hypotension.

The principal concern with using nitrates is the development of tolerance, especially with continuous use. Nitrate preparations producing more constant blood levels (e.g., patches or sustained release preparations) rather than peaks and troughs (ISDN, ointment) may be more likely to produce tolerance. A dosing schedule that allows nitrate-free periods (usually stopping treatment for ten to twelve hours per 24 hours) has been shown to reduce tolerance.

In recent years, many new nitrate preparations have become available for use. New drug delivery systems such as patches and sustained release tablets are slowly replacing the standard, widely prescribed isosorbide dinitrate. It remains to be proven however whether or not these new formulations are more efficacious than isosorbide dinitrate. If so, it needs to be determined if they are worth the extra cost.

An earlier evaluation done by British Columbia Office for Health Technology Assessment compared ISDN to sustained release formulations (Nitrong-SR®, Coradur®, Cedocard-SR®) and found no evidence that one preparation was superior in terms of efficacy, effectiveness, tolerance, compliance, side effects, drug interactions or quality of life.² The CCOHTA commissioned study extended the evaluation to include all other nitrate preparations.
PARAMETERS OF THE EVALUATION

a) Therapy Evaluated

Prophylactic nitrates were compared to isosorbide dinitrate, an older and inexpensive preparation. (Table 1)

<table>
<thead>
<tr>
<th>Nitrate preparation</th>
<th>Proprietary name</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isosorbide dinitrate (ISDN) tablet</td>
<td>Isordil®, Apo-ISDN®, Novo-Sorbide®</td>
<td>Wyeth-Ayerst, Apotex, Novopharm</td>
</tr>
<tr>
<td>ISDN sustained release (SR) tablet</td>
<td>Cedocard-SR®, Coradur®</td>
<td>Pharmascience, Glaxo</td>
</tr>
<tr>
<td>Nitroglycerin (NTG) ointment</td>
<td>Nitrol®, Nitro-Bid®</td>
<td>Rhone-Poulenc Rorer, Hoescht</td>
</tr>
<tr>
<td>NTG patch</td>
<td>Transderm-Nitro®, Nitrodur®, Minitran®</td>
<td>CIBA, Key, 3M</td>
</tr>
<tr>
<td>NTG SR tablet</td>
<td>Nitrogard-SR®, Nitrong-SR®</td>
<td>Astra, Rhone-Poulenc Rorer</td>
</tr>
<tr>
<td>Isosorbide mononitrate (ISMN) tablet</td>
<td>ISMO®</td>
<td>Wyeth-Ayerst</td>
</tr>
<tr>
<td>ISMN SR tablet</td>
<td>Imdur®</td>
<td>Astra</td>
</tr>
<tr>
<td>Pentaerythritol tetranitrate (PETN) tablet</td>
<td>Peritrate®</td>
<td>Parke-Davis</td>
</tr>
</tbody>
</table>

b) Perspective/ Target Audience

The perspective adopted reflected the main target audiences which were the provincial/territorial drug benefit plans as well as other third party payers.

c) Type of Analysis

The commissioned study was a cost-minimization analysis based on a meta-analysis of head to head randomized clinical trials of nitrates. Three provincial drug databases (1992 to 1994 data for British Columbia’s Pharmacare, and 1989 to January 1996 data for New Brunswick Prescription Drug Program and Blue Cross for the Atlantic provinces) were also analyzed to determineduration of therapy and evidence of tolerance. As well, prescribing patterns and trends were obtained from Intercontinental Medical Statistics (IMS) data.

d) Outcomes of Interest

Outcomes of interest evaluated were:
1) from the comparative trials: performance at stress tests, frequency of angina attacks, use of sublingual nitroglycerin, tolerance, patient preferences, and adverse effects;
2) from the databases: dose escalation of the prophylactic nitrate and use of sublingual nitroglycerin over time to determine tolerance, relative duration of nitrate therapy, and switching to a different type of nitrate.
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Efficacy

A comprehensive literature search generated a limited number of randomized controlled studies comparing nitrates against other nitrates. When analyzed by meta-analytic techniques, no evidence could be found to show the superiority of the newer nitrate preparations compared to ISDN. The data available indicated that there were no significant differences between the various nitrates in efficacy or adverse effects.

ISDN vs. Patch
Exercise time to angina was increased with ISDN (overall difference -22.14 seconds, 95% Confidence Interval (CI): -159.04 to 114.76) but this finding was not statistically significant. NTG patches caused fewer headaches (Odds Ratio (OR) 0.40, 95%CI:0.06 to 2.38) but again, this was not statistically significant.

ISDN vs. ISMN-SR
ISMN-SR, although not statistically significant, showed an improvement in: time to 1mm ST depression after acute treatment (overall difference 2.08 seconds, 95%CI: -40.01 to 44.16) time to 1mm ST depression after chronic treatment (overall difference 40.14 seconds, 95%CI: 6.76 to 87.04) time to onset of moderate angina with acute therapy (overall difference 8.64 seconds, 95%CI: -27.29 to 44.57) and time to onset of moderate angina with chronic therapy (overall difference 7.08 seconds, 95%CI: -36.24 to 50.40).

ISMN vs. ISDN-SR
There were fewer adverse effects reported with the use of ISDN-SR (OR 0.73, 95%CI:0.32-1.67) and this was not statistically significant.

ISMN vs. ISMN-SR
Exercise time after two weeks of therapy was increased with ISMN-SR (overall difference 1.70 seconds, 95%CI: -64.74 to 68.14). There were fewer angina attacks per week (overall difference -0.15 attacks, 95%CI: -2.90 to 2.59) less use of sublingual nitroglycerin (overall difference 0.29 tablets, 95%CI: -4.12 to 4.70) but more frequent headaches (OR 0.80, 95%CI:0.31 to 2.03) with ISMN. None of these findings were statistically significant.

Transderm-Nitro® patch vs. Nitrodur® patch
The Transderm-Nitro® group had fewer angina attacks (overall difference -0.024 attacks, 95%CI: -0.65 to 0.60) per week (not statistically significant). However, patients on Nitrodur® required statistically significantly less sublingual nitroglycerin (overall difference 0.31 tablets, 95%CI: -0.52 to -0.11) per week.

Two studies evaluating the effect of nitrates on quality of life have shown that nitrates diminished quality of life because of the headaches associated with their use.

Studies examining patient preferences have been of poor quality. Furthermore, they focused on comparing nitrate patches for factors such as ease of application, adherence of patch and skin irritation.

Effectiveness

Provincial Drug Databases
Surrogate outcomes were used as indicators of effectiveness.

It was determined that patches were the most frequently prescribed nitrate preparation for each of the three databases. NTG-SR and ISDN were the second and third most prescribed nitrates respectively. For these three medications, patients infrequently switched to another nitrate.
Thirty-six to 38% of the patients used prescription sublingual nitroglycerin presumably for acute attacks.

While holding age, sex, and concomitant anti-anginal drug use constant, patients on NTG-SR received this therapy for a longer duration than those receiving ISDN (4 weeks difference). Those on ISDN had 2 to 10 more weeks of treatment than patients on the patch. The ISDN group had the largest dose escalation (9% dose increase) over 30 weeks followed by the patch (6%) and the NTG-SR (2%) groups. However, the ISDN group used less sublingual nitroglycerin.

Modeling to incorporate the influence of treatment allocation bias suggested no significant differences between the three nitrates in dose escalation or use of sublingual nitroglycerin.

IMS Canada
ISDN was the most mentioned* nitrate preparation but its usage dropped from 48% of total nitrates in 1990 to 29% in 1994. From 1990 to 1994, the use of the patches increased whereas NTG-SR usage stayed constant. In 1995, ISDN was still the most mentioned product. The second most mentioned nitrate was NTG-SR until 1992.

Patches and NTG-SR were widely used in Quebec, British Columbia, Alberta, New Brunswick, Nova Scotia, Prince Edward Island and Newfoundland, perhaps due to their different policies regarding the coverage of these products.

Overall, results of the databases analyses did not indicate that one nitrate is better.

**COST**

Cost data were obtained from 1995 provincial formulary claims from seven provinces, a survey of 1996 prices, and from 1994 IMS cost data.

Provincial formulary claims included reimbursement to pharmacies for drug acquisition cost and mark up but not dispensing fees. IMS cost data included prescription fees.

**COST-MINIMIZATION ANALYSIS**

A cost-minimization analysis was conducted given that there was no evidence that any nitrate was superior.

A mean cost per nitrate type was obtained for each province by summing cost per individual nitrate strength weighted by their relative volume of claims. (Table 2)

Also, given that duration of prescription varied between provinces due to the individual province’s regulations concerning number of days supplied per prescription, the costs were not comparable across provinces. However, duration of therapy of other nitrates was adjusted to the mean duration of ISDN therapy to permit comparability within provinces.

* A mention is obtained when a physician voluntarily records the use of a drug product by a particular patient after a visit. It is not obtained from copies of actual prescriptions.
<table>
<thead>
<tr>
<th>Nitrate</th>
<th>Alberta</th>
<th>BC</th>
<th>Man.</th>
<th>NB</th>
<th>NS</th>
<th>Ontario</th>
<th>Quebec</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISDN</td>
<td>0.0235</td>
<td>0.03</td>
<td>0.0367</td>
<td>0.0288</td>
<td>0.0280</td>
<td>0.0458</td>
<td>0.02948</td>
</tr>
<tr>
<td>ISDN-SR</td>
<td>0.3265</td>
<td>0.34</td>
<td>0.3612</td>
<td>0.3404</td>
<td>0.3410</td>
<td>0.3585</td>
<td>0.3454</td>
</tr>
<tr>
<td>NTG ointment</td>
<td>0.1984</td>
<td>0.21</td>
<td>0.2048</td>
<td>0.2074</td>
<td>0.1916</td>
<td>0.2139</td>
<td>0.2037</td>
</tr>
<tr>
<td>Patch 0.2mg/h</td>
<td>0.5667</td>
<td>0.57</td>
<td>0.6664</td>
<td>0.5700</td>
<td>0.603</td>
<td>—</td>
<td>0.5667</td>
</tr>
<tr>
<td>Patch 0.4mg/h</td>
<td>0.6667</td>
<td>0.67</td>
<td>0.7840</td>
<td>0.6700</td>
<td>0.710</td>
<td>0.6400</td>
<td>0.6400</td>
</tr>
<tr>
<td>Patch 0.6mg/h</td>
<td>0.9703</td>
<td>0.97</td>
<td>1.1411</td>
<td>0.9700</td>
<td>1.034</td>
<td>0.6400</td>
<td>0.6400</td>
</tr>
<tr>
<td>Patch 0.8mg/h</td>
<td>1.2167</td>
<td>1.22</td>
<td>1.4308</td>
<td>1.2170</td>
<td>1.296</td>
<td>—</td>
<td>1.1100</td>
</tr>
<tr>
<td>NTG-SR</td>
<td>0.4162</td>
<td>0.416</td>
<td>0.5000</td>
<td>0.4252</td>
<td>0.4250</td>
<td>0.4379</td>
<td>0.4162</td>
</tr>
<tr>
<td>ISMN</td>
<td>—</td>
<td>0.11</td>
<td>0.4926</td>
<td>—</td>
<td>—</td>
<td>0.5190</td>
<td>0.4953</td>
</tr>
<tr>
<td>ISMN-SR</td>
<td>—</td>
<td>0.21</td>
<td>0.6566</td>
<td>0.9095</td>
<td>—</td>
<td>—</td>
<td>0.6681</td>
</tr>
<tr>
<td>PETN</td>
<td>0.3335</td>
<td>0.30</td>
<td>0.3680</td>
<td>0.2879</td>
<td>0.2518</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

aData could not be obtained for Saskatchewan, P.E.I., Newfoundland or the Territories.

bPrices used to determine the average cost of patches and NTG-SR tablets are those of 1996.

Isosorbide dinitrate had the lowest cost per unit for all provinces. Patches were the most expensive, except in New Brunswick and Quebec with isosorbide dinitrate sustained release tablets (Coradur®, Cedocard-SR®) within the range of cost for patches.

Table 3 shows the total spending for nitrates for each province obtained from total reimbursement for claims (calculated from mean reimbursement for each nitrate type for 1995 and quantity of claims for 1995).

Actual ISDN use was based on 1995 utilization data. Variations in prescribing practices between provinces probably reflect the fact that certain provincial drug plans reimbursed only selected nitrates (e.g., Ontario’s drug plan only reimbursed for isosorbide dinitrate tablets and nitrate ointment in 1995).
TABLE 3: ISDN Use and Total Nitrate Spending

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Alberta</td>
<td>2,716.2</td>
<td>4,596,511</td>
<td>18</td>
</tr>
<tr>
<td>British Columbia</td>
<td>3,668.4</td>
<td>9,014,852</td>
<td>16</td>
</tr>
<tr>
<td>Manitoba</td>
<td>1,131.1</td>
<td>1,594,021</td>
<td>61</td>
</tr>
<tr>
<td>New Brunswick</td>
<td>759.3</td>
<td>2,210,940</td>
<td>22</td>
</tr>
<tr>
<td>Nova Scotia</td>
<td>936.7</td>
<td>3,739,013</td>
<td>13</td>
</tr>
<tr>
<td>Ontario</td>
<td>10,927.8</td>
<td>3,908,752</td>
<td>81</td>
</tr>
<tr>
<td>Quebec</td>
<td>7,281.1</td>
<td>20,902,103</td>
<td>18</td>
</tr>
</tbody>
</table>

* in 000’s; source: Statistics Canada

Adjusted for duration of therapy

By extrapolating 1995 utilization data (Table 4), it was estimated that total spending for 1996 would decrease due to a decrease in prices that occurred in 1996 for Nitrong-SR® and the patches. However, savings could still have been realized by substituting ISDN. For example, substituting ISDN 50% of the time would have incurred total national savings of an estimated $9 million for 1996. It should be noted that these savings were most likely underestimated given that data for Saskatchewan, P.E.I., Newfoundland or the Territories were not included in the analysis.

In Ontario, due to the high utilization of isosorbide dinitrate, it was projected that spending would have remained approximately the same for 1996. However, patches were recently introduced on formulary and most likely, their total spending for nitrates will increase.

TABLE 4: Potential Savings of Increased Prescribing of ISDN

<table>
<thead>
<tr>
<th>Province</th>
<th>Estimated spending for nitrates in 1996 ($)</th>
<th>Savings if usage changes to 20% ISDN ($)</th>
<th>Savings if usage changes to 50% ISDN ($)</th>
<th>Savings if usage changes to 70% ISDN ($)</th>
<th>Savings if usage changes to 100% ISDN ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alberta</td>
<td>3,030,778</td>
<td>54,835</td>
<td>1,063,262</td>
<td>1,735,569</td>
<td>2,743,973</td>
</tr>
<tr>
<td>BC</td>
<td>6,338,664</td>
<td>242,532</td>
<td>2,292,904</td>
<td>3,659,818</td>
<td>5,710,189</td>
</tr>
<tr>
<td>Man.</td>
<td>1,130,234</td>
<td>—</td>
<td>—</td>
<td>192,687</td>
<td>810,482</td>
</tr>
<tr>
<td>NB</td>
<td>1,681,361</td>
<td>—</td>
<td>529,503</td>
<td>913,839</td>
<td>1,490,344</td>
</tr>
<tr>
<td>NS</td>
<td>2,449,559</td>
<td>163,458</td>
<td>914,313</td>
<td>1,414,883</td>
<td>2,165,738</td>
</tr>
<tr>
<td>Ontario</td>
<td>3,904,272</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>377,234</td>
</tr>
<tr>
<td>Quebec</td>
<td>12,786,045</td>
<td>234,484</td>
<td>4,265,047</td>
<td>6,952,088</td>
<td>10,982,651</td>
</tr>
</tbody>
</table>

* Adjusted for duration of therapy

Finally, according to IMS data (1994), approximately 2.2 million prescriptions for nitrates were dispensed nationally at a cost of $78 million.
STUDY LIMITATIONS

The commissioned study did not evaluate the use of other classes of drugs in the management of stable angina. Also, it did not assess the use of nitrates in other types of angina and conditions such as congestive heart failure.

The meta-analysis was based on evidence obtained from a limited number of head to head trials. Each nitrate was not necessarily evaluated for all outcomes and was not necessarily compared to all other nitrates. Also, patient characteristics, disease severity, co-morbidity, and concomitant treatment were often poorly described in the trials.

Results of placebo-controlled trials were not incorporated in the meta-analysis, although a review of abstracts indicated that no nitrate appeared to be superior.

The use of drug databases to model effectiveness was limited by the fact that the analysis could not identify motivating factors for prescribing one nitrate over another, nor could it give information on patient outcomes such as worsening of disease, hospitalization or death.
ENDNOTES

